# Book of Abstracts

# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

Faro, Portugal, July 1st - 6th 2007

Title: Eleventh European Symposium on Organic Reactivity - Book of Abstracts

Edited by: Pedro M.L. Gonçalves e M.Lurdes S. Cristiano

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## Organizers

CCMAR - Centro de Ciências do Mar

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UNIVERSIDADE DO ALGARVE

# Welcome Address

Dear Colleagues and Friends,

On behalf of the Organising Committee, I have the pleasure and the honour to welcome you to the Eleventh European Symposium on Organic Reactivity (ESOR XI), at the University of Algarve, in Faro.

It is extremely rewarding that so many leading scientists are participating in this meeting, making ESORXI one of the main scientific events in 2007. We are also very proud that the Symposium is held in Portugal.

The scientific focus of the ESOR Symposia is Organic Reactivity. ESOR XI aims at highlighting recent achievements in this highly interdisciplinary field of research and further enlarge its frontiers. The Symposium comprises state of the art lectures and communications under three major topics: (i) Structure versus chemical reactivity and biochemical functions, (ii) New sustainable processes and (iii) New materials and molecular machines. The scientific level of all contributions will undoubtly meet the usuall critaria of excellence in ESOR Symposia, emphasising once more the primordial role of Physical Organic Chemistry as a core subject in the development of modern science.

We hope that this opportunity to exchange knowledge and create grounds for scientific cooperations will be scientifically challenging and pleasant, under the ever blue sky of Algarve.

We thank you all for your participation, and wish you a fruitfull and delightfull stay in Portugal.

**Prof. Maria de Lurdes Cristiano**
Symposium chairman

# Welcome to the University of Algarve

It is a great pleasure for me to welcome all the participants of ESOR-XI which, this year, takes place at the University of Algarve.

In spite of being one of the youngest of the state Universities in Portugal, the University of Algarve can already claim recognition from the international scientific community.

Our activities emphasize the importance of scientific research as a necessary basis to ensure a high quality teaching, a good capability for knowledge transfer and a committed role in the development of the Algarve region.

Our academic community has just under 10 000 people, distributed across fifty first cycle courses, as well as approximately thirty master courses and in a large number of areas within which the University of Algarve delivers PhD degrees.

The Algarve region, in which the University of Algarve is located, has long-standing traditions and is known for the friendly way in which it treats its visitors. Its relationship with the Mediterranean regions, which have last for thousands of years, and, more recently, also with the North of Europe, have introduced in our customs a special interest in the society of, and in the cooperation with, other peoples.

I hope that your stay in Faro is marked by a high level of scientific debate, as is usual in ESOR meetings, and that you will also enjoy the more informal social gatherings, as well as the exchange of scientific ideas that will make this meeting a successful one.

# International Advisory Board

Peter Chen (Zurich, Switzerland)
Mirjana Eckert-Maksic (Zagreb, Croatia)
Jacques Fastrez (Louvain-la-Neuve, Belgium)
Florian Hollfelder (Cambridge, England)
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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## General Information

## Symposium Location

The symposium will be held at the Campus of the University of Algarve situated in Gambelas, about 5-6 Km away from the city of Faro and 2 Km away from Faro Airport and Praia de Faro.

## Lecture Halls

Plenary and Invited Lectures will be held at the main University Auditorium. In parallel Sessions, the Auditorium will be used for Session A, and Theatre B, located by the Auditorium, for Session B. Both rooms are equipped with facilities for power point presentation and overhead projection.

## Symposium Office

The Symposium desk will be located in the Hall by the Auditorium during Lecture periods and, on Sunday 1st, at the City Museum.

## Symposium Office Hours

| | | |
|---|---|---|
| Sunday, July 01 | 17:00 – 21:30 | City Museum |
| Monday, July 02 | 8.00 - 19.00 | Auditorium Hall |
| Tuesday, July 03 | 8.30 - 13.00 | Auditorium Hall |
| Wednesday, July 04 | 8.30 - 19.00 | Auditorium Hall |
| Thursday, July 05 | 8.30 - 19.00 | Auditorium Hall |
| Friday, July 06 | 8.30 - 13.00 | Auditorium Hall |

# Meals

Lunch is free for active participants and will be served every day from 12:30 to 14:00 at the University Restaurant, situated by the Auditorium ( building 6, please refer to the map of the campus).

Tickets for lunch will be provided to participants at the Registration desk, together with all other Symposium documentation, on arrival.

# Badges

The badge must be worn at all times during the conference.

A colour coding has been adopted for easy identification:

| | | |
|---|---|---|
| Plenary and Invited Speakers | - | Yellow |
| Members of the Organising Committee | - | Orange |
| All other participants | - | White |
| Accompanying Persons | - | Blue |

# Banking

There is a bank with ATM-service at the main entrance of the campus.

Opening hours: 8:30 – 15:00

Closed at Saturday and Sunday

24h ATM-service

# Local Transportation

The organisation will provide a bus service from the hotels to the Campus at 8.00 am on Monday 2d and at 8.30 on the other days, and from the Campus to the hotels at the end of the schedulled program. There are normal buses between Faro and the University Campus every 30 minutes, in case participants need to return earlier to the hotel. The bus drive between the Campus and the city centre "Docas" (marina, in front of hotels Eva and Faro) takes 30 minutes.

# ESOR XI

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## Social Program

## Sunday, 1st of July - Welcome Reception

An informal get-together will be offered to all participants at the City Museum, located in Faro Historical Center, inside the City Walls, behind the Cathedral. The Museum is at walking distance from all Hotels in Faro.

Time: 19:30 - 21:30

## Tuesday, 3rd of July - Conference Excursion

The Conference excursion will be held on Tuesday afternoon and is free to all participants. Buses depart from the University Campus, outside the Auditorium, by 14.30.

### *"Historical Algarve"*

The tour runs along the coast to the west to some of the most interesting parts of the Algarve.

From the Campus we drive to LAGOS one of the most picturesque towns of the ALGARVE. In LAGOS, participants are escorted to appreciate the ancient slave market, the statue of Prince Henry the Navigator and the Golden Chapel of St Anthony.

Then, we proceed to Ponta da Piedade, famous for its beautiful rock formations that you can admire.

On the way back to the hotel we make a stop at SILVES, the former Moorish capital of the ALGARVE and visit it's Castle and Museum. Refreshments will be offered in Silves.

## Wednesday, 4th of July - Concert

After the Poster Session, an informal dinner will be served to all participants. Then, a concert delivered by the Algarve Philarmonic Orchestra will be offered after dinner.

Time: 21:30

## Thursday, 5th of July - Conference Dinner

The conference dinner will be held at Quinta de Nossa Senhora Menina. Tickets are required. Participants that have not included the dinner in their online registration and desire to go, may purchase the tickets at the Conference desk until Tuesday.

The price is € 50.00.

Time: 20:30

## Excursion for acompanying persons

## *"Unspoilt Algarve"*

The excursion starts with a visit to ESTOI, with a chance to explore the palace and its magnificent gardens.

Proceed to OLHÃO, a traditional fishing village, renowned for the cube-shaped white-washed houses. Here you have the opportunity to explore the famous market with its huge selection of fish. There also several stalls where you can bargain hunt for souvenirs.

Continue to TAVIRA, known as the town of the 22 churches. See the Arab fortress and the Roman Bridge dating from the IV century.

The next stop will be at STA. LUZIA, a small fishermen's village known for it's specialty on octopus fishing. Tour ends in FARO the capital of the Algarve where you can visit the Cathedral.

Wednesday 4th, 9.00-1700. The price is € 30.00 per person, for a minimum of 20 persons.

# ESOR XI

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## Scientific Program

## Sunday 01

| | |
|---|---|
| 17:00-19:30 | REGISTRATION (at the City Museum) |
| 19:30-21:30 | WELCOME RECEPTION (at the City Museum) |

## Monday 02

| | | | | |
|---|---|---|---|---|
| 8:30-9:00 | Opening Ceremony | | | |
| **Chairperson** | **Rui Moreira** | | | |
| 9:00-10:00 | PL01 | Gary Posner | | |
| 10:00-11:00 | PL02 | Jean-Marie Aubry | | |
| 11:00-11:30 | Coffee Break | | | |
| **Chairperson** | **Jan Engberts** | | | |
| 11:30-12:00 | IL01 | Andrée Kirsch- De Maesmeker | | |
| 12:00-12:30 | IL02 | Manuel Garcia Basallote | | |
| 12:30-14:30 | Lunch | | | |
| **Chairperson** | **Arturo Santaballa** | | **Rory M. O'Ferral** | |
| 14:30-14:50 | OP01 | M. Schmittel | OP02 | W.J. Spillane |
| 14:50-15:10 | OP03 | G. Saielli | OP04 | H.W. Lee |
| 15:10-15:30 | OP05 | L. Cruzeiro | OP06 | I. Pintanida |
| 15:30-15:50 | OP07 | C. Galli | OP08 | A. O'Donoghue |
| 15:50-16:10 | OP09 | H. Yamataka | OP10 | S. Kobayashi |
| 16:10-16:40 | Coffee Break | | | |
| **Chairperson** | **Tom W. Bentley** | | **Eduardo Humeres** | |
| 16:40-17:00 | OP11 | M. Mishima | OP12 | I. Watt |
| 17:00-17:20 | OP13 | M. Yanez | OP14 | C. McDonnel |
| 17:20-17:40 | OP15 | T.B. Phan | OP16 | F. Schoenebeck |
| 17:40-18:00 | OP17 | G. Gadanji | OP18 | P.M. Ferreira |

## Tuesday 03

| | | | | |
|---|---|---|---|---|
| **Chairperson** | **Manuel Yañez** | | | |
| 9:00-10:00 | PL03 | Yitzak Apeloig | | |
| 10:00-11:00 | PL04 | François Diederich | | |
| 11:00-11:30 | Coffee Break | | | |
| **Chairperson** | **Anthony Kirby** | | | |
| 11:30-12:00 | IL03 | Luigi Mandolini | | |
| 12:00-12:30 | IL04 | Dean J. Tantillo | | |
| 12:30-14:30 | Lunch | | | |
| 14:30 | **CONFERENCE EXCURSION** | | | |

## Wednesday 04

| | | | | |
|---|---|---|---|---|
| **Chairperson** | **François Terrier** | | | |
| 9:00-10:00 | PL05 | William Jorgensen | | |
| 10:00-11:00 | PL06 | Herbert Mayr | | |
| 11:00-11:30 | Coffee Break | | | |
| **Chairperson** | **Michael Page** | | | |
| 11:30-12:00 | IL05 | Shinro Yasui | | |
| 12:00-12:30 | IL06 | Luís Garcia-Rio | | |
| 12:30-14:30 | Lunch | | | |
| **Chairperson** | **Hans U. Siehl** | | **José Ramon Leis** | |
| 14:30-14:50 | OP19 | J. Fastrez | OP20 | H. Maskill |
| 14:50-15:10 | OP21 | S. Grabowski | OP22 | Z. Maksic |
| 15:10-15:30 | OP23 | P. Guthrie | OP24 | O. Al-Dusouqui |
| 15:30-15:50 | OP25 | M.J. Queiroz | OP26 | N. El-Awadi |
| 15:50-16:10 | OP27 | R. Goumont | OP28 | C. Bravo-Diaz |
| 16:10-16:40 | Coffee Break | | | |
| **Chairperson** | **Carlos Afonso** | | | |
| 16:40-17:10 | IL07 | Rui Fausto | | |
| 17:10-17:40 | IL08 | Gerd Kaupp | | |
| 17:40 | **POSTER SESSION (late-afternoon mixer)** | | | |
| 21:30 | **Concert** | | | |

# Thursday 05

| | | | | |
|---|---|---|---|---|
| **Chairperson** | **Gianfranco Scorrano** | | | |
| 9:00-10:00 | PL07 | Cinzia Chiappe | | |
| 10:00-11:00 | PL08 | José Artur Martinho Simões | | |
| 11:00-11:30 | Coffee Break | | | |
| **Chairperson** | **Michael Schmittel** | | | |
| 11:30-12:00 | IL09 | Addy Pross | | |
| 12:00-12:30 | IL10 | John Richard | | |
| 12:30-14:30 | Lunch | | | |
| **Chairperson** | **Masaaki Mishima** | | **Jacques Fastrez** | |
| 14:30-14:50 | OP29 | A.J. Kirby | OP30 | S. Fornarini |
| 14:50-15:10 | OP31 | M.I. Page | OP32 | P. Burk |
| 15:10-15:30 | OP33 | I.B. Engberts | OP34 | L. Branco |
| 15:30-15:50 | OP35 | T.W. Bentley | OP36 | E. Humeres |
| 15:50-16:10 | OP37 | B. Cardey | OP38 | M.C. Rezende |
| 16:10-16:40 | Coffee Break | | | |
| **Chairperson** | **Mirjana Eckert-Maksic** | | **Marie Françoise Ruasse** | |
| 16:40-17:00 | OP39 | R.More O'Ferral | OP40 | Z. Rappoport |
| 17:00-17:20 | OP41 | J.A. Santaballa | OP42 | M. Charton |
| 17:20-17:40 | OP43 | H. U-Siehl | OP44 | F. Holfelder |
| 17:40-18:00 | OP45 | A. Sartorel | OP46 | C. Cardellicchio |
| 18:00-18:20 | OP47 | A Stanger | OP48 | A. Lapi |
| 20:30 | **CONFERENCE DINNER** | | | |

# Friday 06

| | | |
|---|---|---|
| **Chairperson** | **Carlo Galli** | |
| 9:00-10:00 | PL09 | Ben Feringa |
| 10:00-11:00 | PL10 | Colin Suckling |
| 11:00-11:30 | Coffee Break | |
| **Chairperson** | **Amnon Stanger** | |
| 11:30-12:30 | PL11 | Sebastião Formosinho |
| 12:30-13:00 | **CLOSING REMARKS** | |

# Journal of Physical Organic Chemistry Award

The 2007 Journal of Physical Organic Chemistry Award for Early Excellence in the Field of Physical Organic Chemistry

This award is given annually to recognize the accomplishments of an individual working in the field of physical organic chemistry or applying the principles of this field to other areas. In even-numbered years, the award is presented at the Reaction Mechanisms Conference (RMC). In odd-numbered years, it is presented at the European Symposium on Organic Reactivity (ESOR). The awardee will present a lecture at the meeting. The award consists of a stipend of $5000 (from which travel expenses are paid) and a plaque. There are no limitations on nationality. At the time of nomination, the nominee must be no more than six years from the beginning of the first independent appointment.

Nominations shall contain (1) a statement in fewer than 1000 words of the nominee's research accomplishments, (2) a list of publications in print or in press, and (3) a curriculum vitae. The CV must include biographical information, lists of honors, financial support, invited talks, and arranged talks (those submitted to conferences or arranged for a tenure tour). The nominee or a designee may prepare the nomination. In addition, at least two seconding letters should be submitted from individuals knowledgeable in the nominee's field.

Nominations and seconding letters should be submitted to the editor of the Journal of Physical Organic Chemistry by electronic mail before February 1 2007 (jlambert@northwestern.edu).

**The 2007 Journal of Physical Organic Chemistry Award was attributed to Dean J. Tantillo, Assistant Professor at University of California-Davis.**

# Plenary Lectures

| | |
|---|---|
| **PL01** | Trioxanes: From Mechanistic Understanding Toward Chemotherapy<br>**Gary Posner**<br>*The Johns Hopkins University, Baltimore, Maryland, USA* |
| **PL02** | Chemical Generation of Singlet Oxygen in Single Phase and Multiphase Microemulsion Systems for the Catalytic Oxidation of Organic Substrates<br>**Jean-Marie Aubry**<br>*ENSCL, Cité Scientifique, Villeneuve d'Ascq, France* |
| **PL03** | Recent Studies of Reactive Tri-Coordinate Silicon Intermediates<br>**Yitzhak Apeloig**<br>*Israel Institute of Technology, Haifa, Israel* |
| **PL04** | Advanced Materials by Acetylene and Fullerene Scaffolding<br>**François Diederich**<br>*Laboratorium für Organische Chemie, Zürich, Switzerland* |
| **PL05** | QM/MM Simulations of Organic and Enzymatic Reactions<br>**William L. Jorgensen**<br>*Yale University, Connecticut, USA* |
| **PL06** | Do General Nucleophilicity Scales Exist?<br>**Herbert Mayr**<br>*Universität München, München, Germany* |
| **PL07** | Structure of Ionic Liquids and Their Solvent Properties<br>**Cinzia Chiappe**<br>*Università Pisa, Pisa, Italy* |
| **PL08** | Energetics of Free Radicals<br>**José A. Martinho Simões**<br>*Universidade de Lisboa, Lisboa, Portugal* |
| **PL09** | Molecular Switches and Motors at Work<br>**Ben L. Feringa**<br>*University of Groningen, Nijenborgh, Groningen, The Netherlands* |
| **PL10** | Structure and Selectivity in the Binding of Small Ligands to DNA and their Consequences<br>**Colin J. Suckling**<br>*University of Strathclyde, Glasgow, Scotland* |
| **PL11** | Absolute rate calculations of proton transfers in solution and in enzymes, and the rates of $S_N2$ reactions and their relation to molecular and solvent properties<br>**Sebastião J. Formosinho**<br>*University of Coimbra, Portugal* |

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| **IL01** | Ru(II) complexes, DNA, and light, for the construction of biomolecular tools.<br>**A. Kirsch – De Mesmaeker**<br>*Université Libre de Bruxelles, Bruxelles, Belgium* |
| **IL02** | The Mechanism of "Slow" Proton Transfers to Metal Hydrides in Organic Solutions: The Proton Donor and Acceptor, the Solvent and the Ion Pairs Provide a Variety of Reaction Pathways<br>**Manuel G. Basallote**<br>*Universidad de Cádiz, Puerto Real, Cádiz, Spain* |
| **IL03** | The Dynamic Covalent Chemistry of Cyclophane Formaldehyde Acetals<br>**Luigi Mandolini**<br>*Università La Sapienza, Roma, Italy* |
| **IL04** | Mechanistic Studies on Carbocation Cascades Occurring During the Biosynthesis of Polycyclic Natural Products<br>**Dean J. Tantillo**<br>*University of California—Davis, USA* |
| **IL05** | Kinetics-Energetics Relationship in the Electron Transfer from Trivalent Phosphorus Compounds to the Singlet Photo-Excited Sensitizers<br>**Shinro Yasui**<br>*Tezukayama University, Nara, Japan* |
| **IL06** | Investigation of Surfactant-Cyclodextrin Mixed Systems by Means of Chemical Kinetics<br>**Luis García-Río**<br>*Universidad de Santiago, Santiago de Compostela, Spain.* |
| **IL07** | Ground and Excited State Photochemistry of Matrix-Isolated Organic Molecules<br>**Rui Fausto**<br>*University of Coimbra, Portugal* |
| **IL08** | Waste-free synthesis and production all across chemistry with the benefit of self-assembled crystal packings<br>**Gerd Kaupp**<br>*University of Oldenburg, Germany* |
| **IL09** | How Can a Chemical System Act Purposefully?<br>**Addy Pross**<br>*University of the Negev, Beer Sheva, ISRAEL* |
| **IL10** | Utilization of Phosphate Binding Energy in Catalysis by Small and Large Molecules<br>**John P. Richard**<br>*University at Buffalo, Buffalo, NY, USA* |

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| **OP01** | Non-statistical dynamic effects before and after the transition state! Intra *versus* intermolecular kinetic isotope effects suggest a broad transition state<br>**Michael Schmittel,** Chandrasekhar Vavilala, and Ralph Jaquet<br>*Universität Siegen, Siegen, Germany* |
| **OP02** | Aminolysis of Sulfamate Esters – Models for Enzymatic Reactions<br>**William J. Spillane,** Cheryl J. A. McCaw and Andrew O'Byrne<br>*National University of Ireland, Galway, Ireland* |
| **OP03** | Fries Rearrangement of Aryl Formates: a Mechanistic Study by Means of $^{1}H$, $^{2}H$ and $^{11}B$ NMR Spectroscopy and DFT Calculations<br>A. Bagno, W. Kantlehner, R. Kress, **G. Saielli** and E. Stoyanov<br>*Istituto per la Tecnologia delle Membrane del CNR, Sezione di Padova, Italy* |
| **OP04** | Kinetics and Mechanism of the Aminolysis of Aryl Phenyl Chlorothiophosphates with Anilines<br>**H. W. Lee**, B-S. Lee, C. K. Kim, A. K. Guha, S. Dey, E. U. Hoque, C. H. Lim<br>*Inha University, Incheon, Korea* |
| **OP05** | Proteins multi-funnel energy landscape and misfolding diseases<br>**L. Cruzeiro**<br>*University of Algarve, Faro, Portugal* |
| **OP06** | Interactions of bis-urea bridged bis-phenanthridines with DNA and RNA<br>**Ivo Piantanida**, Marijana Radić Stojković<br>*Ruđer Bošković Institute, Zagreb, Croatia* |
| **OP07** | Oxidation of Amides Employing Aminoxyl Radicals: Mechanistic Features<br>**C. Galli**, P. Gentili, and R. Vadalà<br>*Università 'La Sapienza', Roma, Italy* |
| **OP08** | Origin of the Catalytic Specificities of *Methylglyoxal Synthase* and *Triosephosphate Isomerase*<br>**AnnMarie C. O'Donoghue**, Barry J. Dodd, and Terence Flynn<br>*University of Durham, UK* |
| **OP09** | A combined Experimental-Computational Study on the Proton-Transfer Reaction of Phenylnitromethane<br>**Hiroshi Yamataka**, Nobuyoshi Yoshimura, Yutaka Kitamura, Munetoshi Shibata, Daigo Sawaki, and Hisashi Shimazu<br>*Rikkyo University, Tokyo, Japan* |
| **OP10** | DABCO or DMAP – What Makes Their Difference in Organocatyalysis?<br>**S. Kobayashi**, M. Baidya, and H. Mayr<br>*Universitaet München, München, Germany* |

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| **OP11** | Nucleophilicity of Alcohols and Acids in the Reaction of Carbocations<br>M.N. Kumara, T. Nakahara, and **M. Mishima**<br>*Kyushu University, Fukuoka, Japan* |
| **OP12** | Kinetiks Isotope Effects in Thermoneutral Intramolecular Proton Transfers from Carbon Acids<br>Nick Backstrom and **Ian Watt**<br>*The University of Manchester, Manchester, UK* |
| **OP13** | Reactivity of Model Biochemical Systems with Divalent Metal Cations<br>**M. Yáñez**<br>*Universidad Autónoma de Madrid, Madrid, Spain* |
| **OP14** | By How Much is Protonated Benzene Stabilised by Coordination to Iron Tricarbonyl? - Investigating A Route from *Cis*- to *Trans*-Arenedihydrodiols<br>**C. Mc Donnell**, M. Galvin and R. A. More O'Ferrall<br>*Dublin Institute of Technology, Dublin, Ireland* |
| **OP15** | Can the Change from $S_N1$ to $S_N2$ Mechanism be Predicted?<br>**T. B. Phan** and H. Mayr<br>*LMU München, München, Germany* |
| **OP16** | Organic Super Electron Donors:<br>The First Powerful Reductions Performed By Neutral Organic Molecules<br>**F. Schoenebeck**, S.-Z. Zhou, and J. A. Murphy<br>*University of Strathclyde, Glasgow, UK* |
| **OP17** | Interfacing experiment and quantum chemical calculations in transition metal chemistry:<br>A comparative study of structural and magnetic properties of [$(Ligand)_nNi$--$CH_2$-$CH_2$-COO-] complexes and their role in a hypothetic catalytic cycle towards acrylic acid<br>**G.Gadanji** and H.-U. Siehl<br>*University of Ulm, Germany* |
| **OP18** | Reactivity of Dehydroamino Acid Derivatives Towards *N*-Bromosuccinimide<br>**P. M. T. Ferreira**, L. S. Monteiro, M. G. Pereira and L. Ribeiro<br>*University of Minho, Braga, Portugal* |
| **OP19** | Why is the penicillin binding protein of *T. elongatus* not a β-lactamase?<br>C. Labarbe, C. Evrard, J.-P. Declercq, P. Soumillion and **J. Fastrez**<br>*Université Catholique de Louvain, Louvain-la-Neuve, Belgium* |
| **OP20** | Mechanism and substituent effects in the acid-catalysed hydrolysis of methoxy-substituted trityl 2,2,2-trifluoroethyl ethers<br>M. Canle-Lopez, I. Demirtas, and **H. Maskill**<br>*University of Newcastle, Newcastle, UK* |

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| **OP21** | Different types of H…H interactions<br>**S.J. Grabowski**<br>University of Łódź, Łódź ,Poland |
| **OP22** | The Origin of Aromaticity – Important Role of the Sigma Framework<br>**Z.B. Maksić**<br>*Faculty of Science and Mathematics, Zagreb, Croatia* |
| **OP23** | Predicting the rates of organic reactions in solution:<br>The aldol addition reaction.<br>**J. Peter Guthrie**<br>*University of Western Ontario, Ontario, Canada* |
| **OP24** | Qualitative/Quantitative Correlation of Acidities and Rates of Gas-Phase Pyrolysis of Picolinic Acids and Corresponding Ethyl Esters<br>Nouria A. Al-Awadi, Moayyad A. Al-Sawah, Hicham H. Dib,<br>**Osman M. E. El-Dusouqui**<br>*Kuwait University, Safat, Kuwait* |
| **OP25** | Rectivity of Methyl Esters of *N*-Boc-β,β-disubstituted Dehydroamino Acids Towards the Synthesi of Lactams ans Lactones<br>**M-J.R.P. Queiroz**, P.M.T. Ferreira, A.S. Abreu, M.S.D. Carvalho, R.C. Calhelha<br>*University of Minho, Braga, Portugal* |
| **OP26** | Kinetics, Mechanism and Element / Substituent Effects of<br>Gas-Phase Pyrolysis of (P) and (As) Ylides<br>**Nouria A. Al-Awadi**, Rasha F. Al-Bashir, Osman M. E. El-Dusouqui<br>*Kuwait University, Safat, Kuwait* |
| **OP27** | The Versatile Reactivity of a Superelectrophilic Nitroolefin : 4-Nitrobenzodifuroxan.<br>**R. Goumont**, S. Lakhdar, G. Berionni, T. Boubaker and F. Terrier<br>*University of Versailles, Versailles, France* |
| **OP28** | O-Copuling Reactions: Formation and Decomposition of Transient Diazo Ethers in the Course of Reactions between Arenediazonium Ions and different alcohols.<br>**Bravo-Díaz, C.**, Pazo Llorente, R., Fernández-Alonso, A., Losada-Barreiro, S., Sánchez-Paz, Verónica.<br>*Universidad de Vigo, Vigo, Spain* |
| **OP29** | Thoughts on enzymes and models<br>**Anthony J. Kirby**<br>*University Chemical Laboratory, Cambridge, UK* |

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| **OP30** | Mimicking Compound I by Naked, High-valent Oxo Iron Intermediates<br>M. E. Crestoni, and **S. Fornarini**<br>*Università di Roma, Roma, Italy* |
| **OP31** | What is the Role of the Metal-ion in Metallo β-Lactamases?<br>**M. I. Page** and A. Badarau<br>*University of Huddersfield, Huddersfield, UK* |
| **OP32** | The limits of growth for superacidity and superbasicity of neutral Brønsted acids and bases<br>**Peeter Burk**, Ilmar A. Koppel, Ivo Leito, and Kaido Tämm<br>*Institute of Chemical Physics, University of Tartu, Tartu, Estonia* |
| **OP33** | pH-Dependent Aggregation of Sugar-based Gemini Surfactants<br>Jaap E. Klijn, Marc A.C.Stuart, Marco Scarzello and **Jan B.F.N.Engberts**<br>*University of Groningen, Groningen, The Netherlands* |
| **OP34** | Ionic Liquid Interactions with Organic Solutes<br>**L.C. Branco**, S. Otto, J.G.Crespo and C.A.M. Afonso<br>*Instituto Superior Técnico, Lisboa, Portugal* |
| **OP35** | Substituent Effects on the Formation of Cations from Acid Chlorides<br>**T. W. Bentley**<br>*University of Wales, Swansea, UK* |
| **OP36** | Reactivity of the Intermediates of the Reduction of $SO_2$ on carbons. The Use of XPS Spectra for the Study of Reaction Mechanisms<br>**Eduardo Humeres**, Karen Mendes de Castro, Regina de F.P.M. Moreira, Maria da Gloria B. Peruch, Wido H. Schreiner, Abil E. Aliev, Moisés Canle, J. Arturo Santaballa, Isabel Fernández.<br>*Universidade Federal de Santa Catarina, Brazil* |
| **OP37** | Mechanism of thiol oxidation by the superoxide radical : a theoretical study<br>**B. Cardey**, S. Foley, M. Enescu<br>*University of Franche-Comté, Besançon, France* |
| **OP38** | Hardness as an intrinsic property for the prediction of solvatochromic behaiour<br>**Marcos Caroli Rezende** and Moisés Domínguez<br>*Universidad de Santiago, Santiago, Chile* |

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| **OP39** | Stereoselectivity in the Formation and Reaction of β-Hydroxycarbocations<br>J. R. Keeffe, J. Kudavalli, **R. A. More O'Ferrall**, D. A. Lawlor and S. N. Rao<br>*University College Dublin, Dublin, Ireland* |
| **OP40** | The First Solid Enols of Anhydrides<br>Jinhua Song, Yi Xiong Lei and **Zvi Rappoport**<br>*The Hebrew University, Jerusalem, Israel* |
| **OP41** | Radical Species Derived from s-Triazine Pesticides: Geometry, Thermodynamics and Kinetics<br>M. I. Fernández, Josep M. Oliva, M. Canle L., and **J.A. Santaballa**<br>*University of A Coruña, Coruña, Spain* |
| **OP42** | The relationship between group electronegativities and substituent constants.<br>**Marvin Charton**<br>*Pratt Institute, Brooklyn, New York, USA* |
| **OP43** | Quantum Chemical Investigation of Carbon-Carbon<br>Spin-Spin Coupling Constants<br>**Hans-Ullrich Siehl**, Innokentiy Elanov<br>*University of Ulm Albert Einstein Allee 11, Ulm, Germany* |
| **OP44** | Polyethelene Imine Derivatives Accelerate Phosphate Transfer in the Absence of Metal<br>F. Avenier, J. Domingos, L. D. Van Vliet and **Florian Hollfelder**<br>*University of Cambridge, Cambridge, UK* |
| **OP45** | Asymmetric Tetraprotonation of γ-$[(SiO_4)W_{10}O_{32}]^{8-}$ triggers catalytic Epoxidation with $H_2O_2$<br>**A. Sartorel**, M. Carraro, A. Bagno, G. Scorrano and M. Bonchio<br>*University of Padova, Padova, Italy* |
| **OP46** | Enantioselective Oxidation of Aryl Benzyl Sulfides in the Presence of Chiral Titanium Complexes: a Proposed Model<br>**C. Cardellicchio**, F.Naso, and M. A.M. Capozzi<br>*University of Bari, Bari, Italy.* |
| **OP47** | A simple and intuitive description of C-H bond energies.<br>**Amnon Stanger**<br>*Technion – Israel Institute of Technology, Haifa, Israel* |
| **OP48** | The Singlet Oxygen Oxidation of Chlorpromazine and Some Phenothiazine Derivatives. Products and Reaction Mechanisms<br>**A.Lapi**, E. Baciocchi, T. Del Giacco, O. Lanzalunga and D. Raponi<br>*Università "La Sapienza," Rome, Italy.* |

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| **PP01** | Reactivity of pure stereoisomers of *N*-Boc-β-dibenzothienyldehydrophenylalanines in a metal-assisted C-N intramolecular cyclization to heterocyclic compounds<br>**Ana S. Abreu**, M. Solange D. Carvalho, Paula M.T. Ferreira, Maria-João R.P. Queiroz<br>*Universidade do Minho, Braga, Portugal* |
| **PP02** | Reactivity control by micellar aggregates: Inhibition of the reaction between 4-nitrobenzenediazonium ions and hydrophilic aminoacids.<br>**Alejandra Fernández-Alonso**, Sonia Losada-Barreiro, Verónica Sánchez-Paz, Carlos Bravo-Diaz<br>*Universidad de Vigo, Vigo, Spain* |
| **PP03** | Structural Analysis of N,N-dimethyl-1,2-benzisothiazol-3-amine 1,1-dioxide by means of Matrix Isolation FTIR Spectroscopy and Quantum Chemical Calculations<br>**R. Almeida**, A. Gómez-Zavaglia, A. Kaczor, M.L. Cristiano and R. Fausto<br>*University of Coimbra, Coimbra, Portugal* |
| **PP04** | New DNA Directed Trioxanes as Potential Antimalarial Agents<br>**Nuna C. P. Araújo**, M. L. Cristiano, P. M. O'Neill<br>*Universidade do Algarve, Faro, Portugal* |
| **PP05** | Functionalised Side-chain 5,9-Diaminobenzo[a]phenoxazi nium Salts: Synthesis and Antimicrobial Activity<br>**S.A. Barros**, V.H.J. Frade, M.J. Sousa, J.C.V.P. Moura and M.S.T. Gonçalves<br>*Universidade do Minho, Braga, Portugal* |
| **PP06** | Catalysis of Aromatic Nucleophilic Substitution Reactions by Glymes and Crown Ethers<br>**Nuno Basílio**, Luis García-Río, Moisés Pérez-Lorenzo<br>*Universidade de Santiago de Compostela, Santiago de Compostela, Spain.* |
| **PP07** | Synthesis of a New Class of Phenanthrolines bearing a Arylthienylimidazo Conjugation Pathway as Nonlinear Optical Chromophores<br>**R. M. F. Batista**, S. P. G. Costa, M. Belsley, C. Lodeiro and M. M. M. Raposo<br>*University of Minho, Braga, Portugal* |
| **PP08** | Kinetics and mechanism of the reaction between 4-hexadecylbenzenediazoni um ions and vitamin C in an emulsified system: Formation of a 3-O-diazo ether intermediate<br>**Carlos Bravo-Díaz**; María José Pastoriza-Gallego; Alejandra Fernández-Alonso; Sonia Losada-Barreiro; Verónica Sánchez-Paz<br>*Universidad de Vigo, Spain* |
| **PP09** | Nucleophilic Reactivity of Imide and Amide Anions<br>**M. Breugst**, T. Tokuyasu, and H. Mayr<br>*Ludwig-Maximilians-Universität, München, Germany* |

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| **PP10** | New Potential *Plasmodium* Cysteine Proteases Inhibitors Incorporating Tetrazoles<br>**Andreia Bringela**, Nuna Araújo, M. Lurdes S. Cristiano<br>*Universidade do Algarve, Faro, Portugal* |
| **PP11** | Reactions of Aryl Chlorothionoformates with Quinuclidines. A Kinetic Study<br>Enrique A. Castro, M. Aliaga, **P. R. Campodonico**, J. R. Leis, L.García-Río, and José G. Santos<br>*Universidad del Desarrollo, Santiago, Chile* |
| **PP12** | Direct Photodegradation and $TiO_2$-photocatalyzed Degradation of Anilide-based Herbicides<br>**M. Canle L.**, M.I. Fernández, S. Rodríguez, J.A. Santaballa, and E. Vulliet<br>*University of A Coruña, A Coruña, Spain.* |
| **PP13** | Oxidation of Pyrimidine Bases: Mechanism of Thymine Chlorination<br>**E. Carro**, M. Canle L., M. Fernández, and J. A. Santaballa<br>*University of A Coruña, A Coruña, Spain* |
| **PP14** | Nitration Mechanism Discussion based in the Correlation of Statistical Models constructed by Experimental Design<br>**Erika C.A.N. Chrisman**<br>*University of Rio de Janeiro, Rio de Janeiro, Brazil* |
| **PP15** | The Elimination Kinetics and Mechanisms of Some Organic Orthoesters in the gas phase<br>Edgar Marquez, Rosa María Domínguez, Armando Herize, Maria Tosta, and **Gabriel Chuchani**<br>*Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela* |
| **PP16** | The Kinetics and Mechanisms of the Gas Phase Elimination of Some Aminoketals<br>José R. Mora, Rosa María Domínguez, Armando Herize, Maria Tosta, and **Gabriel Chuchani**<br>*Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela* |
| **PP17** | Theoretical Study at the MP2 Level of the Gas Phase Elimination Kinetics of N,N-Dimethylglycine, N-Phenylglycine, Picolinic Acid and Their Corresponding Ethyl Esters.<br>Johan R. Perez, M. Loroño, **Tania Córdova**, and Gabriel Chuchani<br>*Universidad Central de Venezuela, Caracas, Venezuela* |
| **PP18** | Living Polymerization of Tri-*O*-propyl-(4-ethynyl)benzyloxy-*p*-*t*-butylcalix[4]arene by a Rh-based Ternary Catalytic System: Synthesis of a Novel Conjugated Calixarene Polymer with Controlled Molecular Weight and MWD<br>**Alexandra I. Costa**, José V. Prata<br>*Instituto Superior de Engenharia de Lisboa, Lisboa, Portugal* |

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| **PP19** | Chlorine Transfer between Amines: A Mechanistic Study<br>Paula Calvo, **Juan Crugeiras**, and Ana Ríos<br>*Universidade de Santiago de Compostela, Santiago de Compostela, Spain* |
| **PP20** | Ester Aminolysis Catalyzed by Polyethilene Glycols<br>N. Basilio, L. García-Río, S. Pérez-Feas, M. Pérez-Lorenzo and **P. Rodríguez-Dafonte**<br>*Universidade de Santiago de Compostela, Santiago de Compostela, Spain* |
| **PP21** | Contribution of Substrate Phosphodianion Group to<br>Enzymatic Catalysis by Methylglyoxal Synthase<br>**Barry J.Dodd**, Terence Flynn and AnnMarie C. O'Donoghue<br>*University of Durham, Durham, UK* |
| **PP22** | Acetylenic Alcohols Used as Corrosion Inhibitors in Acidic Media: Correlation Between Inhibition and Efficiency and Chemical Structure<br>**E.C.S. Elias**, and E.C.A.N. Chrisman<br>*Federal University of Rio de Janeiro, Rio de Janeiro, Brazil* |
| **PP23** | Kinetic Studies on the Photocleavage of Fluorescent Neurotransmitter Conjugates<br>**M. J. G. Fernandes**, M. S. T. Gonçalves and S. P. G. Costa<br>*University of Minho, Braga, Portugal* |
| **PP24** | Reduction of aldimines by heterogeneous catalytic transfer reduction<br>**C. S. C. Fonseca**, R.A.W.Johnstone<br>*University of Algarve, Faro, Portugal* |
| **PP25** | Mechanistic Investigations on the Photochemistry of 5-Allyloxy-1-phenyl-1H-tetrazoles in Solution<br>**L.M.T. Frija**, I.V. Khmelinskii, M.L.S. Cristiano, C. Serpa and R. Fausto<br>*University of Algarve, Faro, Portugal* |
| **PP26** | Influence of Colloid Suspensions of Humic Acids upon the alkaline hydrolysis of N-Methyl-N-Nitroso-P-Toluene Sulfonamide<br>M. Arias, **D. Fernández-Gándara**, L. García-Río, J.C. Mejuto<br>*University of Vigo at Ourense, Ourense, Spain* |
| **PP27** | Activation of double and triple bonds in unsaturated hydrocarbons by the Ru(001) surface<br>**Ana. R. Garcia**, Ricardo B. Barros and Laura M. Ilharco<br>*Instituto Superior Técnico, Lisboa, Portugal* |
| **PP28** | Photophysics of Environmentally Relevant Phenylurea Herbicides<br>**C. Martínez García**, M. Canle L., and J.A. Santaballa<br>*University of A Coruña, A Coruña, Spain* |

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| **PP29** | Use Of Physical Organic Chemistry Methodology As A Tool To Investigate The Properties Of Complex Systems Formed By Cyclodextrins And Surfactants<br>**L. García-Río**, M. Méndez<br>*Universidad de Santiago, Santiago de Compostela, Spain.* |
| **PP30** | Kinetics and Mechanims of the Pyridinolysis of S-Aryl Chlorodithioformates<br>Enrique A. Castro, **Marcela Gazitúa**, and José G. Santos<br>*Pontificia Universidad Católica de Chile, Santiago, Chile.* |
| **PP31** | Site-directed Mutagenesis of Laccase from Fungus *Trametes Versicolor*: Investigating effects responsible for the Reactivity of Substrates<br>C. Galli, **P. Gentili**, C. Jolivalt, and R. Vadalà<br>*Università 'La Sapienza', Roma, Italy* |
| **PP32** | Dipeptide reactivity towards 2,5-diketopiperazine formation:<br>in search of suitable carriers for intramolecularly-activated prodrugs<br>**José R. B. Gomes** and Paula Gomes<br>*Universidade do Porto, Porto, Portugal* |
| **PP33** | Kinetic Study of Nitrosation of Guanidines<br>I. Fernández, **P. Hervés**, M. Parajó<br>*University of Vigo, Vigo, Spain* |
| **PP34** | Effects of Micellar Aggregates of SDS on the Reaction of Local Anaesthetics with Nitrous Acid<br>**E. Iglesias**, I. Brandariz, and F. Penedo<br>*University of La Coruña, La Coruña, Spain* |
| **PP35** | An experimental study of an $S_N2$ reaction pathway<br>of acyl compounds<br>**Mika Katayama**, Nobuyoshi Yoshimura, and Hiroshi Yamataka<br>*University of Rikkyo, Tokyo, Japan* |
| **PP36** | Electrophilicity of Substituted Diethyl Benzylidenemalonates<br>**O. Kaumanns** and H. Mayr<br>*Ludwig-Maximilians-Universität, München, Germany* |
| **PP37** | The Influence of *O*-Methylation on *cis*/*trans* Rate Ratios in the Acid-catalysed Dehydration of Arene Dihydrodiols<br>D. D. Coyne, **J. Kudavalli**, D. A. Lawlor, R. A. More O'Ferrall and S. N. Rao<br>*University College Dublin, Dublin, Ireland* |
| **PP38** | Water Interaction With Oxo-Thione Derivatives of 2,7-Dimethyl-1,2,4-Triazepines<br>**Al Mokhtar Lamsabhi**<br>*Universidad Autónoma de Madrid, Madrid, Spain* |

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| **PP39** | Cis-trans Selectivity of Nucleophilic Attack on β-Hydroxyarenonium Ions<br>Rory A. More O'Ferrall and **David A. Lawlor**<br>*University College Dublin, Dublin, Ireland* |
| **PP40** | Mechanism-Guided Studies of Asymmetric Organocatalysis of the Mannich Reaction.<br>**A. G. Lindsay** and A. C. O'Donoghue<br>*Durham University, Durham, UK* |
| **PP41** | The Exocyclic Amino Group of a Neighbouring Adenosine Moiety is Involved in the Transesterification of Phosphodiester Bonds of RNA<br>**H. Linjalahti** and S. Mikkola<br>*University of Turku, Turku, Finland* |
| **PP42** | Pseudo-zero order reaction in solution<br>**Rui M. S. Loureiro**, R. A. W. Johnstone and J. Phillip Sankey<br>*University of Liverpool, Liverpool, UK* |
| **PP43** | Hydrolysis of Sulfamate Esters and Sulfamoyl Chlorides<br>**Neil P. Maguire**, Cheryl J. A. McCaw and William J. Spillane<br>*National University of Ireland, Galway, Ireland* |
| **PP44** | Synthesis and Aromatisation Reactions of Arene Hydrates<br>**M. J. O'Mahony** and A. C. O'Donoghue<br>*Durham University, Durham, UK* |
| **PP45** | Acid-Catalysed Hydrolysis of N-Acylsulfamate Esters<br>**Jean-Baptiste Malaubier** and William J. Spillane<br>*National University of Ireland, Galway, Ireland* |
| **PP46** | Evaluation of Binding Constants of Different Flavours to Cyclodextrins<br>G. Astray, L. García-Río, **J.C. Mejuto**<br>*University of Vigo at Ourense, Ourense, Spain* |
| **PP47** | Transesterification of RNA model in buffer solutions in $H_2O$ and $D_2O$<br>N. Virtanen, V. Nevalainen, T. Lehtinen and **S. Mikkola**<br>*University of Turku, Turku, Finland* |
| **PP48** | Prototropic Tautomerism of Selenouracils<br>Cristina Trujillo, **Otilia Mó** and Manuel Yáñez<br>*Universidad Autónoma de Madrid, Cantoblanco, Madrid, Spain.* |
| **PP49** | Application of LSER methodology to the modelling of Quinoline-Solvent (Alkan-1-ol/DMF Mixtures) Intercation Mechanism of Solvation<br>**M.L. Moita** and L.M. Pinheiro<br>*Universidade de Lisboa, Lisboa, Portugal* |

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| **PP50** | *O*-(*tert*-Butyloxycarbonyl) hydroxyamino acids: synthesis and reactivity<br>**L. S. Monteiro**, P. M. T. Ferreira, M. G. Pereira and L. Silva<br>*University of Minho, Braga, Portugal* |
| **PP51** | A kinetic study of oxygen transfer from an oxygen donor to the complex Dichlorodi oxomolybdenum(VI)-bis(N,N-dimethylformamide), an effective epoxidation catalyst<br>**José A. Moreira**, Márcia Pessêgo, André D. Lopes, João P. Lourenço, Carla Grosso and Isabel S. Goncalves<br>*University of the Algarve, Faro, Portugal* |
| **PP52** | 2-Aryl-4-chloro-3-halogenoquinolines as Substrates for the Synthesis of 2,3-Disubstituted Primary 4-Aminoquinoline Derivatives<br>**Malose J. Mphahlel** and Vathiswa Mtshemla<br>*University of South Africa, Pretoria, South Africa* |
| **PP53** | Reactivity of 4-Oxo-β-Lactams as Novel Inhibitors of Elastase<br>**J. Mulchande**, W. Tsang , M. I. Page, J. Iley and R. Moreira<br>*University of Lisbon, Lisbon, Portugal* |
| **PP54** | Theoretical Study on the Hydration Structures<br>Determining the Relative Acidities of Substituted Phenols<br>**K. Nakata**, M. Fujio, K. Nishimoto, and Y. Tsuno<br>*Hosei University, Tokyo, Japan* |
| **PP55** | Application of LSERs to the Solution Enthalpies of Adamantane Derivatives in Protic and Aprotic Solvents at 298.15 K<br>**N. Nunes**, **L. Moreira**, R. E. Leitão, and F. Martins<br>*Instituto Superior de Engenharia de Lisboa, Lisboa, Portugal* |
| **PP56** | C–H Bond Dissociation Enthalpies in Indene and Indane<br>**Paulo M. Nunes**, Rui M. Borges dos Santos, and José A. Martinho Simões<br>*Universidade de Lisboa, Lisboa, Portugal* |
| **PP57** | Investigation of a Metal Complexing Route to Form Arene *Trans*-dihydrodiols<br>**C. O'Meara**, C. McDonnell and R. More O'Ferrall<br>*Dublin Institute of Technology, Dublin, Ireland* |
| **PP58** | Ion pair formation process between an ionic dye and an anionic surfactant<br>L. García-Río, P. Hervella, J. C. Mejuto, **M. Parajó**<br>*Universidad de Santiago, Santiago de Compostela, Spain* |
| **PP59** | Supramolecular tuning of reversible Diels-Alder reaction<br>**S. Pasquale** and B. Masci<br>*University La Sapienza, Rome, Italy* |

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| **PP60** | Hydride Affinities of Some Unsaturated Small Organic Molecules – Triadic Analysis<br>**N.Peran**, R. Vianello, and Z.B. Maksić<br>*Ruđer Bošković Institute, Zagreb, Croatia* |
| **PP61** | Sensitivity of reaction rates of Acidolysis of N-Acyl-N,α,α-Trialkyl-Glycine Amides to the electronic contributions of Substituents<br>**S.M.M.A. Pereira-Lima**, F.C.S.C. Pinto, C. Ventura, L. Albuquerque, R. Gonçalves-Maia and H.L.S. Maia<br>*University of Minho, Braga, Portugal* |
| **PP62** | Controlling Fluorescent Signal In self-assembling α,γ-Cyclic Peptides<br>**M. J. Pérez-Alvite**, R. J. Brea, L. Castedo, J. R. Granja.<br>*Universidad de Santiago de Compostela, Santiago de Compostela, Spain* |
| **PP63** | Nitrosative deamination of Purine and Pyrimidine Bases: Implications in DNA Mutagenesis<br>**M. Pessêgo**, J. A. Moreira, and A. M. Rosa<br>*University of the Algarve, Faro, Portugal* |
| **PP64** | Creation of hydrogen bonded 1D networks by co-crystalization of dithiooxamide with nitrogen heterocycles.<br>**Barbara Piotrkowska**, Aleksandra Wasilewska, Maria Gdaniec, Tadeusz Polonski<br>*Technical University, Gdansk, Poland* |
| **PP65** | Kinetic study of the oxidation of propionaldehyde by peroxynitrite<br>**F.J. Poblete**, B. Cabañas, P. Corrochano and C.J. Sanchez<br>*Universidad de Castilla-La Mancha, Ciudad Real, Spain* |
| **PP66** | A Computational and Experimental Study on Specific Solvent Effects on Some Common Organic Reactions in RTILs<br>**C.S. Pomelli**, C. Chiappe, and R. Bini<br>*Università di Pisa, Pisa, Italia* |
| **PP67** | Synthesis of $N^{\gamma}$-Alkyl Derivatives of Glutamine - Potential Inhibitors of Glucosamine-6-phosphate Synthase<br>**Marta Prokop**, Maria J. Milewska<br>*Gdansk University of Technology, Gdańsk, Poland* |
| **PP68** | Modelling the Active Site of Peroxidases<br>**D.R. Ramos**, M.V. García, M. Canle L., and J.A. Santaballa<br>*University of A Coruña, A Coruña. Spain* |
| **PP69** | Carbon-halogen heterolysis in tertiary alkyl halides: a kinetic and theoretical study<br>**M. Reis**, F. Agapito, L. Moreira, R. E. Leitão, F. Martins<br>*Universidade de Lisboa, Lisboa, Portugal* |

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| **PP70** | Structure-Reactivity Effects on Kinetic Isotope Effects for Protonation of Ring Substituted α-Methoxystyrenes.<br>**John P. Richard** and W.-Y. Tsang<br>*University at Buffalo, NY, USA* |
| **PP71** | On the Importance of Leaving Group Ability in Reaction of Ammonium, Oxonium, Phosphonium, and Sulfonium Ylides<br>**R. Robiette**, V. K. Aggarwal, and J. N. Harvey<br>*Université catholique de Louvain, Louvain-la-Neuve, Belgium* |
| **PP72** | *Computing the 1H NMR Spectrum of Bulk Ionic Liquids based on Imidazolium Cations from Snapshots of Classical and Car-Parrinello Molecular Dynamics Simulations*<br>*A. Bagno, F. D'Amico, and* **G. Saielli**<br>*Istituto per la Tecnologia delle Membrane del CNR, Padova Italy.* |
| **PP73** | Kinetics and Mechanism of the Aminolysis of *S*-Phenyl 4-Nitrophenyl Thiocarbonate in Aqueous Ethanol.<br>Enrique A. Castro, Margarita Aliaga, and **José G. Santos**<br>*Pontificia Universidad Católica de Chile, Santiago, Chile.* |
| **PP74** | Intramolecular Hydride Transfer of Acyloin Anion:<br>Analysis of Solvation Structure Dynamics<br>**Makoto Sato** and Hiroshi Yamataka<br>*University of Rikkyo, Tokyo, Japan* |
| **PP75** | Nucleophilicity of metal carbonyl anions towards vinyl halides:<br>An unusually Broad Nucleophilicity scale<br>**P.K. Sazonov**, G.A. Artamkina, and I. P. Beletskaya<br>*M.V. Lomonosov Moscow State University, Moscow, Russia* |
| **PP76** | Direct Observation of Intermediate Carbocations in Solvolysis Reactions<br>**H. F. Schaller** and H. Mayr<br>*Ludwig-Maximilians-Universität, München, Germany* |
| **PP77** | A physical model for the energetics of protein conformational changes<br>**P.A.S. Silva** and L. Cruzeiro<br>*University of Algarve, Faro, Portugal* |
| **PP78** | Reactivity of 2-Dialkylamino Thioisomünchnones Towards Azodipolarophiles: a Theoretical Approach of a Versatile Process<br>**G. Silvero**; B. Sánchez; J. L. Bravo<br>*Universidad de Extremadura, Cáceres, Spain* |

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| **PP80** | Computational study of triguanide cyclization<br>**Vjekoslav Štrukil**, Zoran Glasovac, Mirjana Eckert-Maksić<br>*Rudjer Bošković Institute, Zagreb, Croatia* |
| **PP81** | MD studies of properties of Guanidinium ionic liquids<br>**M. Tanaka** and H.-U. Siehl<br>*University of Ulm, Ulm, Germany* |
| **PP82** | Dimethyl Carbonate Reactions Under Microwave Irradiation<br>**P. Trošelj**, I. Zrinski-Antonac, D. Margetić, M. Eckert-Maksić<br>*Institute Ruđer Bošković, Zagreb, Croatia* |
| **PP83** | Gas-Phase Reactions Between Thiourea and $Ca^{2+}$, Similarities and Differences With $[Ca (Urea)]^{2+}$<br>**Cristina Trujillo**, Otilia Mó, Manuel Yáñez, Jean-Yves Salpin and Jeanine Tortajada<br>*Universidad Autónoma de Madrid, Madrid, Spain.* |
| **PP84** | Substituent Effects on Photosolvolysis of Benzylthioacetates in Aqueous Solution<br>**S. Usui** and T. Hirahara<br>*Niigata University, Niigata, Japan* |
| **PP85** | Characterization of new 8-aminoquinoline derivatives using electrospray ionisation-ion trap mass spectrometry<br>**Nuno Vale**, Joana Matos, Rita Capela, Rui Moreira and Paula Gomes<br>*Faculdade de Ciências do Porto, Porto, Portugal* |
| **PP86** | Comparative QSAR Analysis of Anti -Tubercular Compounds using Artificial Neural Networks and Multiple Linear Regressions<br>**C. Ventura**, J. Manso, D. Latino and F. Martins<br>*FCUL, Lisboa, Portugal* |
| **PP87** | Peptidic-like Inhibitors of Plasmodium Falciparum: Development of New Antimalarials<br>**Edite Veríssimo**, Paul M. O'Neill, M. Lurdes S. Cristiano<br>*Universidade do Algarve, Faro, Portugal* |

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| **PP88** | UV Photolysis of γ-lactams<br>**S. Vilariño**, M. Canle L., Jayanta K. Ray and J.A. Santaballa<br>*University of A Coruña, A Coruña, Spain* |
| **PP89** | π–π Stacking and Secondary Bonding Interactions in Cocrystals of Benzo-2,1,3-selenodiazole<br>**A. Wasilewska**, M. Gdaniec, and T. Połoński<br>*University of Technology, Gdansk, Poland* |
| **PP90** | Pure Steric Effects In Reactions Of Aliphatic Carboxylic Acids<br>Andrew Regan and **Ian Watt**<br>The University of Manchester, Manchester, UK |

# ESOR XI

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## Abstracts

### Plenary Lectures

# Trioxanes: From Mechanistic Understanding Toward Chemotherapy

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The public health crisis posed by drug-resistant malaria and the urgent need for safe and effective new therapies are widely recognized. Ancient Chinese herbal remedies to combat malaria involve an active ingredient that is a 1,2,4-trioxane. We have elucidated much of the mechanism of action of such trioxanes when they are triggered by ferrous iron. A cascade of chemical transformations occurs leading to reactive intermediate carbon-centered radicals and high-valent iron-oxo species as well as to a neutral reactive alkylating epoxide; one or more of these species kills the malaria parasites inside malaria-infected human erythrocytes. This mechanistic understanding has allowed rational design of some simple endoperoxides that are potent antimalarials. Also, some dimeric trioxanes show not only fast-acting but also long-lasting antimalarial activity as well as potent and selective anticancer activity. These various aspects of trioxanes will be discussed.

# Chemical Generation of Singlet Oxygen in Single Phase and Multiphase Microemulsion Systems for the Catalytic Oxidation of Organic Substrates

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In the last few years there has been a surge of interest in the first excited state of oxygen "singlet oxygen" $^1O_2$ ($^1\Delta_g$) because it was found to be the key species in many important biological and photochemical processes and in the synthesis of valuable organic compounds.

Singlet oxygenation is usually carried out by dye-sensitized photooxidation that requires gas/liquid photo-reactors which are seldom available in research laboratories or industrial plants. By contrast, "dark" singlet oxygenation provides a safe and inexpensive alternative to photooxidation that can be carried out in ordinary multi-purpose plant stirred tank reactors.

Many chemical sources of $^1O_2$ are known, but the most efficient one involves the disproportionation of $H_2O_2$ catalyzed by molybdate anion. Due to the hydrophilicity of reactants, this method is particularly efficient in water which is not a suitable medium for the oxidation of hydrophobic substrates. Microemulsions constitute an excellent way to circumvent reagents incompatibility because they may dissolve simultaneously organic compounds and inorganic salts. Thanks to the small droplet size (≈ 50 nm), the short-lived $^1O_2$ (4 µs) generated in the aqueous microdomains can diffuse, before deactivation, to the organic phase where it reacts with the substrate.

The first generation of oxidizing microemulsion was based on a quinary system SDS / $CH_2Cl_2$ / $H_2O$ / $Na_2MoO_4$ / BuOH. Once formulated in appropriate proportions, this mixture affords a transparent, thermodynamically stable, one-phase microemulsion which was used to oxidize various electron-rich substrates by adding aqueous $H_2O_2$.[1]

However, this type of medium suffers several drawbacks for large scale transposition: (i) use of a chlorinated solvent (ii) tedious recovery of products (iii) demixing of the microemulsion upon addition of high amount of $H_2O_2$.

Several major improvements have been brought to the formulation of microemulsion in order to overcome these problems (i) replacement of chlorinated solvents by "green" solvents, (ii) combination with a pervaporation membrane that enables a continuous dewatering (iii) development of two-phase microemulsion systems in which the microemulsion is in equilibrium with a solvent phase to facilitate the recovery of products in the oil phase.[2]

The most advanced reaction media are three-phase microemulsion systems based on "well-balanced catalytic surfactants". A mere mixing of those amphiphilic catalysts with water and an appropriate organic solvent give a three-phase system (Solvent / Microemulsion / Water). The oxidation products, are readily recovered since they are extracted in the organic excess phase as they are formed. The water arising from the catalytic process is expelled in the aqueous excess phase whereas the amphiphilic catalyst, specifically localized in the middle microemulsion phase, may be reused.

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# Recent Studies of Reactive Tri-Coordinate Silicon Intermediates

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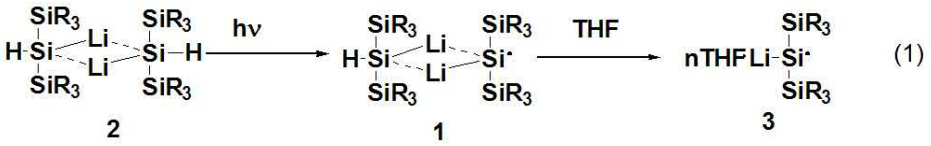
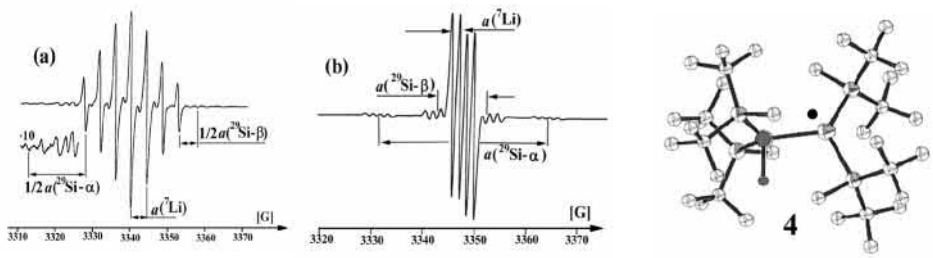
Silyl radicals and silyl anions are important reactive intermediates in many modern technological processes and in synthetic chemistry. Yet, fundamental knowledge for these intriguing reactive species is scarce. In this lecture I will discuss some of our recent studies on these tri-coordinated silicon compounds.

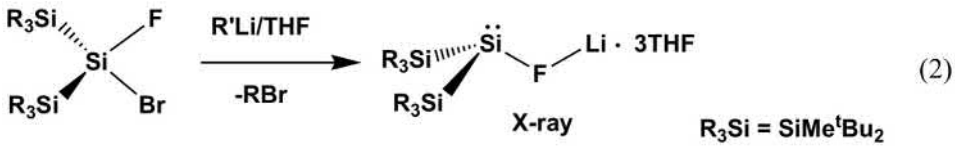
Silyl radical 1 ($R_3Si$ = $SiMe^tBu_2$) was generated by photolysis of silyl lithium aggregate 2 (eq. 1). 1 shows a characteristic EPR septet (Fig. a) resulting from interaction of the unpaired electron with two equivalent Li atoms. Upon controlled addition of THF to 1 a new stable silicon centered radical 3 is formed (eq. 1, Fig. b).

We also report on the synthesis and characterization by X-ray crystallography of a stable silyl radicals, e.g., $(R_3Si)_2HSi(R_3Si)_2Si^{\bullet}$ (4), and report on its interesting photolysis.




The first known fluoro-silylenenoid was synthesized (eq. 2) and characterized by X-ray crystallography and its reactions are reported.



# Advanced Materials by Acetylene and Fullerene Scaffolding

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The first part of the lecture describes the synthesis and photophysical properties of multinanometer-sized oligoporphyrin-fullerene arrays, capable of undergoing an exceptional number of reversible oxidation and reduction steps. STM studies on nano-patterned surfaces of oligoporphyrins with hosting properties are reported. An unprecedented set of experiments reveals the formation of one- and two-dimensional fullerene networks upon evaporation of pristine $C_{60}$ on the preorganized porphyrin monolayers. Repositioning experiments with the STM tip demonstrate that the $C_{60}$ molecules can be easily relocated without disrupting the underlying porphyrin layers. An example for a supramolecular single-molecule rotor, that can be brought to motion using the STM tip, will be presented.

The second part of the lecture reports the construction of new chromophores by acetylenic scaffolding, starting from a versatile library of ethynylated building blocks. Examples for carbon-rich acetylenic macrocycles are perethynylated dehydroannulenes, expanded radialenes, and radiaannulenes. Peripheral donor groups stabilize these delicate, electron-accepting all-carbon chromophores and greatly enhance their optoelectronic properties. The self-assembling properties of tetrathiafulvalene-fused dehydroannulenes are discussed. Cyanoethynylethenes and 1,1,4,4-tetracyanobutadienes are introduced as new classes of powerful organic electron acceptors. Among the interesting properties of these new advanced materials are exceptional electron uptake and storage capacity, electronic transitions extending into the near infrared, as well as strong nonlinear optical properties and efficient two-photon absorption cross-sections. Many of these chromophores feature high thermal stability and can be sublimed undecomposed. This has enabled formation of highly ordered thin films for potential device applications. The lecture finishes with the presentation of unprecedented dendritic donor-acceptor molecules, that can be multiply charged in a very large number of reduction steps. New AB-type oligomers have become accessible in a cascade reaction, involving repetitive sequences of [2+2]cycloadditions, followed by retro-electrocyclizations. The regular AB sequence is controlled by the electronic nature of the involved acetylenes that are being functionalized.

of the switching process, including the effects of different solvents, has been gained. Switching of the cavitands is observed both in solution and, unprecedented, also in Langmuir monolayers. A molecular switch undergoing large molecular motions, with reversible changes from a 0.7 nm sized contracted to a 7 nm sized expanded form, is presented. This switching can be monitored by fluorescence resonant energy transfer (FRET) as well as by excimer emission. First evidence is presented for the electrochemical switching of a resorcin[4]arene cavitand bearing tetrathiafulvalene moieties at the upper rim. The first container molecules for constrictive cycloalkane binding, a molecular basket and a molecular tube featuring reversible switchable portals for guest uptake and egress, are reported. The thermodynamics and kinetics of guest binding provide new insights into the control of molecular recognition phenomena by solvent effects.

# QM/MM Simulations of Organic and Enzymatic Reactions

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Quantum mechanics (QM) and Monte Carlo statistical mechanics (MC) simulations have been used by us since the early 1980s to study reaction mechanisms and the origin of solvent effects on reaction rates. A goal was always to perform the QM and MC/MM calculations simultaneously in order to obtain free-energy surfaces in solution with no geometrical restrictions. This was achieved by 2002 and complete free-energy profiles and surfaces with full sampling of solute and solvent coordinates can now be obtained through one job submission using BOSS [JCC 1689 (2005)]. Speed and accuracy demands also led to development of the improved semiempirical QM method, PDDG-PM3 [JCC 1601 (2002); JCTC 817 (2005); JPCA 13551 (2006)]. The combined PDDG-PM3/MC/FEP methodology has provided excellent results for free energies of activation for many reactions in numerous solvents. Recent examples include Cope, Kemp and E1cb eliminations [JACS 8829 (2005), 6141 (2006); JOC 4896 (2006)], as well as enzymatic reactions catalyzed by the putative Diels-Alderase, macrophomate synthase, and fatty-acid amide hydrolase [JACS 3577 (2005); JACS 16904 (2006)]. The presentation will focus on the accuracy and mechanistic insights that can be obtained in such QM/MM studies.

# Do General Nucleophilicity Scales Exist?

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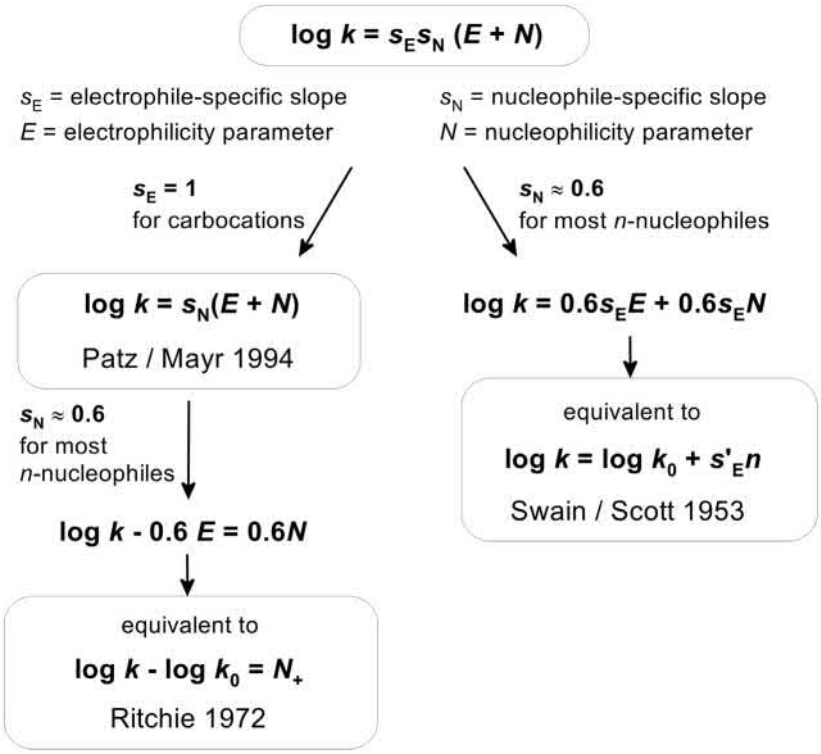
The benzhydrylium ion based nucleophilicity scale which has been used for the characterization of π-, n-, and σ-nucleophiles is the most comprehensive nucleophilicity scale presently available.[1] We have found that the nucleophile-specific parameters *s*N and *N*, which have been derived from the rates of reactions of nucleophiles with benzhydrylium ions and structurally related quinone methides, can also be used for describing the rates of $S_N2$ reactions, if our 1994 equation is extended by an electrophile-specific slope parameter. A novel equation is presented which includes the Ritchie and Swain-Scott equations as special cases.[2]




Practical applications of the reactivity parameters *E* and *N* in organocatalysis will be discussed.

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# Structure of Ionic Liquids and Their Solvent Properties

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Room temperatures ionic liquids (ILs)- salts with melting points below 100 °C- have attracted considerable attention as novel reaction media over the last decade.[1] By virtue of their nonflammability, thermal stability and nonvolatility ILs have been proposed as alternative solvents receiving serious consideration with the promise of both environmental and technological benefits. Structurally, most of the ILs that have been investigated to date are based on imidazolium, ammonium and pyridinium cations associated with polyatomic anions, such as chloroaluminates, tetrafluoroborate, hexafluorophosphate and bis-triflimide.

Bulk properties, such as melting point, viscosity, density, refraction index have been determined[2] for many ILs and several attempts have been made to correlate these properties to structural features.[3] Also the question "How polar are ionic liquids" has been addressed by many methods that previously have been used to characterize the polarity of common molecular solvents. Moderate dielectric constant values have been evaluated for many ILs, using indirect methods[4] and by microwave dielectric spectroscopy.[5] Furthermore, the microscopic properties of ILs (i.e. the ability of these media to interact with specific dissolved species) have been measured and several polarity scales, previously developed for common molecular solvents, have been extended to ILs.[2,6]

Theoretical and experimental studies have evidenced that the strong ion-ion interactions present in the ILs lead to high ordered three-dimensional supermolecular polymeric networks of anions and cations linked by hydrogen bonds and/or Coulombic interactions, producing a completely different environment with respect molecular solvents. ILs can be therefore considered nanostructurally organized materials, with ionic networks permeated by non-polar region.[7]

Recent kinetic and product distribution studies, performed on typical organic reactions (cycloadditions, aliphatic nucleophilic substitutions, keto-enol equilibria and so on), will be discussed at the light of the physico-chemical properties of ILs.

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# Energetics of Free Radicals

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To gain a better understanding of free radical solvation energetics and to obtain chemically accurate bond dissociation enthalpy (BDE) data are two major research goals of our laboratory.

Although most available BDEs refer to the gas phase, many important chemical and biochemical processes involving free radicals occur in condensed phases. As BDEs are relevant to predict reactivity, it is important to relate solution- and gas-phase data. This implies a better knowledge of the solvation enthalpies of radicals, which can be achieved by comparing experimental gas-phase and solution-phase BDEs or by developing theoretical models suitable to describe solvation energetics. In our laboratory we use time-resolved photoacoustic calorimetry (TR-PAC) to determine solution-phase BDEs and several theoretical methodologies to estimate radical solvation energetics (in collaboration with a computational chemistry group).

The second research goal mentioned above stems from a trivial, but surprising, finding. Contrary to a widespread belief, BDE data for many basic species are unreliable, i.e. the uncertainty intervals assigned to the enthalpies of formation of many of those radicals are much larger thanca. 4 kJ. .mol$^{-1}$. This hinders not only our ability to ascertain BDE trends and to predict new data but also our quantitative evaluation of effects such as hyperconjugation and resonance. Our goal is therefore to improve the accuracy of the enthalpies of formation of selected radicals by using both experimental (TR-PAC) and computational tools and then reassess familiar structure-energetics relationships.

# Molecular Switches and Motors at Work

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Inspired by Nature we design molecular systems in which the control of molecular dynamics is coupled to specific functions. Toward the bottom up construction of photo- and electro-active systems the focus is on light- or redox induced switching and control of motion. In this lecture *molecular switches* for the control of organization and self-assembly and chirality as well as nanomechanical devices are presented.

*Molecular motors* stand out among the most challenging goals in nanoscience and will provide the heart of future molecular level machinery. Both linear and rotary motors are shown and the dynamic processes and mechanism discussed. Progress in the construction of an artificial nanoscale "windmill park" powered by light and the application of molecular motors to perform useful functions is shown.

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# Structure and Selectivity in the Binding of Small Ligands to DNA and their Consequences

**Colin J. Suckling[1], Abedawn Khalaf[1], David Breen[1], John Parkinson[1], Gavin Donoghue[1], Roger Waigh[2], Simon Mackay[2], Nahoum Anthony[2], Elizabeth Ellis[2], Iain Hunter[2], Curtis Gemmell[3], and Keith Fox[4].**

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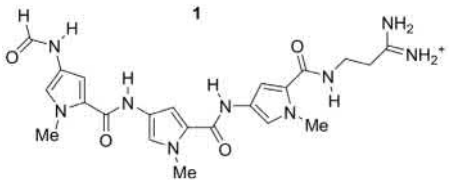
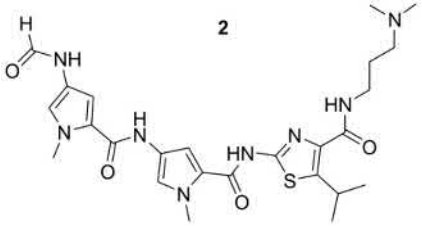
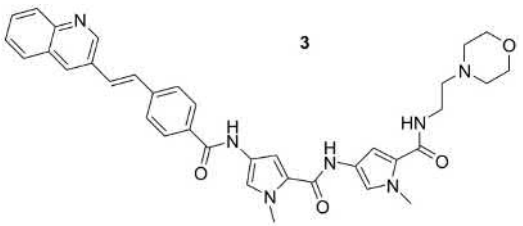
Several classes of natural products that bind to the minor groove of DNA have been discovered and have become of interest as starting points for the development of drugs. The minor groove binders (MGBs) related to distamycin (**1**) have attracted particular attention because of the great scope for the systematic modification of its structure. Distamycin itself strongly prefers AT rich regions of DNA but if an N-methylpyrrole is replaced by an N-methylimidazole, binding adjacent to GC base pairs in a DNA duplex becomes possible. Highly selective binding has been reported for long MGBs in which the sequence of heterocycles has been designed to match the DNA target. Although such molecules have exquisite sequence selectivity and bind strongly to DNA, they do not possess the structural characteristics typical of drugs. Distamycin itself is toxic but analogues have been found with selective biological actions including anticancer and antibacterial activity. The effectiveness of such compounds depends upon a combination of their binding mechanism to DNA and upon the physicochemical properties that control their access to DNA duplexes within the target cells.




At Strathclyde, we took the view that improved antibacterial activity in particular could be obtained by preparing more lipophilic analogues of distamycin using several design strategies: a. increasing the size of the N-alkyl group, b. introducing a more non-polar head group than formyl, c. replacing N-alkylimidazole by C-alkylthiazole, and d. selecting the pKa of the tail group to be significantly lower than that of the amidine in distamycin. Application of these strategies in various combinations first led to the highly selectively binding MGB, thiazotropsin A (**2**) and more recently to alkene-containing analogues such as (**3**), which are active antibacterial compounds in vivo and have commercial potential. The selectivity of binding of these and related compounds to DNA has been examined by footprinting and capillary electrophoresis and the details of their DNA complexes have been established by NMR. The affinity of binding has been measured by isothermal titration calorimetry and by melting temperature measurements. The development of the antibacterial agents will be described from the point of view physicochemical properties and structure.



# Absolute rate calculations of proton transfers in solution and in enzymes, and the rates of $S_N2$ reactions and their relation to molecular and solvent properties

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The reaction pathway of the Interacting-State Model[1] is used in the Transition-State Theory with the semiclassical correction for tunneling (ISM/scTST) to calculate the rates of proton-transfer reactions from hydrogen-bond energies, reaction energies, electrophilicity indices, bond lengths and vibration frequencies of the reactive bonds[2]. ISM/scTST calculations do not involve adjustable parameters. The calculated proton-transfer rates are within one order of magnitude of the experimental ones at room temperature, and cover very diverse systems, such as deprotonations of nitromethane, acetylacetone, HCN, carboxylic acids, and excited naphthols, as well as the breaking of C-H bonds by enzymes. The calculated temperature dependencies and kinetic isotope effects are also in good agreement with the experimental data[3]. These calculations elucidate the roles of the reaction energy, electrophilicity, structural parameters, hydrogen bonds, tunneling and solvent in the reactivity of acids and bases.The efficiency of the method makes it possible to run calculations through the Internet[4].

The studies of proton transfers in solutions were extended to enzyme catalysis. One salient feature is the role of hydrogen bonding CH···O along the reaction coordinate that can lead to very high tunnelling corrections (up to 100) and inflated kinetic isotope effects (up to 50) at room temperature. The sensitivity of the reaction path to small changes in this H-bonding accounts for the influence of protein dynamics in the reaction rates. A relevant example is the case of soybean lipoxygenase-1 where the formal H-abstraction is a proton coupled electron transfer. The KIE of 44 at 25 °C results from a thin and high-energy barrier, and the relevant conclusion from our theoretical study is that the TST view of catalyzes is not incompatible with the large KIE observed in enzyme reactions at room temperature[5].

The history of $S_N2$ reactions closely parallels the development of concepts such as structure-reactivity relationships and solvent effects as a probe of mechanisms. The relation between the mechanisms of $S_N2$ and electron transfer reactions has also been explored extensively in recent times. In order to address some of these issues the energy barriers of symmetrical methyl exchanges in the gas phase are also calculated with the reaction path of the Intersecting/Interacting-Sate Model (ISM). Reactive bond lengths increase along a column of the Periodic Table and compensate for the decrease of force constants, explaining the near constancy of the intrinsic barriers in the series of nucleophiles $F^- \approx Cl^- \approx Br^- \approx I^-$. This compensation is absent along the rows of the Periodic Table, and the reactivity trend is dominated by the increase of the electrophilicity index of the nucleophile in the series C<N<O<F. Solvent effects are quantitatively incorporated in ISM through a correlation between electrophilicity and the solvent acceptor number. This correlation is transferable between nucleophiles and solvents, and allows for the calculation of methyl transfer rate constants in solution with a remarkable simplicity and accuracy[6]. Considering only ET self-exchanges, the low resonance in apolar solvents cannot be much reduced by polar solvents, and static solvent effects should be much smaller than for symmetrical methyl transfers. The weak solvent dependence of ET self-exchanges has been experimentally observed[7] and is the basis for the success of ISM applications to electron transfer reactions[8].

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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## Abstracts

### Invited Lectures

# Ru(II) complexes, DNA, and light, for the construction of biomolecular tools.

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Since many years, our research team has focused its interest on different types of Ru(II) complexes with polyazaaromatic ligands and has studied their photophysics and photochemistry in solution, more particularly in the presence of biomolecules. Some of these compounds induce an electron transfer from a guanine moiety of DNA[1, 2] or from a tryptophane unit of a peptide[3], towards the excited complex. The recombination of the produced ion pair generates an adduct of the metallic complex on the guanine base or on the tryptophane unit.

In this presentation, we will show how it is possible to take advantage of these photoreactions by studying different biomolecular models. Thus Ru-derivatized oligonucleotides bearing or not a guanine unit in their different sequences have been prepared as probe-sequences. The Ru(II) complexes have been chemically linked to the oligonucleotide by an imine linkage. When these Ru-probe single strands recognize their target-sequences (complementary sequences), they irreversibly attach to the target strand under illumination via the formation of the photo-adduct.

We will show also that such photocrosslinkings between oligonucleotide strands are possible by using free complexes (thus non chemically Ru-derivatized oligonucleotides). In such cases each oligonucleotide strand must contain a guanine base. These two guanines, which will be crosslinked, must be localized at a specific distance from each other, depending on the type of complex which is chosen. This application works particularly well with a dinuclear complex formed with a TPAC (TPAC = tetrapyrido[3,2-a:2′,3′-c:3″,2″-h:2‴,3‴-j]acridine) bridging ligand[4]. The study of this dinuclear species is extended to telomeric sequences.

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*Acknowledgements*: We thank the FNRS (Fonds National pour la Recherche Scientifique) for its financial support and the COST D35 for the collaboration.

# The Mechanism of "Slow" Proton Transfers to Metal Hydrides in Organic Solutions: The Proton Donor and Acceptor, the Solvent and the Ion Pairs Provide a Variety of Reaction Pathways

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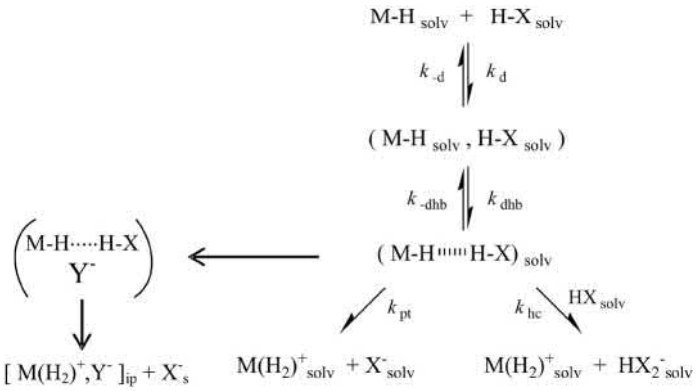
The activation of molecular $H_2$ is a topic of current interest because of its chemical, industrial and biological relevance. The discovery of dihydrogen complexes, in which $H_2$ is coordinated to a metal centre without the breaking of the H-H bond, has allowed in the last two decades a better understanding of these activation processes. One of the most interesting properties of the dihydrogen complexes is its capability to behave as acids transferring a proton to a base ($L_nM(H_2)^+ + B \rightarrow L_nMH + HB^+$). The reverse reaction, protonation of a coordinated hydride ($L_nMH + HX \rightarrow L_nM(H_2)^+ + X^-$), is one of the most common synthetic procedures for preparing dihydrogen complexes. Except for a few cases, these proton transfer processes are carried out in organic solution and occur in the time scale of ms to minutes; i.e. they are "slow" proton transfer processes when compared with classical acid-base reactions. Proton transfers to metal-hydride bonds occur with the initial attack by the acid, yielding M-H…H-X adducts known as dihydrogen-bonded species. However, these species can evolve to the reaction products through a variety of mechanistic pathways that include direct conversion to products; assistance by a second molecule of acid with formation of the homoconjugated $HX_2^-$ species, and reaction through ion pairs formed with external anions. Examples of recent kinetic and DFT studies [1-3] illustrating the different pathways will be discussed.

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*Acknowledgements*: This work was funded by Junta de Andalucía (Grupo FQM-137) and by the Spanish M. E. C. and the E.U. FEDER program (project CTQ2006-14909-C02-01).

# The Dynamic Covalent Chemistry of Cyclophane Formaldehyde Acetals

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The acid-catalyzed transacetalation of formaldehyde acetals (formal metathesis) is a suitable reaction for the generation of well-behaved Dynamic Libraries of cyclophane formals. The composition of the equilibrated mixtures solely depends on concentration, and is totally independent of whether the feedstock is any of the pure cyclic oligomers, or a mixture of oligomers/polymers. Effective Molarities related to the formation of the lower cyclic oligomers were directly measured as their equilibrium molar concentrations above the critical monomer concentration. The finding that silver cation acts as a selective binder toward the cyclic dimer $C_2$, coupled with the "proof reading and editing" capability of our quickly equilibrating system, translated into significant amplifications of $C_2$ when the equilibrated mixtures were exposed to the action of the silver template. These results highlight the potential of Dynamic Combinatorial Chemistry as a powerful tool for the preparation in synthetically useful amounts of an otherwise elusive macrocyclic compound. The possibility of using a mixture of high molecular weight byproducts as feedstock adds considerably to the practical value of the procedure.

Important insight has been obtained into the mechanism of the acid-catalyzed transacetalation process. The order of appearance of the lowest oligomers in the early stages of the equilibration reaction is fully consistent with ring-fusion/ring-fission processes in which oxonium ion intermediates undergo $S_N2$ reactions, according to an acid-catalysed bimolecular (A2) mechanism. The alternative acid-catalysed monomolecular (A1) reaction path, based on "back-biting" processes of carbenium ions generated by $S_N1$-type cleavage of oxonium ion intermediates, predicts sequences that are in marked contrast with experimental findings.

# Mechanistic Studies on Carbocation Cascades Occurring During the Biosynthesis of Polycyclic Natural Products

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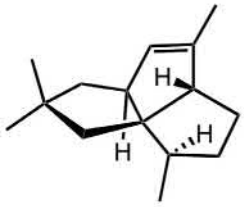
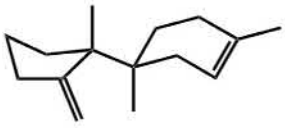
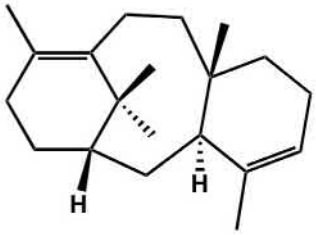
Many complex terpenes are formed in Nature by enzyme-catalyzed polycyclizations of acyclic, achiral precursors. Possible polycyclization pathways leading to the sesquiterpenes pentalenene[1] and trichodiene[2] and the diterpene taxadiene[3] have been studied using quantum chemical calculations. These natural products are the biosynthetic precursors of the pentalenolactone antibiotics, the trichothecene mycotoxins, and taxol, respectively. Many unusual and unexpected carbocation intermediates have been uncovered in these studies (such as the so-called "proton sandwiches"[4]) and their structures have motivated the design of various biochemical and physical organic experiments and new mechanistic probe molecules.




**pentalenene**



**trichodiene**




**taxadiene**

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*Acknowledgements*: This work was supported by UC Davis, the American Chemical Society's Petroleum Research Fund, and the US National Science Foundation.

# Kinetics-Energetics Relationship in the Electron Transfer from Trivalent Phosphorus Compounds to the Singlet Photo-Excited Sensitizers

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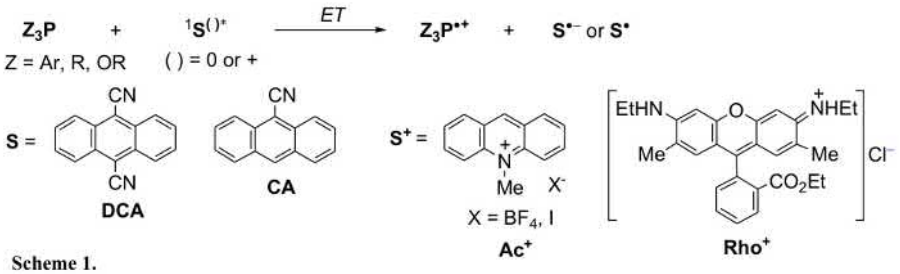
Trivalent phosphorus compounds $Z_3P$ undergo electron transfer (ET) to electron-deficient compounds. Thus, $Z_3P$ quenches the singlet photoexcited states of neutral sensitizers such as 9,10-dicyanoanthracene (**DCA**)[1] and 9-cyanoanthracene (**CA**) as well as cationic sensitizers such as acridinium cations (**Ac**$^+$) and rhodamine 6G (**Rho**$^+$)[2] through ET mechanism. In this work, the Stern-Volmer analyses were performed on the ET quenching of these sensitizers by $Z_3P$'s having various oxidation potentials. It was found that dependency of ET rate constant kET on free-energy change of the ET step $\Delta G_0$ is weaker than that predicted by the Rehm-Weller theory (Figure 1). More interestingly, the deviation from the theoretical prediction is larger for charge separation (CS) type ET ($Z_3P$ + $^1S^*$) than for the charge shift (CSh) type ET ($Z_3P$ + $^1S^{+*}$).




**Scheme 1.**

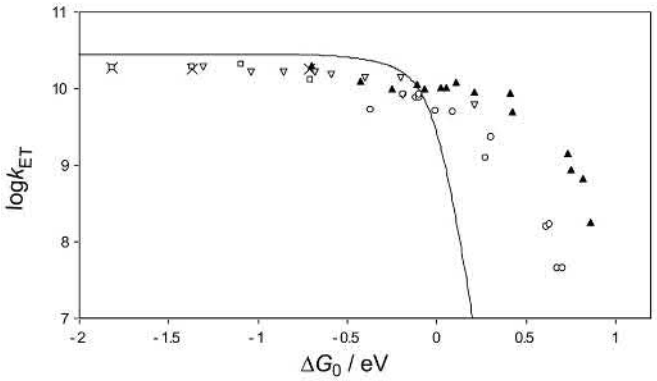



**Figure 1**. Plot of $\log k_{ET}$ vs $\Delta G_0$ for the ET from $Z_3P$ to $^1S(\ )^*$ in the air. S( ) = ▲; CA, ▽; DCA, O; Rho$^+$, □; **Ac**$^+$ (iodide salt), ×; **Ac**$^+$ (tetrafluoroborate salt). The line represents the prediction by the RW theory.

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# Investigation of Surfactant-Cyclodextrin Mixed Systems by Means of Chemical Kinetics

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Surfactant aggregates and cyclodextrins (CD) have the ability to alter chemical reactivity. The most studied cyclodextrins are α-, β- and γ-cyclodextrins, which consist in six, seven and eight glucose units, respectively. Regardless of the finer details of their structure, the most important feature of CDs is their cavity, because this enables them to form inclusion complexes with a great variety of substrates. Cyclodextrins as drug complexing agents have been the object of intense interest for both fundamental aspects and practical purposes for a long time. Recently, this attention has turned to the problem of biological photosensitisation oby drugs. Indeed, despite their excellent therapeutic activity, many pharmacologically important chemicals such as antibacterials, antimicotics and non-steroidal anti-inflammatory drugs can induce phototoxic, photoallergic and photomutagenic phenomena strictly related to the drug photochemical reactivity. It has been reported that in some cases such effects can be substantially decreased in the presence of CDs with model cellular systems. Application of CDs was, therefore, suggested as a useful strategy to minimise the biological damage induced by drugs and increase drug photostability. However, it should be stressed that drug-CD complexes usually dissociate once introduced into the body, where there is also exposure to a wide range of endogenous species.

In order to study the drug-CD dissociation into the body we mimic biological membranes by mean of surfactant aggregates. We use micelles and phospholipids liposomes or synthetic amphiphile vesicles, because the architecture of these artificial membranes is considerably simpler than that of cell membranes. In order to modulate the behavior of cyclodextrins in the presence of surfactant aggregates we studied the acid/basic hydrolysis of nitrosocompounds, ester hydrolysis and solvolysis of sulfonyl chlodries. From our results, certain characteristics of cyclodextrin-surfactant mixed systems can be highlighted: *(i)* At surfactant concentrations lower than the micellization point, a complexation equilibrium between the surfactant and the cyclodextrin is established. As the surfactant concentration increases, the concentration of uncomplexed surfactant monomers in equilibrium with the CD is sufficient for the micellization process to begin. *(ii)* The critical micelle concentration has been found to shift to higher values in the presence of CD. The critical micelle concentration of a micellar system in the presence of a cyclodextrin is equivalent to the combined concentrations of surfactant monomers complexed to the CD and of free dissolved monomer in equilibrium with the micellized surfactant. *(iii)* Once the micellization process has begun, interactions will not be established between the CD and the micellar system.

# Ground and Excited State Photochemistry of Matrix-Isolated Organic Molecules

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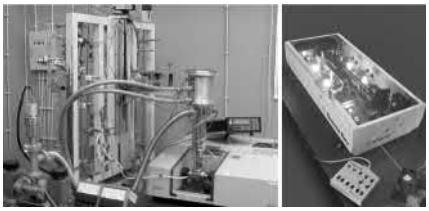
When used together with conventional spectroscopic methods (*e.g.*, FT-IR spectroscopy), matrix isolation constitutes a very powerful technique to investigate the photochemistry of single molecules. In matrix-isolation spectroscopy the sample to be studied is prepared by deposition under high vacuum conditions of the necessary amounts of the target substance and support gas (usually an inert gas such as argon or xenon) on a suitable optical substrate cooled at a temperature of a few degrees Kelvin. Under these conditions the spectral resolution strongly increases due to the band narrowing effects associated with both the extreme low work temperature and matrix rigidity (molecular diffusion as well as rotational and vibrational hot transitions is suppressed). Once a matrix of a given substance has been prepared, selective *in situ* irradiation can be undertaken in order to promote photochemical processes such as conformational isomerization,[1,2] tautomerization[3] or fragmentation (including photo-degradation).[4]

In this communication, recent results obtained in the *Laboratory for Molecular Criospectroscopy and Biospectroscopy* (Department of Chemistry – University of Coimbra) using the methodology above described will be presented. These will include both ground and excited states photochemical investigations in selected organic molecules.



Matrix-isolation set-up and MOPO system available at the *LMCB – Univ. of Coimbra*

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*Acknowledgements:* Credits shall be given to my co-workers for their outstanding contribution to the studies to be summarized in this talk: M.Räsänen, L.Kriachtchev, M.Pettersson, M.Nowak, L.Lapinski, M.L.Cristiano, I.D.Reva, A.Gómez-Zavaglia, A. Kaczor, E.M.S.Maçôas, S.Jarmelo, A.Sharma, S.Breda, L.Frija, P.Mobili, S.Lopes, A.Borba, N.Kuş, J.Junior, R.Almeida, C.Nunes L.Duarte and A.P.Simão. Financial support from Fundação para a Ciência e a Tecnologia (POCTI/458937/QUI/2004) is acknowledged.

# Waste-free synthesis and production all across chemistry with the benefit of self-assembled crystal packings

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Molecular crystals are the most general self-assembled systems in three dimensions. Their profitable benefit, which enables extraordinary selectivities, is still not widely used in synthetic chemistry. Rather the available bargain of the alignment is wasted by dissolving crystals prior to reaction, while the solvated molecules also become less reactive. Reactions within crystals proceed rapidly and completely due to lowest reaction order. We started to change the habit of not using self-assembly with more than 1000 waste-free gas-solid and solid-solid reactions in more than 25 reaction types all across chemistry for the sake of a better environment by also avoiding purifying workup. The exploratory work has been developed in Oldenburg since 1985 and the preparative use at the kg scale became possible due to the experimental three-step "phase-rebuilding mechanism" as deduced from our nanotechnological investigations (atomic force microscopy AFM, scanning near-field optical microscopy SNOM, grazing incidence diffraction GID, and nanoscratching). None of these reactions were foreseen by the unduly acclaimed Schmidt's "topochemistry" hypothesis that strangely claims "minimal atomic and molecular movements" in the crystal for isomerizations and photoreactions despite their very poor predictive power (e.g. too short distances can be impeding, etc). Conversely, long-range anisotropic molecular migrations have been secured by all of the various nanotechniques used . This applies to all reaction types among the different solid-state reaction techniques and not only to intra-crystalline situations.

The reason for the molecular migrations is the physical impossibility to adopt the enormous pressures that would build up within the infinite crystal lattice by the geometric change of the molecules upon chemical reaction if there were no release by immediate migration. Such pressure release requires the presence of cleavage planes or channels or voids in the crystal: no chemical reaction does occur in their absence. On the other hand, producing "vacuum" by shrinking without considerable distortion of the crystal packing can also be impeding if the migrations stop as soon as too large gaps are created in the crystal. In between are the very few exceptional topotactic reactions without geometric change that do not "evacuate" or produce pressure. Only these do not exhibit migrations, as secured by AFM with molecular precision. Gas-solid and inter-crystalline reactions require cleavage planes or channels also for reagent transport. Only the latter reactions require milling for multiple contacts. But grinding or milling of reactants is *not* "mechanochemistry" if regular bonds are not mechanically broken as with explosives, polymers and infinite covalent crystals.

Clearly, solid state reactivity predictions cannot be based on distances of reacting centers but they must analyze the crystal packing. This provides the answers to the anisotropy of the reactions with single crystals. The shapes of cleavage planes and channels (11 basic types) will be classified, limiting cases pointed out. The influence of gaseous or solid reagents is comprehended by their molecular size. All three steps in the solid-state mechanism that are experimentally secured (1. phase rebuilding, 2. phase transformation, 3. crystal disintegration) must occur in solid-state syntheses with geometric change. The strict application of this mechanistic knowledge indicates how the gas-solid and stoichiometric solid-solid reactions should be performed to give 100% yield at a large scale in a short time, or how they should be engineered if the steps 2 and/or 3 provide difficulties. Local submicro-melting can be detected by AFM. It stops reaction when it occurs, as melt reactions require much higher temperatures. But cooling down below eutectics will enable then. detected by AFM. It stops reaction when it occurs, as melt reactions require much higher temperatures. But cooling down below eutectics will enable then.

# How Can a Chemical System Act Purposefully?

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Chemistry enables us to understand the properties of chemical systems based on their chemical structure. For example, we understand why water is soft, why ice is hard, and why metals are shiny and conduct electricity. However this kind of understanding is lacking for the basic properties of living systems. In particular, one of living systems' most striking characteristics is their purposeful (teleonomic) character, but a **chemical** understanding of that character and, in particular, how it might have emerged, remains missing. In this talk we will explore the chemical nature of purpose (teleonomy) within a general framework that attempts to further clarify the physico-chemical relationship between animate and inanimate systems. A key element of the analysis is our proposal that all living systems constitute a **kinetic state of matter**, as opposed to the traditional thermodynamic states that dominate the inanimate world. According to this view transformations in animate systems are primarily governed by **kinetic** factors, in contrast to those in "regular" chemical systems, which are primarily governed by **thermodynamic** ones. We will attempt to demonstrate that it is this difference in the relative importance of kinetic and thermodynamic factors within the two worlds that leads to the special character in living systems that we term "purposeful".

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# Utilization of Phosphate Binding Energy in Catalysis by Small and Large Molecules

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Many enzymes have flexible loops, which open to expose the substrate binding pocket and then close around a nonreacting phosphate of substrate so as to encapsulate the ligand at the active site. The binding interactions between the phosphate group and such loops serve the mundane functions of fixing the substrate at the enzyme active site. We have shown that the binding interactions also provide specific stabilization of the transition states for proton transfer catalyzed by triosephosphate isomerase and decarboxylation catalyzed by orotidine 5′-monophosphate decarboxylase (OCDase), because they are expressed in the absence of a covalent connection between phosphate and the reacting substrate. The specificity of dianion binding, and the mechanism for the specific expression of the phosphate binding interactions at the transition state for these two enzyme-catalyzed reactions will be discussed.

# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## Abstracts

### Oral Presentations

# Non-statistical dynamic effects before and after the transition state! Intra- versus intermolecular kinetic isotope effects suggest a broad transition state

**Michael Schmittel,[1] Chandrasekhar Vavilala,[1] and Ralph Jaquet[2]**

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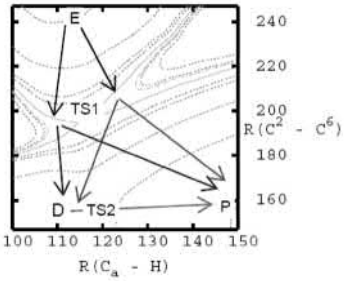
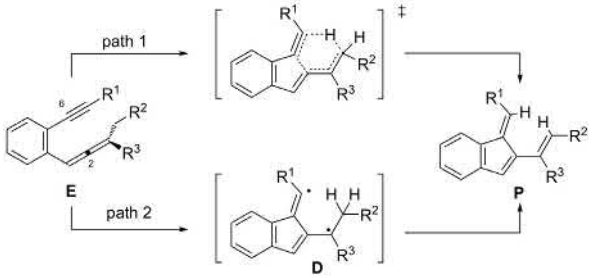
While in the first decades following the birth of physical organic chemistry, a set of firm paradigms has guided our conception of reactive intermediates, transition states and reaction coordinates, the significance of dynamic effects in organic reactions has lately become evident through the seminal work of Carpenter, Singleton, Doubleday, Hase and others.[1] It was suggested, quite often in the context of unimolecular reactions proceeding at the concerted vs. stepwise boundary, that dynamic effects cause a behavior differing from what is predicted by statistical kinetic models, such as the transition state theory.

So far, experimental substantiation of non-statistical dynamic effects, mostly based on kinetic isotope effects (KIE) or stereochemical information, was usually limited to just one single case study and thus needed to be complemented by computational dynamic simulations. Herein, we describe how dynamic effects become manifest in experimental inter- and intramolecular data[2] at the concerted/stepwise boundary of the thermal $C^2$-$C^6$ cyclization of enyne-allenes. The experimental intra- and intermolecular KIEs seen at the stepwise-concerted boundary can be reconciled with a broad plateau as "transition state" allowing thermalized trajectories to proceed from E to P directly or *via* D. Hence, dynamic effects are operating not only after, but also before the transition state.




**Scheme/Fig. 1.** The thermal $C^2$-$C^6$ cyclization of enyne-allenes as a model reaction for the study of dynamic effects (middle). Computed energy hypersurface of the thermal $C^2$-$C^6$ cyclization of enyne-allenes (top).

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*Acknowledgements:* This work was partly funded by the Deutsche Forschungsgemeinschaft.

# Aminolysis of Sulfamate Esters – Models for Enzymatic Reactions

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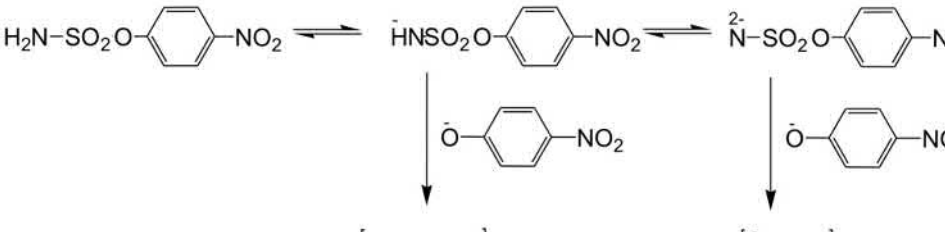
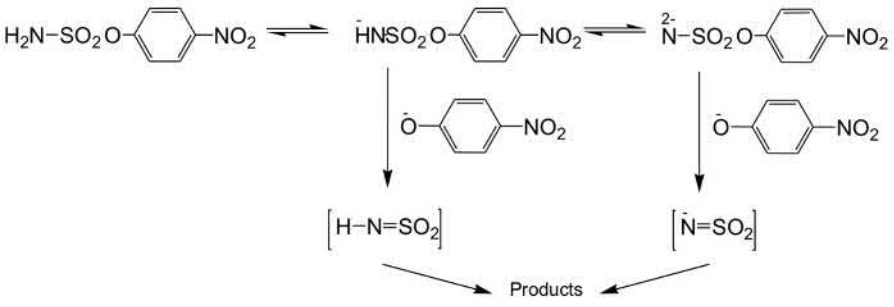
There has been an upsurge of interest in sulfamate esters $RNHSO_2OR'$ over the last 12 or so years because of their potential in medicinal chemistry where certain types of ester, particularly those of type $NH_2SO_2OR$ have been showing considerable promise in a wide variety of applications. To take a few important examples, some sulfamates inhibit steroidal sulfatases (STS) and carbonic anhydrase (CA) and thus the synthesis of those steroids that encourage the growth of hormone-dependent cancers like breast and prostrate cancer and other diseases[1] can be blocked. The results of phase I clinical trials on 667-Coumate (**1**), an STS inhibitor, which shows promise in the treatment of breast cancer have appeared recently[2] and Emate (**2**) and other sulfamates has also been the subject of many studies.

These esters act by blocking enzymatic pathways in the body and it is thought that they act by sulfamoylating amino acid residues in the enzyme thus inactivating it.



Little is known about the mechanism of action of these esters but at ESOR X we presented[3] some preliminary data on this and now further details of the mechanisms in acetonitrile and water are known and will be given here. In particular evidence to support the following scheme will be presented:

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# Fries Rearrangement of Aryl Formates: a Mechanistic Study by Means of 1H, $^{2}$H and $^{11}$B NMR Spectroscopy and DFT Calculations

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We present an experimental and computational study of the reaction mechanism of the Fries rearrangement of aryl formates promoted by boron trichloride. $^{1}$H and $^{2}$H NMR spectroscopy has been used to study the kinetics of the reaction by monitoring the substrate, while $^{11}$B NMR spectroscopy allowed monitoring the Lewis acid. DFT calculations were employed to investigate the energetics of several reaction paths and to calculate NMR chemical shifts of key intermediates and products. By comparing experimental and calculated data a consistent picture has emerged[1,2]: the rearrangement proceeds in two steps, beginning with the cleavage of the ester bond and the release of formyl chloride in situ which, in turn, acts as a formylating agent introducing an aldehydic functionality into the aromatic ring, see Figure 1. The high regioselectivity (only the *ortho*- product is obtained) is also accounted for by the proposed intermolecular, Lewis acid assisted, mechanism.

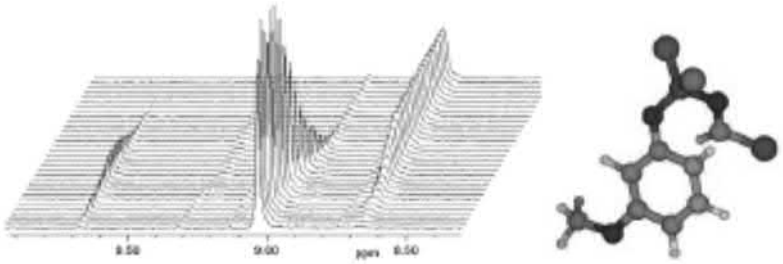

**Fig. 1**. Left: $^{1}$H NMR of the reaction mixture at +7 °C: the signal at *9.70* ppm is attributed to the intermediate formyl chloride. Right: Calculated structure of the transition state for the *ortho*- acylation.

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# Kinetics and Mechanism of the Aminolysis of Aryl Phenyl Chlorothiophosphates with Anilines

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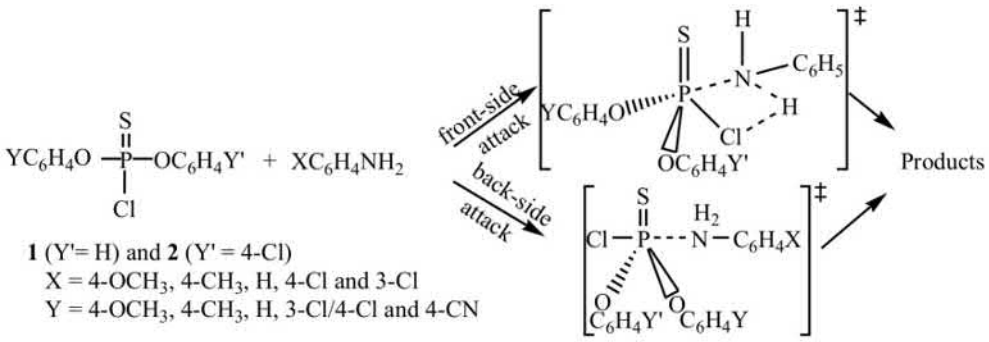
Kinetic studies of the reactions of aryl phenyl chlorothiophosphates (1) and aryl 4-chlorophenyl chlorothiophosphates (2) with substituted anilines in acetonitrile at 55.0 oC are reported. The negative values of the cross-interaction constants $\rho XY$ ($\rho XY = -0.22$ and $-0.50$ for 1 and 2, respectively) between substituents in the nucleophile (X) and substrate (Y) indicate that the reactions proceed by concerted $S_N2$ mechanism. The primary kinetic isotope effects ($k_H/k_D$ = 1.11–1.13 and 1.10–1.46 for 1 and 2 respectively) involving deuterated anilines ($XC_6H_4ND_2$) nucleophiles are obtained. Front- and back-side nucleophilic attack on the substrates is proposed mainly based on the primary kinetic isotope effects. A hydrogen-bonded, four-center type transition state is suggested for a front-side attack while the trigonal bipyramidal pentacoordinate transition state is suggested for a back-side attack. The MO theoretical calculations of the model reactions of dimethyl chlorothiophosphate (1′) and dimethyl chlorophosphate (3′) with ammonia are carried out. Considering the specific solvation effect, the front-side nucleophilic attack can be occurred competitively with the back-side attack in the reaction of 1′.

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# Proteins multi-funnel energy landscape and misfolding diseases

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Proteins are the machines of life, they mediate most of the processes that go on in living cells. In order to work, they must first acquire a well-defined three dimensional structure, the native structure. An outstanding problem in Biology is the protein folding problem which consists in knowing how a given sequence of amino acids eventually assumes the native structure. Since the experiments by Anfinsen[1] one answer to the protein folding problem has been the thermodynamics hypothesis, that is, the idea that the native structure corresponds to the minimum of the (free) energy of the corresponding sequence. This hypothesis has been further developed by linking it to the supposed funnel shaped (free) energy landscape of proteins[2]. In this presentation, evidence will be presented for that the same amino acid sequence can assume several, very different, structures, with the same (free) energy as the native structure, and in the same thermodynamic conditions. This means that the (free) energy landscape of proteins is not a single funnel, but rather, a multi-funnel and that the native structure is not acquired by the simple thermodynamic principle of energy minimization. How then do proteins fold? In a multi-funnel picture, transient deterministic forces are needed to select the native funnel from all other funnels that the protein can potentially fall into[3]. Following in the footsteps of McClare[4], Davydov[5], and Scott[6], the suggestion here is that such transient, deterministic forces arise from vibrational excited states[3], something that has recently been designated as the VES hypothesis[7]. This presentation ends with an application of the VES hypothesis to a protein involved in a misfolding disease.

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# Interactions of bis-urea bridged bis-phenanthridines with DNA and RNA.

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Low weight organic molecules interacting with DNA and/or RNA are of continuously high scientific interest.[1] Our recent results have pointed out that selectivity of bis-phenanthridinium derivatives toward various DNA/RNA sequences could be controlled by the steric effects[2] or by electrostatic (pH controlled) interactions with DNA/RNA backbone and/or nucleobases.[3] Since urea-containing aromatics have shown many biologically interesting features,[4] we have introduced two urea moieties into the linkers connecting phenanthridines with the idea that urea could offer recognition of various DNA/RNA sequences by hydrogen bonding.

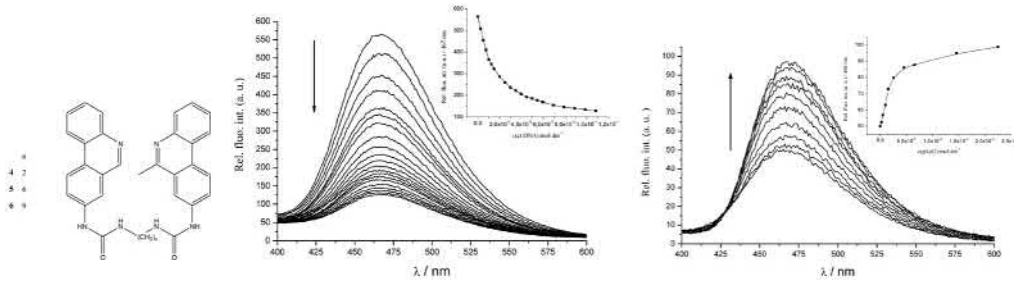


Fig. 1. Synthesized bis-urea bridged bis-phenanthridines 4-6. Changes in fluorescence spectrum of 6 ($c=1.0\times10^{-6}$ mol $dm^{-3}$, pH=5): A) upon titration with ct-DNA; B) upon titration with poly A- poly U.

Novel bis-phenanthridine derivatives bridged by bis-urea linkers of variable length (Fig. 1) were synthesized and spectroscopicaly characterized. Spectroscopic study (UV/vis, fluorescence) revealed that interactions of 4-6 with DNA and RNA are strongly dependent on the length of the linker, as well as on the polynucleotide basepair constitution and DNA/RNA secondary structure. In addition, 6 could be considered as a specific fluorescence probe for poly A – poly U (Fig. 1B, strong fluorescence increase) and poly dA-poly dT, since addition of ct-DNA (Fig. 1A) and poly G – poly C results in quenching of 6 fluorescence.

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*Acknowledgements:* This work was funded by the Ministry of Science, Education and Sport of Croatia (project 098-0982914-2918).

# Kinetics and Mechanism of the Aminolysis of Aryl Phenyl Chlorothiophosphates with Anilines Oxidation of Amides Employing Aminoxyl Radicals: Mechanistic Features

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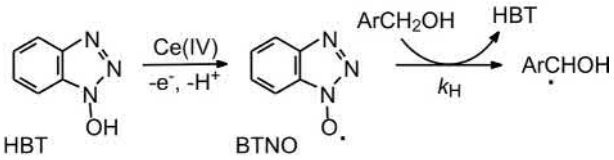
The aminoxyl radical BTNO is generated from 1-hydroxybenzotriazole (HBT) by using the one-electron oxidant cerium(IV)ammonium nitrate (*viz*. CAN) in MeCN solution.[1] It features a broad absorption band in the 400-600 nm region ($\lambda_{max}$ at 474 nm, ε 1840 $M^{-1}$ $cm^{-1}$), which decays with a half-life of 110 s. An EPR spectrum compatible with the structure of BTNO has been recorded by mixing CAN and HBT solutions in MeCN at 25 °C.[1]




**Scheme 1**

An extensive kinetic study of the H-atom transfer (*HAT*) oxidation by BTNO with a number of H-donor substrates presenting C-H bonds of suitable energy ($BDE_{C-H}$), for example benzylic or allylic alcohols or hydrocarbons, has been published.[2] In a new spectrophotometric investigation we have determined rate constants ($k_H$) of H-abstraction by BTNO from a series of six X-substituted-benzylacetamides, at 25 °C in MeCN.

$$ArCH_2NHCOMe + BTNO \xrightarrow{k_H} ArCHO + ArC(O)NHCOMe + HBT$$

**Scheme 2**

Plotting the log $k_H$ data *vs*. σ+ yields ρ = -0.63, a value in keeping with a *HAT* process by the electrophilic radical BTNO. The kinetic isotope effect $k_H/k_D = 8$ (using $PhCD_2NHCOMe$) gives also compelling evidence for a rate determining H-abstraction by BTNO. Comparison with data analogously obtained in the oxidation of amides using the aminoxyl radical PINO generated from N-hydroxyphthalimide (HPI) by means of the Co(II)/$O_2$ system[3] will be made. Through the determination of the activation parameters with $PhCH_2NHCOMe$, and use of the Evans-Polanyi correlation of *Ea vs*. $BDE_{C-H}$ previously reported,[2] we provide quantitative evidence for a substantial weakening of the benzylic C-H undergoing cleavage, as due to a stereoelectronic effect from the amide-nitrogen in α.[4] An appropriate alignment of the benzylic C-H bond with the nitrogen lone-pair orbital causes a high rate of H-abstraction, which is the more pronounced the better the eclipsing between the two orbitals.

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# Origin of the Catalytic Specificities of Methylglyoxal Synthase and Triosephosphate Isomerase

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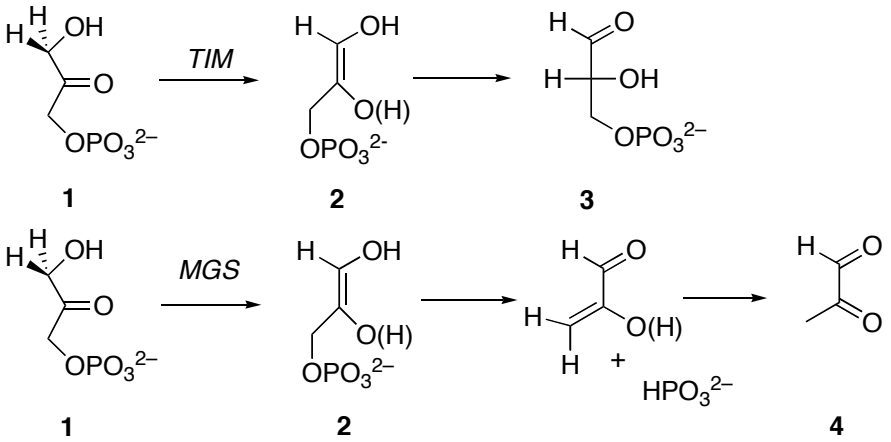
The design or selection of catalysts to rival natural enzymes often focuses solely on achieving large catalytic rate enhancements. However enzymes also offer remarkable specificities. Therefore, to gain a fuller understanding of enzyme catalysis we must address both issues in concert. We are addressing the factors determining the different product outcomes of the reactions of *methylglyoxal synthase* (MGS) and *triosephosphate isomerase* (TIM), which operate upon the same substrate. The TIM and MGS systems serve as prototypes for many enzymatic processes involving proton transfer at carbon that do not involve cofactors. MGS and TIM catalyze elimination and isomerisation reactions of dihydroxyacetone phosphate **1**. In both cases deprotonation of the α-carbon in the first step yields an enediol(ate)-enzyme intermediate **2**: in the TIM reaction this intermediate is reprotonated to give isomerisation product glyceraldehyde 3–phosphate **3**, whereas MGS catalyses the elimination of orthophosphate from the intermediate to give methylglyoxal **4**.




**Scheme 1** Enzymatic reactions of *triosephosphate isomerase* (TIM) and *methylglyoxal synthase* (MGS).

The long-held stereoelectronic explanation of these different product outcomes was recently disputed by a computational study, which considered differential electrostatic binding of the substrate phosphodianion group the critical factor.[1] We are investigating the relative contributions of phosphodianion intrinsic binding energies to the enzymatic rate acceleration for MGS and TIM to provide experimental clarification.[2] In this paper we will present recent results on the contribution of the phosphodianion group to the MGS reaction. We have prepared a series of mutant substrates lacking the phosphodianion group and have studied the enzymatic and solution reactions of these substrates using high resolution NMR spectroscopy.

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# A Combined Experimental-Computational Study on the Proton-Transfer Reaction of phenylnitromethane

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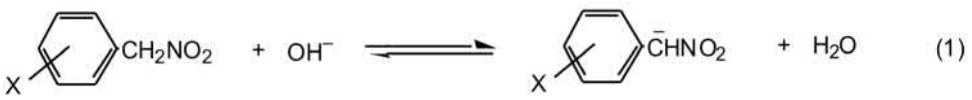
Anomalous relation between rates and equilibrium for the proton-transfer reactions of nitroalkanes is known as nitroalkane anomaly. In a typical example, the reactivity of nitromethane in acid-base reactions was shown to be much lower than expected from the Brønsted plot for the reactions of a series of carbon acids with $OH^-$ in water.[1] In another example, an anomaly was illustrated by Bronsted α coefficients of 1.3-1.5 for the reactions of $XC_6H_4CH_2NO_2$ with bases (eq 1).[2] Computational study revealed that the anomaly observed for these reaction systems could not be reproduced by the MP2-PCM method with a cluster model.[3] One may argue that the computational method is too simple to reproduce the experimental observations. Alternatively, it is possible that the reaction actually occurs in solution is not as simple as shown in eq 1.




We have carried out a combined experimental-computational study in order to clarify what actually happens in the deprotonation-protonation reactions of phenylnitromethane. Kinetic study has shown that the deprotonation step in basic media gives a large negative Hammett ρ value as expected, whereas the protonation process yields a negative ρ value of similar size. Gas-phase calculations have revealed that anomalous results in the Brønsted plots mentioned above do not arise from a kinetics term as often assumed but that a thermodynamic term plays an important role. Detailed analyses of these and other results suggested that the deprotonation-protonation reaction of nitroalkane is more complex than normally thought.

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# DABCO or DMAP – What Makes Their Difference in Organocatyalysis?

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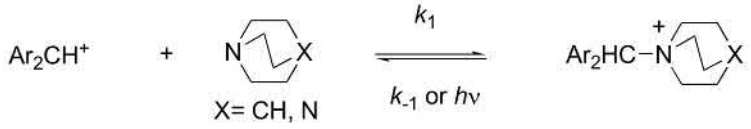
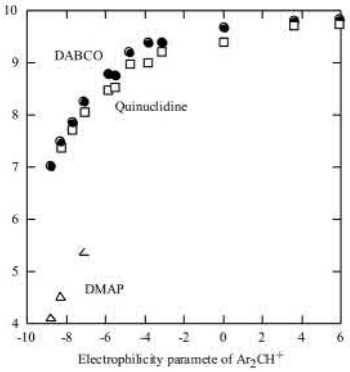
Teratiary amines, like diazobicyclooctane (DABCO), quinuclidine, and dimethylamino-pyridine (DMAP) are important as organocatalysts.[1] In order to elucidate the different behavior in organocatalysis, we determined the rates and equilibria of the reactions of tertiary amines with benzhydrylium ions, an extensively studied class of carbon electrophiles. [2]




The exponential decay of laser flash photolytically generated benzhydrylium ions in the presence of amines was used for determination of the nucleophilicities of the tertiary amines in acetonitrile.

It is found that DABCO and quinuclidine are significantly stronger nucleophiles than DMAP but at the same time much stronger nucleofuges. A comparison with other tertiary amines, triethylamine, N-methyl-pyrrolidine, N-methylpiperidine, and N-methylmorpholine will also be reported.

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# Nucleophilicity of Alcohols and Acids in the Reaction of Carbocations

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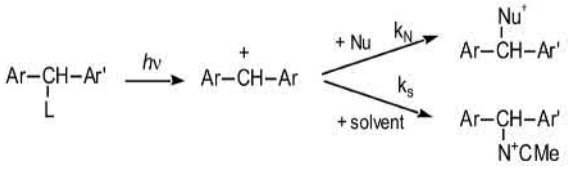
Nucleophilicity is one of the most important concepts in organic chemistry. "Solvent nucleophilicity" has been of central interest in the solvolytic reactions for several decades and several empirical scales have been proposed. These scales involve the effects of different solvation in addition to intrinsic effects arising from their molecular structures. To clarify an essential relationship between nucleophilicity and molecular structures it is necessary to elucidate the nucleophilicity of a solvent molecule.




$$k_{decay} = k_s + k_N [Nu]$$

In this study, the rate constants of the reactions of alcohols and acids with highly reactive diarylmethyl cations in acetonitrile solution were determined using a laser flash photolysis technique. The log ($k_N$) value for each alcohol was correlated linearly with Mayr's electrophilicity parameters ($E$)[1] of diarylmethyl cations that are less reactive than *p*-Tol(Ph)CH$^+$, giving the nucleophilicity paprameter *N* values. It was found that the N value decreases in the order of *n*-BuOH, *n*-PrOH, EtOH, MeOH > *i*-PrOH > $H_2O$ > *t*-BuOH.

Contrary to alcohols, acidic nucleophiles including trifluoroethanol showed a nearly flat curve like that observed for a diffusion-controlled reaction. However, the rate constants at the plateau are far from the diffusion limit rate constant ($5x10^9$ – $10^{10}$ $s^{-1}$, e.g., $CF_3CH_2NH_2$). The rate constants at the plateau seem to be related to their $pK_a$'s, i.e., the stronger acid shows the higher reactivity, suggesting the importance of the dissociation process of their nucleophiles. In addition, it was found that these log $k_N$ values for MeOH, EtOH, AcOH, TFE, and $H_2O$ at the plateau are correlated linearly with the solvent nucleophilicity scales ($N_1$ or $N_{OTs}$'). These results will be discussed.

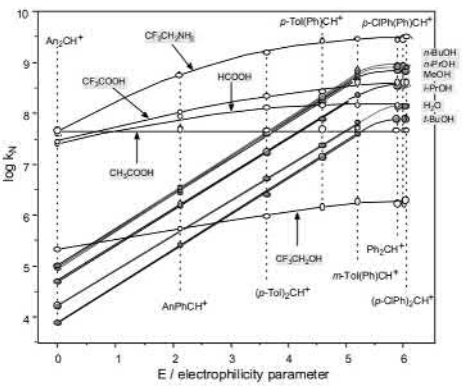



**Fig. 1.** Plot of log $k_N$ for the reaction of diarylmethyl cations with alcohols and acids against the electrophilicity parameter ($E$) of the cations.

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# Kinetic Isotope Effects In Thermoneutral Ntramolecular Proton Transfers From Carbon Acids

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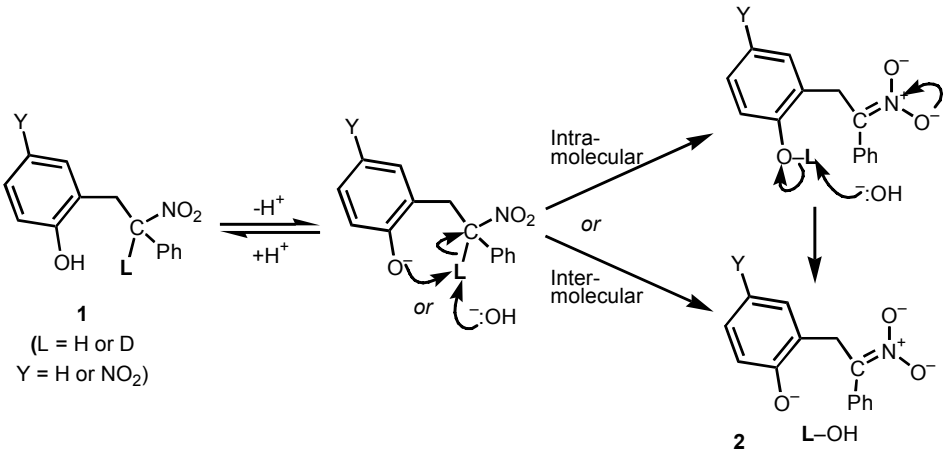
Recent examinations and re-examinations of kinetic hydrogen isotope effects in enzymecatalysed proton, hydride, and hydrogen atom transfers have suggested that large tunnelling contributions are common in such processes and have been accompanied by theorising as to how enzymes might promote tunnelling. As an experimental contribution to this debate, we compare kinetic isotope effects in proton transfers between stabilised carbanions and intermolecular and intramolecular bases, and will present our results on the behaviour of the phenolic nitroalkanes, **1**(Y = H or $NO_2$) and their conversions to di-anions, **2**.




Inter- and intra-molecular reactions have been observed, mass balances fully established, and effective molarities for the intramolecular deprotonations measured. Kinetic hydrogen isotope effects for the deprotonations ($k_H/k_D$) and their temperature dependences will be reported and discussed.

# Reactivity of Model Biochemical Systems with Divalent Metal Cations

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The interactions of different model biochemical systems such as urea, glycine, thiourea, and uracil with divalent metal cations have been investigated by means of electrospray mass spectrometry techniques and density functional theory (DFT) calculations. In this survey both alkaline-earth dications such as $Ca^{2+}$ and transition metal dications such as $Cu^{2+}$, $Ni^{2+}$ and $Zn^{2+}$ have been considered. The interactions of transition metal divalent cations ($M^{2+}$) with different solvent molecules (L) is followed by an immediate deprotonation of the system so that only $[M(L\text{-}H)]^+$ monocations are observed in the gas phase. These deprotonation processes[1] are a direct consequence of the oxidation of the base triggered by the divalent metal cation.[2] This oxidation plays also a significant role in the keto-enol tautomerization of systems like thymine[3]. Conversely, $Ca^{2+}$ is not able to oxidize the base and the deprotonation processes become endothermic. The first important consequence is that $[ML]^{2+}$ doubly charged species are stable in the gas phase and its unimolecular reactivity can be easily investigated through the use of electrospray mass spectrometry techniques. Interestingly, in the reaction with urea,[4] besides the expected coulomb explosions the loss of neutral fragments is also observed, so that new doubly charged species, such as $[CaNH_3]^{2+}$ are formed along the reaction. Surprisingly in the case of glycine only coulomb explosions are experimentally observed, in agreement with the topology of the potential energy surface obtained by DFT calculations.[5]

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# By How Much is Protonated Benzene Stabilised by Coordination to Iron Tricarbonyl? - Investigating A Route from Cis- to Trans-Arenedihydrodiols

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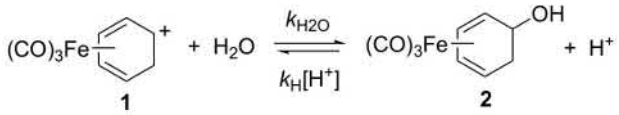
Arene *trans*-dihydrodiols are potentially important chiral synthons that provide access to new structures of interest including inositols and conduritols. As part of an investigation into the conversion of *cis*-benzenedihydrodiols to the corresponding *trans*- isomers *via* nucleophilic substitution of an iron tricarbonyl coordinated carbocation intermediate,[1] the stablity of some cyclohexadienyl cation complexed to iron tricarbonyl has been examined.

Among reactive intermediates, the benzenonium ion (cyclohexadienyl cation) is known as an example of instability and reactivity. The lifetime of this species in aqueous solution is less than 100 picoseconds and, in one molar acid, less that one molecule per mole of benzene exists in the protonated form. The discovery over fifty years ago that the same ion coordinated to an iron tricarbonyl group **1** can be recrystallised from water[2] is a striking example of the effect of metal complexation on carbocation stability. Another remarkable observation is that reaction of the metal complex with hydroxide ion leads not to deprotonation but to nucleophilic reaction at the formal charge centre to yield the coordinated benzene hydrate (5-hydroxy-1,3-cyclohexadiene) **2**.[2]




$$K_R = \frac{[2][H^+]}{[1]} = \frac{k_{H2O}}{k_H[H^+]}$$

**Scheme 1**.

Conversion of **1** to its hydrate **2** in aqueous sodium bicarbonate[2] implies that the equilibrium constant $K_R$ between the two species (Scheme 1) should be measurable at mildly acidic pH. We have found that monitoring the dependence of an absorbance change at 250 nm upon pH in cacodylic and acetic acid buffers produces a titration curve consistent with $pK_R = 4.74$. This value may be compared with $pK_R = -2.1$ for the uncoordinated cyclohexadienyl cation.[2]

The implications of these results for the interconversion of *cis*- and *trans*-arenedihydrodiols will also be discussed.

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# Can the Change from $S_N1$ to $S_N2$ Mechanism be Predicted?

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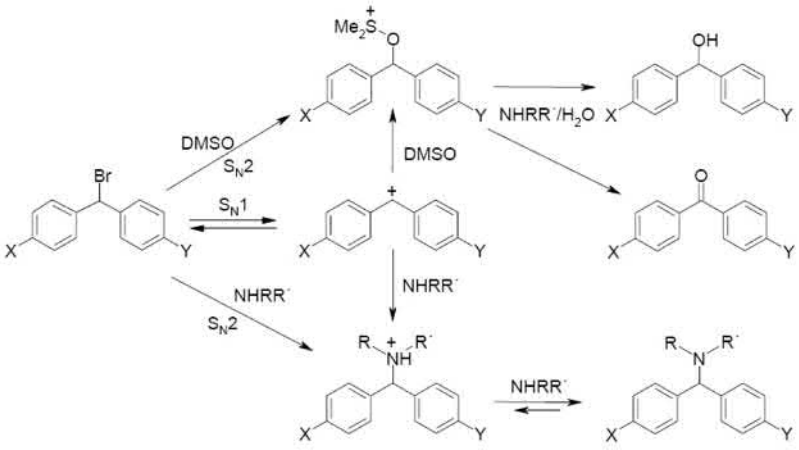
The change between $S_N1$ and $S_N2$ mechanisms is of general interest for mechanistic as well as for synthetic organic chemistry. Jencks and Richard have analyzed this problem by studying solvolyses of 1-phenylethyl halides[1] and demonstrated that a change of mechanism takes place when the lifetime of the potential intermediate becomes equal to that of a bond vibration ($10^{-13}$s).[2,3]

$$\log k\ (20\ °C) = s(E + N) \qquad (1)$$

We now report on the kinetics of the reactions of benzhydryl bromides with various amines in DMSO. Because equation (**1**) allows one to calculate the rates of the reactions of the benzhydrylium ions with the amines from the electrophilicity parameters *E* of the benzhydrylium ions and the nucleophilicity parameters *N* and s of the amines,[4] it becomes possible to predict the preferred mechanisms.

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# Organic Super Electron Donors: The First Powerful Reductions Performed By Neutral Organic Molecules

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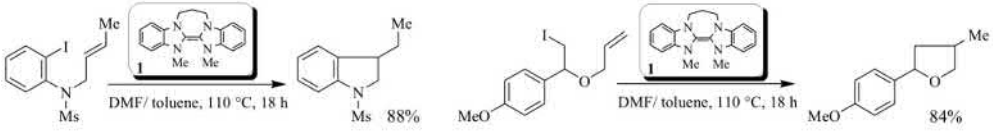
We have entered the age of organocatalysis, but will organic reagents ever be able to take the place of metals? The sternest test would be to prepare 'organic sodium', i.e. a neutral organic reagent with extraordinary reducing power. To achieve this goal we recently developed bisbenzimidazolylidene **1**; this is the first neutral organic donor that is capable of transferring a single electron to an unactivated aryl or alkyl iodide, leading to products in high yields resulting from intermediacy of aryl radicals. [1]




**Scheme 1.**

However, despite having great reducing ability, donor **1** is not powerful enough to master even tougher challenges. The highly powerful neutral organic donor **2** [exhibiting a reduction potential of -1.2 V vs. S.C.E.] has therefore been synthesised and its exceptional reactivity has been explored. Donor **2** is the first neutral organic molecule that is capable of producing an aryl anion from an aryl halide, giving xanthone **4** upon cyclisation of the aryl anion derived from substrate **3**.[3] Furthermore, donor **2** is able to reduce anthracene to its dihydro counterpart in the absence of any metals, highlighting its enormous reductive power.


**Scheme 2.**

Investigations on sulfones and sulfonamides were carried out, and a mild and yet highly powerful protocol was developed, allowing their reductive cleavage in an efficient fashion.


**Scheme 3.**

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# Interfacing experiment and quantum chemical calculations in transition metal chemistry: A comparative study of structural and magnetic properties of [(Ligand)$_n$Ni-CH$_2$-CH$_2$-COO-] complexes and their role in a hypothetic catalytic cycle towards acrylic acid

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Metal mediated reactions modelled after nature are promising for $CO_2$ activation and transformation and are of general interest for oxo-functionalization of simple organic compounds.

The fixation of carbon dioxide to a nickel(0) complex and an ethylene molecule results in the formation of a nickelalactone (**1**). Among a variety of interesting synthetic applications nickelalactones could also be considered as possible intermediates in the formation of industrially valuable acrylic acid (**4**). In a recent paper D. Walther et al.[1] addressed the formation of the nickel-acrylate complex (**2**) to be the key step in a to date hypothetical catalytic cycle towards acrylic acid (Figure 1.).

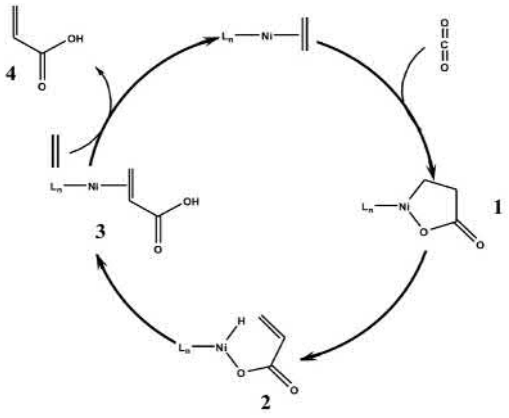


**Fig. 1**. Hypothetical catalytic cycle leading to the formation of acrylic acid

We have performed a quantum chemical computational study of the structural and magnetic properties of niceklalactone type complexes (**1**) and in addition explored the reaction path interlinking complex (**1**) with a complex bound acrylic acid (**3**).[2] The results of the ab initio calculations compared to experimental X-ray data and $^{13}C$ NMR chemical shifts measured in solution will be presented and the results of the IRC computations will be discussed.

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# Reactivity of dehydroamino acid derivatives towards N-bromosuccinimide

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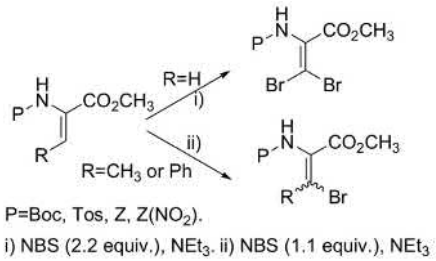
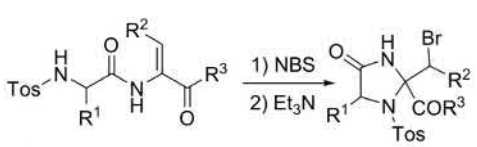
The reactivity of dehydroamino acid and dehydropeptide derivatives towards NBS was studied.[1a] Thus, the methyl esters N-protected dehydroamino acids, were reacted with 2.2 or 1.1 equivalents of NBS, followed by treatment with $NEt_3$, to give β,β-dibromodehydroalanines and β-bromo-β-substituted dehydroamino acids, respectively (Scheme 1). The β,β-dibromodehydroalanines were obtained in good to high yields (52-86%) using as substrate dehydroalanine derivatives. β-Alkyl, β-bromo and β-aryl, β-bromodehydroalanines were prepared in yields ranging from 80% to 97%, by reacting β-substituted dehydroalanines namely dehydroaminobutyric acid (ΔAbu) and dehydrophenylalanine (ΔPhe), respectively. In these cases a mixture of E and Z isomers was obtained, with a higher stereoselectivity towards the Z-isomer for the dehydrophenylalanine derivative and when the 4-toluenesulphonyl group was used as protecting group.




| Product | Yield / % | E/Z ratio |
|---|---|---|
| Boc-ΔAla(β,β-Br)-OMe[1b] | 52[1b] | --- |
| Z-ΔAla(β,β-Br)-OMe | 86 | --- |
| Z($NO_2$)-ΔAla(β,β-Br)-OMe | 75 | --- |
| Boc-ΔAbu(β-Br)-OMe | 92 | 1/1 |
| Z-ΔAbu(β-Br)-OMe | 89 | 4/3 |
| Z($NO_2$)-ΔAbu(β-Br)-OMe | 80 | 1/1 |
| Tos-ΔAbu(β-Br)-OMe | 94 | 1/9 |
| Boc-ΔPhe(β-Br)-OMe[1c] | 97[1c] | 1/2[1c] |

**Scheme 1**

Dehydropeptides were also reacted with NBS, followed by treatment with $NEt_3$. It was found that, when the N-protecting group was other than a 4-toluenesulphonyl group, the corresponding β-bromodehydrodipeptides were isolated. However, when this group was present, the only products isolated were N-(4-toluenesulphonyl)-4-imidazolidinone derivatives in good to high yields (Scheme 2). We believe that the initial step in the formation of these compounds is the bromination of the dehydroamino acid residue by NBS, followed by cyclization, which occurs via a nucleophilic attack of the nitrogen atom of the sulphonamide moiety on the α-carbon atom of the second amino acid residue.




$R^1$=H, $R^2$=H, $R^3$=$OCH_3$, 92%;
$R^1$=H, $R^2$=$CH_3$, $R^3$=$OCH_3$, 94%;
$R^1$=$CH_3$, $R^2$=$CH_3$, $R^3$=$OCH_3$, 74%;
$R^1$=H, $R^2$=$C_6H_5$, $R^3$=$OCH_3$, 86%;
$R^1$=$CH_3$, $R^2$=$C_6H_5$, $R^3$=$OCH_3$, 91%;
$R^1$=$CH_3$, $R^2$=H, $R^3$=$OCH_3$, 88%;
$R^1$=H, $R^2$=H, $R^3$=$NHCH_2CO_2CH_3$, 82%.

**Scheme 2**

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# Why is the penicillin binding protein of T. elongatus not a β-lactamase?

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DD-peptidases, enzymes involved in bacterial walls synthesis, are also called "Penicillin Binding Proteins" (PBPs) since they form stable acyl-enzymes with β-lactam antibiotics, the stability of these complexes being responsible for the antibiotic effect. Some bacteria are resistant to β-lactams thanks to the production of β-lactamases, enzymes capable of hydrolysing these antibiotics up to $10^8$ times faster than PBPs following a mechanism implying an acyl-enzyme. It is generally accepted that β-lactamases have evolved from an ancestral PBP by dramatically increasing the rate of deacylation. In order to better understand this mechanism of molecular evolution, we have attempted to evolve a DD-peptidase into a β-lactamase.

The PBP-A from *Thermosynechococcus elongatus* was chosen as starting protein. This enzyme belongs to a new family of PBPs that appears to be the most closely related to the class A β-lactamases. Biochemical analyses on this protein indicate that it is indeed a DD-peptidase. Since sequences alignments suggested that Leu158 could be located in the active site in a position similar to that of Glu166, a residue essential for efficient deacylation in the class A β-lactamases, the L158E mutation was performed. It leads to only a 90-fold increase in the rate of deacylation of an acyl-enzyme formed with penicillin. Structural analyses of the wild-type enzyme and the L158E mutant indicate that the active site of the mutant enzyme is very similar to that of class A β-lactamases, most catalytic residues being in nearly identical positions. In an attempt to evolve PBP-A into β-lactamase, a directed evolution approach was implemented in which two libraries of mutants were created either by replacement of a region of the sequence thought to be essential for deacylation by semi-random sequences or by error-prone amplification of the full gene. A selection protocol developed in our laboratory was then applied on these libraries. It has allowed selecting enzymes with significantly improved rates of acylation. However, no mutant deacylating significantly faster than the L158E mutant could be isolated. The possible reasons why PBP-A and its mutants are not β-lactamases will be discussed.

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# Mechanism and substituent effects in the acid-catalysed hydrolysis of methoxy-substituted trityl 2,2,2-trifluoroethyl ethers

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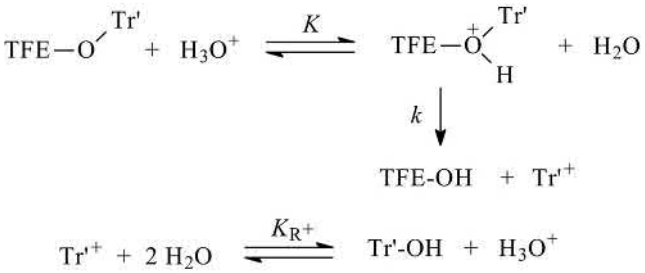
Detritylation of the methoxy-substituted trityl (Tr') 2,2,2-trifluoroethyl (TFE) ethers under aqueous acidic conditions led to trifluoroethanol and equilibrium mixtures of the substituted trityl carbenium ions and the corresponding trityl alcohols (Scheme). The kinetics of the detritylations were investigated by our usual method of monitoring the rate of increase in UV absorption due to the formation of the (substituted) trityl cation. Reactions of the trimethoxy- and dimethoxy-trityl (TMT and DMT) TFE ethers were carried out at acid concentrations up to 1 mol $dm^{-3}$, and 1 mol $dm^{-3}$ constant ionic strength. The monomethoxytrityl (MMT) analogue was insufficiently reactive under these conditions so higher acid concentrations were used; consequently, this compound was investigated at 3.0 mol $dm^{-3}$ constant ionic strength.




**Scheme.** Cleavage of substituted trityl TFE ethers (Tr'-O-TFE) in dilute aqueous acidic solution.

For all three methoxy-substituted compounds, the increase in *pseudo*-first-order rate constants with increasing acid concentration was initially linear, which allowed determination of second-order rate constants for the hydronium ion catalysed reaction ($k_H$). In all three cases, extrapolation of data indicated finite reactivity ($k_o$) at zero hydronium ion concentration. All three methoxy-substituted compounds also showed increasingly upward curvature at higher acidities. However, absence of a correlation between $k_{obs}/[H_3O^+]$ and $[H_3O^+]$ for the monomethoxy compound established that this upward curvature was not simply due to the intrusion of a second-order term in the rate law. Results for substituted trityl TFE ether cleavages will be compared with results for ionisation of the corresponding trityl alcohols and the deamination of the corresponding tritylamines which we reported previously.

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# Different types of H…H interactions

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There are different types of H…H interactions, they exist not only in crystal structures but also in small complexes. The strongest H…H interactions (dihydrogen bonds – DHBs[1]) are characterized by binding energies exceeding 20 kcal/mol and possessing characteristics typical for covalent bonds [2] while the weakest H…H interactions are attributed to van der Waals contacts with binding energies amounting to less than 1 kcal/mol.[3]

The Bader theory [4] is applied to characterize H…H interactions, one can see the broad range of characteristics connected with them (Fig 1). For some of DHBs the bond paths of H…H interactions mimic typical covalent bonds since there are the great values of electron densities at H…H BCPs and negative values of the corresponding Laplacians. The other H…H interactions may be treated as closed-shell interactions what is supported by their characteristics. There are also so-called stabilizing H-H interactions analyzed very recently.[5]

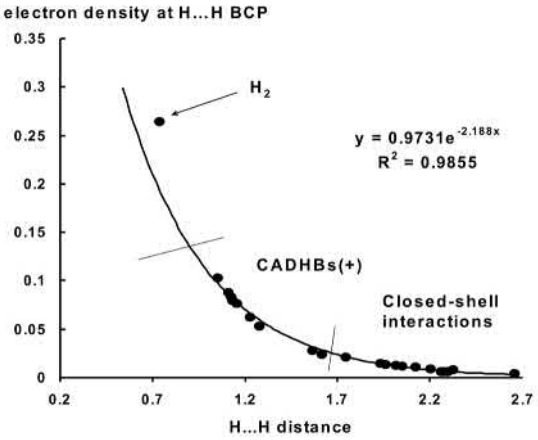


**Fig. 1.** The H…H distance (in Å) vs. the electron density at the corresponding bond critical point (in au); the regions of weaker closed-shell interactions and the charge-assisted dihydrogen bonded are designated; also the $H_2$ molecule for comparison is indicated.

It is worth mentioning that H…H interaction in dihydrogen bonded system may be treated as a preliminary stage of the formation of gaseous molecular hydrogen.[6] Hence the deeper insight into H…H contacts allows to explain numerous chemical processes.

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# The Origin of Aromaticity – Important Role of the Sigma Framework

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Aromaticity is one of the most important concepts in organic chemistry despite the fact that it cannot be rigorously defined. The question of origin of this elusive (pseudo) phenomenon is very interesting. Traditionally, aromaticity is attributed to the π electrons in planar molecular systems. This "dogma" was challenged by Shaik and coworkers[1,2], who put forward arguments in favour of the sigma framework. Our analyses of the total electronic energies based on the stockholder partitioning criterion confirm that the σ-framework exerts a decisive influence.[3] Moreover, it was convincingly shown that Clar' s sextet rule is also a consequence of the σ-framework.[4] Surprisingly, Hückel (4n+2) $\pi$ electron rule still works being useful in determining stability of the bond-strech isomers.[5,6]

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# Predicting the rates of organic reactions in solution: the aldol addition reaction.

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"No Barrier Theory" asserts that when only one thing happens in a chemical reaction there is no kinetic barrier, but only a quadratic potential function, and that the kinetic barriers associated with almost all chemical reactions result from the need for more than one simple thing to happen simultaneously for the reaction to occur. This theory permits calculation of the free energies of activation for chemical reactions given only the equilibrium constants in solution and the distortion energies corresponding to the hypothetical "one thing at a time" transformations. The calculations are much less demanding than direct calculation of the structure and energy of the solvated transition state and generally come within 2 kcal of the observed value. No Barrier Theory also provides a qualitative way to think about the magnitude of the intrinsic barrier for a reaction.

This approach has now been applied to the hydroxide catalyzed aldol addition reaction. As has been shown for the addition of water to carbonyl compounds, the No Barrier Theory approach allows calculation of the rate constants corresponding to a mechanism of reaction.

*Acknowledgements:* This work was funded by NSERC, Canada.

# Qualitative/Quantitative Correlation of Acidities and Rates of Gas-Phase Pyrolysis of Picolinic Acids and Corresponding Ethyl Esters

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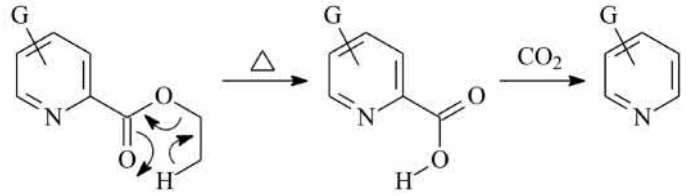
Substituted picolinic (2-pyridinecarboxylic) acids (PAs) and their ethyl esters enjoy a wide range of applications in the pharmaceutical, agrochemical, nutrition, enzyme assay, and microbiological domains. Structure/activity-reactivity correlation studies constitute an integral part of the study of PAs and their alkyl esters.

In the present investigation, the effects of substituents (-CH3; -Cl/Br; -OR; -$NO_2$) at the 3, 4, 5 and 6 positions of the heteroaryl picolinic ring on acid strength (pKa values) and rates ($k/s^{-1}$) of gas-phase pyrolysis of the ethyl esters are assessed both qualitatively and quantitatively. Quantitative (LFER) correlation addressed Hammett (K/σ and k/σ) relations, as well as Hammett-type analysis of thermodynamic (pK) and kinetic (pk) data. It is noteworthy that the pyrolysis pathway of the ethyl ester involved a 6-membered transition state leading to the picolinic acid, which in turn could decarboxylate into a pyridine derivative.




The aza moiety of PA constitutes an important replacement substituent. In earlier studies, we have provided the first record of gas-phase Hammett replacement substituent constants of heteroaryl groups,[1] and data on the molecular reactivity of diaza replacement substituents.[2] Here, we assess the cumulative effects of electron-donating/withdrawing groups and heteroaryl replacement substituents of PA and derivatives.

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*Acknowledgements.* College of Graduate Studies and ANALAB & SAF grants # GS 01/01 and GS 03/01 are gratefully acknowledged.

# Reactivity of Methyl Esters of N-Boc-β,β-disubstituted Dehydroamino Acids Towards the Synthesis of Lactams and Lactones

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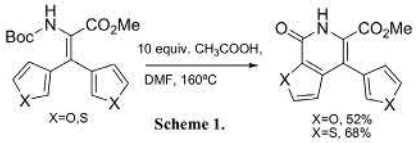
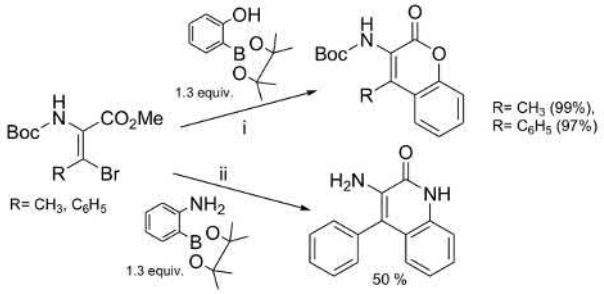
Several methyl esters of N-(t-butoxycarbonyl)-β,β-heteroaryldehydroamino acids were prepared from a β,β-dibromodehydroalanine derivative[1] and heteroarylboronated compounds, using a bis-Suzuki coupling. These coupling products were cyclized in presence of acetic acid at 160 ºC in DMF, to give δ-lactams in good yields by attack of the heterocyclic ring on the carbonyl of the Boc group (Scheme 1).




**Scheme 1.**

We were able to obtain in a one pot two steps procedure, δ-lactams and δ-lactones from 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol or aniline and (*E*)-β-bromo-β-substituted dehydroamino acids. In this method a Suzuki coupling2 is followed by an intramolecular cyclization involving the amino or the hydroxy groups and the carbonyl of the ester (Scheme 2).




**Scheme 2**

To our knowledge it is the first time that δ-lactams and δ-lactones were obtained from methyl esters of *N*-Boc-β,β-disubstituted dehydroamino acids, taking advantage of the reactivity of the protecting groups.

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# Kinetics, Mechanism and Element / Substituent Effects of Gas-Phase Pyrolysis of (P) and (As) Ylides

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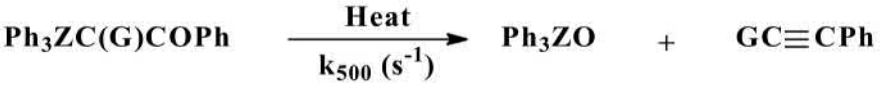
Research in the field of ylide chemistry is rich and diverse, with emphasis so far being placed on structure, synthesis and mechanisms of reaction. An important aspect of current interest in this area is flash vacuum pyrolysis (FVP) of stabilized ylides. We have now extended the investigation of ylide gas-phase pyrolysis to the study of the kinetics of reaction in order to correlate reactivity with structure and to lend support thereby to proposed reaction mechanisms.[1-3]

In this communication, we outline the synthesis of ten stabilized (P) and (As) benzoylmethylene-triphenylphosphorane and triphenylarsorane ylides and report on the kinetic and mechanistic investigation of their FVP and static thermal gas-phase elimination reactions.




**Z: P; As & G: H; $C_2H_5$; Ph; SPh; COPh; $CO_2C_2H_5$**

Pyrolysis of the (P) ylides involved the extrusion of Ph3PO as the inorganic elimination fragment, while the pyrolysates of the (As) ylides included both $Ph_3AsO$ and $Ph_3As$. Analysis of the kinetics and products of reaction underpin the mechanism proposed for the elimination pathway which was in turn used to rationalize relative ylide molecular reactivities.

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# The Versatile Reactivity of a Superelectrophilic Nitroolefin : 4-Nitrobenzodifuroxan.

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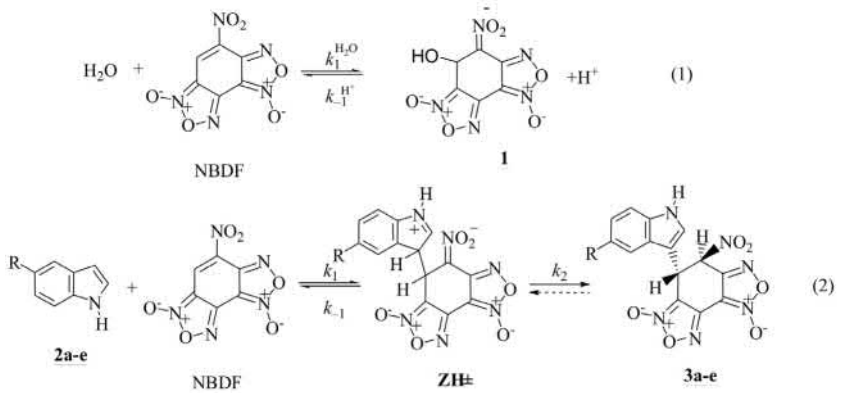
This communication will emphasize the exceptional electrophilicity of the nitro activated C4-C5 double bond of 4-nitrobenzofuroxan (NBDF).[1,2] As a first example of this behaviour, NBDF is found to undergo complete covalent hydration in the absence of any added base in aqueous solution. The $pK_a^{H_2O}$ and $k_1^{H_2O}$ (in s-1) values for formation of the adduct **1** (eq. 1) are equal to 3.00 and 0.04 respectively, making NBDF much more electrophilic than such common activated olefins as benzylidenemalonitrile ($pK_a^{H_2O}$ = 10.07 and $k_1^{H_2O}$ = 1.2x10-4), β-styrene ($pK_a^{H_2O}$ = 10.37 and $k_1^{H_2O}$ = 2.2x10-6 in 50% H2O) or benzylidene Meldrum's acid ($pK_a^{H_2O}$ = 5.43 and $k_1^{H_2O}$ = 0.55). Another remarkable illustration of the high electrophilic character of NBDF is that this compound readily reacts with a series of 5-X-substituted indoles **2a-e**, affording the Michael adducts **3a-e** in acetonitrile. A kinetic study of reaction (2) has allowed the ranking of NBDF on the comprehensive electrophilicity scale of Mayr.3 With an E value of -6.15, the reactivity of NBDF approaches that of such a cation like the 4-nitrobenzenediazonium cation (E = -5.10).




**a)** R = $NH_2$; **b)** R = OMe; **c)** R = Me; **d)** R = H; **e)** R = Cl

The reactivity of NBDF extends to normal and inverse electron-demand Diels-Alder reactions. Several interactions will be discussed focussing especially on the UV-visible and kinetic evidence that most of the cycloadditions proceed through a two-step addition-cyclization pathway, i.e. they are very polar in nature.

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# O-Copuling Reactions: Formation and Decomposition of Transient Diazo Ethers in the Course of Reactions between Arenediazonium Ions and different alcohols.

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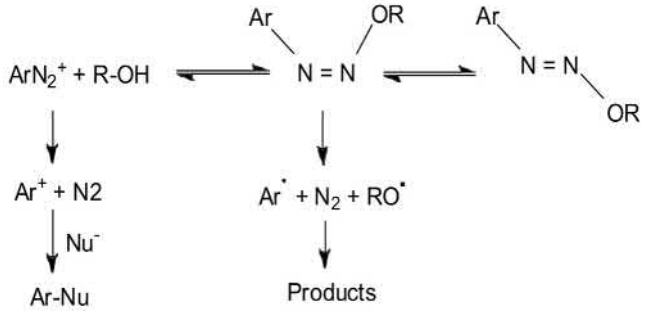
In this work we present the results of studies carried out in the last years related with the formation and decomposition of diazo ethers in the course of O-coupling reactions between arenediazonium ions, $ArN_2^+$, and different alcohols. $ArN_2^+$ ions spontaneously decompose through a $D_N + A_N$ mechanism leading to ArNu derivatives, Scheme 1, but there exist a diversity of reactions where O-nucleophiles add to diazonium ions at $N_\beta$ to give Z-adducts as kinetically controlled products, i.e., Ar-N=N-O-R (R= alkyl, aryl). In most cases analyzed, the nucleophile must possess a charge, such as $OH^-$, $CN^-$, $RO^-$ or ascorbate ions, and experimental conditions are chosen so that substantial concentrations of the anionic form of the nucleophile are present;[1-4] but formation of Z-diazoethers with neutral nucleophiles has also been reported.[5-7] Diazo ethers of the general structure ArN=NOR (with R = alkyl, aryl) are rarely formed as stable products because they are sensitive to acid and base as well as light.




**Scheme 1** Basic illustration of the spontaneous decomposition of $ArN_2^+$ ions ($D_N + A_N$ mechanism) leading to ArNu products and the formation of transient diazoehters that may undergo homolytic scission, yielding reduction products, or undergoing isomerization to give the thermodinamically stable E-diazo ether.

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# Thoughts on enzymes and models

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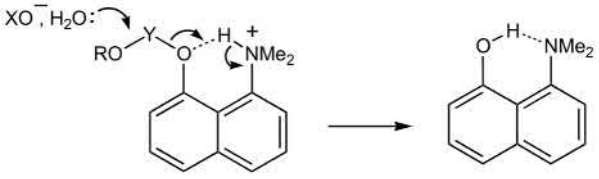
The objective of our work on intramolecular catalysis is to understand generic catalytic mechanisms used by enzymes, by studying the same basic reactions in simple systems. Proton and phosphate transfer are between them the most common enzyme catalyzed reactions – and some of the most difficult to pin down, even in quite simple systems. We report new results for systems designed to reveal details of hydrogen-bonding in reactant and transition states relevant to catalytic efficiency in phosphate transfer. The reactions concerned involve proton transfer to oxygen, mostly concerted with the breaking of bonds to phosphorus. Catalysis in these model systems is highly efficient if – *and only if* - the proton transfer takes place via a strong intramolecular hydrogen bond.

Results with a series of phosphate[1-3] and sulfate[4] esters (Scheme, Y = $PO_2^-$ (etc.) or $SO_2$) show that hydrogen bonding in systems derived from 8-dimethylamino-1-naphthol supports highly efficient general acid catalysis of phosphate and sulfate transfer to nucleophiles. In some cases the hydrogen bond is strong in the reactant as well as the product, but it must be strongest in the transition state for the reaction. These results have implications for a wide range of enzyme reactions will be touched.




**Scheme**

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# Mimicking Compound I by Naked, High-valent Oxo Iron Intermediates

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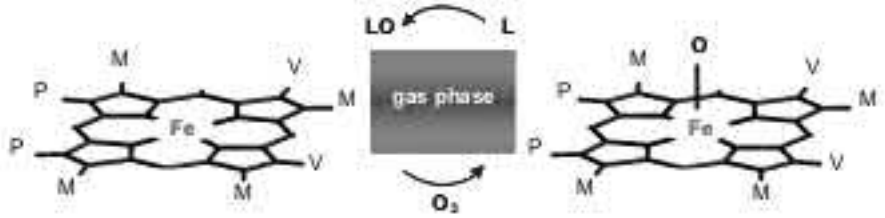
High valent iron porphyrins at the formal Fe(V) oxidation level are well-established as Compound I intermediates for heme proteins such as peroxidases and catalases as well as for their synthetic model compounds.[1-2] A dominant feature of these processes is the dramatic change in product patterns and selectivities that Compound I may exhibit under the influence of reaction conditions. In this context, gas phase studies may have great potential in revealing the individual contributions of solvent, counterions, and aggregation/ligation, thus allowing the intrinsic reactivity of the active species to be elucidated at a molecular level. Electrospray ionization (ESI) in combination with Fourier transform ion cyclotron resonance mass spectrometry is used to characterize the gas phase reactivity of high-valent oxoiron intermediates formed by two distinct procedures. In the first one, the oxoiron(IV) porphyrin cation radical intermediate, $[(TPFPP)\cdot^{+}Fe^{IV}=O]^{+}$ (TPFPP = 5,10,15,20-tetrakis (pentafluoroph enyl)porphinato dianion) ion is prepared in solution by the reaction of the iron(III) porphyrin chloride, $[(TPFPP)Fe^{III}]Cl$, and $H_2O_2$ in methanol and then transferred to the gas phase by ESI.[3] Alternatively, the naked core of Compound I is synthesized by the reaction of iron-protoporphyrin-IX (heme) ions, $[(PP\text{-}IX)Fe^{III}]^{+}$, with ozone in the gas-phase, namely in a dielectric medium resembling to some extent the low polarity environment surrounding the prosthetic group within a hemeprotein. The formation of the oxo-complex, described as a gaseous iron(IV)-oxo protoporphyrin IX radical cation species, $[(PP\text{-}IX)\cdot^{+}\ Fe^{IV}=O]^{+}$, allows a viable entry to a species that proves to be elusive in solution where it evolves presumably by activating the rapid growth of degradation products.




The reactivity properties of the so-obtained high valent oxo iron intermediates with exemplary biologically active molecules and model compounds of naturally occurring substrates of hemeproteins are reported.

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# What is the Role of the Metal-ion in Metallo β-Lactamases?

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The mechanistic role of the metal-ion in enzymes that catalyse the hydrolysis of amides is usually attributed to either providing a metal-bound nucleophilic hydroxide-ion or to acting as a Lewis acid to polarise the carbonyl group and stabilise the oxyanion tetrahedral intermediate. Metallo-β-lactamases are native zinc enzymes that catalyse the hydrolysis of β-lactam antibiotics, but are also able to function with other metal-ions and require one or two metal-ions for catalytic activity. The hydrolysis of cefoxitin, cephaloridine and benzylpenicillin catalysed by cobalt substituted β-lactamase from *Bacillus cereus* (BcII) has been studied at different pHs and metal-ion concentrations. An enzyme group of $pK_a$ 6.5±0.1 is found to be required in its deprotonated form for metal-ion binding and catalysis. The $k_{cat}/K_m$ for cefoxitin and cephalexin with cadmium substituted BcII is dependent on two ionising groups on the enzyme: one of $pK_{a1}$=8.7±0.1 required in its deprotonated form and the other of $pK_{a2}$=9.3±0.1 required in its protonated form for activity. The pH-dependence of the competitive inhibition constant, Ki, for CdBcII with L-captopril indicates that $pK_{a1}$=8.7±0.1 corresponds to the cadmium bound water. For the manganese substituted BcII, the pH dependence of kcat/Km for benzylpenicillin, cephalexin and cefoxitin similarly indicated the importance of two catalytic groups: one of $pK_{a1}$=8.5±0.1 which needs to be deprotonated and the other of $pK_{a2}$=9.4±0.1 which needs to be protonated for catalysis; the $pK_{a1}$ was assigned to the manganese bound water. The metal substituted species have similar or higher catalytic activities compared with the zinc enzyme, albeit at pHs above 7. Interestingly, with cefoxitin, a very poor substrate for ZnBcII, both kcat and $k_{cat}/K_m$ increase with increasing $pK_a$ of the metal bound water, in the order Zn<Co<Mn<Cd. A higher pKa for the metal-bound water for cadmium and manganese BcII leads to more reactive enzymes than the native zinc BcII suggesting that the role of the metal-ion is predominantly to provide the nucleophilic hydroxide, rather than to act as a Lewis acid to polarise the carbonyl group and stabilise the oxyanion tetrahedral intermediate.

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# The limits of growth for superacidity and superbasicity of neutral Brønsted acids and bases

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The principles of designing superstrong neutral Brønsted acids and bases are discussed. The design of neutral superacids implies the fulfillment of several of the following preconditions in the neutral acid and its conjugated anion: accumulation of highly polarizable strong electron-acceptor substituents, delocalization of the negative charge in the anion, its coplanarity and aromaticity or three-dimensional sigma-aromaticity, the lack of pi-electrons and/or lone-electron pairs, high symmetry, etc.

The design of neutral superbases assumes the presence of polarizable electron-donor substituents, localization of negative charge on the basicity center, extensive resonance stabilization of the protonated form and delocalization of its positive charge, and lack of extra-stabilization (e.g., resonance, H-bond) of the neutral base.

Comparison of extreme values of acidity and basicity scales shows that the spontaneous gas-phase proton transfer between neutral superacid and superbase is achievable. Comparisons between gas-phase and solution (aqueous and nonaqueous solvents) acidity and basicity scales are made.

# pH-Dependent Aggregation of Sugar-based Gemini Surfactants

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We have made an extensive study of a large series of novel (reduced) carbohydrate-based gemini surfactants (**1**) carrying two amine functionalities.This structural feature allows

(RBC)(R)N- (spacer)- N(R)(RCB)
**1**, R = C(1) – C(18), RBC = (reduced) carbohydrate group

variation of the protonation state between zero and two, leading to a rich pH-dependent aggregation behavior, including formation of spherical and worm-like micelles, vesicles, inverted phases and oil droplets[1]. The morphological changes have been examined by cryo-electron microscopy, static and dynamic light scattering, ç-potential measurements and fluorescence spectroscopy. The packing parameter concept was helpful in the interpretation of the data[2]. Around neutral pH, the almost uncharged vesicular aggregates flocculate, but, most remarkably, a small further increase of the pH leads to redispersal of the vesicles. Charge reversal has occurred due to adsorption of hydroxide ions to the vesicular surface. An MD simulation supported this interpretation[3].This explanation has now been further substantiated by experiments with selected geminis that cannot bind hydroxide ions by hydrogen bonding[4].

The phase transitions can also be affected by molecular variations in the gemini structure such as changes in the length and saturation of the alkyl tails R, the length and nature (hydrophobic vs. hydrophilic) of the spacer, the size and stereochemistry of the carbohydrate groups and shortening or removal of the carbohydrate units.

The overall results show a fascinating interplay between hydrophobic interactions and hydrogen-bonding effects. The gemini structural features, including the protonation state, determine how the aggregation properties respond to the aqueous medium offered to the amphiphilic solutes.

Apart from their fundamental interest, the present insights are also useful in our studies of the application of the gemini surfactants as DNA carriers in gene delivery[5].

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# Ionic Liquid Interactions with Organic Solutes

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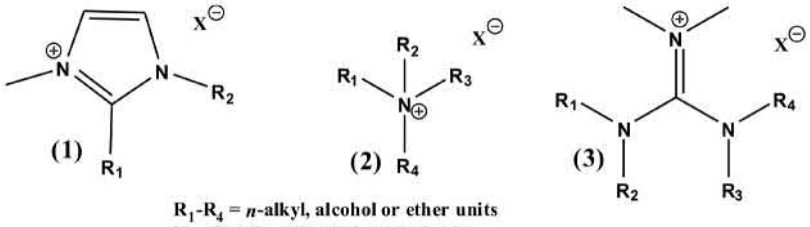
Ionic Liquids (ILs) are attracting increasing interest as new media, mainly because some peculiar physical and chemical properties[1] such as high conductivity, wide electrochemical window, near non-volatility, high thermal stability, low flammability, tuneable viscosity and controllable solubility in water and in common organic solvents as well as good extractability for several organic solutes and metal ions.

As a result of these properties ILs are emerging as an alternative recyclable, environmentally benign reaction medium in analytical chemistry, catalysis and biocatalysis, synthesis, separation science and nanotechnology processes. [2]

Herein, we discussed some interactions between ILs and organic solutes using ILs as potential extractants, liquid membranes (LMs) or supported liquid membranes (SLMs). In 2002, we showed that SLM based on ILs possess a high potential for the continuous highly selective separation of isomeric amines between two organic phases that are structurally similar and have comparable boiling points.[3]

From these experiments, we conclude that the appropriate combination of selected ILs based on imidazolium (**1**), ammonium (**2**) or guanidinium (**3**) cation units with several anions and supporting membranes is crucial for achieving good selectivity to specific organic solutes.[4]




$R_1$-$R_4$ = *n*-alkyl, alcohol or ether units
X = Cl, $PF_6$, $BF_4$, $NTf_2$, chiral units

Additionally, recent studies in the literature have been focused on liquid-liquid phase behaviour of ionic liquids in various solvents.[5] In this context, we have studied the partition coefficients between ionic liquid/water biphasic systems for representative pharmaceutical organic compounds. These partition coefficients were compared with conventional two-phase systems such as 1-octanol/water in the hope of obtaining a better model for phospholipids/water partitioning..

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# Substituent Effects on the Formation of Cations from Acid Chlorides

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A recent G3 theoretical calculation[1] gives a thermoneutral transfer (ΔH = -0.3 kcal/mol) of chloride ion in the gas phase from *t*-butyl chloride to the acetyl cation (eqn. 1), in good agreement with the latest experimental data (ΔH = -1.2 kcal/mol):[2,3]

$(CH_3)_3CCl + CH_3CO^+ = (CH_3)_3C^+ + CH_3COCl$ (1)

Important aspects of these and related results are:

(a) Contrary to widespread perceptions, hydrolysis of acetyl chloride may proceed via a cationic mechanism, similar to that for t-butyl chloride, as proposed earlier from experimental data.[4]

(b) Lower level calculations (especially B3LYP) predict significantly less reliable results:

HF/6-31G(d) gives ΔH = -5.4 kcal/mol (compared with the experimental value of -1.2),[3] and B3LYP/6-31G(d) gives an even worse result, ΔH = -10.7 kcal/mol.[1,3]

New G3 calculations will be reported for carboxylic acid and sulfonyl chlorides, and corresponding cations (acylium and sulfonyl cations). To further establish the reliability of the G3 calculations, results will be compared with experimental data for protonation of small molecues (e.g. ketene) and with heterolytic bond dissociation enthalpies for C-Cl in $CH_3COCl$ (eqn. 2), and S-Cl in $CH_3SO_2Cl$. G3 calculations will then be used to guide the applications of lower level calculations to larger molecules (e.g. arenesulfonyl chlorides) for which G3 calculations are currently too time-consuming.

$CH_3COCl = CH_3CO^+ + Cl^-$ (ΔH = heterolytic bond dissociation enthalpy) (2)

Heterolytic bond dissociation enthalpies are predicted to vary by over 70 kcal /mol from 4-methoxybenzoyl chloride to $SO_2Cl_2$. Some implications for mechanism and reactivity in solution will be suggested.

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# Reactivity Of The Intermediates Of The Reduction Of $SO_2$ On Carbons. The Use Of Xps Spectra For The Study Of Reaction Mechanisms

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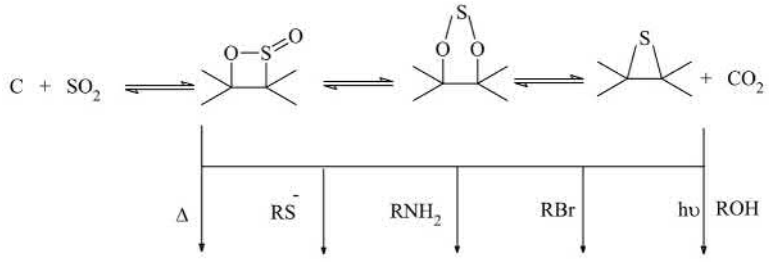
It has been proposed that the reduction of $SO_2$ on carbons proceeds through reactive intermediates bound to the carbon matrix, which were postulated to be 1, 2-oxathiene 2-oxide (or sultine), and 1, 3, 2-dioxathiolane that decomposes to produce an episulfide and $CO_2$.[1-4]




Modified activated carbon containing the intermediates was obtained at 630 ºC after reaction with $SO_2$. Consistent mechanisms for several reactions were postulated for these intermediates from the XPS spectra, considering the changes of atomic composition of the surface after a reaction. When modified activated carbon obtained at 630 ºC was heated at 900 ºC, it was observed that the changes of the XPS spectrum resulted from the forward reaction of decomposition of the oxidized intermediate with S-transfer to produce the episulfide and $CO_2$, and the reverse reaction with extrusion of $SO_2$. Basic hydrolysis hydrolyzed the sultine intermediate and the attack of hydroxide ion on the episulfide formed a sulfide anion, eliminating $S^{2-}$ in a consecutive step. The reactions of alkylthiol, alkylamine, alkyl halide, and laser photolysis in *t*-butanol with modified activated carbon, showed the insertion of the organic moiety in the carbon matrix.

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# Mechanism of thiol oxidation by the superoxide radical : a theoretical study

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The superoxide radical anion ($O^{2\bullet-}$) is one of the most important reactive oxygen species (ROS) responsible for oxidative stress in bio-organisms. The preferred target of $O^{2\bullet-}$ are the thiols , whose oxidation affects the intracellular redox equilibrium.

In spite of the large quantity of experimental work focused on this reaction, its mechanism still remains controversial[1,2]. Moreover, the reported experimental reaction rates are also abnormaly inconsistent, ranging from 10 to 105 $dm^3\ mol^{-1}\ s^{-1}$.

In the present paper we analyse in a systematic manner and at a high level of the ab initio molecular orbital theory (QCISD(T)/6-311+G(2df,2pd)//UMP2/6-311+G(d,p)) the interaction between thiol and the superoxide radical in both anionic ($O_2^{\bullet-}$) and protonated ($HO_2^{\bullet}$) forms. The reaction pathways are determined and the reaction energy barriers are calculated, both in vacuo and in aqueous solution.

Calculations predict that the main reaction pathway consists of the formation of a three-electron-bonded adduct (AD) followed by the elimination of the hydroxide anion, giving the sulfinyl radical ($RSO^{\bullet}$) as the reaction product.

An alternative reaction pathway consisting of hydrogen atom transfer from the thiol to the protonated superoxide radical was also identified. However, its reaction energy barrier is significantly higher. A comprehensive scanning of the potential energy surface did not show any other competitive reaction pathway.

The present results provide a useful basis for the interpretation of the complex experimental data related to thiol oxidation by superoxide radical in a biological environment.

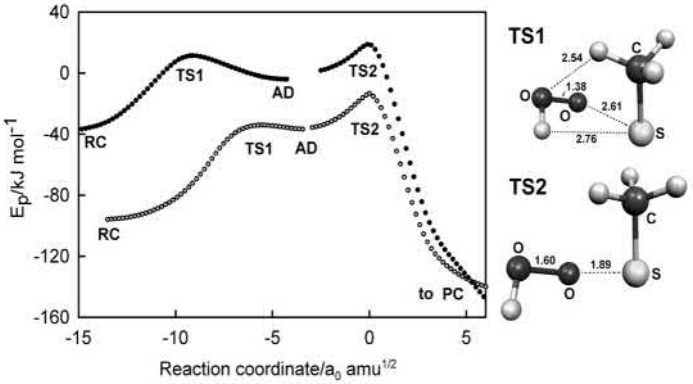


**Fig. 1**. Energy profile of the main reaction path in gas phase (open circles) and aqueous solution (solid circles) ; structures of transition states TS1 and TS2.

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# Hardness as an intrinsic property for the prediction of solvatochromic behaviour

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Solvatochromism is classified as positive or negative depending on the observed batho- or hypsochromism of the shifting band with increasing solvent polarity. A solvatochromic reversal occurs when a given compound changes its behaviour as the polarity of the medium is varied. The lack of an intrinsic property of these molecules correlating with their solvatochromic behaviour led us to investigate 22 compounds in the literature. A previous work on the solvatochromic behaviour of merocyanines[1] suggested the use of hardness as a predictive parameter. Since we employed the ET(N) scale of polarity [2] in our comparisons, our set of compounds comprised as donors phenoxides or related fragments, present in the ET(30) probe[3]. Acceptors included pyridinium or related systems, indolinium, benzothiazolium and benzimidazolium.

The hardness of each donor and acceptor fragment, following Koopman's approximation, was calculated as its HOMO-LUMO gap, by the AM1 method. The total hardness of each molecule was obtained by summation of the hardnesses of its constituting fragments. The results suggest that the calculated hardness of these solvatochromic probes might provide an indication of their behaviour. Dyes exhibiting negative solvatochromism were harder (average $2\eta$=395±18 kcal.mol$^{-1}$, N=8) than those showing a positive behaviour (average $2\eta$ =343 ±5 kcal.mol$^{-1}$, N=3). A solvatochromic reversal corresponded to intermediate hardnesses (average $2\eta$=366 ± 4 kcal.mol$^{-1}$, N = 11).

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# Stereoselectivity in the Formation and Reaction of β-Hydroxycarbocations

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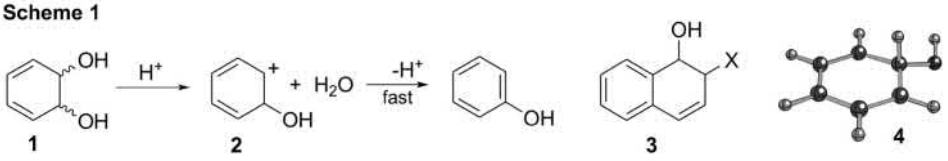
Arene dihydrodiols undergo acid-catalysed dehydration to phenols as illustrated for benzene dihydrodiol **1** in Scheme 1. Substituent effects and comparisons with the dehydration of alcohols to alkenes suggest that the reaction proceeds via rate-determining formation of a β-hydroxycarbocation intermediate **2**.[1,2] Remarkably, the ratio of reactivities of cis- and trans-dihydrodiols is very large, $k_{cis}/k_{trans}$ = 4500, despite the fact that both dihydrodiols should react through a common intermediate. For the 1,2- and 9,10-dihydrodiols of naphthalene and phenanthrene $k_{cis}/k_{trans}$ = 440 and 55 respectively.

**Scheme 1**




Some additional measurements and calculations are helpful in interpreting this behaviour. In a separate abstract it is reported that trapping of the β-hydroxyphenanthrenonium ion with water yields an unusually high ratio of *cis* to *trans* dihydrodiol products, [*cis*]/[*trans*] > 15. Studies of 2-X-substituted-1,2-dihydro-1-naphthols 3 show that ratios of reactivities of *cis* and *trans* isomers ($k_{cis}/k_{trans}$) for the dehydration reactions are much larger for X = OH (440) than for CH3 (8.4), Ph (3.8) or $Bu^t$ (12.7).

These results are consistent with the formation of different transition states for *cis* and *trans*-dihydrodiols with the carbocation centre for that from the cis-isomer strongly stabilised by hyperconjugation with a β-carbon-hydrogen bond. The influence of hyperconjugation is supported by DFT calculations which show a single stable conformation for the β-hydroxybenzenonium ion with a β-hydrogen in a pseudoaxial position and OH pseudo-equatorial, **4**. Distortion of this ion to achieve a conformation in which the C-OH bond is close to pseudoaxial, as presumably it is in the transition state fror the trans-dihydrodiol, leads to a substantial increase in energy. Interestingly, preliminary measurements with cis- and trans-1,2-tetrahydrodiols of naphthalene suggest that the high stereoselectivity of β-hydroxy carbocations formally derived from aromatic double bonds does not extend to carbocations from non-aromatic double bonds.

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# The First Solid Enols of Anhydrides

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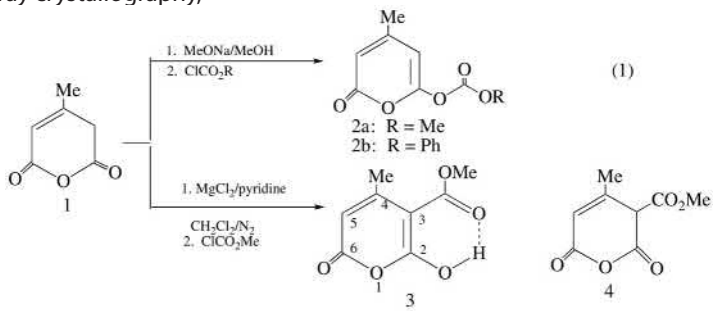
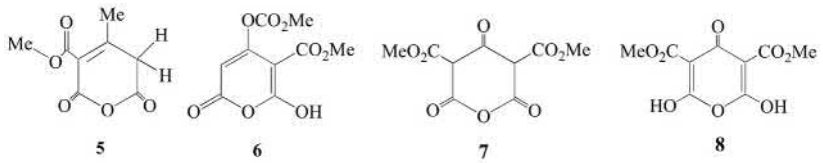
Enols of anhydrides are rare species, and none of them was prepared unequivocally as a solid species. We report here the first preparation of such solid enols. Reaction of α-methylglutaconic anhydride ***1*** with NaOMe followed by reaction with methyl or phenyl chloroformate gave the corresponding *O*-methoxy (and *O*-phenoxy) carbonylation derivatives **2a** and **2b**. Reaction of **1** with $MgCl_2$/pyridine, followed by methyl chloroformate gave C-methoxycarbonylation at C3 of **1** to give **3** (eq 1), which was previously suggested by calculation1 to be the enol of the anhydride **4**. This is confirmed by X-ray crystallography,




which show a C-OH and C1-C2 bond lengths of 1.297 Å and 1.388 Å, respectively, and OH…O=C(OMe) of 2.479 Å, i.e., **3** is the first **solid** enol of anhydride. In $CDCl_3$, $CD_3CN$ or $C_6D_6$ solution **3** displays a broad δ(OH) signal at ca. 15 ppm, with a hydrogen bond to the $CO_2Me$ group. With D2O in $CDCl_3$ the OH and the C5H protons exchange rapidly. The isomeric anhydride **5** is formed in polar solvents. In solution, anhydride **4**/enol **3** equilibria are rapidly established with $K_{Enol}$ of 6.40 ($C_6D_6$, 298 K), 0.52 ($CD_3CN$, 298 K), 9.8 ($CDCl_3$, 298 K), 22.8 ($CDCl_3$, 240 K), and decreasing $K_{Enol}$ in CDCl3:$CD_3CN$ mixtures with increasing the % $CD_3CN$. The % of **5** in $CDCl_3$: $(CD_3)_2CO$ increases with the increased % $(CD_3)_2CO$. Deuterium isotope effects on the δ($^{13}$C) values were determined. An analogous enol of anhydride **6** was prepared and its structure was confirmed by X-ray crystallography (C-OH 1.298 Å, O…O 2.513 Å); δ(OH) = 12.04-13.22 in $CDCl_3$. THF-$d_8$, $CD_3CN$ and DMSO-$d_6$ and $K_{Enol}$ = ≥ 100, 7.7, 3.4, (≥ 100), respectively. 3,5-Dimethoxycarbonyl-2,4,6-pyrantrione (**7**) was prepared and it gives the dienol **8** according to NMR data in $CDCl_3$-DMSO-$d_6$ solution.

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# Radical Species Derived from s-Triazine Pesticides: Geometry, Thermodynamics and Kinetics

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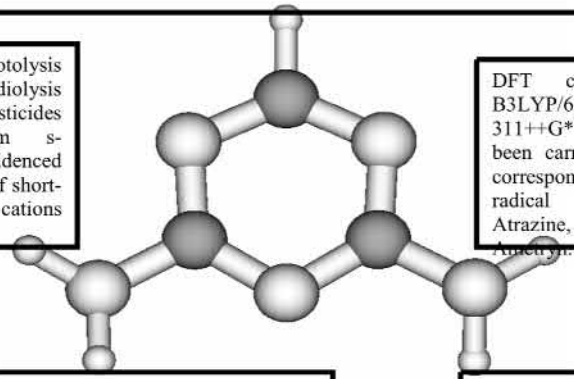
Derivatives of sym-Triazine are systemic herbicides acting as photosynthesis inhibitors.[1] Some of them, e.g. Atrazine or Simazine, are considered dangerous pollutants,[2] not easily destroyed by usual water treatments. Advanced oxidation procedures (AOPs), like UV-Vis photodegradation, have been proposed to minimize the presence of those persistent organic pollutants (POPs) in waters.

Laser flash photolysis and pulse radiolysis studies on pesticides derived from s-Triazine evidenced the existence of short-lived radical cations and anions.

DFT calculations at B3LYP/6-311++G**level, have been carried out on the corresponding neutral and radical species of Atrazine, Atraton and Ametryn.



We report optimised geometries of neutral and singly charged species. Triazine ring and exo $NR_2$ groups are all planar but in radical anions. Optimised structures of the radical cations and radical anions undergo respectively an in-plane and out-of-plane Jahn-Teller distortion due to the presence of doubly degenerate HOMOs and LUMOs.

Calculated spectroscopic features of those radical cations and radical anions, thermodynamic properties (red-ox potentials and pKa values), and kinetic parameters are compared with experimental results.

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# The relationship between group electronegativities and substituent constants.

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Group electronegativities have been shown to be useful in correlating a number of substituent effects on some physical properties such as nmr chemical shifts and coupling constants, and bond dissociation energies. A number of reports have appeared regarding relationships between electrical effect substituent constants and atomic or group electronegativities , ϰM and χX respectively. We have published equations of the type,

$$\sigma_{MZn} = \chi_M + \Sigma\sigma I\, Z + \Sigma\sigma d\, Z + \Sigma\sigma e\, Z + a_0 \quad (1)$$

where $X = MZ_n$.

It seemed likely tha the χX values are composite substituent parameters in which case a knowledge of their composition would be useful .We have therefore correlated twenty sets of χX values taken from the literature with the equation,

$$\chi X = a_{M\,\chi M} + L_{\sigma I\,X} + D_{\sigma d\,X} + R_{\sigma dX} + A_{\alpha X} + a_0 \quad (2)$$

Significant correlations were obtained for all data sets other than Set 6. A dependence on the electronegativity of the atom M in the group which is bonded to the remainder of the species being studied is found in almost all the χX data sets studied and is the major contributor to χX in these sets. The exception is a set that is large but contains no π bonded groups and therefore does not represent a wide range of substituent types. A dependence on σI is almost always observed and a dependence on α is frequently found.

Group electronegativity involves the electrons in the bond between the group and the remainder of the molecule, 1. The inductive effect is a possible mode of transmission of the electrical effect from substituent to active site and must traverse chemical bonds that lie between the initial atom of the group and the atom of the active site that is responsible for some observable phenomenon. Thus the inductive effect is a proposed mode of transmission of the electrical effect of X though the skeletal group G to the reaction site Y in **2**. χX applies to the direct interaction of X with Y in **1**.

| X – Y | X – G – Y |
|---|---|
| **1** | **2** |

The dependence of properties on $\chi_X$ is not evidence for the existence of the inductive effect. In fact, there is no extant evidence that transmission of electrical effects in **2** involves the inductive effect. The available evidence strongly supports transmission by the field effect. The inductive effect does not seem to exist.

# Quantum Chemical Investigation Of Carbon-carbon Spin-spin Coupling Constants

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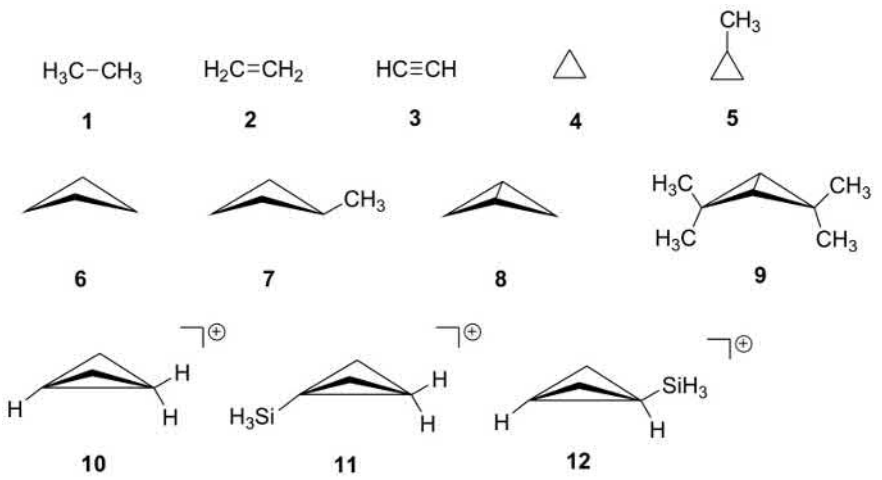
The experimental determination of Nuclear spin spin coupling constants is a well known fruitful and straightforward tool for elucidating details of chemical bonding. In addition to the most often measured J(H,H) and J(C,H) couplings, J(C,C) coupling constants are highly diagnostic and characteristic for particular C-C-bonds. On the other hand, several studies have demonstrated that spin-spin coupling constants are among the most difficult parameters to predict quantitatively.[1]

We will present preliminary results of calculations of carbon-carbon coupling constants for simple organic molecules and some carbocations **1 – 12** and show a comparison with available experimental data.[2] Similar to recent benchmark studies[3] the Lee-Yang-Parr (B3LYP) hybrid functional has been used for modelling the n-electron space. It is shown that reliable data are obtained if appropriate models for the one-electron space (basis sets) are used.

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# Polyethelene Imine Derivatives Accelerate Phosphate Transfer in the Absence of Metal

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The efficient integration of binding, catalysis and multiple turnovers remains a challenge in building enzyme models. We report that systematic derivatisation of polyethylene imine (PEI) with alkyl ($C_2$-$C_{12}$), benzyl and guanidinium groups gives rise to catalysts ('synzymes') for phosphate transfer reactions that show rate accelerations ($k_{cat}/k_{uncat}$) of up $10^4$ in absence of metal. The synzymes exhibit saturation kinetics and up to 180 turnovers per active site. Catalysis can be specifically inhibited by anionic and hydrophobic small molecules.

The efficacy of catalysis is determined by the PEI derivatisation pattern. The derivatisation reagents exert a synergistic effect, i.e. combinations of derivatisation increase catalysis more than the sum of each single modification. The pH rate profile for $k_{cat}/K_M$ is bell shaped with a maximum at pH 7.85 and can be explained as a composite of two effects that both have to be operative for optimal activity: (a) $K_M$ increases at high pH, due to deprotonation of PEI amines that bind the anionic substrate and (b) the availability of hydroxide decreases at low pH. Thus catalysis is based on substrate binding by positively charged amine groups and the presence of hydroxide ion in active sites with a medium that is tuned for catalysis. Inhibition studies suggest that differential molecular recognition of the doubly negatively charged transition state (over singly charged ground state and product) is responsible for the ability to turn over multiple times by releasing product and makes a 5-10-fold contribution to catalysis.

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F. Avenier, J. Domingos, L. D. Van Vliet and Florian Hollfelder *J. Am. Chem. Soc.* (2007), in the press.

# Asymmetric tetraprotonation of γ-$[(SiO_4)W_{10}O_{32}]^{8-}$ triggers catalytic epoxidation with $H_2O_2$

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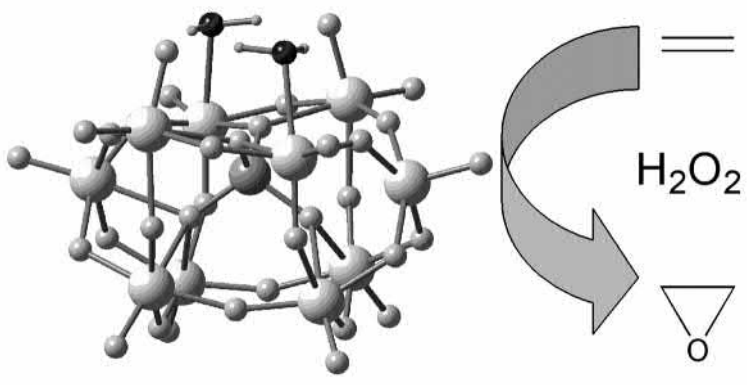
Polyoxometalates (POM) are the inorganic alternative to classical transition metal coordination catalysts. Their structural and solution chemistry is pivotal in the design of catalytically active sites with properties tunable at the molecular level. Recently, a fast catalytic epoxidation of both terminal and internal double bonds with $H_2O_2$ was found to be promoted by the tetraprotonated form of the lacunary γ-$[(SiO_4)W_{10}O_{32}]^{8-}$, **1**, with >99% selectivity and $H_2O_2$ utilization.[1] The assignment of the protonation sites and their role within the catalytic mechanism, are a matter of current debate.[2] We present herein a combined kinetic, spectroscopic, and computational study to address the electronic and structural factors dictating protonation equilibria of **H4-1** as well as their impact on catalysis. In the epoxidation of *cis*-cyclooctene catalyzed by **H4-1**, the turnover frequency (TOF) drops linearly upon addition of the first two equivalents of ($_nBu_4N$)OH, then levels off to a plateau value. This result points out the major role played only by two, out of four, acidic protons on the POM surface, in promoting oxygen transfer. Solution speciation by $^1H$, $^{29}Si$ and $^{183}W$ NMR, FT-IR and relativistic DFT calculations support a regioselective double protonation of two oxygens of the POM surface, leading to the localization of two water molecules on the POM lacunary site (scheme 1).[2]




Scheme 1. Epoxidation with $H_2O_2$ catalysed by $(Bu_4N)_4H_4$γ-$[(SiO_4)W_{10}O_{32}]$.

This asymmetric proton distribution is associated to a stabilizing chiral compression of the POM backbone, known as Pfeiffer effect, resulting in an alternate sequence of long and short *trans* O-W-O bonds. Fast catalysis is likely prompted by the two W-$OH_2$ functions, carrying an incipient leaving group, thus fostering ligand exchange within the coordination sphere of each independent catalytic site.

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# Enantioselective Oxidation of Aryl Benzyl Sulfides in the Presence of Chiral Titanium Complexes: a Proposed Model

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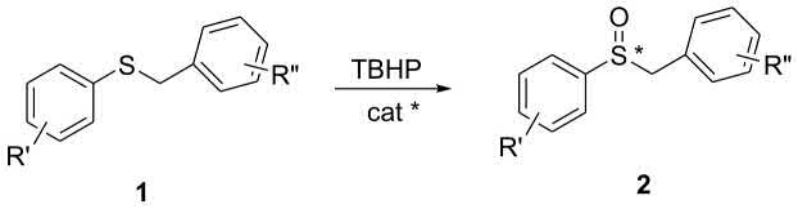
In previous papers we reported that *tert*-butyl hydroperoxide (TBHP) oxidises with high ee values (94->98% ee) some classes of sulfides in the presence of chiral titanium complexes.[1-4] In particular, TBHP-oxidation in the presence of catalytic amounts of a complex between titanium and (*S, S*)- or (*R, R*)-hydrobenzoin[2] yielded several benzyl haloaryl sulfoxides with high ee values (up to >98% ee) and high isolated yields (80-85%).




**1** **2**

cat* = Ti(O-*i*-Pr)$_4$/(*S,S*)-hydrobenzoin

**Scheme 1**. Enantioselective oxidation of aryl benzyl sulfides in the presence of a titanium/hydrobenzoin catalyst.

Since we had observed that the use of chiral nonracemic 1,2-dialkyldiols as titanium ligands produces a low enantioselectivity in the oxidation of the sulfides cited above, we formulated the reasonable hypothesis that π-π-stacking of the aryl groups could play a crucial role. Accordingly, a preliminary reactivity model was drawn (Spartan 5.1.3-Unix). Then, we decided to perform a systematic investigation of the enantioselective TBHP-oxidation of sulfides in the presence of the titanium/hydrobenzoin catalyst to confirm or to disprove the model.

In a first instance, we focused our investigation on aryl benzyl sulfides bearing electron-withdrawing or electron-releasing groups on the phenyl rings of the substrates, since the presence of these substituents should affect the degree of π-π-stacking and, consequently, the reactivity. Then, we used hydrobenzoin-like molecules, as chiral ligands of the titanium. Finally, we oxidised sulfides which have structural similarity with aryl benzyl sulfides.

Stereochemical results were in agreement with the proposed model whose validity will be briefly discussed.

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# A simple and intuitive description of C-H bond energies.

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Several attempts to understand C-H bond dissociation energies (BDHs) have been proposed in the last two decades. Measures such as energy density over interatomic distances, atomization energies, and hyperconjugation have been invoked. It was proposed that in strained rings BDEs are connected to the ring strain although the strain lies in the C-C bonds.[1]

Organic chemists tend to think in VB terms, namely resonance structures and hybridizations. The above-mentioned studies yielded accurate results but the qualitative picture and predicting ability was lost. This paper presents the simple yet quite accurate connection between hybridization and BDEs using hybrid DFT calculations at the B3LYP/6-311G(d) level and NBO analysis.

Propane, 1-butene and propene were used as models to study the effect of hybridization on alkylic, allylic and vinylic C-H bonds, respectively. This was done by calculating the BDEs at imposed CCC angles ranging from 70 to 160 degrees. Each type of C-H bond correlates to the hybridization through a different function.

The dependence of the BDEs as functions of hybridizations as obtained from the model studies were applied for the analysis of thirty five different C-H bond dissociation energies in cycloalkanes and cycloalkenes, including secondary, tertiary, allylic and vinylic, in hydrocarbons, bridgehead CH-bonds in bi- and tricyclic hydrocarbons, difluoro, tetrafluoro, disilyl and tetrasilyl derivatives. Despite the large verity of systems and substitution types, it is shown that all these BDEs can be rationalized to a large extend using the hybridization of the lobe that forms the C-H bond which breaks and the stabilization (reorganization energy) of the radical.

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# The Singlet Oxygen Oxidation of Chlorpromazine and Some Phenothiazine Derivatives. Products and Reaction Mechanisms

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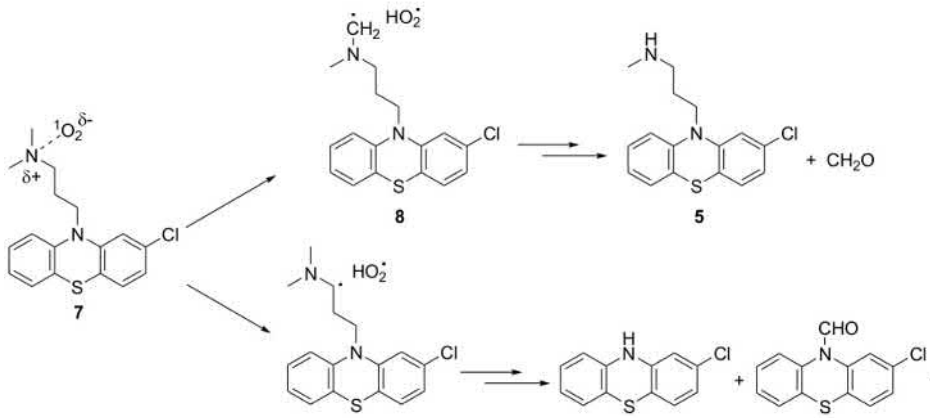
The reactions of chlorpromazine **1**, N-methylphenothiazine **2** and N-ethylphenothiazine **3** with $^1O_2$ have been investigated in MeOH. **1** undergoes exclusive side chain cleavage giving 2-chlorophenothiazine **4**, as the major product, the N-demethylation product **5**, N-formyl-2-chlorophenothiazine **6**, DMF and formaldehyde. No side-chain cleavage products are instead observed in the reactions of **2** and **3**, which afford only the corresponding sulfoxides. On the basis of kinetic information and the parallel study of a piperidyl analog of chlorpromazine, a very reasonable reaction mechanism has been proposed involving the initial formation of a charge transfer complex at the dimethylamino nitrogen in the side-chain (**7**) followed by the formation of the radicals **8** and **9**. **8** leads to **5** and $CH_2O$ whereas **9** leads to **4**, **6** ad DMF (Scheme). Thus, the side-chain reactivity of chlorpromazine is exclusively due to the dimethylamino functionality.[1] This explains the no side-chain reactivity of **2** and **3** that, as aromatic tertiary amines, generally exhibit only physical quenching of $^1O_2$. Sulfoxide formation is however observed for **2** and **3** and, interestingly, the rate constant for sulfoxidation of **2** is significantly higher than expected for a diaryl sulfide, suggesting an anchimeric assistance by the neighboring nitrogen.




Scheme.

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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## Abstracts

### Poster Presentations

# Reactivity of pure stereoisomers of N-Boc-β-dibenzothienyldehydrophenylalanines in a metal-assisted C-N intramolecular cyclization to heterocyclic compounds

**Ana S. Abreu, M. Solange D. Carvalho, Paula M.T. Ferreira, Maria-João R.P. Queiroz**

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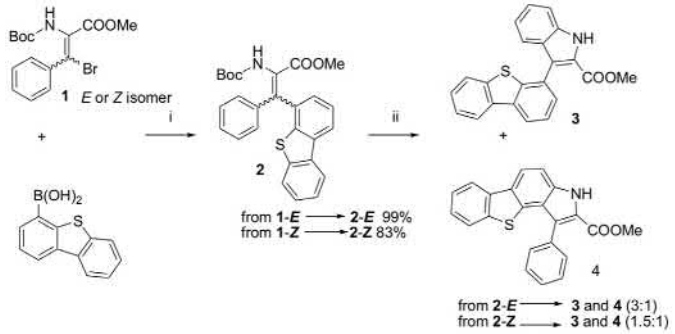
Recently our research group had developed a new metal-assisted (palladium and/or copper) intramolecular C-N cyclization reaction of β,β-bis(benzo[b]thienyl)dehydroalanines or β-(benzo[b]thienyl)dehydrophenylalanines to benzo[b]thienopyrroles, thienoindoles or indoles.[1,2]

Here we describe the synthesis of methyl esters of N-Boc-(*Z*) or (*E*)-β-(dibenzothien-4-yl)dehydrophenylalanines in high yields by Suzuki cross-coupling of pure stereoisomers of β-bromodehydrophenylalanine[3] **1-*E*** or **1-*Z*** with dibenzothien-4-yl boronic acid, maintaining the stereochemistry of the starting material. The coupling products **2-*E*** or **2-*Z*** were submitted to our intramolecular C-N cyclization conditions, giving in both cases two new heterocyclic compounds, indole **3** and benzothienoindole **4**, in different ratios, resulting from either direct cyclization or cyclization after isomerisation of the starting materials (Scheme).




i) 1.5 equiv. boronic acid, 15 mol% $PdCl_2(dppf).CH_2Cl_2$ (1:1), 1.4 equiv. $Cs_2CO_3$,THF/$H_2O$ (1:1), 90ºC, 1h 30 min.
ii) 50 mol% $Pd(OAc)_2$, 3 equiv. $Cu(OAc)_2$, DMF, from **2-*E***, 3h 30 min. 130ºC + 3h 30 min. 160ºC, and from **2-*Z***, 5h 130ºC + 2h 160ºC.

**Scheme**

With these results we can conclude that in these conditions the isomerization of either **2-*E*** or **2-*Z*** occurs in different ratios to give two compounds by a Pd(II) assisted cyclization. After extrusion of Pd(0) it is thought that $Cu(OAc)_2$ reoxidizes it to Pd(II), avoiding the use of a stoichiometric amount of $Pd(OAc)_2$. As acetic acid is formed, the Boc group is removed.[2]

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# Reactivity control by micellar aggregates: Inhibition of the reaction between 4-nitrobenzenediazonium ions and hydrophilic aminoacids.

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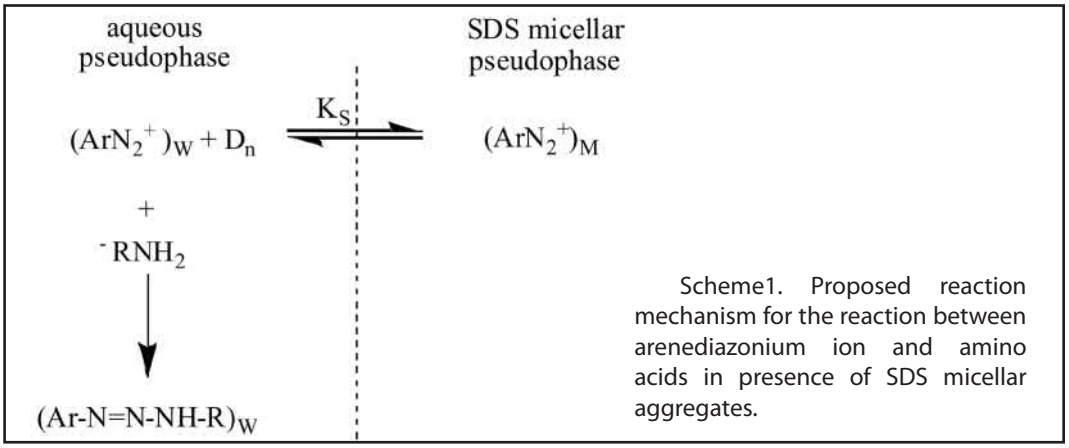
We have explored the kinetics and mechanism of the reaction between 4-nitrobenzenediazonium ions, 4NBD, and the hydrophilic amino acids, AA, glycine and serine in the presence and absence of sodium dodecylsulfate, SDS, micellar aggregates. In aqueous acid (buffer controlled) solution, the observed rate constants $k_{obs}$ increase linearly with [AA] and show an inverse dependence on acidity, suggesting that the reaction takes place through the non-protonated amino group of the amino acid. Addition of SDS inhibits the reaction because of the micellar-induced separation of reactants originated by the electrical barrier imposed by the SDS micelles; $k_{obs}$ values are depressed by factors of 10 (glycine) and 6 (serine) on going from [SDS] = 0 up to [SDS] = 0.05 M. The hypothesis of a micellar induced separation of the reactants was confirmed by $^1$H-NMR spectroscopy, which was employed to investigate the location of 4NBD in the micellar aggregate; the results showing that the aromatic ring of the arenediazonium ion is predominantly located in the vicinity of the α-β carbon atom of the surfactant chain, and hence the reactive $-N_2^+$ group is located in the Stern layer of the micellar aggregate. The kinetic results can be quantitatively interpreted in terms of the pseudophase kinetic model, allowing estimations of the association constant of 4NBD to the SDS micelles. Similar results are expected if cationic surfactants such as cetyltrimethylammonium halides, CTAX, are employed instead of SDS. The electrical nature of CTAX micelles, whose head groups $-(CH_3)_3N^+$ are positively charged, makes the α-amino carboxylate form of the amino acid to be associated to the micellar aggregates but will exclude 4NBD ions from the Stern layer because of the electrical repulsion. The global effect should be again an effective separation of reactants and hence decreasing the local concentration of the reactive form of the amino acid in the vicinity of the 4NBD ions.




Scheme1. Proposed reaction mechanism for the reaction between arenediazonium ion and amino acids in presence of SDS micellar aggregates.

*Acknowledgements*: Financial support from the following institutions is acknowledged: Ministerio de Educación y Ciencia (CTQ2006-13969-BQU), Xunta de Galicia (PGDIT06PXIB314249PR), FEDER and Universidad de Vigo.

# Structural Analysis of N,N-dimethyl-1,2-benzisothiazol-3-amine 1,1-dioxide by means of Matrix Isolation FTIR Spectroscopy and Quantum Chemical Calculations

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Saccharin (1,2-benzisothiazol-3(2H)-one-1,1-dioxide) is a commonly known substance as it is the oldest artificial sweetener. More recently, some of its derivatives have also been attracting an increased attention, as they show herbicidal, antimicrobial and antifungal activity and can also participate in enzymatic inhibition[1]. Because the benzisothiazole moiety is strongly electron-withdrawing, benzisithiazolyl ethers can be efficiently used as intermediates for selective reductive cleavage of C-O bonds, using catalytic trasnsfer methods[2]. In contrast, amino derivatives of benzisothiazole were inert to hydrogenolysis. Considering the syntheticrelevance of methodologies for mild and selective C-N cleavage, for instance in bioorganic chemistry, it was decided to further investigate the structure of aminobenzisothiazoles. In this work, the amino-substituted derivative of saccharin, N,N-dimethyl-1,2- benzisothiazol-3-amine 1,1-dioxide (DiMeBAD) was isolated in solid argon and xenon and studied by matrix isolation FTIR spectroscopy and quantum chemical calculations. Since the computational description of saccharins is difficult because of the presence of the hypervalent S=O bonds in their structures, different computational methods (HF, B3LYP, MP2) implemented with basis sets of different sizes were applied to predict the geometry and vibrational frequencies of the studied compound. The experimentally obtained spectra could be successfully predicted at the B3LYP/6-311++G(3df,3pd) level of theory, stressing the adequacy of the B3LYP functional and of the Pople's type 6-311 basis set, when dulyaugmented by extensive sets of polarization functions to study the considered family of compounds.

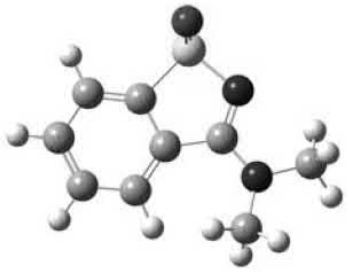

**Fig. 1**. Structure of N,N-dimethyl-1,2-benzisothiazol-3-amine 1,1-dioxide (DiMeBAD)

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We acknowledge the "Cyfronet" Computer Center, Krakow (Grant KBN/SGI/ORIGIN_2000/UJ/ 044/1999) for computing time and the Portuguese Science Foundation (Grant #SFRH/BPD/ 17081/2004 and projects POCI/QUI/2004: 59019 and 58937). AGZ is member of the Research Career Conicet, Argentina.

# New DNA Directed Trioxanes as Potential Antimalarial Agents

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In this project we aim to develop synthetic routes to produce DNA-directed endoperoxides, combining a DNA binding moiety[1] with a known antimalarial function, which represents also a promising anticancer agent. This strategy is based on the ability of Fe (II) to selectively cleave the peroxide bridge of the artemisinin type of drugs, generating radicalar species capable of damaging parasitic biomolecules[2].

We proposed to build two different classes of endoperoxide hybrids (compounds 1 and 2, Fig. 1) and exploit their mechanism and site of action as well as their biological activity.

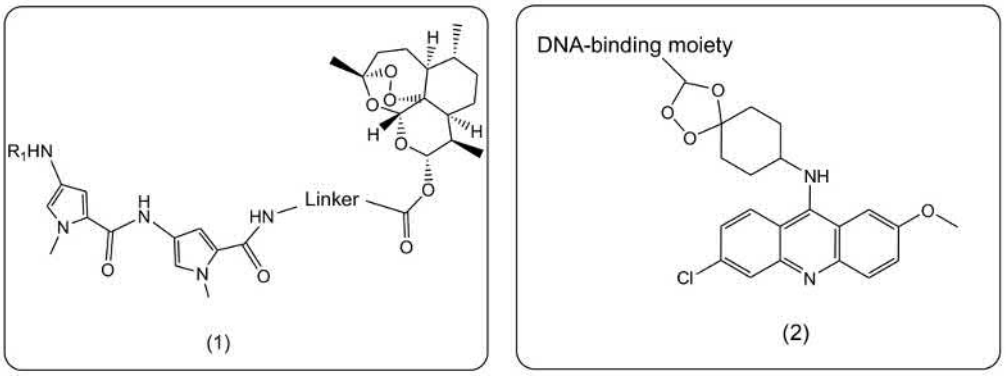


**Fig. 1**. Target hybrid-drugs.

We expect that this comparative study will contribute to the elucidation of the general mechanism of action of endoperoxide-type compounds.

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*Acknowledgements*: We acknowledge FCT for the grant SFRH / BPD/ 20587 / 2004.

# Functionalised Side-chain 5,9-Diaminobenzo[a]phenoxazinium Salts: Synthesis and Antimicrobial Activity

**S.A. Barros,[1] V.H.J. Frade,[1] M.J. Sousa[2], J.C.V.P. Moura[1] and M.S.T. Gonçalves[1]**

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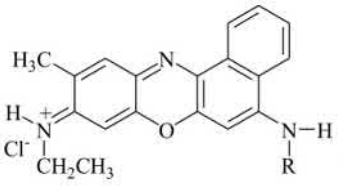
Benzo[*a*]phenoxazinium salts are a polycyclic cationic heterocycle system, possessing several interesting properties. They exhibit an intense long-wavelength absorption superior to 600 nm and red fluorescence. As a result, they have been used as fluorescent probes in various applications, such as for monitoring hydrophobic surfaces in proteins, as lipid stains in membranes and also to study the interaction with DNA and its application in electrochemical recognition.[1-3] Furthermore, activity against leukemia and solid tumor cell lines at submicromolar concentrations has also been reported.[4]

In the present work, a series of functionalised 5,9-diaminobenzo[*a*]phenoxazinium salts were prepared by condensation of 5-ethylamino-4-methyl-2-nitrosophenol hydrochlorides with *N*-alkylated derivatives. These heterocycles were linked to valine, by coupling them with the aid of *N,N'*-dicyclohexylcarbodiimide (DCC) assisted by 1-hydroxybenzotriazole (HOBt) under standard conditions. All these compounds were evaluated against *Saccharomyces cerevisiae* W303-1B, in a microdilution broth assay.

The determination of the Minimum Inhibitory Concentrations (MIC) for the different compounds showed that activity was dependent on the substituent groups, the most effective compounds presenting MIC values of 15 μM. The examination of structure - activity relationships of these heterocycles will be discussed.



R = alkyl-$R^1$, $R^1$ = $CO_2H$, OH, $NH_2$, Val-OMe, Val-Boc, O-Val-Boc

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# Catalysis of Aromatic Nucleophilic Substitution Reactions by Glymes and Crown Ethers

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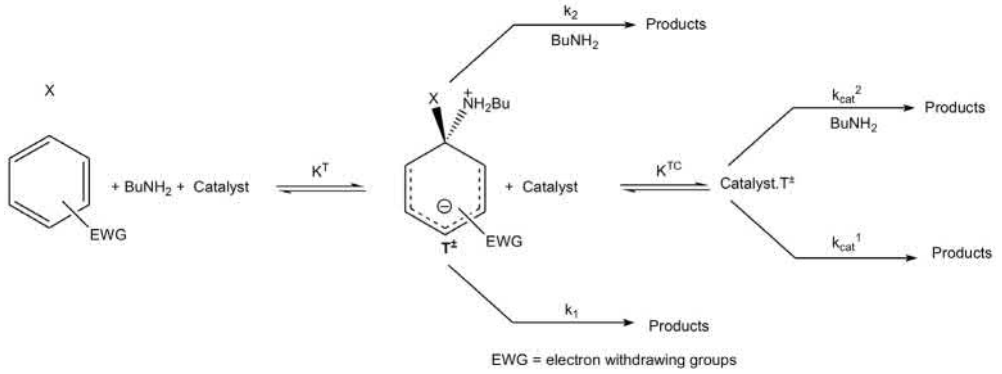
The aromatic nucleophilic substitution reactions (SnAr) involving primary or secondary amines as nucleophiles is know to proceed trough a two step mechanism. Nucleophilic attack of amine on the aromatic substrate generates a zwitterionic intermediate. In the presence of phase transfer catalysts (crown ethers or glymes) the intermediate and/or the transition structure could be complexed and the stabilization acquired lead to catalysis. We have studied the kinetics of the reaction between *n*-butylamine and 1-chloro-2,4-dinitrobenzene (CDNB) and 1-fluoro-4-nitrobenzene in chlorobenzene in the presence of various glymes and crown ethers and shown that the kinetics of the reaction obey to the general rate equation

$$k_{obs} = k_A[BuNH_2] + k_B[BuNH_2]^2 + k_C[BuNH_2][Catalyst] + k_D[BuNH_2]^2[Catalyst]$$

In the case of the CDNB substrate the $k_D$ term was not observed. For the mononitro compound (FNB) we do not observe the spontaneous decomposition ($k_A$) of the intermediate but the base catalysed step of the complexed intermediate was observed (in contrast with CDNB). Catalysis by phase transfer catalysts required that the decomposition of the intermediate is rate limiting. In the basis of the kinetic results we propose the general mechanism for the SnAr reactions in chlorobenzene catalysed by phase transfer catalysts




**Scheme 1**

We find that the glyme with four oxygens is the optimal catalyst for the reaction. According to Hogan and Gandour's studies on the aminolysis of esters catalysed by glymes, the relationship between catalysis and structure suggests that the ammonium ion part of the transition structure is recognized by the catalyst.

*Acknowledgements*: Financial support from Fundação para a Ciência e Tecnologia (Lisboa) (PhD grant to Nuno Basilio) is gratefully acknowledged.

# Synthesis of a New Class of Phenanthrolines bearing a Arylthienylimidazo Conjugation Pathway as Nonlinear Optical Chromophores

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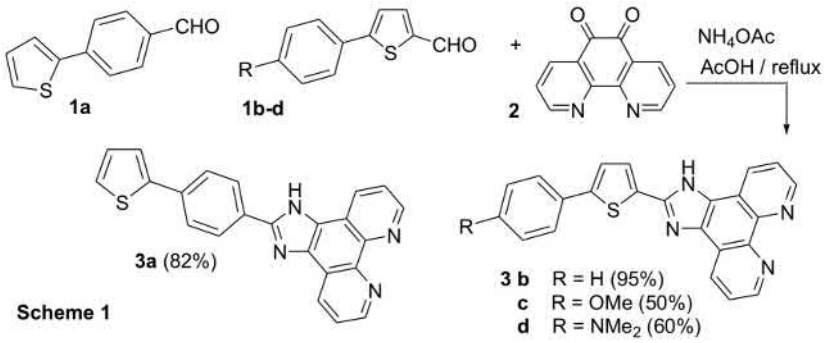
Organic compounds such as phenanthrolines, containing metal binding sites within their molecular backbones are of general interest in coordination and in materials chemistry.[1] The planarity, the extension of conjugation and the deficiency of electron density on the ring C atoms of phenanthroline moiety, leads to an interesting building block which could be used as the acceptor group in the design of new efficient NLO chromophores. Imidazole derivatives have received increasing attention as nonlinear optical (NLO) chromophores due to their excellent thermal stability in guest-host systems.[2] The incorporation of thiophene rings is also desirable to enhance molecular nonlinearity.[3] As a result of the optical an conductive properties, conjugated materials containing thiophene and imidazole heterocycles have found many applications including uses in OLED/PLEDs, in flexible light displays, solar cells, flat panel displays, field effect transistors, NLO materials, sensors, etc. Owing to synthetic difficulties, most of NLO imidazoles developed so far, possess short conjugation pathways (spacers) such as phenyl. Following our interest in heterocyclic derivatives for optical applications,[4-5] we report in this communication the synthesis and the characterization of the linear and nonlinear optical properties of NLO chromophores **3** (scheme 1), containing a functionalized arylthienyl $\pi$ conjugated bridge linked to the imidazo-phenanthroline system, which is original and different from other related reports.




**Scheme 1**

***References***

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*Acknowledgements*: Thanks are due to Foundation for Science and Technology (Portugal) for financial support through the Centres of Chemistry and Physics (Universidade do Minho).

# Kinetics and mechanism of the reaction between 4-hexadecylbenzenediazonium ions and vitamin C in an emulsified system: Formation of a 3-O-diazo ether intermediate

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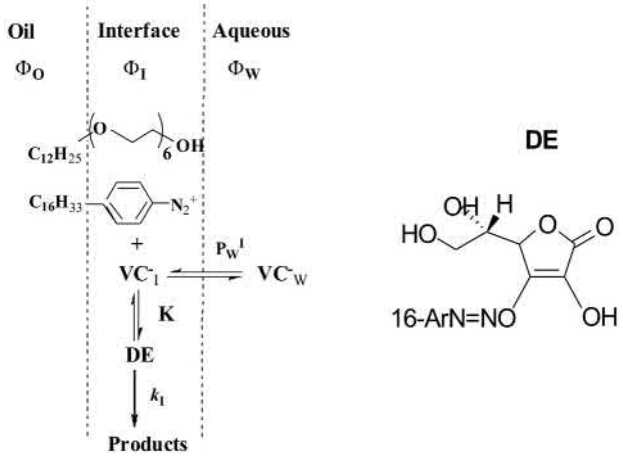
We have explored the kinetics and mechanism of the reaction between 4-hexadecylbenzenediazoniu m ions, 16-$ArN_2^+$, and vitamin C, VC, in a model macroemulsion composed of octane, water (HCl, pH = 2.5) and the nonionic emulsifier hexaethylene gluycol monododecyl ether, $C_{12}E_6$. Because emulsions are opaque, we employed the electrochemical linear sweep voltammetry, LSV, technique to investigate the kinetics of the reaction .

Emulsions are thermodynamically unstable systems that can be visualized as composed of three distinct regions, the oil, aqueous and an interfacial region where most of the emulsifier is located, Scheme 1. Because of the hydrophobic tail of 16-$ArN_2^+$, the reactive $-N_2^+$ group will be located in the interfacial region of the emulsion and thus the reaction with ascorbic acid will take place exclusively in that region.

Voltammograms of 16-$ArN_2^+$ show a reduction peak at Ep ≈ -0.1 V. Upon addition of VC, the reduction peak of 16-$ArN_2^+$ dissapears and a new voltammetric peak at Ep ≈ -0.25 V, not observed in the absence of VC, is detected. Voltammetric titration of VC shows that a 1:1 complex is formed. The peak current of this new peak at Ep ≈ -0.25 V decreases with time, indicating that the formed intermediate, a diazo ether, is not stable. Observed rate constant, kobs, for diazo ether loss were determined by fitting the corresponding $i_p$-t data to the integrated first order equation, and linear plots (cc > 0.999) were obtained for more than 3 $t_{1/2}$. The variation of $k_{obs}$ with $[VC_T]$ follows a saturation kinetics profile, suggesting that the reaction mechanism is the same as that observed in aqueous solution, that is, formation of an intermediate **DE** in a pre-equilibrium step that further decomposes, Scheme 1.




**Scheme 1**. Proposed reaction mechanism for the reaction between 16-$ArN_2^+$ and Vitamin C in a macroemulsion formed with octane, water and $C_{12}E_6$ and structure of the formed diazo ether DE.

*Acknowledgements*: Financial support from the following institutions is acknowledged: Ministerio de Educación y Ciencia (CTQ2006-13969-BQU), Xunta de Galicia (PGDIT06PXIB314249PR), FEDER and Universidad de Vigo.

# Nucleophilic Reactivity of Imide and Amide Anions

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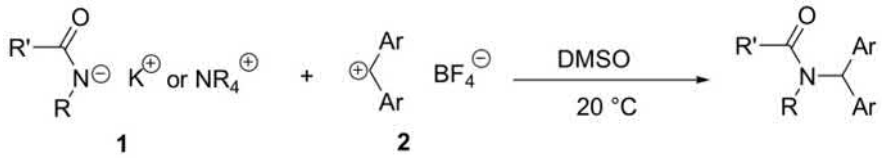
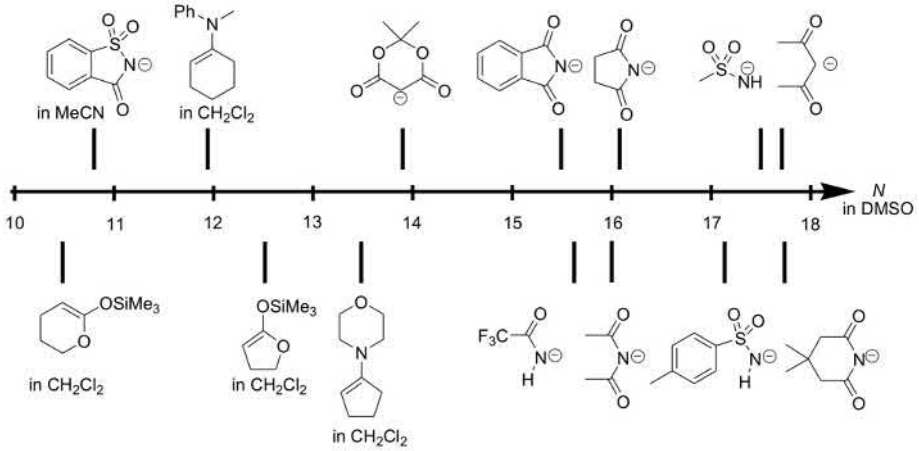
More than 100 years ago Gabriel developed a synthesis of primary amines by alkylation of potassium phthalimide and successive removal of the phthaloyl group.[1] Due to the high reliability of the Gabriel synthesis, this reaction has been investigated to a large extent.[2]

We have examined the nucleophilicity of several imide and amide anions **1** by determining the rate constants of their reactions with benzhydrylium ions and structurally related quinone methides **2** in DMSO. The nucleophilicity of these anions can be quantified according to the correlation equation $\log k_2$ (20 °C) = $s(N + E)$, where $s$ and $N$ are nucleophile-specific parameters and $E$ is an electrophilicity parameter.[3,4]




**Scheme 1.** Reaction of imide and amide anions **1** with several reference electrophiles **2**.

It is found that a sulfonyl group has a similar effect on the nucleophilicity of amide anions as two acetyl groups. As shown in the figure below, the nucleophilicity of amide anions is higher than that of enamines and silyl ketene acetals but lower than that of carbanions with comparable p$K_{aH}$ values.

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# New Potential *Plasmodium* Cysteine Proteases Inhibitors Incorporating Tetrazoles

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Cysteine proteases inhibitors are potential chemotherapeutic targets for malaria treatment. *Falcipain-2* is a typical cysteine proteases of the papain-family, that plays an important role in the parasite life cycle by degrading erythrocyte proteins, in specific hemoglobin[1]. Hemoglobin degradation is essential for the growth of erythrocytic *Plasmodium falciparum* providing free amino acids for parasite protein synthesis[2].

I*n vivo* results performed with specific classes of dipeptides, fluoromethyl ketones and vinyl sulfones (Figure 1), demonstrated that inhibition of enzyme *Falcipain-2* prevents parasite maturation[3,4].

In the present investigation and based on structure-activity results for such type of compounds, we have introduced structural modifications on the target inhibitors. Tetrazoles are known to be very stable metabolically at physiologic pH, and are incorporated in many important drugs in order to increase bioavailability and efficiency[5]. Accordingly, it is expected that insertion of a tetrazol moiety into the antimalarial prototype will confer different chemical properties to the final dipeptide and that will result in an improvement on the balance between good water solubility and good membrane permeability.

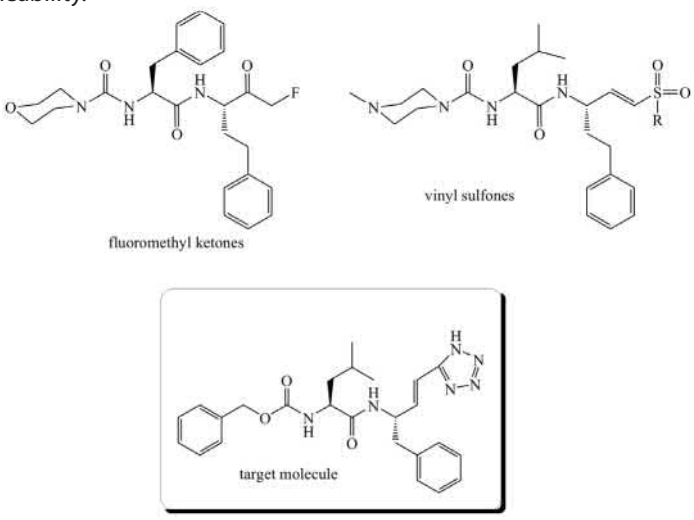


**Fig. 1.** Inhibitors of enzyme *Falcipain-2*.

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# Reactions of Aryl Chlorothionoformates with Quinuclidines. A Kinetic Study

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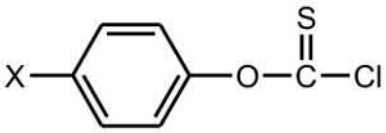
The kinetics of the aminolysis of oxyesters have been extensively studied and their mechanisms are well-established; those for the reactions of thio derivatives such as chlorothionoformates[1] have been less investigated compared with their carbonyl analogues.[2]

In this work we have studied the kinetics of the reactions of quinuclidines with phenyl, 4-cyanophenyl and 4-nitrophenyl chlorothionoformates (PClTF, CNPClTF and NPClTF, respectively). The reactions were followed spectrophotometrically. Under amine excess, pseudo-first-order rate coefficients ($k_{obsd}$) were found. For all these reactions, plots of $k_{obsd}$ *vs*. free amine concentration at constant pH were linear, the slope ($k_N$) being independent of pH. The Bronsted-type plots (log $k_N$ *vs* p$K_a$ of the aminium ions) were linear, with slopes (β) in accordance with stepwise mechanisms through a tetrahedral intermediate.




X = H PClTF
X = CN CNPClTF
X = $NO_2$ NPClTF

The objectives of this study are to assess the influence of the nonleaving and electrophilic groups on the reactivity of the substrates.

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# Direct Photodegradation and $TiO_2$-photocatalyzed Degradation of Anilide-based Herbicides

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Some of the commonest herbicides used nowadays are anilides. They are frequently used for post-emergence control of broad-leaved and grass weeds in different crops, such as rice. Their degradation rate is highly dependent on environmental conditions, relatively rapid in lakes, with half-lifes, up to 6 days,[1] but highly persistent in ground-waters, with $t_{1/2}$ > 8 months.[2] Therefore, investigating the ways of degradation of anilides in water is of high environmental concern. Photodegradation is one of the main photodegration pathways for water pollutants. Moreover, photocatalytic oxidation with semiconductors, such as $TiO_2$, is commonly used for the remediation of polluted waters.

We have investigated the direct photodegradation and the $TiO_2$ photocatalyzed degradation of anilides, with particular emphasis on Propanil (3,4-dichloropropionanilide). It undergoes monophotonic VUV photoionization with very low quamtum yield ($\Phi_{PI}$ . 4%), yielding a radical cation (Propanil$^{\bullet+}$). The VUV irradiation of Propanil yields the corresponding photo-Fries products. Its reduction potential has been estimated as $E^0$ (Propanil$^{\bullet+}$/Propanil) *ca.* 2.3±0.1 V *vs*. NHE. The extinction coefficient of Propanil$^{\bullet+}$ is at 455nm *ca.* 1000 $M^{-1}\cdot cm^{-1}$.

The radical anion, Propanil$^{\bullet-}$, generated by one-$e^-$ reduction, absorbs at about 370 nm. From the corresponding rate constants, the generation of Propanil$^{\bullet-}$ and $O_2^{\bullet-}$ on the surface of photocatalysts may be competitive. $HO^\bullet$ reacts with Propanil via addition and/or $H^\bullet$ abstraction from a saturated carbon, rather than doing it by one-$e^-$ oxidaditon.

Different compounds have been observed upon photocatalytic degradation of Propanil, while only two hydroxychloro derivatives were found after direct 365-nm irradiation. The photocatalytic degradation proceeds by three main pathways: i) substitution of one chorine by an hydroxyl group and ii) hydroxylation of the benzenic ring and iii) oxidation of the alkyl group of the side chain.

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# Oxidation of Pyrimidine Bases: Mechanism of Thymine Chlorination

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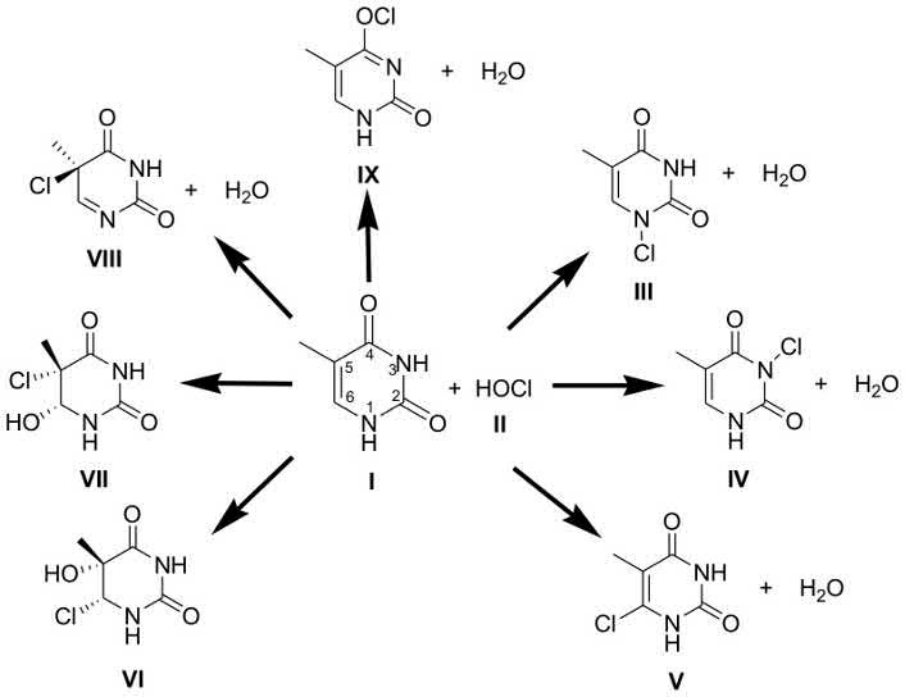
We have studied the in vitro chlorination of the pyrimidine base Thymine at 298.0 K. The process follows second order kinetics, with a rate constant that strongly depends on the pH of the medium, as expected for this kind of compound[1]. The mechanistic possibilities shown in the scheme below can be proposed.




**Scheme**. Alternative products of Thymine Chlorination

A DFT B3LYP/6-31G* theoretical studies have been carried out on each of these pathways. The model used included up to two discrete water molecules. Activation thermodynamic parameters suggest that the preferred pathway is the chlorination on the N1 atom, which leads to product **III**.

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# Nitration Mechanism Discussion based in the Correlation of Statistical Models constructed by Experimental Design

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The statistics being used to many years in the analytical chemistry to increased quality, precision and sensitivity of the results. In organic chemistry is also possible. The literature shows that the most common problems in organic synthesis are solved through the adjustment in the reaction conditions.[1-3] The use of experimental design through multivariable strategies, can be employed in process design and synthesis, to assess key process parameters, to increase the efficiency of synthetic strategies, to identify robust operating regions, and to favour the formation of desired products in preparative reactions. On applying such techniques to a particular reaction combining specific knowledge (or what could be referred to as "chemical insight") we will possibly enable the increase the knowledge about this reaction and facilitate the decisions about it, as long as it allows the description of correlation models among the reaction variables. These methods of factorial analysis and response surface can be applied for the attainment of that model focused, for instance, in the increase of efficiency and/or selectivity of products. The relationship between the response and the independent variables is described by an empirical approximation using a polynomial of order n, that describe the surface under study. When I compare each empirical model obtained to each products, it is possible to learn something about the mechanism of these reactions. To prove it, I applied experimental design in the nitration of aromatic compounds, that has wide information in the literature. It was chosen the nitration with sulphonitric mixture of products like benzene, phenol, ethylbenzene, benzoic acid, bromobenzene and nitrobenzene. First I evaluated the results of nitration of benzene and nitrobenzene. The most important parameter that is responsible for the preferences between each product is the ratio of sulphuric acid on nitric acid, confirming the theoretical concepts about the mechanism of subject. Second, the reactivity of each reagent used was evaluated using the similar conditions and showed the influence of each substance in study. At the end, comparisons of principal parameters of empirical model showed that the factorial analysis is a useful tool for studies of mechanisms and substitution effects in organic reactions with no need of a robust or expensive statistical software.

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# The Elimination Kinetics and Mechanisms of Some Organic Orthoesters in the gas phase

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The elimination kinetics of some organic orthoesters have been examined over the temperature range of 290 – 351$^0$ C and pressure range of 80 – 170 Torr. These reactions, in a static reaction system, were found to be homogeneous, unimolecular and follow a first-order rate law. For triethyl orthoacetate, the overall rate coefficient is expressed by the following Arrhenius equation: log $k_1$ ($s^{-1}$) = (13.28 ± 0.16) – (182.05 ± 1.8)kJ $mol^{-1}$ (2.303 RT)$^{-1}$. In the case of triethyl orthopropionate, the kinetics Arrhenius expression is described as: log $k_1$ ($s^{-1}$) = (13.44 ± 0.29) – (190.36 ± 3.4)kJ $mol^{-1}$ (2.303 RT)$^{-1}$.

The product formation of these eliminations are the corresponding ester, ethanol and ethylene. The probable mechanism according to experimental kinetic and thermodynamic parameters are presented and described.

# The Kinetics and Mechanisms of the Gas Phase Elimination of Some Aminoketals

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The gas phase elimination kinetics of some aminoketals have been determined over the temperature range of 320 – 370$^0$ C and pressure range of 40 – 150 Torr. These reactions, in a static reaction system, are homogeneous, unimolecular and follow a first-order rate law. The 2,2-diethoxy-N,N-diethyl ethylamine undergo elimination by two parallel reactions. Path A, gives ethanol and 1-diethylamine-2-ethoxy-ethene (DEE) in a slow step, which then slowly decomposes to N,N-diethyl methylamine, ethylene, and CO. Path B yields N,N-diethylamine-ethyl acetate and ethane. The rate coefficient for path A is expressed by the following Arrhenius equation: for the log $k_A$ ($s^{-1}$) = (13.91 $\pm$ 0.24) – (202.0 $\pm$ 3.2)kJ $mol^{-1}$ (2.303 RT)$^{-1}$, while Path B by log $k_B$ ($s^{-1}$) = (14.00 $\pm$ 0.60) – (203.5 $\pm$ 7.8)kJ $mol^{-1}$ (2.303 RT)$^{-1}$. In the case of 2,2-diethoxyethylamine eliminates also in two parallel reactions. Path A gives 1-amino-2-ethoxyethene and ethanol following the kinetic equation log $k_A$ ($s^{-1}$) = (13.99 $\pm$ 0.24) – (201.1 $\pm$ 3.2)kJ $mol^{-1}$ (2.303 RT)$^{-1}$. Path B renders amine ethyl acetate and ethane, following the equation $k_B$ ($s^{-1}$) = (13.77 $\pm$ 0.60) – (203.8 $\pm$ 7.8)kJ $mol^{-1}$ (2.303 RT)$^{-1}$. According to the experimental kinetic and thermodynamic parameters, we are describing the most probable mechanisms.

# Theoretical Study at the MP2 Level of the Gas Phase Elimination Kinetics of N,N-Dimethylglycine, N-Phenylglycine, Picolinic Acid and Their Corresponding Ethyl Esters.

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The electronic structure calculations of the Potential Energy Surface (PES) on the elimination kinetics of N,N-dimethylglycine, N-phenylglycine, picolinic acid, and their corresponding ethyl esters in the gas phase, were carried at MP2/6-31G(d,p) level of theory. These amino acids were found to decarboxylate to give the corresponding amino compounds. However, the ethyl esters of these amino acids undergo the elimination of ethylene and the parent acids in the rate determining step. On the basis of these calculations, the mechanisms were found to be concerted and polar in nature. NBO Charges and Bond Orders were calculated for all the species of the reaction coordinates in order to gain insight on the transition state structures and the mechanisms. The calculated kinetic and thermodynamic parameters agree reasonably well with the experimental values.

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# Living Polymerization of Tri-O-propyl-(4-ethynyl)benzyloxy-p-t-butylcalix[4]arene by a Rh-based Ternary Catalytic System: Synthesis of a Novel Conjugated Calixarene Polymer with Controlled Molecular Weight and MWD

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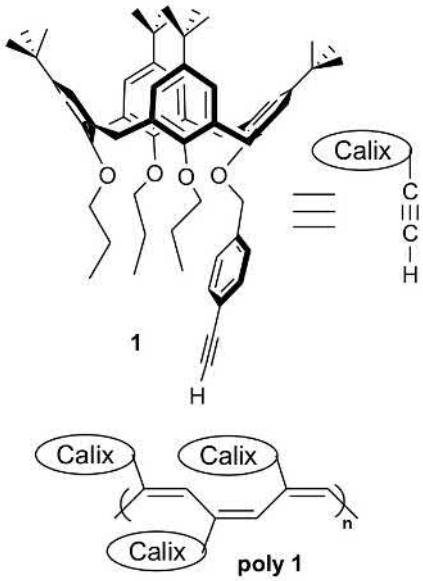
The living polymerization of monosubstituted phenylacetylenes (PAs) using Rh(I) catalysts has been accomplished with three different catalytic systems. Noyori *et al.* first reported that $Rh(C{\equiv}CPh)(nbd)(PPh_3)_2$/4-DMAP[1] and $[Rh(ndb)(OMe)]_2/PPh_3$/4-DMAP[2] systems promote the living polymerization of PA, with initiation efficiencies ($I_{eff}$) of 37% and 72%, respectively. New ternary catalyst systems of the type [Rh(diene ligand)Cl]/$(Ar)_2$-C=C-(Ar)H/$P(4\text{-R-}C_6H_4)_3$ (R=H, F, Cl), achieving quantitative $I_{eff}$, were later developed by Masuda *et al.*.[3]

As part of our ongoing research aiming to produce well-defined calixarene-based conjugated polymers as new materials for use in sensing chemistry, combining the molecular recognition capabilities of the calixarene scaffolds with the unique properties provided by the conjugated main chain polyene, the polymerization of tri-*O*-propyl-(4-ethynyl)benzyloxy-*p*-*t*-butylcalix[4]arene (**1)** was examined. Previous work with this monomer, prepared through a Sonogashira-Hagihara cross-coupling procedure previously developed by us,[4] had shown that the polymerization sluggishly proceeds in toluene or THF when $[Rh(nbd)Cl]_2$ was used, with or without added cocatalysts ($PPh_3$ and/or $NHEt_2$). For instance, at a [Rh]:[monomer] molar ratio of 100:1 in toluene, the yield of the polymer was only 9%, in addition to *ca.* 30% of oligomeric products and 61% of starting **1**, after 5h at 30ºC. A remarkable effect was witnessed when **1** was polymerized by a ternary catalytic system prepared *in situ* from $[Rh(nbd)Cl]_2$, 1,1-diphenyl-2-phenylvinyl lithium and $PPh_3$ in toluene, not only in the polymerization yield, which was quantitative (GPC analysis), but also in its selectivity, since no oligomeric materials were formed. Using different catalyst-to-monomer molar ratios (200:1; 100:1; 50:1 and 25:1), a linear relationship could be obtained between the number-average molecular weight ($M_{n(GPC)}$) of **poly 1** and the [Rh]:[**1**] feed ratio, showing that the polymerization of **1** has proceeded in a living fashion. High $I_{eff}$ and narrow polydispersities were achieved with this ternary system.

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# Chlorine Transfer between Amines: A Mechanistic Study

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Nucleophilic substitution reactions at carbon are among the most studied of all reactions in Physical Organic Chemistry. However, the information on the mechanism of the similar nucleophilic reactions involving the attack of a nucleophile on a halogen atom (halophilic reactions) is scarce. We have studied the reversible chlorine transfer between N-chlorotaurine and different amines:

$$^{-}O_3SCH_2CH_2NHCl + R^1R^2NH \rightleftarrows {}^{-}O_3SCH_2CH_2NH_2 + R^1R^2NCl$$

Chlorine transfer reactions from chloramines require protonation at nitrogen before or during the chlorine transfer step to avoid the formation of the unstable amine nitranion. Two different situations were observed depending on the $pK_a$ of the amine to which the chlorine is transferred:

**i)** For chlorine transfer from N-chlorotaurine to amines of similar $pK_a$ as taurine ($\Delta pK_a<2$) the reaction shows specific acid catalysis, consistent with a mechanism involving protonation of N-chlorotaurine in a fast preequilibrium step.

**ii)** In the case of amines with $pK_a$ values more than two units higher or lower than the $pK_a$ of taurine, the reaction is subject to general acid catalysis, which suggests that a proton is being transferred in the rate determining step.

The different mechanisms involved in these chlorine transfer reactions will be analyzed.

*Acknowledgements*: Financial support from the Spanish MEC is acknowledged.

# Ester Aminolysis Catalyzed by Polyethilene Glycols

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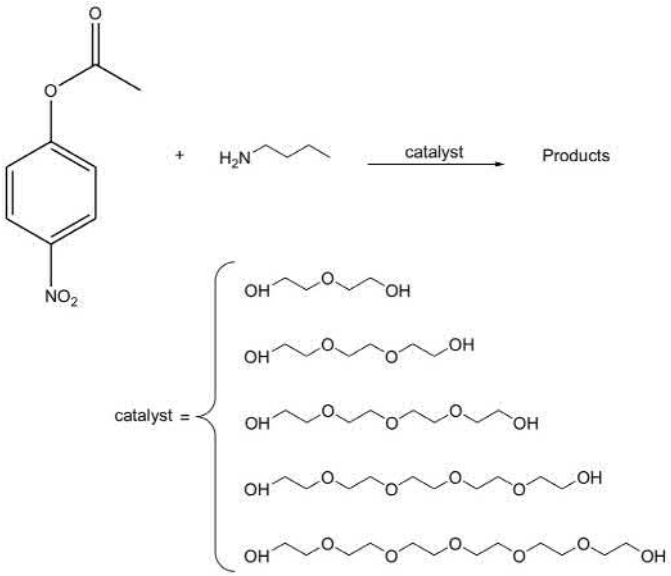
Catalysis by phase-transfer agents of aminolysis reactions of carboxylic esters is a well-studied process. In the present work, we report results obtained in our laboratory by studying the butylaminolysis of 4-nitrophenyl acetate (NPA) in chlorobenzene in the presence of different Polyethylene Glycols (PEGs) (Scheme 1). The generally accepted catalytic mechanism in aprotic solvents implies a nucleophilic attack of n-butylamine on the ester, generating a tetrahedral intermediate $T^{\pm}$. This intermediate may either proceed with the catalytic assistance of a second n-butylamine molecule or form a complex with the phase-transfer agent $C \cdot T^{\pm}$. Subsequently, this complex gives rise to the reaction products in the rate-determining step.

However, in a recent paper our group showed that butylaminolysis of NPA in chlorobenzene in the presence of different kinds of Crown Ethers and Glymes supports the existence of a reaction pathway exhibiting a first-order dependence on the concentration of the phase transfer catalyst and a second-order dependence on the concentration of butylamine. This novel reaction pathway must be included in the mechanism traditionally accepted for the catalysis by phase-transfer agents of aminolysis reactions in aprotic solvents.

From experiments with PEGs with different chain length the values of catalytic rate constants were obtained. Analysis of the catalytic efficiency of PEGs shows that catalysis increases as the number of oxygen atoms increases.




**Scheme 1**

*Acknowledgements*: Financial support from Fundação para a Ciência e Tecnologia (Lisboa) (PhD grant SFRH/BD/29218/2006 to Nuno Basilio) is gratefully acknowledged.

# Contribution of Substrate Phosphodianion Group to Enzymatic Catalysis by *Methylglyoxal Synthase*

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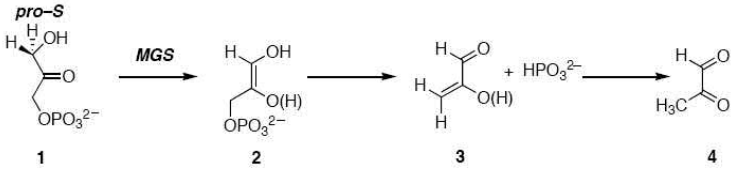
*Methylglyoxal synthase* (MGS) catalyses the elimination of inorganic phosphate from dihydroxyacetone phosphate **1**. Deprotonation of the *pro*–S hydrogen of substrate **1** yields an enediol(ate) intermediate **2**, which upon elimination of inorganic phosphate yields the enol of methylglyoxal **3** (Scheme 1). Tautomerisation of enol **3** to methylglyoxal **4** occurs in solution and not at the enzyme active site.1 We are probing the contribution of the phosphodianion group of substrate to enzymatic catalysis by MGS using a range of mutant substrates: dihydroxyacetone **5**, dihydroxyacetone sulphate **6**, dihydroxyacetone thiophosphate **7**, 4–hydroxy–3–oxobutylphosphonate **8**, and bromohydroxyacetone **9** (Figure 1).




**Scheme 1** Enzymatic reaction of *methylglyoxal synthase* (MGS).

Prior to looking at the turnover of the mutant substrates by MGS it is necessary to fully characterize the solution elimination reactions. Enzymatic rate acceleration may be quantified from a comparison between the second order rate constant for the general base catalysed elimination reaction of mutant substrate in solution and the $k_{cat}/K_M$ value for the analogous MGS–catalysed reaction at the same pH. The contribution of the phosphodianion group to catalysis of the isolated enolisation step may be probed by deuterium exchange experiments using high resolution $^1$H NMR spectroscopy. Our recent experimental results for mutant substrates **5–9** will be presented.

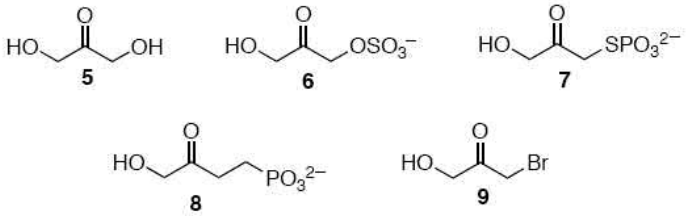



**Figure 1** Substrate analogues of dihydroxyacetone phosphate **1**.

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# Acetylenic Alcohols Used as Corrosion Inhibitors in Acidic Media: Correlation Between Inhibition and Efficiency and Chemical Structure

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Acid solutions are widely used in the petroleum industry. The most important application is the oil-well acidizing for enhancing oil production through the increase of the permeability of the reservoir rock. The drawback of this treatment is the corrosion of oil-well equipments made of mild steel, which is not resistant to acidic media. The corrosion inhibitors are widely used to prevent or reduce the corrosion rate of metallic materials [1-4]. In general, a corrosion inhibitor can be defined as any chemical substance in which when added, in low concentration, to an aggressive system diminishes the metal loss significantly due to corrosion attack [1].

Organic compounds have been used successfully as corrosion inhibitors with long hydrocarbon chains containing heteroatoms of high electronic density such as sulphur, nitrogen, oxygen in various functional groups, as well as triple bonds or aromatic rings in their molecular structures [2]. These compounds form strong co-ordination bonds with Fe atoms (ferric complex) leading to the adsorption of species and film formation on the metallic surface [1,5].

The acetylenic alcohols have been the subject of research of many authors in the last decade. These compounds are shown to be an excellent class of inhibitors to reduce the corrosion rates of steels in acidic environments [6]. Especially the inhibition of propargyl alcohol (PA), is one of the acetylenic alcohols has been investigated extensively The decisive of triple bonds of acetylenic alcohol molecules due to the π-electrons interaction with the metallic surfaces is generally accepted [7].

The aim of this work is to investigate the inhibition properties of propargyl alcohol (PA), ($CH_3C{\equiv}C\text{-}OH$) and the relationship between the chemical structure and their ability to inhibit the corrosion on the carbon steel surface in a solution of organic acids mixture (5 wt % acetic acid + 7 wt% formic acid) and 1,5 %wt HF. Weight loss measurements were carried out to study the effect of addition, in different concentration (1-2 wt%) of this compound on the corrosion rate of the steel in acidic media. All the tests were performed using steel coupons of the dimensions 20 mm x 5 mm x 5 mm immerged in 250 mL of acid solution in the cylindrical autoclave that was closed and placed inside the rolls stove previously heated. The immersion time ranged from 3 to 5 hours and temperature from 333 to 353 K.

The percentage inhibition efficiency (% IE) and the parameter (θ) which represents the part of metal surface covered by the inhibitor molecule were calculated using the following equations:

$$\%IE = \left[1 - \frac{W_{add}}{W_{free}}\right] \times 100$$

$$\theta = \left[1 - \frac{W_{add}}{W_{free}}\right]$$

where Wfree and Wadd are the weight loss of carbon-steel coupon in free and inhibited acid solution, respectively.

The calculated values of inhibition efficiency (%IE), obtained from weight loss, increase with increasing the inhibition concentration resulting in a decrease of the corrosion rate values. Also, it was observed that the corrosion rate is reduced with the increasing of the immersion time. This can be explained by the formation of an inhibitor layer (θ) whose protection against corrosion increases with the time of treatment.

Based on the previous results, the effectiveness of the acetylenic alcohols on iron can be assumed by the adsorption of the inhibitor by the interaction of the C≡Cπ bond and the d orbital on the Fe atoms. So, it promotes the formation of protective films which act as a physical barrier between the acidic solution and the iron surface.

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# Kinetic Studies on the Photocleavage of Fluorescent Neurotransmitter Conjugates

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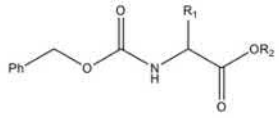
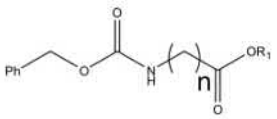
The controlled temporal and spatial release of biomolecules from photolabile precursors, known as caged compounds, has become increasingly important in biological studies, medicine and materials sciences (1-3). Caged compounds, i.e. molecules whose activity in biological recognition events is masked with a photochemically removable protecting group, can be used to deliver bioactive materials such us neurotransmitters, ATP or simply $Ca^{2+}$ ions rapidly to small, addressable target sites, at the desired time and position by a photochemical reaction using UV radiation, and thereby enable biologists to follow the course of physiological events in real time (4,5). Flash photolysis with UV light cleaves the caging group and generates the biologically active molecule. In this way, fast jumps in the concentration of the biomolecule can be achieved at a define location, allowing the study of the spatial and time dependent aspects of cellular processes.

In this work, the behaviour of a series of fluorescent conjugates derived from model neurotransmitters (Figure 1) was studied in different cleavage conditions, namely the wavelength of irradiation and the use of different solvents, in a photochemical reactor equipped with monochromatic lamps of 254, 300, 350 and 419 nm. Cleavage kinetics studies were undertaken in the above mentioned conditions and monitored by HPLC/ UV detection.





**1 a** $R_1 = CH_3$, $R_2 = CH_2Flu$
**b** $R_1 = CH_2CH_2COOCH_2Flu$, $R_2 = CH_3$
**c** $R_1 = CH_2CH_2COOCH_3$, $R_2 = CH_2Flu$

**1 d** n = 1, $R_1 = CH_2Flu$
**e** n = 2, $R_1 = CH_2Flu$
**f** n = 3, $R_1 = CH_2Flu$

Flu = fluorophore

**Fig. 1**. Structure of fluorescent neurotransmitter conjugates.

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# Reduction of aldimines by heterogeneous catalytic transfer reduction

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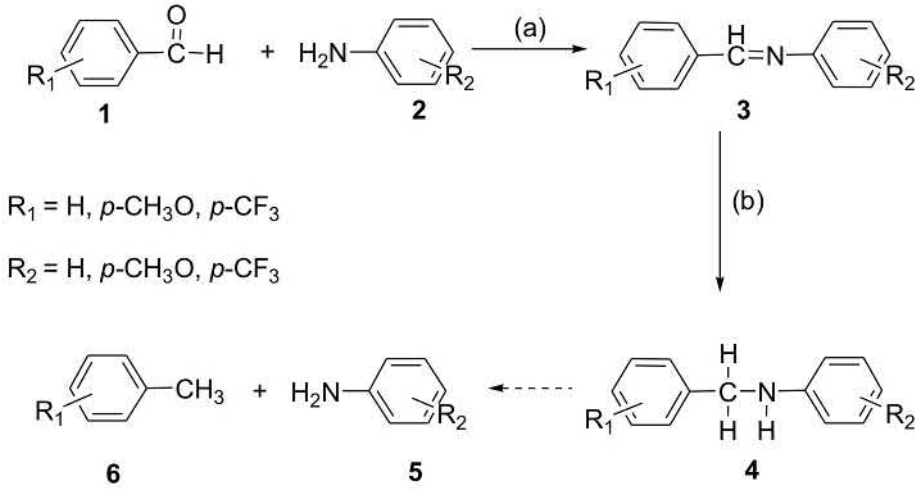
Earlier, we have proposed a mild and highly efficient synthetic procedure for reduction of C=O bond.[1] Presently, we study the reactivity of C=N bond in previously synthesized imines (**3**), in reductive conditions.

The synthesis of aromatic imines is easy to perform and involves a reaction between an aromatic aldehyde (Scheme 1, **1**) and an aromatic amine (Scheme 1, **2**) under refluxing petroleum ether.

In order to study the reactivity and elucidate the mechanism of heterogeneous catalytic transfer reduction, substituted imines (**3**) were reduced using two solvent systems already used for reduction of carbonyl group, one employing toluene/water at 90ºC and the other – tetrahydrofuran/water at room temperature, with palladium-on-charcoal catalyst. The hydrogen donor, an aqueous solution of sodium phosphinate, was added dropwise to the stirred mixture of the substrate with the catalyst and the solvent.




**Scheme1**

We conclude that imines are reduced to amines (**4**) (Scheme 1, **b**), or to products of further hydrogenolysis of amines (**4**), namely arene (**6**) and an aniline derivative (**5**). The substituent effects in the reactivity of aromatic imines can be explained taking into account the electronic structure of the substrate and the Pd-H bond polarization.

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*Acknowledgements*: This work was funded by FCT and Centro de Investigação de Química do Algarve (CIQA).

# Mechanistic Investigations on the Photochemistry of 5-Allyloxy-1-phenyl-1H-tetrazoles in Solution

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The importance of substituted tetrazoles in fields such as medicine (as antihypertensive, antiallergic, antibiotic and anticonvulsant agents as well as in cancer and AIDS treatments) and agriculture (as pesticides) is well known[1] and boosted fundamental research in the structure and reactivity of tetrazolyl derivatives. The tetrazolic ring is present in the structure of many highly efficient drugs, increasing potency and bioavailability of the pharmacophore. Tetrazoles are also really interesting compounds from the viewpoint of reactivity – they have demonstrated a very rich photochemistry, strongly influenced by the nature of the substituents present in the tetrazole ring. The structure and reactivity of tetrazolyl ethers have been studied, and these compounds were used successfully as intermediates in the transformation of alcohols.[2] Recently, a research program aiming at the investigation of the photochemistry of tetrazole-based compounds was undertaken, whereby UV-induced photochemistry of selected tetrazolyl derivatives isolated in solid argon matrices and in solution was firstly explored.[3-4]

In view of the widespread interest in tetrazoles, and 5-substituted tetrazoles in particular, and continuing our research on the reactivity of these type of molecules, the mechanism of photocleavage of a series of 5-allyloxy-1-phenyl-1*H*-tetrazoles in solution is presently under investigation. Photoproducts were isolated and characterised, intermediate species were proposed and reaction kinetics and photolysis quantum yields were determined in different experimental conditions. Solvent effects on the mechanism will be discussed for the tetrazole derivatives studied.

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# Influence of Colloid Suspensions of Humic Acids upon the alkaline hydrolysis of N-Methyl-N-Nitroso-P-Toluene Sulfonamide

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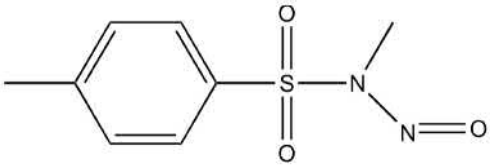
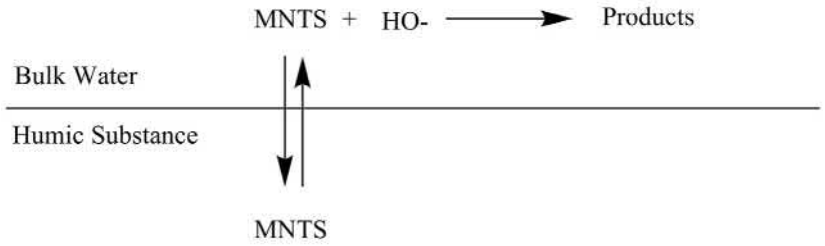
The influence of Humic Substances (HSs) upon the alkaline hydrolysis of N-methyl-N-nitroso-p-toluene sulfonamide (MNTS) has been studied.




Scheme 1. MNTS

Important inhibition of hydrolysis reaction has been reported. This inhibition has been explained in terms of association of carbocations to the humic substances. Kinetic results have been modellised using the micellar pseudophase model.




**Scheme 2**. Distribution and reaction mechanism

# Activation of double and triple bonds in unsaturated hydrocarbons by the Ru(001) surface

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The study of the reactivity of unsaturated hydrocarbons on clean Ru(001) contributes to understanding the metal surface assisted decomposition mechanisms. This is achieved mainly by the identification of the surface species formed at different temperatures and coverages and of their adsorption geometries and sites.[1-3]

The focus of the present work is the reactivity of C6 alkenes and alkynes. It is proposed, based on reflection absorption infrared spectroscopy (RAIRS) results, that 1-hexene chemisorbs at low temperature (90 K) and coverage (0.1 Langmuir) as a di-σ complex, whereas 1-hexyne forms a di-σ/π complex. By thermal activation, these surface complexes dehydrogenate (in C1), yielding hexylidyne, which further decomposes with the formation of surface metallocycles, $\equiv C(CH_2)_4CH_2-$ and $\equiv C(CH_2)_4C\equiv$. Eventually, at 300 K, these species undergo complete C–C bond breaking yielding adsorbed methylidyne (≡CH).

The C6 alkene and alkyne isomers with the unsaturation in secondary carbons may follow two decomposition mechanisms. At low temperatures, they adsorb as the corresponding alkyne di-σ/π complex, which implies a rehybridisation of the $sp^2$ (sp) carbons with reduction of the bond order, plus, for alkenes, the dehydrogenation at the same carbons. These complexes decompose by breaking the C-C bonds adjacent to the surface anchors: C1-C2/C3-C4 in the case of the 2-isomer, yielding methylidyne and propylidyne, and C2-C3/C4-C5 in the 3-isomer, with formation of the ethyne di-σ/π complex and ethylidyne ($\equiv CCH_3$). The second proposed decomposition path has been observed upon direct adsorption at the reaction temperatures. It involves the scission of the multiple bond, with formation of the corresponding short chain alkylidynes: propylidyne (in the case of 3-hexyne and Z-3-hexene), ethylidyne and butylidyne (in the case of 2-hexyne). The reactivity of Z-2-hexene revealed to be different, since there was no evidence for the second decomposition path.

The results on the adsorption and decomposition of E-3-hexene on Ru(001), when compared to those for Z-3-hexene and 3-hexyne, show a remarkable stability. This may be explained by a strong π interaction with the surface, accompanied by a more difficult dehydrogenation due to the spatial arrangement of the ethyl ($C_2H_5$) groups. The chemical behaviour of this isomer is also different: either by annealing a low temperature layer or by adsorbing at high temperature, it dehydrogenates into the intermediate 3-hexyne di-σ/π complex, which is also stabilized, and decomposes exclusively by breaking of the C2-C3 and C4-C5 bonds, yielding ethyne di-σ/π complex and ethylidyne.

In conclusion, it is clear that the geometrical isomerism plays a determining role in the stability and in the decomposition paths of C6 unsaturated hydrocarbons on clean Ru(001), and that the chemical behaviour of such molecules on this surface is determined by the position rather than by the nature of the functionality.

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# Photophysics of Environmentally Relevant Phenylurea Herbicides

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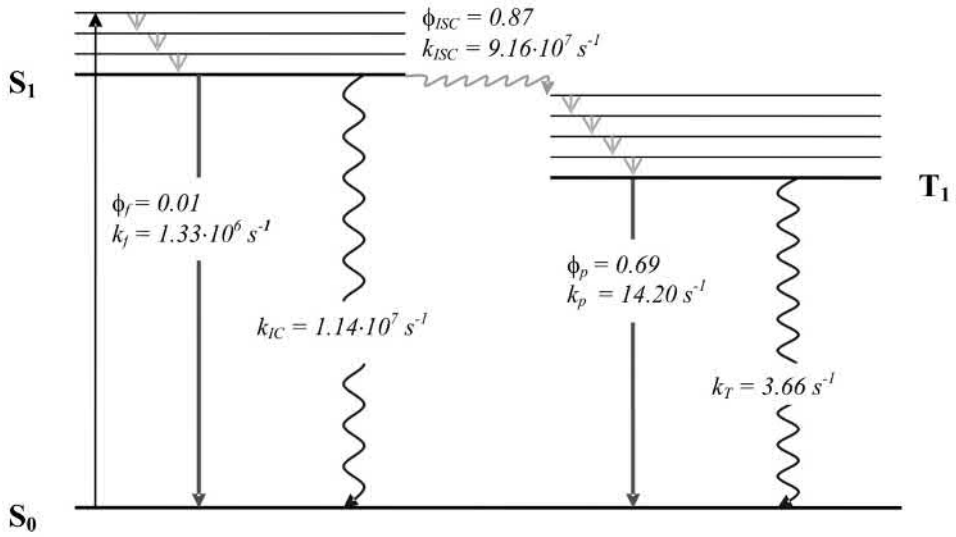
Phenylureas constitute an important group of systemic herbicides, believed to inhibit photosystem-II.[1] They are highly persistent, with half-life times of several months in soil.[2] We have recently reported on their direct photodegradation and the corresponding $TiO_2$-photocatalyzed process.[3]

Quantum yields for photoproducts are low (ca. 10 %), evidencing the existence of alternative modes of deactivation of the initially generated excited states. Here, we report quantum yields and rate constants for different photophysical processes taking place upon light absorption of Fenuron, Monuron and Diuron dissolved in methanol.




**Scheme**. Jablonski diagram for Monuron (1,1-dimethyl-3-(p-chlorophenyl)urea)

Changes in the parameters shown in the Jablonski diagram are also discussed as the chlorine content in the herbicide increases.

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# Use of Physical Organic Chemistry Methodology as a Tool to Investigate the Properties of Complex Systems Formed by Cyclodextrins and Surfactants

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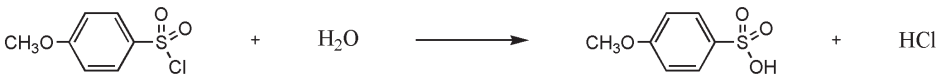
The study of cyclodextrin/ surfactant systems has been of great interest in recent years due to the numerous potencial applications. One of the most important applications is based on the capacity of the cyclodextrin to modulate the physicochemical properties of micellar solutions. To study these systems, we used as a chemical probe the hydrolysis of 4-Methoxybenzenesulfonyl chloride , a molecule whose geometry and polarity is suitable for complex formation with cyclodextrin.




The results obtained allow us to explain the experimental behavior observed in the mixed systems cyclodextrin-surfactant and confirm the validity of the kinetic model proposed. This model has enabled us to highlight certain characteristics of these systems. (a) Before the micellization point, a complexation equilibrium between the surfactant and the cyclodextrin is established. As the surfactant concentration increases, a situation is reached in which the concentration of the uncomplexed surfactant monomers in equilibrium with the CD is sufficient for the micellization process to begin. (b) The critical micelle concentration has been found to shift to higher values in the presence of CD. The critical micelle concentration of a micellar system in the presence of cyclodextrin is equivalent to the combined concentrations of surfactant monomers complexed to the CD and of free dissolved monomers in equilibrium with the micellized surfactant. (c) Once the micellization process has begun, interactions will not be established between the CD and the micellar system.

# Kinetics and Mechanism of the Pyridinolysis of *S*-Aryl Chlorodithioformates

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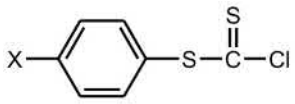
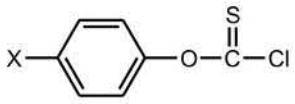
Although there have been some reports on the kinetics and mechanisms of the aminolyses (several types of amines) of alkyl and aryl chloroformates,1 and aryl chlorothionoformates,2 there have been no investigations concerning the kinetics of the aminolyses of S-aryl chloro dithioformates.

To extend our investigations on the mechanism of the pyridinolysis and aminolysis of chloroformates, in this work we undertake a kinetic investigation on the reactions of pyridines with the S-aryl chlorodithioformates, 1 and 2.



1: X = H
2: X = $NO_2$



3: X = H
4: X = $NO_2$

A specific objective is to assess the influence of the nonleaving group of the substrate on the kinetics and mechanisms of these reactions. Other objective is a comparison of the title reactions with those of the O-aryl chlorothionoformates **3** and **4**.[2b]

The reactions were followed spectrophotometrically. Under amine excess, pseudo-first-order rate coefficients ($k_{obsd}$) were found. For all these reactions, plots of $k_{obsd}$ vs. free amine concentration at constant pH were linear, the slope ($k_N$) being independent of pH.

The Brönsted-type plots (log $k_N$ *vs.* p$K_a$ of the conjugate acids of the amines) were linear with slopes $\beta = 0.30$, consistent with a stepwise mechanism through a tetrahedral intermediate with the formation of the intermediate as rate-determining step.

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*Acknowledgements*: This work was funded by FONDECYT of Chile (project 1060593). M.G. thanks CONICYT of Chile for a doctoral fellowship.

# Site-Directed Mutagenesis of Laccase from the Fungus Trametes versicolor: Investigating Effects Responsible for the Reactivity of Substrates

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Laccases belong to the family of the multi-copper oxidases, and are extensively investigated for their potential environmental (bioremediation) and industrial (pulp and paper) applications. These enzymes are widely distributed in nature, and have broad substrate specificity. In particular, and due to their moderate redox potential (in the 0.4-0.8 V/NHE range), laccases oxidise phenols and arylamines of natural or industrial origin for their conveniently low redox potential. However, aiming to meet specific industrial needs and to widen the range of acceptable substrates, the design of recombinant enzymes is a sought-after issue, and accessible using genetic engineering.

In recent years, a few crystal structures of laccases have been published,[1-3] two of them having an inducer substrate co-crystallized in the active site.[2,3] Thus, a unique opportunity to appreciate prominent binding interactions of a substrate with aminoacidic residues of the active site has become available. In the attempt to improve the enzymatic catalytic properties, structure-based site-directed mutagenesis of the laccase from the fungus *Trametes versicolor* (TvL) has been undertaken. Because the crystal structure of TvL reveals the important role of the Asp206 residue for dragging a substrate inside the binding pocket,[2] due to polar or H-bond interactions with polar groups of the substrate, the Asp206 has been replaced with Glu, Ala or Asn by using protein engineering tools, and the expression system of the yeast *Yarrowia lipolytica*.[4] A preliminary investigation with the mutants has revealed that the transformation efficiency towards ABTS, a non-phenolic substrate, remains within the same range. In contrast, the Asn mutation has led to a significant shift of the optimal pH of activity against a phenolic substrate.[4]

By using substrates of different size and nature with respect to ABTS, we now present results that show how the transformation efficiency of the above mutants may indeed reflect the changed interactions between the active site and a substrate more severely. Additional site-directed mutations are also in progress, in order to change the aminoacidic residues that restrict the access of sterically hindered substrates to the active site. Hopefully, these site-directed mutagenesis experiments will enable to tailor laccase efficiency more finely.

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# Dipeptide reactivity towards 2,5-diketopiperazine formation: in search of suitable carriers for intramolecularly-activated prodrugs

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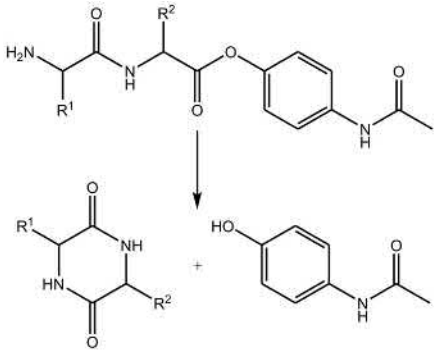
The dose-dependent toxic effects of relevant hydroxylated drugs such as paracetamol or AZT, associated with their low oral bioavailability, limit their clinical usefulness. For example, large doses of paracetamol lead to excessive accumulation of a toxic N-acetylquinone-imine metabolite in the liver, resulting in glutathione depletion and tissue necrosis. Therefore, continued efforts are being done aimed at the elimination of the side-effects ascribed to the use of high doses of hydroxylated drugs such as those written above by, for instance, esterification of these drugs with peptide carriers.[1-2] Further, it is known that dipeptides can deliver the parent drug through enzyme-independent processes, namely, the intramolecular cyclization of the dipeptide moiety to a 2,5-diketopiperazine (DKP). Therefore, there is a strong interest in the establishment of a reactivity scale for dipeptides as prospective carriers in intramolecularly-activated prodrugs, which will provide a basis for future modulation of drug release kinetics.

Herewith, we will present a systematic computational study, based on the density functional theory, on the energetics of ring-closure after cis-trans isomerization of the amide bond for several different dipeptides linked to paracetamol. For each of these dipeptide esters of paracetamol, the energetics of paracetamol release will be also described.




**Scheme 1**. Paracetamol release from its dipeptide ester through intramolecular cyclization of the peptide moiety.

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# Kinetic Study of Nitrosation of Guanidines

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The nitrosation of amines, ureas, amides has received much attention, due in large part to the potential carcinogenic properties of the *N*-nitroso products formed. Nitrosation of amines in acidic medium occurs with rate limiting attack of the nitrosating agent on the free base form of the substrate, while that of amides and ureas involves fast *O*-nitrosation followed by slow proton transfer from the substrate and a fast internal rearrangement to yield the N-nitroso products. Guanidines can be considered nitrogenated analogues of ureas. However, their peculiar structure makes them compounds of great basicity, and in this sense, are more similar to amines than ureas. This situation makes the kinetic study of the nitrosation of guanidines, molecules that combine characteristics of both functional groups, very interesting and provides a bridge between amines and ureas1.

In the present work we report the results of a kinetic investigation in acid media of the nitrosation of N-, N´-dimethyl-cyanoguanidine, dicyanoamide, aminoguanidine and guanidine. The reaction mechanism is (except for aminoguanidine) similar to those found for the nitrosation of amides and ureas. The value of the equilibrium constant, and the values of the rate constants for direct and reverse reaction have been calculated.

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# Effects of Micellar Aggregates of SDS on the Reaction of Local Anaesthetics with Nitrous Acid

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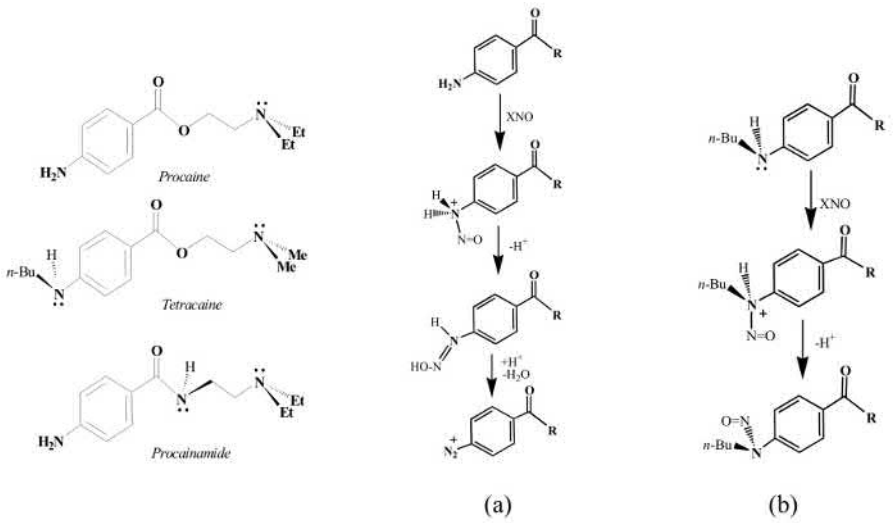
The ingestion or inhalation of nitrosating agents has been know to cause in vivo nitrosation, whose significance greatly increases with the discovery of endogenous NO synthesis and the emergence of NO-releasing drugs. NO is unable to react with nucleophiles under oxygen free conditions, suggesting that its higher oxides, such as $N_2O_3$ were actually nitrosylating agents and that the oxidation of NO to $N_2O_3$ is facilitated by micellar catalysis.[1]

In this work, we analysed the kinetic characteristics of the nitrosation reaction of the primary or secondary amine groups of three local anaesthetics (see Scheme)[2]. The reaction yields the diazonium ions or the N-nitroso amine, depending of the nitrosation of primary or secondary amines. The kinetic study has been performed in mild acid conditions of acetic acid-acetate buffers in the absence or presence of anionic micelles of SDS.




**Scheme**. Molecular structures of local anaesthetics and (a)steps of diazotization of primary amines and (b) of nitrosation of secondary amines in aqueous acid media.

***References***

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# An experimental study of an $S_N2$ reaction pathway of acyl compounds

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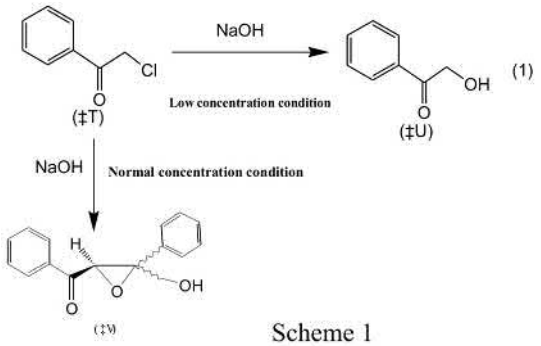
The $S_N2$ reaction rate of an α-haloketone is known to be accelerated by an adjacent carbonyl group. The rate acceleration is normally considered to arise from the TS stabilization through the resonance effect by the carbonyl function. In the present study, we have examined the origin of the acceleration by computational and experimental methods.

Computational study revealed that the reaction with chloride ion proceeds through the normal SN2 reaction pathway with a symmetrical TS. On the other hand, when a nucleophile is hydroxyl ion the reaction goes through an tetrahedral intermediate at the carbonyl carbon.

When the reaction with hydroxyl ion is carried out in aq EtOH, dimer (III, Scheme 1) was obtained under normal conditions (e.g. [I] = 50 mM, [NaOH] = 100 mM). In contrast, the reaction at low concentrations of I (e.g. [I] = 0.8 mM, [NaOH] = 100 mM) gave the normal substitution product (II).




Scheme 1

On the bases of these as well as other kinetic results, it is proposed that the substitution reaction with hydroxide ion proceeds through the carbonyl addition intermediate.

# Electrophilicity of Substituted Diethyl Benzylidenemalonates

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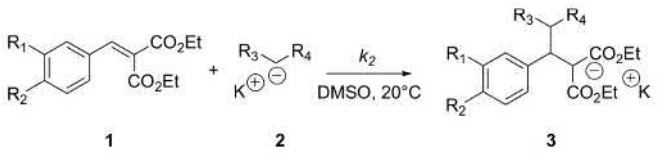
Equation (1), where s and *N* are nucleophile-specific parameters and *E* is an electrophilicity parameter, has been used for the construction of the most comprehensive nucleophilicity scale presently available.[1]

$$\log k_2 = s(N+E) \qquad (1)$$

Benzhydrylium ions and structurally related quinone methides have been employed as reference electrophiles for the characterization of nucleophiles with -4 < *N* < 20 (toluene to diethyl malonate anion).2,3 We report now that benzylidenemalonates are suitable reference electrophiles of lower reactivity (-18 > *E* > -23) which can be used to assign nucleophilicity parameters of carbanions of p$K_{aH}$ values between 9 < p$K_{aH}$ < 27.



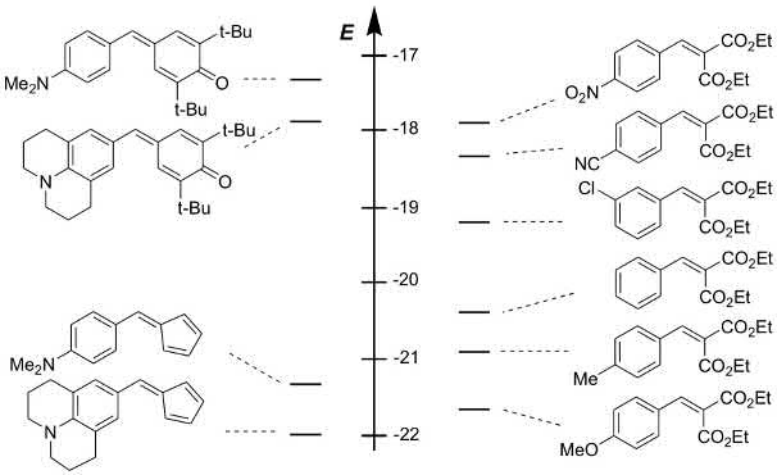




**Figure 1**. Electrophilicity parameters of quinone methides, fulvenes, and benzylidenemalonates.

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# The Influence of *O*-Methylation on *cis/trans* Rate Ratios in the Acid-catalysed Dehydration of Arene Dihydrodiols

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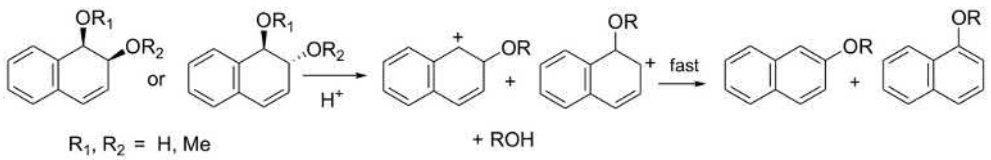
Arene dihydrodiols and their methyl ethers undergo acid-catalysed dehydration to the corresponding phenol or methoxy arene. The reaction is believed to occur with rate determining formation of a carbocation intermediate which reacts rapidly to yield the aromatic product(s), as shown for naphthalene 1,2-dihydrodiols and their methyl ethers in Scheme 1.[1]

**Scheme 1**




A distinctive feature of these reactions is the large difference in reactivities between reactants with *cis* and *trans* configurations of hydroxy or methoxy groups. For benzene dihydrodiols $k_{cis}/k_{trans}$ = 4500 while for 1,2-naphthalene dihydrodiols $k_{cis}/k_{trans}$ = 450 and for 9,10-phenanthrene dihydrodiols $k_{cis}/k_{trans}$ = 55.

As discussed elsewhere in the conference these differences are thought to derive from the conformational dependence of stabilization of a carbocation intermediate by hydrogen hyperconjugation. In this paper, the effect of *O*-methylation on the *cis-trans* reactivity ratio is examined. In the case of benzene dihydrodiols $k_{cis}/k_{trans}$ for the diols and their dimethyl ethers is 4500 and 3700 respectively. The similarity of these ratios suggests that there is little difference in the behaviour of hydroxy and methoxy groups. To our surprise, however, for naphthalene dihydrodiol $k_{cis}/k_{trans}$ is reduced from 440 for the 1,2-dihydrodiols to 20 for their dimethyl ethers.

As shown in Scheme 1 aromatisation of naphthalene dihydrodiols and their methyl ethers is complicated by the formation of two products depending on whether reaction occurs at the 1- or 2-position. In an attempt to elucidate the effect of methylation, fourteen rate constants have been evaluated from a combination of kinetic measurements and product analyses, for the diols themselves and their mono- and di-methyl derivatives. These have been combined with measurements for the corresponding diols and methyl derivatives of 9,10-dihydrophenanthrene in an attempt to explain this unusual effect.

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# Water interaction with oxo-thione derivatives of 2,7-dimethyl-1,2,4-triazepines

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Water traces in organic solutions are difficult to avoid in synthesis processes which has a non negligible effect on the reactional mechanism. Our objective in this study is to explore the interaction between water and thio/oxo derivatives of triazepine. As these compounds present many basic centers, the hydrogen bond donation and attraction of water molecule have been well examined with theoretical tools. The DFT calculations have been carried out at B3LYP/6-311+G(d,p) level in order to establish the most stable water-triazepine complexes. The electron localization function (ELF) analysis method has been used to explore the electronic changes.

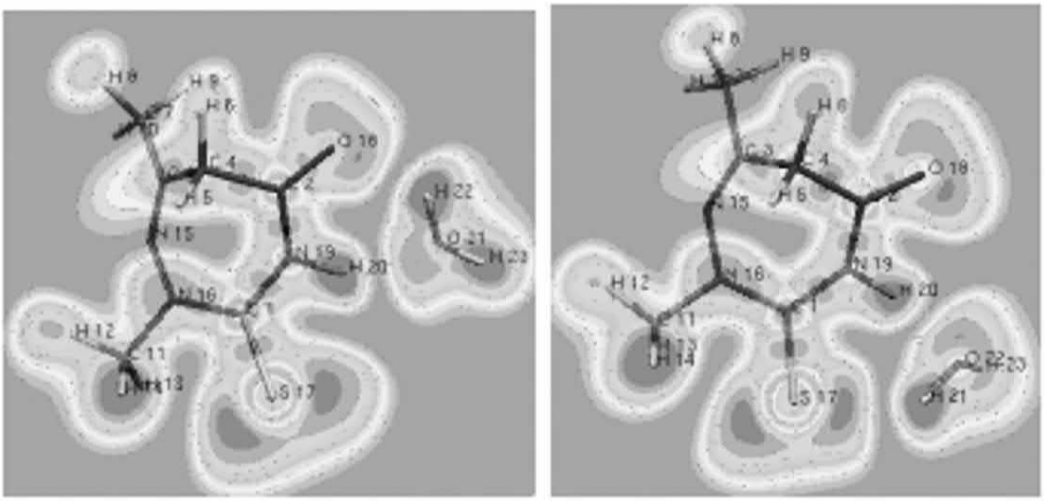

**Fig**: The projection of the ELF function in the most stable structures of the 3-thiotriazepine-water complex.

# Cis-trans Selectivity of Nucleophilic Attack on β-Hydroxyarenonium Ions

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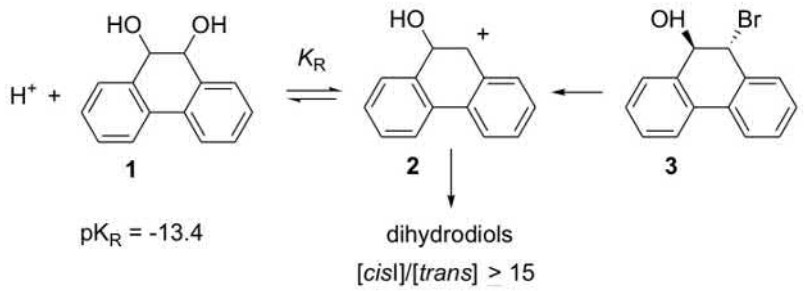
In this paper trapping by azide ions is used to evaluate the stability of and *cis-trans* selectivity towards nucelophilic attack upon a β-hydroxycarbocation. The carbocation is the 9-hydroxy-10-phenanthrenonium ion **2** which has been generated from solvolysis of the *trans*-9,10-bromohydrin of phenanthrene **3**. The measurements yield a $pK_R$ value for the carbocation and ratios of *cis*- to *trans*-dihydrodiol products formed (in addition to the major product phenanthrol) as summarised in Scheme 1.

**Scheme 1**




The almost exclusive formation of *cis*- rather than *trans*-dihydrodiol from the carbocation is consistent with the much greater reactivity exhibited by *cis*- than *trans*-dihydrodiols in their acid-catalysed dehydration reactions, for which the reverse formation of the β-hydroxy carbocation is considered to be rate-determining.[1] For the phenanthrene 9,10-dihydrodiols 1 the ratio of rate constants is $k_{cis}/k_{trans} = 55$, while for 1,2-naphthalene and benzene dihydrodiols $k_{cis}/k_{trans} = 440$ and 4500 respectively. In so far as the *cis*- and *trans*- dihydrodiols differ in stability by no more than a factor of 2 or 3, a much greater stability is implied for the transition state for reaction and formation of the *cis*- than *trans*-dihydrodiols.

The formation of *cis*-dihydrodiol from solvolysis of the bromohydrin 3 ([*cis*]/[*trans*] > 15) contrasts with the preferred formation of its trans-isomer from acid-catalysed ring-opening of phenathrene oxide in water[2] or methanol.[3] Hitherto it has been supposed that the *trans*-product from this reaction arisse from trapping of a β-hydroxy carbocation intermediate. The present results suggest, however, that it is formed not from the carbocation but from $S_N2$ attack by water on the protonated epoxide. Such a mechanism is kinetically indistinguisable from the previously implied SN1 mechanism for opening the (protonated) epoxide.

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# Mechanism-Guided Studies of Asymmetric Organocatalysis of the Mannich Reaction.

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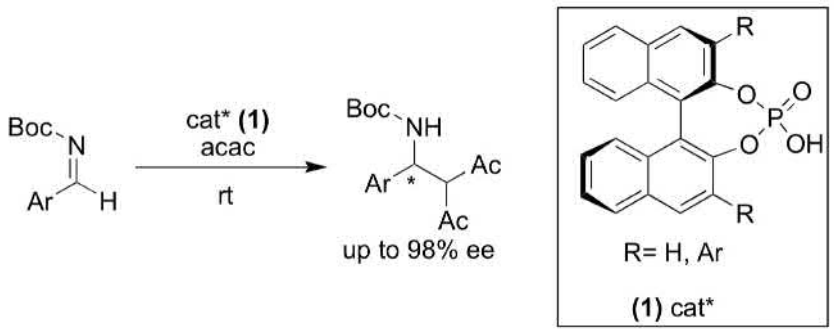
The design and application of small non-metal organocatalysts is becoming increasingly important in industry given the high cost of purchase and disposal of metal analogues. In particular, asymmetric Brønsted acid and base organocatalysis has recently emerged as a useful tool in synthetic methodology.[1] However, the success of a given Brønsted catalyst is highly substrate and solvent dependent and few broadly successful catalysts exist. More importantly the mechanism of asymmetric Brønsted acid and base organocatalysis is not clear.

Asymmetric Mannich reactions of aldimines with enolate components are one of the most important carbon–carbon bond forming reactions. These reactions provide useful routes to optically active β–amino ketones which are versatile chiral building blocks for the preparation of many nitrogen-containing, biologically important molecules. Recently, enantioselective variants of the Mannich reaction have been developed using several organocatalysts including planar chiral phosphoric acid catalyst **1**.[2] This reaction has been suggested to involve asymmetric Brønsted acid organocatalysis.




**Scheme 1** Asymmetric Mannich reaction of N-Boc arylimines and acetyl acetone.

It is assumed that chiral Brønsted acids/bases show recognition by proton transfer to/from a single enantiotopic face of substrate. However, the origin of the asymmetry and the nature of the proton transfer step are not clear. To address these mechanistic questions we are applying a quantitative structure-reactivity approach to probe the origin of asymmetric catalysis. We have determined rate constants for reaction of a family of aryl imines with acetyl acetone in the presence of different phosphoric acid catalysts 1 and thiophosphoryl analogues. pKa values for the conjugate acid of imine substrates and for the phosphoric acids catalysts have been determined. These rate and equilibrium data have been correlated using the Brønsted equation. Mechanistic insight could be obtained from the magnitude of the resulting α or β value. Finally, a comparison where relevant of the α or β value with the reaction enantioselectivity (ee) could suggest the extent of proton transfer necessary for optimal selectivities.

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# The Exocyclic Amino Group of a Neighbouring Adenosine Moiety is Involved in the Transesterification of Phosphodiester Bonds of RNA

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Previous studies have shown that a base composition of even a short RNA oligonucleotide can affect significantly the reactivity of phosphodiester bonds within the sequence.[1] Phosphodiester bonds in certain sequences were more reactive than freely rotable phosphodiester bonds of oligo-U. It has been suggested[2] that adenine base can be involved in the cleavage of a phosphodiester bond by forming hydrogen bonds to the phosphorane transition state.

In order to study this influence, the cleavage of heterosequence oligonucleotides with a U-A scissile bond has been studied under neutral conditions and the reactivity has been compared to that of an oligo-U sequence and an oligonucleotide containing an $N^6$,$N^6$-dimethyladenosine as the leaving group nucleoside.

The results obtained show that under neutral conditions a U-A phosphodiester bond in the middle of a short oligonucleotide can be more 200 times more reactive than a U-U bond in an oligo-U sequence. Experiments with an oligonucleotide with $N^6$,$N^6$-dimethyladenosine as the 5´-linked nucleoside suggests that the exocyclic amino group is involved in the reaction influencing on the reactivity of the neighbouring phosphodiester bond. Methylation renders the phosphodiester bond up to 20 –times less reactive in comparison to a U-A bond next to an unmodified adenosine.

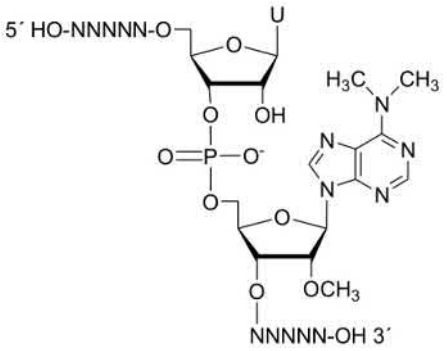


**Fig. 1**. A 12-mer oligonucleotide with $N^6$,$N^6$-dimethyladenosine as the 5´-linked nucleoside.

***References***

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# Pseudo-zero order reaction in solution

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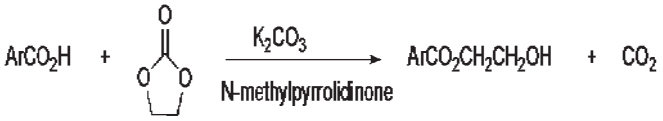
Esterefication of $ArCO_2H$ (**1**) by reaction with ethylenecarbonate (**2**) is catalysed by KI.[1] Studies of the reaction mechanism ascribe the effect of KI (and $Br^-$, $Cl^-$) as being due to the formation of an intermediate iodoethylcarbonate, which is then attacked by $ArCO_2H$.[2] However, $ArCO_2H$ is not a good nucleophile and it is difficult to see how the rapid formation of the iodo intermediate could accelerate the reaction.

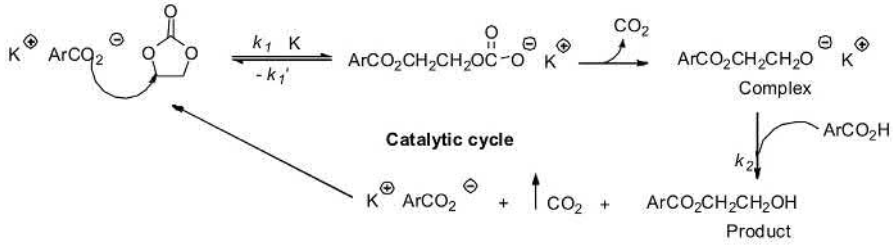



**1** **2** **3** **4**

The same esterification is also catalysed by $K_2CO_3$ with N-methylprrolidinone as solvent so that halogen anion seems to be an unnecessary requirement. The reaction could be expected to follow second order kinetics, especially as the reactants **1**,**2** are normally used in equimolar concentrations, [A] and [C]. Also, there are no significant side-products in the process so that $[A_0\text{-}P] = [A]$, where $A_0$ is the initial concentration of A. The rate equation can be written, $d[P]/dt = k[A].[C] = k[A_0\text{-}P].[C]$. In stark contrast, we observed that the process showed no second order character nor even that of *pseudo* first order and, instead, the reaction appeared to follow zero order or steady state behaviour during up to over 90% conversion to product, P. The rate of formation of **3** and the rate of disappearance of **1** or **2** was constant throughout reaction, *viz*., $d[P]/dt = -d[A]/dt = k$. In a classic test of reaction order, the rate of reaction was unchanged on doubling [A] or [C] but when [P] was increased to 2[P] and $[K_2CO_3]$ was also doubled at the same time, the rate only doubled. In keeping with $K_2CO_3$ being the catalyst, the rate varied only with and proportionately to $[K_2CO_3]$ at constant temperature. In the first few seconds of reaction, there was vigorous effervescence as $CO_2$ was liberated and the true catalyst must be $K^+$, the common denominator of $K_2CO_3$, KI, KBr and KCl.

We propose that reaction of **1** with **2** proceeds through a catalytic cycle similar to that shown in Scheme 1, in which a steady state is quickly reached by rapid formation of an intermediate, $ArCO_2CH_2CH_2OK$ and its slower change to product, $ArCO_2CH_2CH_2OH$, as $K^+$ is exchanged for $H^+$. Adding one mole proportion of KI to this reaction also doubles the reaction rate, in keeping with Scheme 1.

The apparent zero order process is caused by the need for the intermediate potassium complex of Scheme 1 to react with $ArCO_2H$ to give the product **3** and more catalyst, $ArCO_2K$. The ionization needed for the exchange of $K^+$ and $H^+$ is known to be poor in many solvents. It appears that the reaction is actually steady state rather than zero order.

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*Acknowledgements*: This work was funded by Sericol ltd.

# Hydrolysis of Sulfamate Esters and Sulfamoyl Chlorides

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The importance of various types of sulfamate esters **$RNHSO_2OR$** in medicinal chemistry is well documented over the last decade or so and some have proved to be efficacious in the prevention of breast cancer, as anti-glaucoma agents, anti-cholesterol drugs and other applications have been found or indicated. However little detail is available with regard to their mode of action [1,2] and in this work some mechanistic studies under aqueous conditions will be reported for sulfamate esters of type **(1)** since these type of esters tend to represent simple models of the biologically important compounds.

**$NH_2SO_2OAr$**

**(1)**

The mechanism of aqueous hydrolysis of compounds **(1)** has been explored by looking at the pH-rate profiles in water/acetonitrile and water alone, $pK_a$ measurements, various structure-reactivity relationships, kinetic solvent isotope effect and thermodynamic data. The conclusions from earlier data are largely reinforced and extended in this present work.

Some studies have been reported on the solvolysis and aminolysis of sulfamoyl halides of type $R_1R_2NSO_2X$ [3] and the aminolysis (anilines) of arylsulfamoyl halides has been studied.[4] In this communication some preliminary results on the rapid hydrolysis of some sulfamoyl halides of type **(2)** will be presented.

**$RNHSO_2Cl$**

**(2)**

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# Synthesis and Aromatisation Reactions of Arene Hydrates

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Aromatic compounds (**1**), upon ingestion or inhalation, are metabolised by the *cytochrome P450* enzymes in the mammalian liver (Figure 1). These formal oxidation products are known as oxidative metabolites and include the arene oxides (**2**), arene hydrates (**3**) and the arene *trans*-dihydrodiols (**4**).[1] Oxidative biotransformation of arenes (**1**) in bacterial systems yields arene *cis*-dihydrodiols (**5**). We are probing the mechanism of decomposition of these oxidative metabolites in solution. This work has synthetic and environmental impact as these metabolites are both important chiral synthons and are implicated in the mutagenic metabolism of aromatic hydrocarbons.

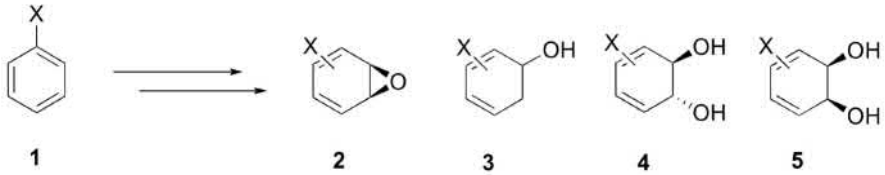


**Figure 1** Oxidative metabolism of aromatic compounds.

One of the main pathways for decomposition of the oxidative metabolites (**2**) – (**5**) in solution is *via* aromatisation. This paper will address the aromatisation reactions of arene hydrates (**3**). An *E1*-mechanism for aromatisation of polycyclic aromatic hydrates is well established. This has generally been assumed to be the case for simple monocyclic benzene hydrates although recent results suggest otherwise. We will present our results of a detailed mechanistic study of the aromatisation of a series of benzene hydrates including pH-rate profiles for aromatisation and a Hammett structure-activity correlation. Results will be compared with data for analogous dihydrodiols (**4**) and (**5**).[2,3]

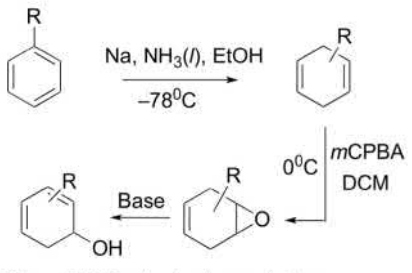


**Figure 2(a)** Synthesis of arene hydrates.

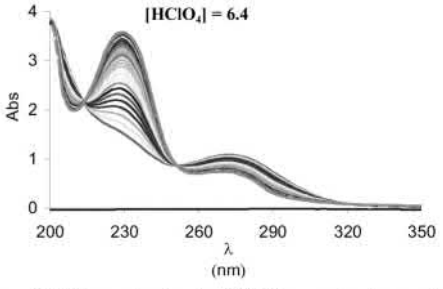


**Figure 2(b)** Aromatisation by UV-Vis spectrophotometry.

Synthetic routes to arene hydrates have not been developed to date and we have optimized new routes to a range of arene hydrates (Figure 2(a)). UV-Vis spectrophotometry is used to follow the reactions; a typical trace for the aromatization reaction is shown (Figure 2 (b)).

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# Acid-Catalysed Hydrolysis of N-Acylsulfamate Esters

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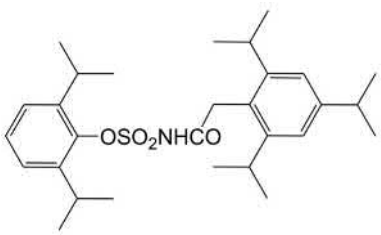
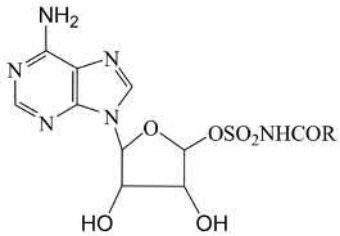
Interest in sulfamate esters, $\mathbf{R_1OSO_2NR_2R_3}$ and sulfamides, $\mathbf{R_1R_2NSO_2NR_3R_4}$ has been widespread over the last decade or so and this is mainly though not entirely due to their many potential and proven uses in medicinal chemistry. Some biomolecules containing the closely related N-(oxycarbonyl)- and N-(carbonyl) sulfamate moieties i.e. -**$OSO_2NHCOO$**- and -**$OSO_2NHCO$**- respectively have also been shown to be very important in biological chemistry and a very thorough mechanistic investigation of the former type was made some years ago.[1] The latter class which may be called N-acylsulfamates includes the important anti-atherosclerotic agent Avasimibe (**1**), which reached phase III of clinical trials,[2] sulfamate esters of type (**2**), which are competitive inhibitors of the pantothenate synthetase-catalysed condensation of D-pantoate and β-alanine to form, pantothenate[3] and certain isoleucylsulfamates which inhibit methionyl-tRNA and isoleucyl-tRNA synthetases.[4]




Despite its obvious importance the chemistry of the acylsulfamate group has not been explored and now in this present communication the hydrolysis of a series of N-acylsulfamates of type $\mathbf{XC_6H_4OSO_2NHCOPr}$ have been studied.

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# Evaluation of Binding Constants of Different Flavours to Cyclodextrins

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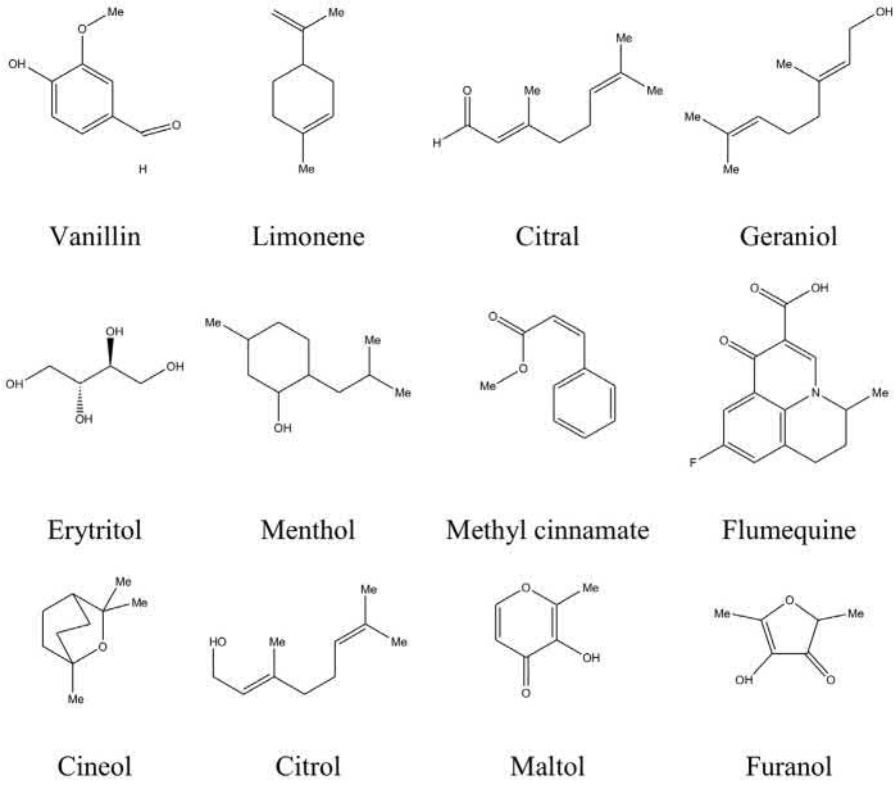
The formation of inclusion complexes between different flavours (see scheme 1) and β-cyclodextins has been studied. Changes in the UV-Vis spectrum of flavours have been analized as a function of β-cyclodextin concentration. These UV-Vis spectrum changes allow us to evaluate the binding constant of both flavours to the β-cyclodextin´s cavity. In both cases the inclusion complexes were 1:1.




**Scheme 1**. Flavours

# Transesterification of RNA model in buffer solutions in $H_2O$ and $D_2O$

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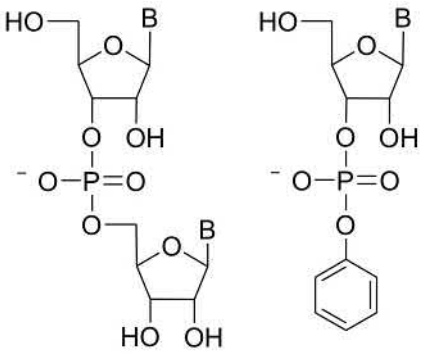
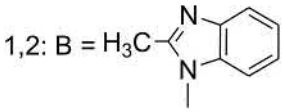
The transesterification of RNA models **1** and **2** has been studied in buffer solutions in $H_2O$ and $D_2O$. The work had two aims. One is to determine kinetic solvent deuterium isotope effect values of transesterification reactions proceeding *via* different pathways. The other is to study the mechanisms of the transesterification reactions, which, despite extensive research, are not fully understood.




1 2




Cleavage and isomerisation of a dinucleoside monophosphate was studied in various buffer solutions (*e.g.* imidazole and MOPSO) under neutral conditions. Rate constants were determined at different buffer ratios as a function of buffer concentration in $H_2O$ and $D_2O$.

The main results are: (i) While imidazole buffers modestly promote the cleavage of **1**, the effect of MOPSO is clearly less significant, (ii) The effect of imidazole buffers on the isomerisation of **1** and cleavage of **2** is very modest; MOPSO has no effect on these reactions, (iii) Rate constants of imidazole promoted cleavage of 1 do not depend linearly on the buffer concentration (iv) significant solvent isotope effect values were obtained only in imidazole solutions.

It can be concluded that imidazole promotes the cleavage of phosphodiester bonds of RNA by a unique mechanism. The system is even more complex than has been believed, and in addition to several parallel first-order processes, a process that shows a second-order dependence in imidazole concentration, was observed. The difference between imidazole and MOPSO most probably depends on charge and/or sterical hindrance that prevents the interaction between the buffer base and the phosphate group.

# Prototropic Tautomerism of Selenouracils

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The relative stability of the different tautomers of the 2-, 4-selenouracil and 2,4-diselenouracil has been studied using density functional theory (DFT) methods. Geometries were optimized at the B3LYP/6-31G(d,p) level. Final energies have been obtained in single point B3LYP/6-311+G(3df,2p) calculations. For all the compounds the most stable tautomer is the oxo-selenone form. The relative stabilities of enol and selenol tauromers changed from one derivative to the other, but they followed similar trends to those find before for the uracil thioderivatives[1] even though the energy gaps between the different tautomers of selenouracils are smaller than for thiouracils. The tautomerism activation barriers are high enough as to conclude that only the oxo-selenone or the diselenone structures should be found in the gas phase, as well as in solution due to the high dipole moment of these forms. For 2- and 4-selenouracils, the most favorable tautomerization process corresponds to a hydrogen transfer towards the selenium atom the activation barriers for transfer towards the oxygen atom being much higher. For 2,4-diselenouracil the most favorable tautomerization corresponds to the H shift from N1 to the selenium atom at C2. However, only for 2-selenouracil and for 2,4-diselenouracil the corresponding selenol tautomer is favored both thermodynamically and kinetically.

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# Application of LSER methodology to the modelling of quinoline-solvent (alkan-1-ol/DMF mixtures) interaction mechanism of solvation

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The quinoline ring systems are present in many natural and synthetic compounds and exhibit a wide range of biological activities. Solvatochromic effects on quinoline in pure and binary solvent mixtures have already been studied[1,2] and it is well reported that they depend fundamentally on non-specific and specific solute-solvent interactions being the dipolarity/polarizability and the HBA capacity of solvent the two main factors (Fig.1). In order to provide a better insight into the physicochemical nature and extent of quinoline solvent interactions we applied the Linear Solvation Energy Relationships (LSER) methodology to the molar transition energies of quinoline $E_T$(Q) *versus* some empirical "polarity" solvent parameters for the binary MeOH/DMF, PrOH/DMF and PeOH/DMF solvent mixtures. The results were analyzed by means of two truncated reference equations: the Taft, Abboud, Kamlet, and Abraham[3] (equation 1), and the Gonçalves, Albuquerque and Simões[4] (equation 2). The non-specific solvent contributions as the microscopic dipolarity/polarizability (π*) parameter on equation 1 and the macroscopic polarizability (g(n)) parameter on equation 2 are the dominant factors that describe the solvent effects on the wave number of the absorption maximum spectrum of quinoline molecule.

$$E_{\mathrm{T}}(Q) = E_{\mathrm{T}}(Q)_0 + s\pi^{\bullet} + a\alpha \qquad [1]$$

$$E_T(Q) = E_T(Q)_0 + a_1 g(\mathrm{n}) + a_2 E_{\mathrm{T}}^{\mathrm{N}} \qquad [2]$$

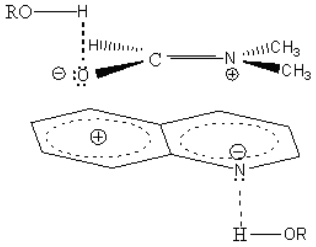


**Fig. 1. Interaction quinoline-solvent model.**

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*Acknowledgements*: This work was funded by FCT.

# *O*-(*tert*-Butyloxycarbonyl) hydroxyamino acids: synthesis and reactivity

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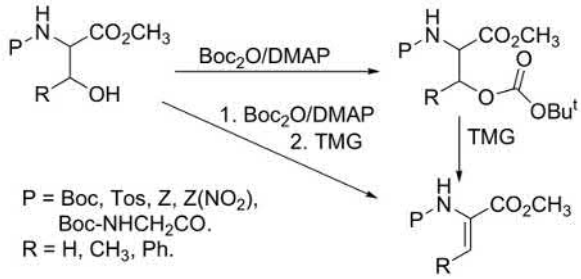
In our laboratories we have been interested in developing efficient methods for the synthesis of dehydroamino acid derivatives and in the study of their reactivity.[1] Herein, we report the high yielding synthesis of several *O-tert*-butylcarbonates by reacting β-hydroxyamino acid derivatives with 1.1 equivalentes of *tert*-butyldicarbonate in the presence of dimethylaminopyridine (DMAP). These compounds were reacted with trifluoroacetic acid giving the initial β-hydroxyamino acid derivatives. However, reaction with *N,N,N',N'*-tetramethylguanidine (TMG) gave dehydroamino acid derivatives in high yields (Scheme 1, Table 1). In the case of dehydroaminobutyric acid (ΔAbu) and dehydrophenylalanine (ΔPhe) only the Z-isomer was isolated.




**Scheme 1**

Table 1 - Yields obtained in the synthesis of O-(tert-butyloxycarbonyl) hydroxy -amino acid and dehydroamino acid derivatives.

| *ert*-Butyloxycarbonyl) xyamino acid derivative | Yield / % | Dehydroamino acid derivative | Yield / % |
|---|---|---|---|
| er(*O*-Boc)-OMe | 80 | Boc-ΔAla-OMe | 87 |
| *O*-Boc)-OMe | 86 | Z-ΔAla-OMe | 82 |
| )-Ser(*O*-Boc)-OMe | 83 | Z($NO_2$)-ΔAla-OMe | 85 |
| hr(*O*-Boc)-OMe | 87 | Boc-*Z*-ΔAbu-OMe | 98 |
| *O*-Boc)-OMe | 86 | Z-*Z*-ΔAbu-OMe | 84 |
| )-Thr(*O*-Boc)-OMe | 89 | Z($NO_2$)-*Z*-ΔAbu-OMe | 95 |
| ır(*O*-Boc)-OMe | 90 | Tos-*Z*-ΔAbu-OMe | 91 |
| he(*O*-Boc)-OMe | 82 | Boc-*Z*-ΔPhe-OMe | 88 |
| ly-Ser(*O*-Boc)-OMe | 67 | Boc-Gly-ΔAla-OMe | 65 |
| ly-Thr(*O*-Boc)-OMe | 79 | Boc-Gly-*Z*-ΔAbu-OMe | 92 |

Dipeptides with β-hydroxyamino acids reacted in the same way, except when a 4-toluenesulfonyl group is attached to glycine. In these cases the corresponding piperazines were isolated in good yields. The study of the reactivity of the *O-tert*-butylcarbonates towards several nucleophiles is also being carried out.

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*Acknowledgements*:This work was funded by FCT through project POCI/QUI/59407/2004

# A kinetic study of oxygen transfer from an oxygen donor to the complex Dichlorodioxomolybdenum(VI) bis(N,N-dimethylformamide), an effective epoxidation catalyst

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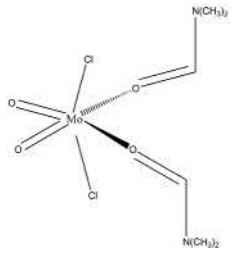
Molybdenum(VI) dioxo complexes are involved in many industrial catalytic processes including the epoxidation of olefins.

The dichlorodioxomolybdenum(VI) bis(N,N-dimethylformamide) complex has proved to be an efficient catalyst for the epoxidation of cyclooctene, limonene and norbornene.




Kinetic studies show that the formation of the catalyst precursor–oxygen donor complex is first-order in tert-butyl hydroperoxyde (TBHP) and in the metal complex, $[MoO_2Cl_2(DMF)_2]$. A specific rate of 3.2$mol^{-1}dm^3s^{-1}$ was found for catalyst formation at 25 ºC.

Activation parameters for this reaction have also been measured: ($\Delta H^{\neq}$ =58±8 kJ $mol^{-1}$, and $\Delta S^{\neq}$ =-80±30 J $mol^{-1}$ $K^{-1}$).

Although the kinetic results found for this complex are similar to the previously obtained for the $[MoO_2Cl_2\{p\text{-tolyl}(CH_3DAB)\}]$[1] and $[WO_2(C_2H_5)_2(4,4'\text{-di-}tert\text{-butyl-}2,2'\text{-bipyridine})]$[2] complexes, nevertheless the DMF complex shows a higher catalytic activity than the p-tolyl($CH_3$DAB) derivative. This finding leads us to conclude that the different catalytic activities observed for these complexes must be imputed to the oxygen transfer from the active species of the catalyst to the substrate.

***References***

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*Acknowledgements*: This work was funded by FCT-Portugal - POCTI/QUI/56109/2004.

# 2-Aryl-4-chloro-3-halogenoquinolines as Substrates for the Synthesis of 2,3-Disubstituted Primary 4-Aminoquinoline Derivatives

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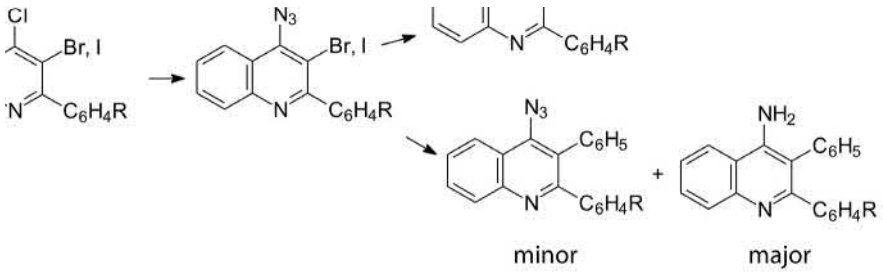
The 2-aryl-4-azido-3-bromo/iodoquinolines derived from 2-aryl-4-chloro-3-halogenoquinolines undergo Staudinger reaction with PPh3 in THF under reflux to afford the 2-aryl-3-iodo-4-(triphenyl phosphoranylideneamino)quinolines. The latter were, in turn, subjected to dilute acetic acid under reflux to afford the primary 4-amino-2-aryl-3-(bromo/iodo)quinolines as structural analogues of the medicinally important 4-aminoquinoline derivatives.




The observed results of Staudinger reaction coupled with the potential for the 3-iodo atom to facilitate metal-catalyzed carbon-carbon formation prompted us to develop a versatile direct one-pot method for the synthesis of primary 4-amino-2,3-diarylquinoline derivatives by means of palladium–catalyzed Suzuki-Miyaura reaction. From the reaction mixture we isolated by chromatography in sequence, two products characterized using combination of spectroscopic techniques as 2,3-diaryl-4-azidoquinoline (minor) and 4-amino-2,3-diarylquinoline (major).

# Reactivity of 4-Oxo-β-Lactams as Novel Inhibitors of Elastase

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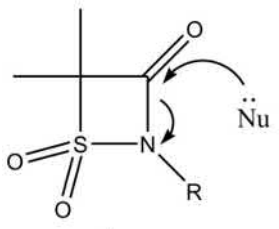
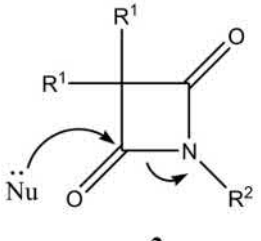
β-Lactams are serine protease inhibitors that acylate the serine residue of a wide range of enzymes, including elastase.[1] Recently, 3-oxo-β-sultams, **1**, were reported as potent inhibitors of elastase. [2] We now report that the isosteric analogues 4-oxo-β-lactams, **2**, are potent inhibitors of porcine pancreatic elastase PPE. Our goal was to evaluate the effect of different amide leaving groups by C-N fission on the kinetics of alkaline hydrolysis and enzyme inhibition. We found that 4-oxo-β-lactams, **2**, are time-dependent active site directed irreversible inhibitors of PPE, while presenting considerably less reactivity towards non specific nucleophiles such as hydroxide when compared to 3-oxo-β-sultams, **1**. The most reactive N-aryl-4-oxo-β-lactam derivatives, containing an electron-withdrawing substituent on the aromatic ring, are also the most active ones against PPE. This is another example that supports the use of $k_{OH}$ value for alkaline hydrolysis as a crude guide to determine the inhibitory potential of an enzyme acylating agent.[3] Comparasions of ρ values for enzyme inactivation and alkaline hydrolysis will be made and the implications of the results discussed.




**1**




**2**

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# Theoretical Study on the Hydration Structures Determining the Relative Acidities of Substituted Phenols

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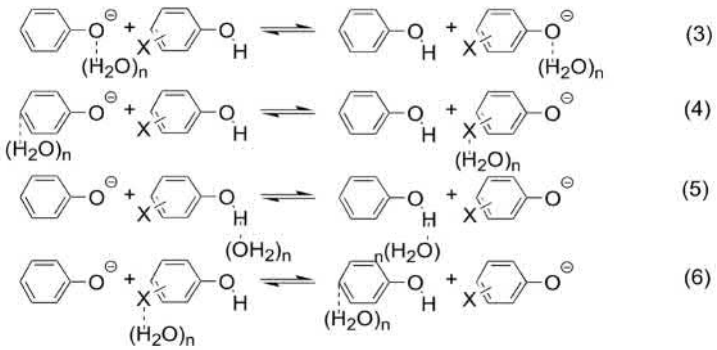
The Yukawa-Tsuno substituent effect analysis on the gas phase acidities of phenols gives the resonance demand r value of 0.6, which is significantly decreased from the r value of unity in corresponding aqueous phase. It is speculated that the specific solvation to para electron withdrawing groups stabilizing the anion by through resonance brings the changes of their substituent constants in this system.[1] Here we investigated theoretically to obtain the proof of the importance of specific hydration to the ring substituents in phenoxide ions.

Energies of all species were determined by ab initio calculation. Relative acidities of ring substituted phenols in gas phase were determined by the energy difference ($\Delta E_x(1)$, Eq. (2)) of proton transfer equilibria Eq. (1). X represents ring substituents.


(1)

$$\Delta E_x(1) = E_x(O^-) + E_H(OH) - E_x(OH) - E_H(O^-) \qquad (2)$$

Energies of phenoxides hydrated at the anion centers or at the ring substituents and phenols hydrated at the hydroxyl groups or ring substituents were also calculated. Energies ($\Delta E_x(3)$, $\Delta E_x(4)$, $\Delta E_x(5)$, $\Delta E_x(6)$) for proton transfer equilibria (3) - (6) were determined and compared with $\Delta E_x(1)$ in gas phase and experimental $\Delta G_v(aq)$ in water phase.



(3)

(4)

(5)

(6)

While the reactions (3), (5), and (6) showed the same substituent effect with (1), the reaction (4) showed a characteristic tendency. $\Delta Ex(4)$ of para electron withdrawing derivatives deviate upward from the correlation line for para electron releasing and meta derivatives and gives excellent linear correlation against $\Delta Gx(aq)$. We will discuss a new model to determine acidities for various compounds.

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# Application of LSERs to the Solution Enthalpies of Adamantane Derivatives in Protic and Aprotic Solvents at 298.15 K

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Recent studies have shown that adamantyl compounds and their derivatives evidence promising antibacterial and antiviral activity.[1] This fact *per se* justifies a growing interest in the physicochemical characterization of these compounds, particularly the knowledge of their behaviour in solution. One of the most used techniques to study molecular interactions in solution is solution calorimetry.

In a series of previous papers, we have reported solution enthalpies of

1-bromoadamantane in water-aprotic mixtures[2] and in hydroxylic solvents.[3] Also, the solution enthalpies at infinite dilution, $\Delta_S H^{\infty}$, at 298.15 K for three adamantane derivatives, namely

1-bromoadamantane (1-AdBr), 1-adamantanol (1-AdOH) and 2-adamantanone (2-AdO), in a set of aprotic solvents have been presented elsewhere. [4]

In this work, we integrate all the previously reported results and include a set of new solution enthalpies for the three referred adamantane derivatives in hydroxylic solvents.

The thermochemical data are analysed in terms of linear solvation energy relationships of the type $\Delta_S H_{\infty} = f$ (solvent descriptors). This scrutiny showed that the consideration of a "true" cavity contribution is crucial for the rationalization of the differences observed for the three solutes.

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# C–H Bond Dissociation Enthalpies in Indene and Indane

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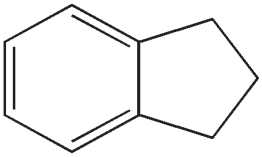
The gas-phase C-H bond dissociation enthalpies (BDEs) in indane 1 and indene 2 have been determined by time-resolved photoacoustic calorimetry (TR-PAC). The obtained results were 359±6 kJ mol$^{-1}$ and 360±6 kJ mol$^{-1}$, respectively. The measured C-H BDE for indane in this work is, to our knowledge, the first experimental determination of this quantity in this molecule. Our result for indene is in good agreement with a previous literature value[1] and *c.a.* 20 kJ mol$^{-1}$ higher than a more recent value calculated from the gas-phase electron affinity of indene.[2] However, the TR-PAC results are consistent with the similarity of the hydrogen atom abstraction rate constants for these two compounds.[3] These results will be discussed in light of the allyl and benzyl stabilization of the corresponding radicals.



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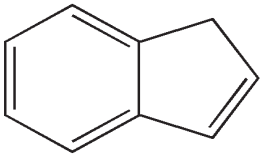

2

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# Investigation of a Metal Complexing Route to Form Arene Trans-dihydrodiols

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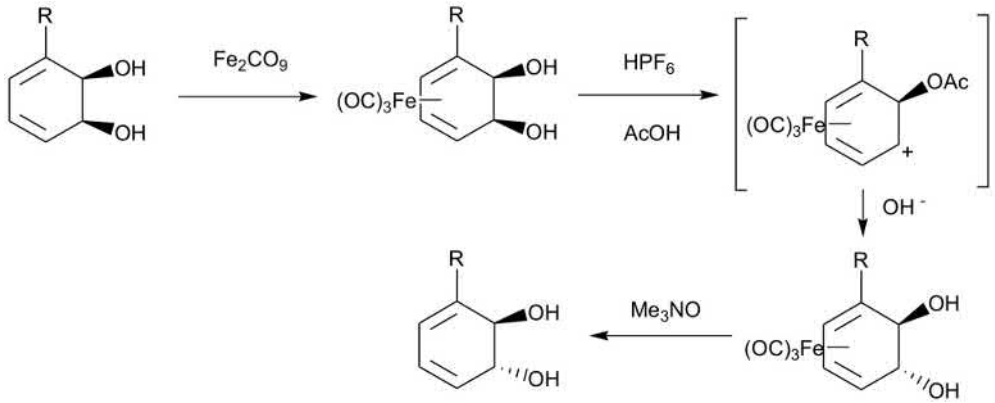
Arene oxides, arene hydrates and arene cis- and trans-dihydrodiols are oxidative metabolites formed by the action of mono and dioxygenase enzymes on aromatic and dihydroaromatic molecules. Arene cis-dihydrodiols can be produced in significant quantities from biotransformations using mutant and recombinant strains of bacteria.[1] They are important chiral precursors for the formation of enantiopure products of synthetic and industrial importance. Investigations are ongoing to develop efficient methods for conversion of *cis*-arene dihydrodiols to a variety of industrially important products, including phenols, catechols (1,2-diphenols) and arene *trans*-dihydrodiols.

Our work has concentrated on developing a viable route for conversion of arene *cis*-dihydrodiols to their *trans*-isomers. The trans-dihydrodiols are not yet obtainable by large scale fermentation and are potentially important chiral synthons. They can provide access to new structures of interest including inositols and conduritols. The synthetic route being examined involves the formation of iron tricarbonyl complexes as intermediates*2* and the transformations involved are summarised in the scheme below.




**Scheme 1**. Synthetic route for conversion of substituted arene *cis*-dihydrodiols to their *trans*-isomers.

Current work involves optimisation of each step in this synthetic sequence and an examination of the reactivity of the intermediates formed.

***References***

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# Ion pair formation process between an ionic dye and an anionic surfactant

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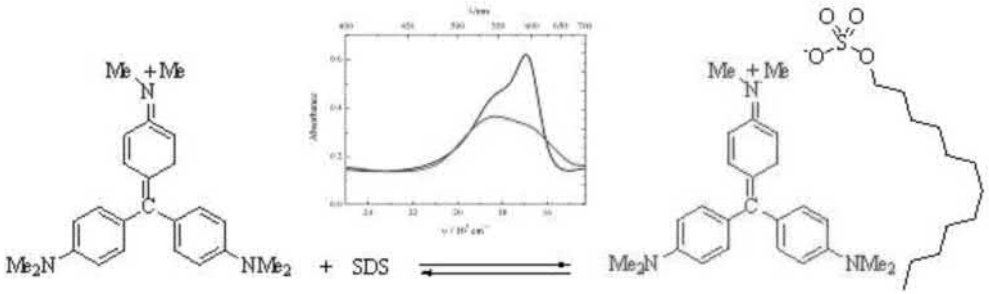
Dye-surfactant interactions are of great interest in dyeing and photographic industries, in biological and medicinal photosensitization and in analytical and environmental sciences. Freshly prepared aqueous solutions of oppositely charged surfactant and dyes exhibit a broad absorption spectrum, not similar to the known spectrum of the monomeric or dimeric forms of the dye. Information on interactions between dyes and ionic surfactants can add to our understanding of combined electrostatic-hydrophobic interactions.

The interaction between crystal violet (CV) and SDS has been kinetically and spectroscopically studied. Kinetic results are consistent with an ion pair formation process. In the absence of surfactant, the CV absorption spectrum is decomposed in two sub bands centred at 17953cm$^{-1}$ (λ=557nm) and 16807cm$^{-1}$ (λ=595nm). In the presence of SDS we observe the formation of two new sub bands centred at 18939cm$^{-1}$ (λ=528nm) and 16000cm$^{-1}$ (λ=625nm). The addition of surfactant results in an increase of the area of these sub bands until they reach a maximum value for [SDS]≈1x10$^{-3}$M and, afterwards diminish. At [SDS]≈8x10$^{-3}$M there are not significant changes related to SDS addition. This behaviour has been explained considering the formation of ionic pairs between dye and SDS monomers. At one SDS concentration, the premicellar aggregation results in a destruction of SDS-$CV^+$ ionic pairs. Later, an increase of SDS concentration yields the micelle formation and the dye incorporation on the micellar surface.



# Supramolecular tuning of reversible Diels-Alder reaction

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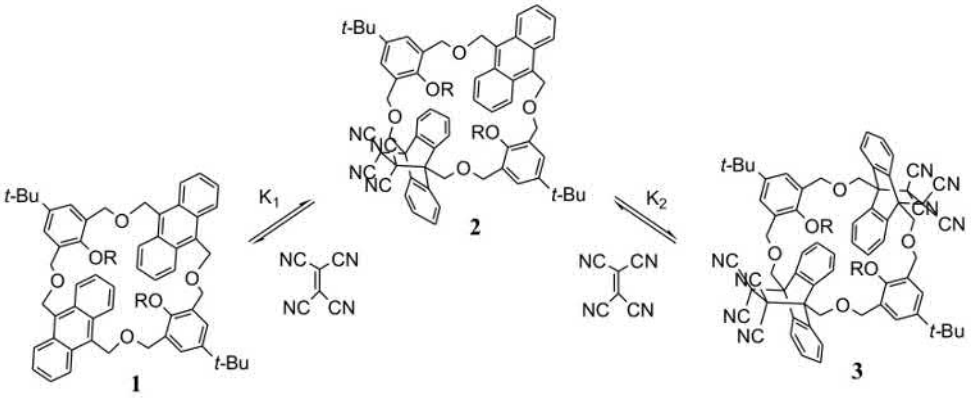
DCC (Dynamic Combinatorial Chemistry) relies on target-driven selection of an optimal species from a dynamic library whose covalent units are products of reactions under thermodynamic control1. Recently efforts have been made to use Diels-Alder reactions in DCC,2 but in this field an effective supramolecular control has not been reported yet. In order to achieve such a control Diels-Alder reactions should be easily reversible at room or moderate temperature, moreover the involved ligands should be capable of strong host-guest interactions.

We developed a new class of photoactive cyclophanes, containing two opposite anthracene moieties, by exploiting the template effect of tetramethylammonium ion in the cyclization step. The strong binding ability of these receptors towards tetraalkylammonium and alkylviologen cations has been investigated in $CDCl_3/CD_3CN$ mixtures through $^1H$ NMR and UV-visible techniques and in the solid state through single crystal X-ray diffraction.

The two anthracene units behave as strong dienes in the presence of tetracyanoethylene (TCNE), the monoadduct **2** and the diadduct **3** formation being observed in even dilute solution, in a few minutes at room temperature. Distribution of all the involved species on increasing TCNE concentration has been monitored through $^1H$ NMR spectroscopy in order to calculate $K_1$ and $K_2$, with the above distribution being markedly altered in the presence of methylviologen salts, that can only strongly bind ligand **1**. In the present system the modulation of the Diels-Alder reaction course appears to be easily carried out by changing the structure of both the anthracene receptor and of the guest cation, and developments are planned in the field of molecular devices.

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# Hydride Affinities of Some Unsaturated Small Organic Molecules – Triadic Analysis

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Hydride affinities of ethene[1], ethyne[2], methanal and their derivatives are studied at the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) level of theory. Effects of substituents comprising groups greatly varying in their electron donor/acceptor properties were investigated. Comparison with the experimental hydride affinities reveals that the agreement with calculated values is very good, with regression coefficient $R^2 = 0.99$ and average absolute deviation AAD = 1.36 kcal $mol^{-1}$. Therefore, at this level of theory the calculated values could reliably replace the missing experimental data, especially for molecules not easily amenable to laboratory measurements. The sites energetically most susceptible to hydride ion attack are identified, and hydride affinities for alternative positions calculated.

Triadic analysis3 proved as very useful tool in interpreting $H^-$ affinities, and in rationalization of their trend of changes. It turns out that derivatives with high electron accepting groups involving CN, $NO_2$ and $CF_3$ fragments possess positive electron affinities. It is shown that hydride affinities are rather well correlated with the adiabatic electron affinities. Hence it appears that the initial state effect mirrored by Koopmans' term is decisive in determining the hydride affinity of the investigated molecules. The highest values of the $H^-$ affinity are obtained for molecules which are double substituted with $NO_2$ and CN groups.

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# Sensitivity of Reaction Rates of Acidolysis of *N*-acyl-*N*,α,α-trialkyl-glycine amides to the electronic contributions of substituents

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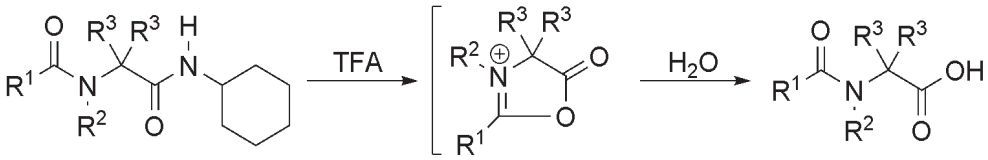
*N-Acyl-N*,α,α-trialkyl glycine amides as synthesised by a Ugi-Passerini reaction can be converted into the corresponding *N-acyl*-α,α-dialkyl glycine acids, which are useful for the synthesis of peptides containing these conformationally restricted moieties. This implies cleavage of the C-terminal amide bond and also that of the *N*-alkyl substituent, which are currently achieved by acidolysis [1,2]. The feasibility of these cleavages and the facility with which they can be carried out is a major requirement for the success of this strategy for peptide synthesis.




Thus, we have been concerned with the study of the effect of the various substrate substituents $R^1$ through $R^3$ in the rate of cleavage of cyclohexyl amides, by varying $R^1$ [3] and $R^3$ [3,4] when $R^2$ was the 4-methoxybenzyl group. A temperature investigation was also carried out with N-acetyl compounds having different substituents at $R^3$ [5].

Our work has been concluded with the investigation of the effect of the structure of the N-alkyl group on the behaviour of *N*-benzylacetyl-α,α-dimethyl and *N*-benzyl-acetyl-α,α-dibenzyl glycine cyclohexylamides [6]. Thus, various electron attracting and electron releasing substituents in 4-substituted benzyl and phenyl groups have been tested in connection with both the feasibility of their cleavage from the reaction products and their effect on the rate of amide acidolysis. In this communication, we present our later results with regard to structure/reactivity effects. We analysed the kinetic results at the light of a Hammett treatment. The uniparametric correlation $\log k = \log k_o + \rho\sigma$ was applied to all acidolyses. We also quantified field/inductive and resonance contributions in those cases where the number of results available allowed the most meaningful statistical analysis $\log k = a_0 + a_1 \sigma_R + a_2 \sigma_I$ (where $\sigma_R$ and $\sigma_I$ are the resonance constant and the field/inductive constant, respectively).

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# Controlling Fluorescent Signal In self-assembling α,γ-Cyclic Peptides

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One of the most fundamental and pressing problems in the field of supramolecular chemistry is the control of self-assembly processes through the design of the molecular components[1] and the practical application at the macromolecular level of such supramolecular associations.*2* In the last few years we have been working with α,γ cyclic peptides (α,γ- CPs) and dimmers as supramolecular models*3* of self-assembled peptide nanotubes. Our interest for these type of structures arises for their multiple applications in medicine, materials, biology.[4] Peptide nanonotubes are formed by stacking of two or more CPs by means of hidrogen bonding between their constituent CPs.

Herein, we have designed and synthetized a novel fluorescent modified α,γ cyclic peptide that allowed us to get information about association constant5of our model system

(Ka > $10^7 M^{-1}$), furthermore to control cross-strand side-chain-side-chain interactions in the assembly process and also to control the structures of the supramolecular entities.

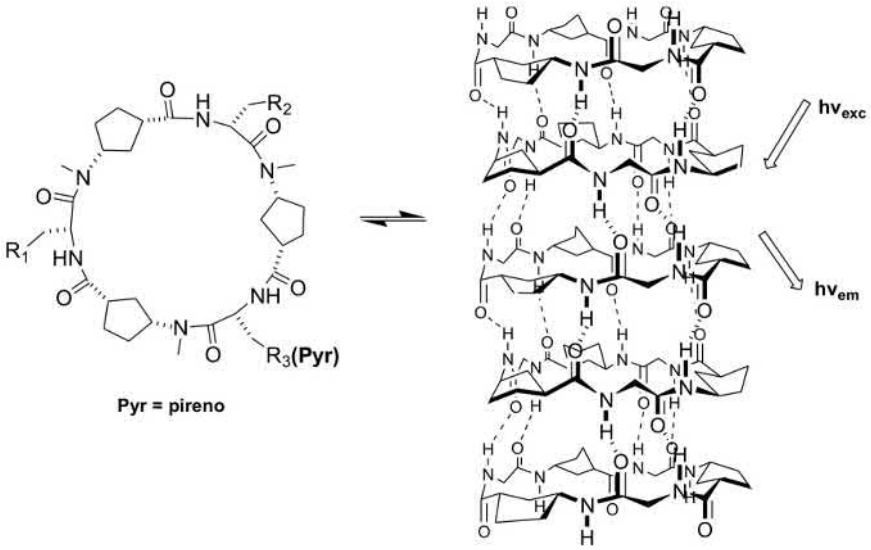


**Fig. 1**. Self-assembled α,γ peptide nanotube formation.

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# Nitrosative Deamination of Purine and Pyrimidine Bases: Implications in DNA Mutagenesis

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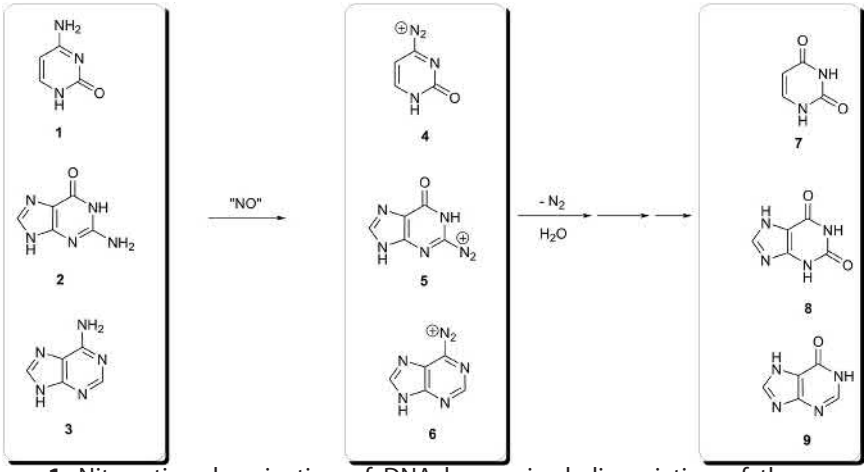
Nitrosative deamination of DNA bases [1], involving either direct reaction with nitroso species [2] or nitroso group transfer from N-nitrosamides [3a] and N-nitrosamines [2d,e], can lead to mutagenesis through misincorporation by DNA polymerase, misrepair, or no repair of the resulting deamination products, which may result in the formation of abasic sites [2b]. The diazonium ions thus formed in bases with an aminic nitrogen (**4-6**) may undergo nucleophilic substitution by water[2d-3] leading to transformation of cytosine (**1**), guanine (**2**) and adenine (**3**) in uracil (**7**), xanthine (**8**) and hypoxanthine (**9**), respectively, (**Scheme 1**).




**Scheme 1**. Nitrosative deamination of DNA bases via dediazoniation of the corresponding diazonium ions.

From the kinetic studies of nitroso group transfer from our model compounds (N-Nitrosobezenessulfonamides) to the above DNA bases, we hope to obtain results that will provide a deeper understanding of the reaction mechanism. Although UV/Vis is broadly used to monitor reaction progress, mainly due to spectral similarities of the involved species, HPLC with diode array detection proved to be a more reliable quantitative methodology. Kinetic results obtained by this method shall be presented.

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# Creation of hydrogen bonded 1D networks by co-crystalization of dithiooxamide with nitrogen heterocycles.

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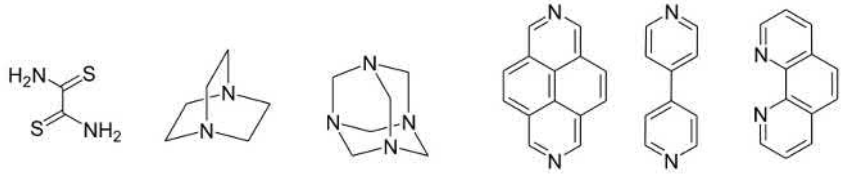
The design and preparation of ordered solid-state structures by means of specific intermolecular interactions is an area of crystal engineering.[1] Particularly hydrogen bonds due to their strength and directionality play a decisive role in controlling the self-assembly of many molecular crystals. They can result in the formation of one-dimensional arrays (tapes or chains), two-dimensional sheets or various three-dimensional networks.[2]

Dithiooxamide (**dtox**), due to acidity of the amide protons is a hydrogen bond donor much better than its oxo analogue and therefore it seems to be an useful candidate for the construction of ordered supramolecular architectures. Since **dtox** contains two equivalent strong proton NH donors, it has potential for formation of 1D polymeric hydrogen bonded chain structures with compounds bearing two hydrogen bond acceptor sites.

Here, we present examples of the crystal structures of supramolecular arrays created by the complexation of **dtox** with several nitrogen heterocycles **1-5**.




The crystal structures of the complexes revealed that **dtox** forms polymeric tapes with the compounds **1-4**, whereas with **5** it creates discrete trimeric associate.

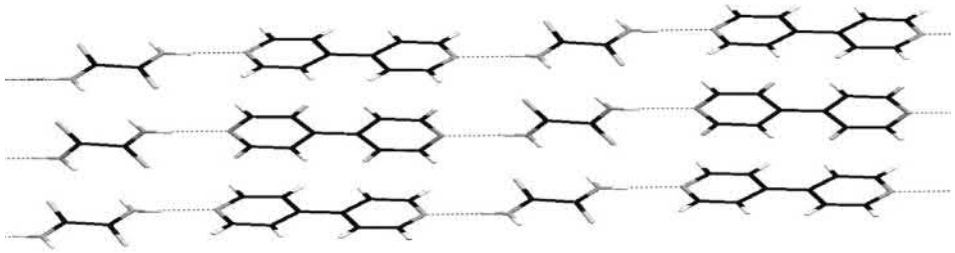


**Fig. 1**. Crystal structure of **dtox • 4**

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# Kinetic study of the oxidation of propionaldehyde by peroxynitrite

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The atmosphere is a complex medium where numerous chemical products are released. In the recent past, tropospheric chemistry of volatile organic compounds (VOCs) was studied only in gaseous phase although the condensate matter is present in the atmosphere. And the multiphase phenomena have been neglected. Recently the studies of atmospheric chemistry pass through of the study the chemistry of water soluble organic compounds (WSOC)[1]. In this way the topic of this work is the study of the oxidation of propionaldehyde, secondary atmospheric pollulant with peroxynitrite, responsible of several oxidation processes in the droplets of clouds or fogg[2].

Peroxynitrite ion is very stable but decomposes in acidic media by homolysing along the O-O bond[3] yielding OH and $NO_2$ free radicals or isomerizing to nitric acid. In basic media the peroxynitrite can form an adduct with $CO_2$ that homolyzes to $NO_2$ and $CO_3$- radicals. This adduct is formed with one of the two C=O bonds of carbon dioxide.

The kinetics of the oxidation of propionaldehyde by peroxynitrite at pH = 4.0 (acetic acid/acetate buffer) has been studied using a spectrophotometric technique. All the kinetic runs were carried out using a SX-18MV Sequential Stopped-Flow apparatus (Applied Photphisics), where peroxynitrite concentrations were evaluated measuring the absorbance at 302 nm. The reaction is first order with respect to peroxynitrite concentration, while present a complex order with respect to aldehyde concentration. A molecular organization has been observed when the aldehyde concentration reach the value of: $3.0 \times 10^{-4}$ M in the kinetic run.

This fact have been also observed by changes in the solution conductivity and UV-Vis spectrum variation. The species responsible of this effect have been identified by NMR and MS.

The reaction mechanism could involve the formation of one adduct between peroxynitrite and the aldehyde.

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# A Computational and Experimental Study on Specific Solvent Effects on Some Common Organic Reactions in RTILs

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The solvent effects on chemical reactivity can be environmental (not specific) or related to a well-defined chemical interaction between the reaction actors and the solvent molecules. Typical examples of such interactions are hydrogen bond, coordination bond, acid-base effects, charge transfer, etc. The phenomenology of these interactions is well known in standard solvents but not in RTILs. In this work we study some common organic reactions and the specific effects of RTILs on the reaction development. From the computational point ab-initio calculations and molecular dynamics on small molecular clusters including also some solvent ions are used. The results of these calculations are compared to experimental evidences and measurements.

# Synthesis of $N^{\gamma}$-alkyl Derivatives of Glutamine – Potential Inhibitors of Glucosamine-6-phosphate Synthase

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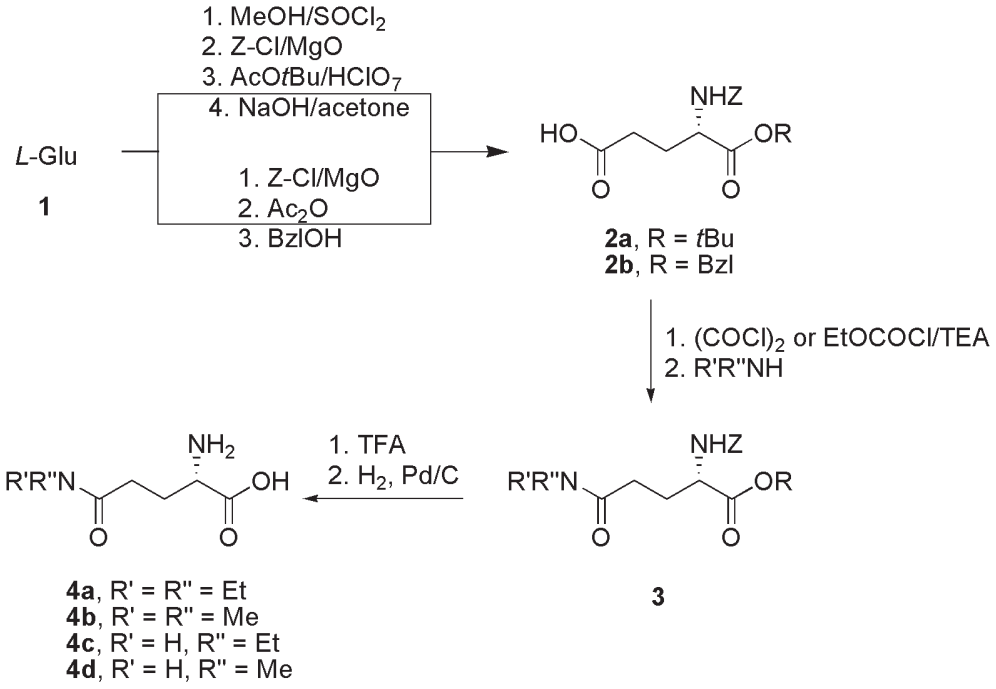
A number of glutamine analogues inhibit glucosamine-6-phosphate synthase activity. Structures of some of them and data characterising their inhibitory potency have already been described.1 Here we report results of our studies on $N^{\gamma}$-alkyl derivatives of glutamine **4a–d** in which one or two hydrogen atoms from amide group of glutamine have been replaced with alkyl (ethyl or methyl). The multiple-way synthesis of this derivatives has started from L-glutamic acid (**1**).




In the recent biochemical studies we have revealed that *L*-glutamic acid γ-monohydroxamate (**4e**, R′=H, R″=OH) and *L*-glutamic acid γ-hydrazide (**4f**, R′ = H, R″ = $NH_2$) exhibit inhibitory activity towards the enzyme, glucosamine-6-phosphate synthase. It has also been observed they can be used as alternate substrates of this enzyme.

In the present communication we report our current results concerning the enzyme inhibitory and substrate properties of $N^{\gamma}$-alkyl derivatives of glutamine.

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# Modelling the Active Site of Peroxidases

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Heme-containing proteins are ubiquitous, this group occurring at the active site of many enzymes. Peroxidases reduce hydrogen peroxide to water and oxidize a wide range of substrates. Their active sites share ferriprotoporphyrin IX and imidazole of a proximal histidine (His336 for myeloperoxidase -MPO-) having the role of the fifth ligand of Fe atom.[1] An oxygen atom acts as the sixth ligand in compounds I and II, while this position seems to be vacant in native Fe(III)-enzymes. Crystallographic studies of several ferric peroxidases show a water molecule in the close vicinity of Fe, which could actually function as ligand. Furthermore, remarkable pH influence on different processes (halide binding, red-ox reactions, etc.) has been observed, allowing the determination of the $pK_a$'s of these intermediates, values varying up to four units.[1] A histidine residue (His95 for MPO) located in the distal cavity, not directly bound to heme but in its environs, able to interact with it and substrates, has been considered responsible for this acidity.[1]

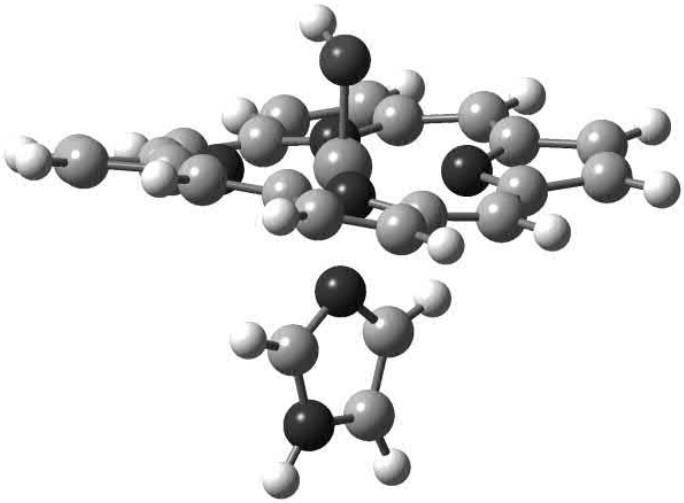

**Figure**. Optimized structure for compound I protonated on the oxo-ferryl center.

The active site was modelled by using porphine and imidazole surrounding Fe atom (see Fig.). Electronic structure calculations have been carried out to examine the effect of protonation or a hydrogen-bonded water molecule, on native enzyme and compounds I and II at different spin states. Thermodynamics and geometries of those species are discussed, results supporting an alternative protonation site to that usually accepted.

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# Carbon-halogen heterolysis in tertiary alkyl halides: a kinetic and theoretical study

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Tertiary alkyl halides undergo solvolysis reactions involving carbon-halogen heterolyses. Their reaction rates (*k*) depend on three main factors: the solvent, the nature of the halide, and the type of carbonated skeleton. This last factor can be divided in two aspects: the carbonated skeleton's ability to stabilize the resulting positive charge and the structural effects arising from its change from a tetrahedral to a trigonal arrangement.

In this work, the solvent effects for three tertiary alkyl halides (3-bromo-3-methylpentane, bromo-methylcyclopentane, and bromo-methylcyclohexane) were investigated using a multiparametric regression approach, the so-called TAKA equation.[1,2] This equation quantifies the solvent effect in terms of its dipolarity/polarizability, hydrogen bond donor and acceptor abilities and its cohesive energy density. Additionally, it also gives a measure of the expected *k* value in an inert solvent or in the gas phase, through its independent term, log $k_0$. The application of the TAKA equation for the three studied substrates showed that the coefficients of the solvent descriptors are very similar, even though their log $k_0$ values differ substantially.

The fact that log $k_0$ refers to an inert solvent or the gas phase makes these reactions particularly suited to be studied by computational chemistry. Density-Functional-Theory (DFT) calculations using the B3LYP hybrid functional[3,4] and Dunning's cc-pVTZ basis set[5] were performed for both heterolysis and isodesmic reactions. The thermodynamic data gathered from these calculations were then used to rationalize the differences in log $k_0$ values for the three substrates.

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# Structure-Reactivity Effects on Kinetic Isotope Effects for Protonation of Ring-Substituted α-Methoxystyrenes.

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We report a simple method for the determination of primary deuterium isotope effects on proton transfer from hydroxylic solvents such as water to carbon, and the application of this method to determine the primary deuterium isotope effect on protonation of vinyl ethers over a broad range of thermodynamic driving force and temperature. Our results provide strong evidence that hydron transfer proceeds by a semiclassical mechanism and passes over the reaction barrier as opposed to tunneling through the barrier. We will also discuss the relationship between the change in the kinetic isotope effects and the change in the transition state structure as measured by the Brønsted coefficients for proton transfer.

# On the Importance of Leaving Group Ability in Reaction of Ammonium, Oxonium, Phosphonium, and Sulfonium Ylides

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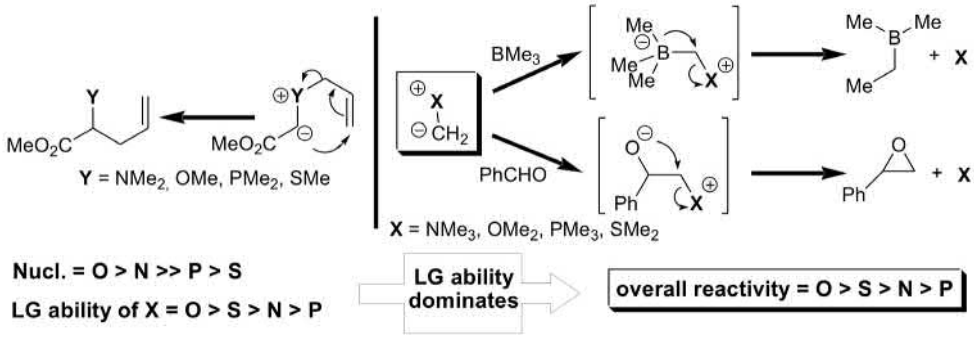
Sulfonium, phosphonium and ammonium ylides undergo various type of reactions in which the reactivity and selectivity of the ylides depend quite strongly on the nature of the central heteroatom. The nucleophilicity of the ylides is one important aspect of their reactivity, and is affected by the degree to which the onium group stabilizes the adjacent negative charge. It has been shown that stabilization increases, and nucleophilicity decreases, in the order O < N << P < S. However, this feature alone does not explain all the observed reactivity. Investigation of their reactions with organoboranes and aldehydes or their [2,3]-σ-rearrangements shows that reactivity of sulfonium, ammonium, phosphonium and oxonium ylides is to a large part determined by the leaving group ability of the corresponding onium group, and this decreases for both intrinsic and thermochemical reasons in the order O > S > N > P. The results are consistent with experimental observations and bring together a general understanding of the factors involved in the different chemical processes.

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# Computing the $^1$H NMR Spectrum of Bulk Ionic Liquids based on Imidazolium Cations from Snapshots of Classical and Car-Parrinello Molecular Dynamics Simulations

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We have investigated the performance of several computational protocols in predicting the NMR spectrum of a molecular ion in a complex liquid phase such as an ionic liquid. Thus, we have computed the proton NMR chemical shifts of the 1-butyl-3-methylimidazolium cation (bmim) in [bmim][$BF_4$] and [bmim][$MeSO_4$][1] and of the 1-ethyl-3-methylimidazolium cation (emim) in [emim][Cl].[2] Environmental effects on the imidazolium ring proton chemical shifts are quite significant and must be taken into account explicitly. Calculations performed on the isolated imidazolium cations as well as on the [emim][Cl], [bmim][$BF_4$] and [bmim][$MeSO_4$] ion pairs grossly fail to reproduce the correct spacing between proton signals. In contrast, calculations performed on clusters extracted from the trajectory of classical molecular dynamics simulation[3] are in much better agreement with the experimental values. For the smaller system [emim][Cl] we also ran a Car-Parrinello molecular dynamics simulation. We have found that subtle details of the liquid phase structure have important consequences on the NMR chemical shifts of the imidazolium ring protons.

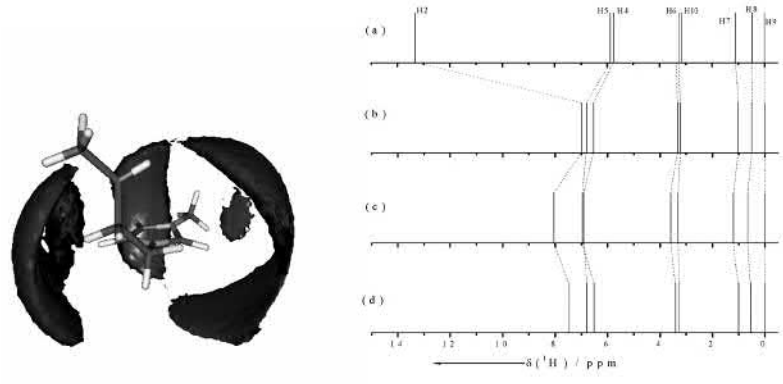


**Fig. 1**. Left: Spatial distribution function of [BF4] anion around the [bmim] cation obtained from classical MD. Right: (a) calculated spectrum of [bmim][BF4] ion pair in vacuo; (b) and (d) calculated spectra of [bmim][BF4] liquid phase with different solvent models; (c) experimental spectrum.

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# Kinetics and Mechanism of the Aminolysis of *S*-Phenyl 4-Nitrophenyl Thiocarbonate in Aqueous Ethanol.

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The aminolysis reactions of O-ethyl S-aryl thiocarbonates are well documented.[1-4] Some of them have been found to be concerted, e.g. the reactions of *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) ethyl thiocarbonates (EDNPTC and ETNPTC, respectively) with secondary alicyclic (SA) amines[1] and quinuclidines[2] and of ETNPTC with anilines.[3] Others have been found to be stepwise, as those of *O*-ethyl *S*-(4-nitrophenyl) thiocarbonate (ENPTC) with pyridines[1], SA amines[2] and quinuclidines[2], those of EDNPTC with pyridines[1] and anilines,[3] those of ETNPTC with pyridines[1] and the reactions of *O*-ethyl *S*-(4-X-phenyl) thiocarbonates (X= $OCH_3$, $CH_3$, H, Cl) with SA amines.[4] In all these reactions the substituted benzenethiolate ion is the leaving group.

On the other hand, the mechanisms of the aminolyses of *O*-aryl *S*-aryl thiocarbonates, where both groups bound to the carbonyl can be the leaving group, have received little attention.

In this work, the reactions of *S*-phenyl *O*-4-nitrophenyl thiocarbonate with a series of SA amines are subjected to a kinetic investigation in 44 wt% ethanol-water, at 25.0º C and an ionic strength of 0.2 M.

The reactions were followed spectrophotometrically. Under amine excess, pseudo-first-order rate coefficients ($k_{obsd}$) were found. For all these reactions, plots of $k_{obsd}$ vs. free amine concentration at constant pH were linear, the slope ($k_N$) being independent of pH.

The Brönsted-type plot (log $k_N$ vs. p$K_a$ of the conjugate acids of the amines) was linear with slope $\beta = 0.85$, consistent with a stepwise mechanism through a tetrahedral intermediate with the breaking of the intermediate as the rate determining step.

A HPLC study shows that 4-nitrophenoxide ion is the leaving group and benzenethiolate ion is the non-leaving group. The reason for this is discussed.

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# Intramolecular Hydride Transfer of Acyloin Anion: Analysis of Solvation Structure Dynamics

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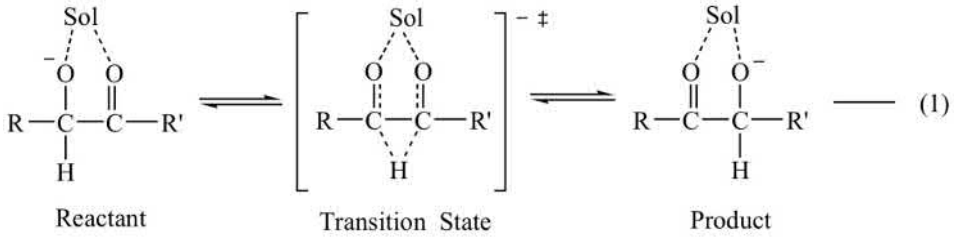
A chemical reaction in solution takes place with concomitant solvation-desolvation events. For the electron transfer reaction, it is known that the electron transfer itself and solvent reorganaization occur in different timescale. In order to understand the mode of solvation and its effect on chemical reactivity, we took a hydride transfer reaction of acyloin anion, and calculated the reaction pathway with quantum mechanical methods.

The local minimum and TS were found for the reactions with different substituents:




(1) R = H, R′ = H, Me, $CH_2F$, $CHF_2$, $CF_3$, $NH_2$, OMe, CN; (2) R = Ph, R′ = $C_6H_4X$ (X = *p*-$NH_2$, *p*-OMe, *p*-OH, p-Me, H, m-Cl, *p*-CHO, p-CN, p-$NO_2$). Then IRC and molecular dynamics (MD) calculations were carried out from the calculated TSs. The Gaussian 98 and Gaussian 03 suites of program were used. HF/6-31+G* and B3LYP/6-31+G* were used as the basis function.

The TS structures (R = R′ = Me) solvated by nH2O (n = 1 ~ 7) were explored. The structure of n = 5 were shown in Fig. 1. The IRC calculation gave that the hydride transfer and solvation—desolvation event occur in a concerted manner, while the MD calculation showed that they react unconcertedly.

In the presentation, the results of MD calculations will be reported in detail.

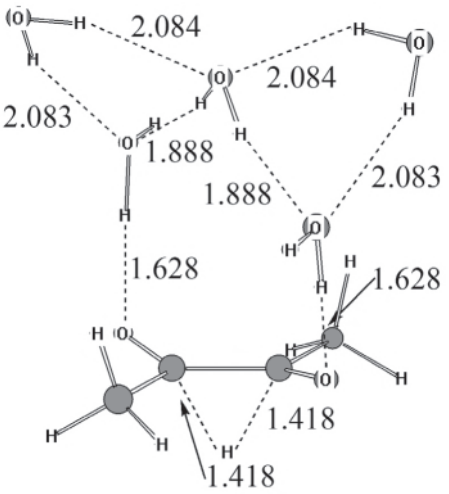



Fig. 1. Cluster structure of R = R′ = Me, n =5 (in Å)

# Nucleophilicity of metal carbonyl anions towards vinyl halides: an unusually broad nucleophilicity scale.

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Metal carbonyl anions ($[M(CO)^nL]^-$) are characterized by a very broad nucleophilicity span, which in aliphatic $S_N2$ reactions[1] increases by eight orders of magnitude from $[Co(CO)_4]^-$ to "supernucleophilic" $[CpFe(CO)^2]^-$. In our studies of nucleophilic vinylic substitution reactions[2] we became more and more aware that the differences in reactivity between metal carbonyl anions are even more pronounced. A careful examination and comparison of nucleophilicity data showed that $[M(CO)^nL]^-$ reactivity increases by 14 orders of magnitued from $[CpMo(CO)_3]K$ to $[CpFe(CO)_2]K$ (Fig. 1). Surprisingly, the reactivity of [M(CO)nL]- in a halogen-metal exchange process (with Z-PhC(CN)=CHI) follows a similar "broad" scale as in addition-elimination ($Ad_NE$) substitution process. A steep dependance of $[M(CO)_nL]^-$ reactivity on their one-electron oxidation potentials ($E_{ox}$) suggests that inner-sphere SET may be a possible mechanistic interpretation.

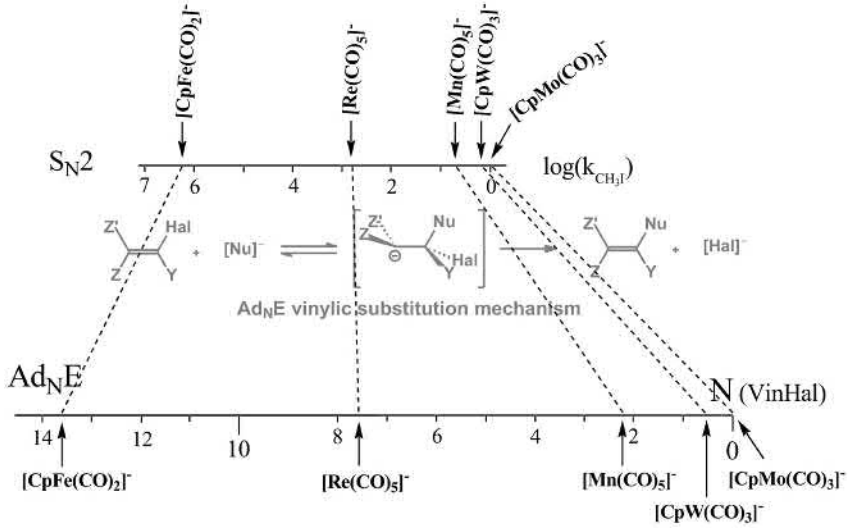


Fig. 1. Comparison of $[M(CO)nL]^-$ nucleophilicity in $S_N2$ and vinylic AdNE reactions.

***References***

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# Direct Observation of Intermediate Carbocations in Solvolysis Reactions

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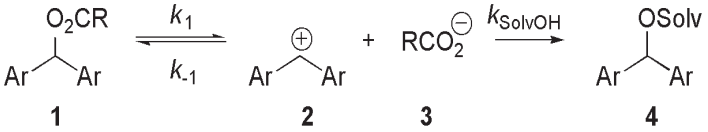
In typical solvolysis reactions (Scheme 1) carbocations are formed as short-lived intermediates, which undergo rapid consecutive reactions with the solvent.




**Scheme 1**. Simplified solvolysis scheme of benzhydryl carboxylates **1**.

In recent work,[1] we have observed the change from the typical $S_N1$ mechanism ($k_1 < k_{SolvOH}$) to the so-called $S_N2C^+$ mechanism ($k_1 > k_{SolvOH}$),[2] where ionization is faster than the consecutive reactions with the solvent.

We will now report on the direct UV-Vis spectroscopic observation of the appearance and disappearance of benzhydrylium ions during the solvolyses of benzhydryl carboxylates **1** in aqueous acetone and acetonitrile.

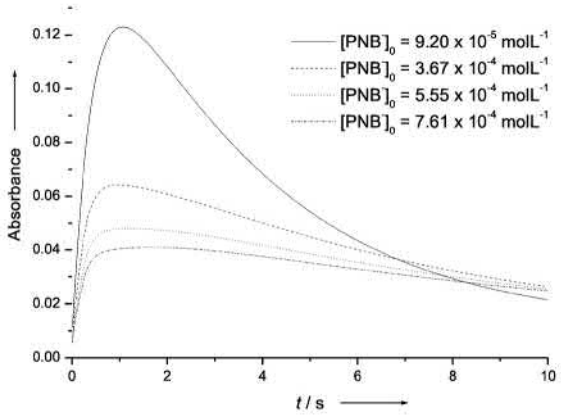



**Fig. 1.** Absorbance at λ = 613 nm during the solvolysis (25°C) of bis(*p*-morpholinophenyl)me thylium *p*-nitrobenzoate (1.02 x $10^{-3}$ molL$^{-1}$) in 20% aqueous acetone in the presence of different amounts of tetrabutylammonium p-nitrobenzoate ($PNB^-$).

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# A physical model for the energetics of protein conformational changes

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Proteins can act like molecular machines converting chemical energy (released by the hydrolysis of ATP) into work. The energetics of these processes is associated with two main questions: (i) In what form is the energy released by the hydrolysis of ATP stored in the protein and, furthermore, how does the system prevent its loss to the environment as heat or radiation? (ii) What is the mechanism for the conversion of that energy into conformational changes and useful work? It has been suggested1 that Vibrational Excited States (VES) can efficiently keep the energy in the protein. The VES hypothesis provides a possible answer to the first question. Moreover, the energy of vibrational excited states can be resonantly transferred from one site in the protein (for instance, the one where ATP hydrolysis occurs) to the site where it is needed for work. Davydov suggested in the 1970's that the actual vibrational mode excited during ATP hydrolysis is a mode of the peptide group known as Amide I2. The development of this idea lead to the conclusion that Amide I excitations can be transferred from site to site in the protein, even at biological temperatures, in tens of picoseconds3. Experimental results indicate that the energy of Amide I excitations does indeed remain in real proteins and model systems for tens of picoseconds4-7. However, the energy is not kept in its initial form. It is transferred to different vibrational modes. The so called Davydov - Scott model provides a description of the storage and transport of energy in the protein but it lacks a mechanism for the observed transfer. In fact, the conservation of the number of Amide I excitations (a consequence of the model) prevents the release of their energy to other forms. A complete theory of the energetics of proteins requires a non number conserving generalization of the model. A non conserving mechanism underlying such a generalization constitutes an answer to the second question.

In this work we explore a non – conserving model in which: (i) the energy is stored and travels along the protein in the form of Amide I excitations, in a Davydov – like manner; (ii) the energy of the excitations is site selectively released and promotes the disruption of structural constraints (such as the hydrogen bonds that stabilize the secondary structures of proteins); the site selection is related to the primary structure of the protein.

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# Reactivity of 2-Dialkylamino Thioisomünchnones Towards Azodipolarophiles: a Theoretical Approach of a Versatile Process

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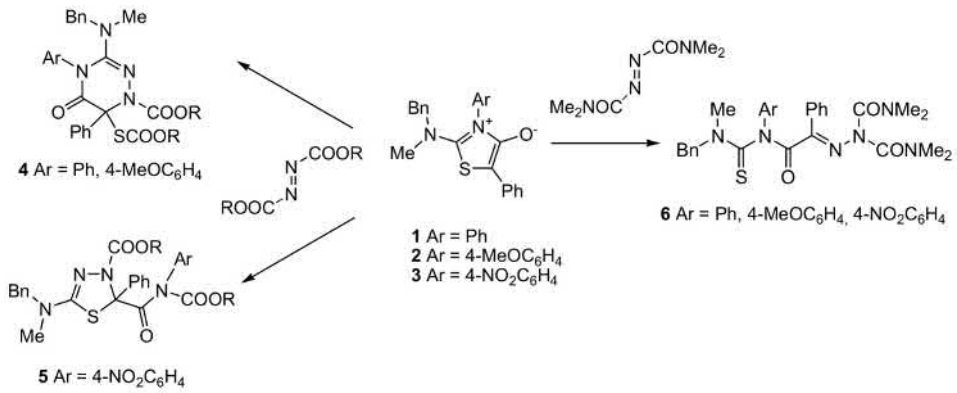
It has been demonstrated the enormous versatility of mesoionic heterocycles as masked dipoles in dipolar cycloaddition reactions. Special attention deserve the anhydro-4-hydroxy-1,3-thiazolium hydroxides, (thioisomünchnones), which are precursors to highly functionalized and often chiral three-, four-, five-, and six-membered rings, by an appropriate choice of reactants and reaction conditions.[1]

In some recent research our group have shown that thioisomünchnones bearing an *N*-benzyl-*N*-methylamino group at C-2 exhibit a particular reactivity. The presence of such dialkylamino substituent constitutes a key stereoelectronic control factor that dictates the subsequent fragmentation pathway of cycloadducts.[2]

According to our experimental results, [3+2] cycloaddition of *N,N*-dialkylamino-substituted thioisomünchnones with azodipolarophiles gives rise to three different types of final products, such as 1,2,4-triazine derivatives **4**, 1,3,4-thiadiazol systems **5**, and acyclic hydrazonoacylthioureas **6** (Scheme 1).[3]

The electronic nature of the group at *N*-3 in the mesoionic moiety along with the azodipolarophile used seem to drive the selective pathway of this process. We have performed a DFT-based theoretical study [B3lyp/6-31G(d)] in order to justify the proposed ring opening-rearrangement mechanism that leads to the final products (**4**-**6**). Results will be described in this communication.




**Scheme. 1.**

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# Determination of Ionization Rates in Solvents of Low Ionizing Power

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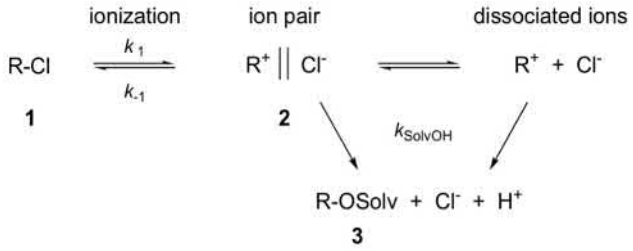
The determination of ionization rates of alkyl halides appears to be difficult in solvents of low ionizing power (i.e. water acetone mixtures) because of the high degree of recombination of the ionic intermediates **2** (Scheme 1).[1]




**Scheme 1**. Simplified solvolysis scheme of alkyl chlorides **1**.

We now report on the kinetics of solvolyses of highly reactive benzhydryl chlorides, which are followed by stopped-flow conductivity measurements. It is found that ion recombination can be suppressed in the presence of amines, while the $S_N2$ mechanism is not yet turned on.

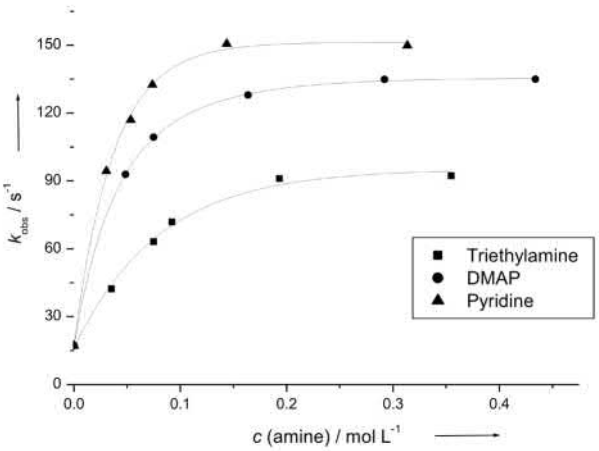



**Fig. 1**. Observed rate constants of the solvolysis of 4,4´-dimethoxybenzhydryl chloride in 80 % aqueous acetone in the presence of variable concentrations of amines.

***References***

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*Acknowledgements*: This work was funded by the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie.

# Computational study of triguanide cyclization

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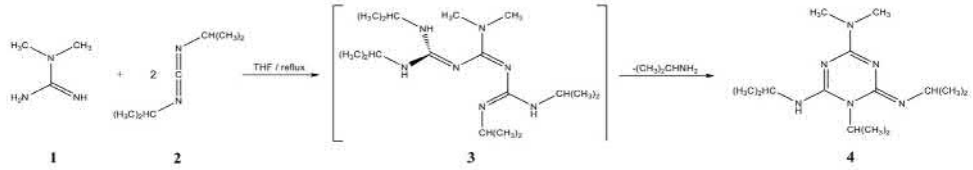
Recently, we prepared series of novel pentasubstituted triguanide derivatives[1] starting from appropriately monosubstituted guanidines and *N,N'*-diisopropylcarbodiimide. In some cases, however, this reaction led to formation of cyclic products which were found to be 1,2,4,6-tetrasubstituted derivatives of 1,3,5-triazine. For instance, in an attempt to prepare triguanide **3** starting from *N,N*-dimethylguanidine (**1**) and *N,N'*-diisopropylcarbodiimide (**2**), the only isolated product was 1,3,5-triazine derivative **4**, as shown in Scheme 1. The product **4** was spectroscopically characterized and its structure confirmed by X-ray diffraction of the perchlorate salt.[2]




**Scheme 1**

In this work, results of computational study on cyclization of hexamethyltriguanide ($CH_3$- instead of $(CH_3)_2CH$- groups in structure **3**) to the corresponding triazine will be presented. Geometry optimizations and vibrational analyses were carried at DFT level of theory using B3LYP/6-31G(d) approach. In addition, single point calculations using B3LYP/6-311+G(d,p) method were carried out. The results indicate that the cyclization proceeds via two-step mechanism with the first step being formation of intermediate heterocyclic structure followed by elimination of methylamine, which results in formation of triazine **4**.

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# MD studies of properties of Guanidinium ionic liquids

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Although there are many applications of ionic liquids (ILs), their properties are quit often not well known. The properties of liquids are determined not only by the molecular properties, but also by the ensemble average of the whole system. We have performed molecular dynamics (MD) simulations to explain properties of guanidinium salts.

The MD simulations are performed for guanidinium chloride, methylguanidinium chloride and hexamethylguanidinium chloride. The OPLS-AA force field and some force field parameters[1] are used. The distribution of anion around guanidinium cation, density and self-difusion coefficients of ions are analiesed. *Ab initio* MO calculations for these salts are also performed for the compison of the tendency of the results from MD simulations.

Fig. 1 shows the radial distribution function (RDF) and its integration number for the distance between the central carbon atom and the chloride ion in the case of guanidinium chloride.[2] It shows a broad peak around 4 Å and the integration number is 7.2. From the result of spacial distribution function (SDF), it is found that this peak comes from the chloride ions located around the molecular plane of guanidinium cation (data not shown).[2] This tendency agrees with the energy relationship between two structures, in-plane (Fig. 2 (A)) and perpendicular (Fig.2 (B)), by means of *ab initio* MO calculation, that the in-plane structure is more stable than the perpendicular one.[2]

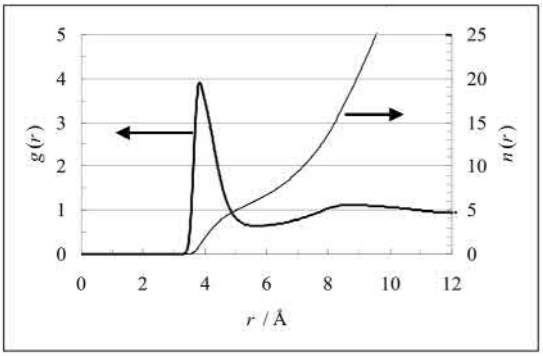


**Fig. 1.** Radial distribution function $g(r)$ and the integration number $n(r)$ for the distribution of chloride ion around the central carbon of guanidinium cation at 300 K, 1 bar.

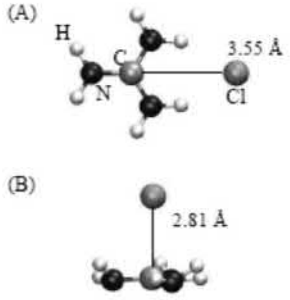


**Fig. 2.** Optimized structures of guanidinium chloride at HF/6-31G*. (A) in-plane, (B) perpendicular.

***References***

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# Dimethyl carbonate reactions under microwave irradiation

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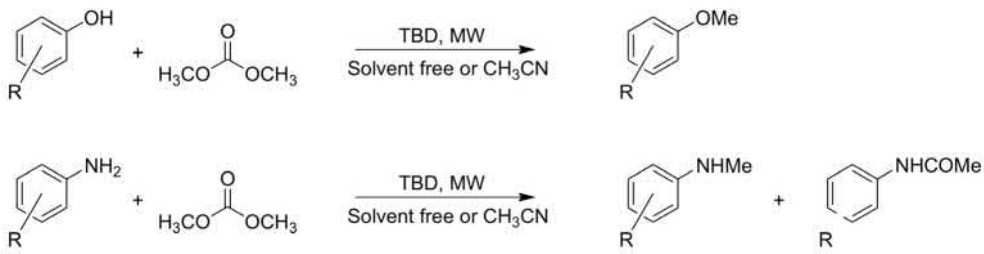
Dimethyl carbonate is, according to its properties and nontoxicity,[1] an environmentally attractive alternative for phosgene, methyl iodide and dimethyl sulfate in carboxy-methylation or methylation reactions.[2]

The influence of temperature and solvent (CH3CN) on reactions of dimethyl carbonate with substituted phenols and anilines, under microwave irradiation, was investigated (Scheme 1). The main purpose was to explore dimethyl carbonate selectivity as methylating or carboxymethylating agent, toward aromatic oxygen or nitrogen nucleophiles. It is known that the use of microwave irradiation[3] allows conduction of organic reactions at much higher temperatures than boiling point of solvent, which leads to higher reaction rates. However, dimethyl carbonate is an ambident electrophile[4] and higher temperatures reduce its selectivity in reactions with nucleophiles. In reactions described in this paper, both products were formed, while reactions of diamino (or dihydroxy) derivatives, gave complex mixtures of products.




**Scheme 1.**

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# Gas-Phase Reactions Between Thiourea and $Ca^{2+}$, Similarities and Differences with [Ca (Urea)] $^{2+}$

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The gas-phase reactions between $Ca^{2+}$ and thiourea were investigated by means of electrospray mass spectrometry techniques. The structures and bonding characteristics of the different stationary points of the [Ca (thiourea)]$^{2+}$ potential energy surface (PES) were theoretically studied by DFT calculations carried out at B3LYP/cc-pWCVTZ level. The gas-phase unimolecular $Ca^{2+}$ ions reactivity towards urea and thiourea share several common features as well as significant dissimilarities. In both processes, the formation of new doubly charged species by the loss of $NH_3$ and HNCS are observed. However, while these processes are dominant with urea [1], they only occur at a minor extent with thiourea. The $H_2NCa^+$ and $NH_4^+$ monocations are also observed in both systems, as a result of typical coulomb processes. The differences between urea and thiourea reactivity are related to the lower ionization potential of the latter, and to the fact that the enthiols are intrinsically more stable than enols with respect to the corresponding keto forms.

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# Substituent Effects on Photosolvolysis of Benzylthioacetates in Aqueous Solution

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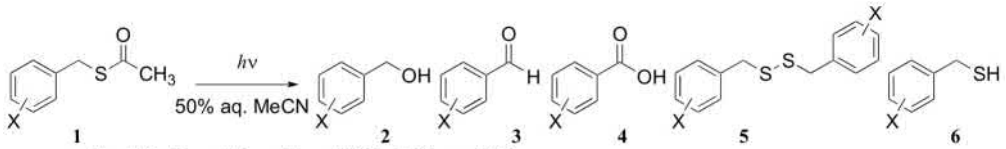
Thioester is one of a major class of compounds in pesticides. Since pesticides are used under open air environment of daylight, the photochemical reaction might be a major route for their decomposition pathway. On this point of view, we are interested in the photochemical reaction of thioesters. In this paper, photosolvolysis mechanism of benzyl thioacetate (1) in aqueous acetonitrile (MeCN) are investigated by the aid of substitutent effect.

Substituted benzyl thioacetates were dissolved into 50% $CD_3CN$ - $D_2O$ solution and were irradiated with 500W Xe lamp under aerobic condition. The Photosolvolysis products were identified and determined by using $^1$H-NMR spectra, MS and HPLC.

Photoirradiation of unsubstituted benzyl thioacetate afforded benzylalcohol (**2**), benzaldehyde (**3**) and benzoic acid (**4**). The first product was derived from the heterolytic $CH_2$-S bond cleavage followed by nucleophilic addition of water, while the latter two compounds were obtained by oxidation of benzyl radical which is generated by the $CH_2$-S bond homolysis. The yields of these compounds are 3.3% for **2** and 52.6% for the sum of **3** and **4**, respectively. The $^1$H-NMR spectrum of the photolyzed solution exhibited two singlet signals at 3.62 and 3.7 ppm as the rest of the photosolvolysis products, and assuming these are benzylic proton signal, the sum of the yield of these compunds was estimated as 46%. Semi-preparative photolysis of m-$CF_3$ derivative revealed that the photosolvoysis product showing $^1$H- NMR signal at 3.6 ppm was identified as benzyldisulfide (**5**), which was derived by coupling of benzylthio radical. Thus, the singlet signal at 3.7 ppm in $^1$H-NMR spectrum was suggested to be benzyl thiol (**6**). The formation of **5** and **6** suggests that the photosolvolysis of benzyl thioacetate involves the thiocarbonyl excited state, which leads to the homolysis of the S-CO bond. In the photosolvolyses of substituted benzyl thioacetates, the S-CO bond homolysis products were obtained in 90.8 %, 88.3 % and 72.8 % for *p*-$CF_3$, *p*-$OCH_3$ and *m*-$OCH_3$ derivatives, respectively. The preference for S-CO bond homolyses in the photosolvolysis of substituted benzyl thioacetates is quite contrast to what has been observed in the photosolovlysis of *m*-$OCH_3$ benzyl acetate,[1] where preferred $CH_2$-O bond heterolysis with no O-CO bond homolysis were observed in the photosolvolysis.




a: X = H, b: X = *p*-$CF_3$, c: X = *p*-$OCH_3$, d: X = *m*-$OCH_3$

***References***

(1) Zimmerman, H. E. and Sandel V. R., *J. Am. Chem. Soc.*, **1963**, 85, 915.

# Characterization of new 8-aminoquinoline derivatives using electrospray ionisation-ion trap mass spectrometry

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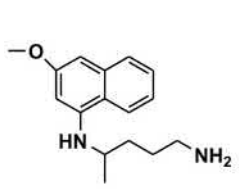
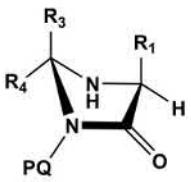
Primaquine (PQ, **1**) is an antimalarial 8-aminoquinoline whose toxicity is mainly due to the metabolites that it generates *in vivo*. PQ derivatives based on the insertion of an imidazolidin-4-one motif (**2**) have been previously prepared in our group and seen to exhibit antimalarial activity *per se*.[1,2] These imidazolidin-4-ones were unexpectedly stable at 37 ºC and pH 7.4 in both phosphate-saline buffer and 80% (v/v) human plasma.[1,2] Thus, the kinetics of their hydrolysis was investigated in the pH range 0.3–13.5 at 60 ºC and data was consistent with a mechanism of hydrolysis involving an $S_N1$-type unimolecular cleavage of the imidazolidin-4-one C2–N3 bond with departure of an amide-leaving group.[3]

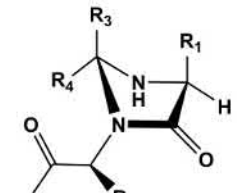
Motivated, on one hand, by the particular characteristics of structures like **2** and, on the other, by previous reports where mass spectrometry fragmentation patterns of drugs was correlated with the distribution of drug metabolites,[4] we decided to study the fragmentation pattern of compounds **2** on ESI-$MS^n$. New imidazolidin-4-ones derived from dipeptide derivatives of PQ were obtained by insertion of the pentagonal ring either at the N-terminal amino group (**3**) or embedded between both the amide groups (**4**) to be also included in this study.[5]



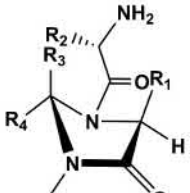

1
(PQ)




2




3




4

The normalized collision energy of the ESI-$MS^n$ technique together with the use of a simple percentile scale will allow to compare these different structures and to foresee the fragments that each of them might typically produce as metabolites *in vivo*.

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*Ackowledgments*: Thanks are due to Fundação para a Ciência e Tecnologia (FCT, Portugal) for financial support through project POCTI/39218/2001 and through plurianual funding to CIQUP and CECF research units. N. Vale thanks FCT for the doctoral research grant SFRH/BD/17754/2004.

# Comparative QSAR Analysis of Anti -Tubercular Compounds using Artificial Neural Networks and Multiple Linear Regressions

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According to the most recent WHO reports[1], in 2005 there were almost 445 000 new tuberculosis (TB) cases registered and more than 66 000 deaths due to TB, just in the European Region. It is estimated that, each year, nearly 9 million people develop active tuberculosis worldwide, and that 1.7 million people die from this disease. In line with the latest estimates[2-3], 10% of all new TB infections are resistant to at least one anti-TB drug. Also, recent reports on multi-drug resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) indicate that rates of drug resistance may be far higher than previously described.[2]

These facts have raised much interest in the scientific community towards the development of new active anti-tubercular compounds and several efforts have been made towards the understanding of the mechanisms of action of active compounds against *Mycobacterium tuberculosis*. Unfortunately, the knowledge on these complex mechanisms is still rather limited.

Due to the large costs involved in the development of new drugs, a reliable quantitative prediction of biological activity prior to the production phase is obviously of great interest to the industry.

In this work we have analyzed 171 active hydrazide compounds, most of them isoniazide related[4] and studied the correlation between their biological activity, as given by their MIC values, and several molecular descriptors of physicochemical, geometrical, steric and electronic nature. With the purpose of disclosing similar structural features and unveil which molecular characteristics are responsible for the anti-tubercular activity of these compounds, we have applied two QSARs methodologies, namely Artificial Neural Networks[5] (Back-Propagation and Kohonen Self-Organizing Maps) and Multiple Linear Regressions. In particular, we compared the flexibility and predictive ability of the back propagation neural networks and the multiple linear regressions approaches and, in a complementary way, we used Kohonen Self- Organizing Maps, a nonlinear technique for pattern recognition which preserves topology, to analyse the compounds similar features.

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*Acknowledgements*: This work was funded by FCT - FCT/SFRH/BPD/2074/2004 (C.Ventura)

# Peptidic-like Inhibitors of *Plasmodium Falciparum*: Development of New Antimalarials

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Malaria is a world threatening disease. Although a number of chemotherapeutic agents are available for the treatment of malaria, the rate at which the parasite has developed resistance has prompted the call for the use of other alternatives, such as drug combinations.[1]

The central importance of haemoglobin degradation to the survival of *P. falciparum* is well estabilished. This process is brought up by the action of several cysteine proteases, from which falcipain-2 has a major role.

Mainly from studies by Rosenthal and co-workers, there are some currently available peptidyl falcipain-2 inhibitors,[2] like Mu-Phe-Ala-$CH_2F$ (Fig. 1a) with activity in the low nanomolar region that have been shown to be active *in vivo* in mouse models of malaria.[3] X-ray crystals of an homologous enzyme of FC-2 covalently bound to this compound, provide clues as to the important bonding interactions at the active site. Also, studies with other cysteine proteases, by Veber and co-workers, have recently shown examples of reversible peptidyl ketones with nanomolar inhibition towards cathepsin K[4] (Fig. 1b). As such, we propose to examine the structure-activity relationships of a series of novel alpha phenoxy carbonyl inhibitors of FP-2 (Fig. 1c).

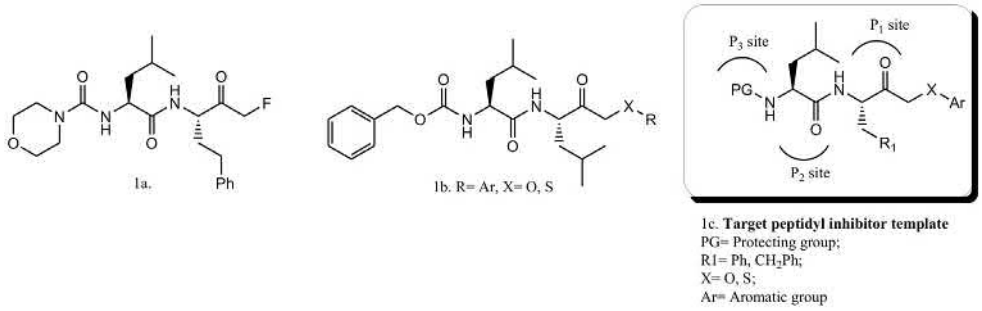


**Fig. 1.** Known FP2 inhibitors and proposed peptidyl inhibitor template.

***References***

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This work was funded by FCT (Portugal) through project grant - FEDER POCTI/FCB/33580/2000 and PhD grant SFRH/BD/6176/2001.

# UV Photolysis of γ-lactams

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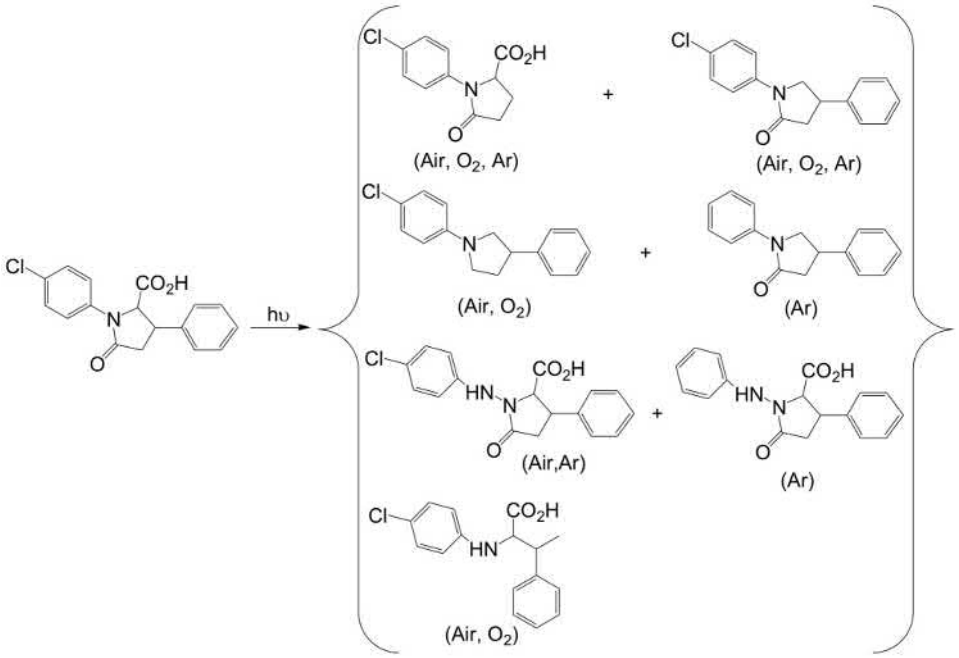
Lactam derivatives, an important groups of antibiotics,[1] may undergo photo-initiated reactions, leading to loss of antibiotic activity or to complete structural modification.[2]

We have investigated the 254 nm photoreactivity of γ-lactams, reported to have substantial antibacterial properties.[3] The Scheme below shows the photoproducts, observed by HPLC/MS/MS, for 1-(4-chloro-phenyl)-5-oxo-3-phenyl-pyrrolidine-2-carboxilic acid upon photolysis in $CH_3CN$.




**Scheme**. Products obtained by 254 nm photolysis of 1-(4-chloro-phenyl)-5-oxo-3-phenyl-pyrrolidine-2-carboxilic acid dissolved in $CH_3CN$

***References***

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# π–π Stacking and Secondary Bonding Interactions in Co-crystals of Benzo-2,1,3-selenodiazole

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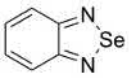
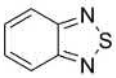
The attractive non-covalent interactions between heavy main group elements and electron pair donors, known as secondary bonding interactions (SBIs), have received increasing attention in recent years because of their significance in crystal engineering. Examples are the halogen bond[1] and chalcogen–nitrogen non-bonded interactions.[2] They result from electrostatic and orbital (charge transfer) contributions, where heavy atoms work as electron acceptors and heteroatoms bearing lone pairs as electron donors. The donor–acceptor character have also interactions between aryl and perfluoroaryl rings.[3]




**1**




**2**


**ipf**


**pfp**

In this communication we present the crystal structures of the supramolecular complexes obtained by co-crystallization of benzo-2,1,3-selenodiazole (**1**) and benzo-2,1,3-thiadiazole (**2**) with iodopentafluorobenzene (**ipf**) or pentafluorophenol (**pfp**). The crystals of **1·ipf** are composed of tetramers containing two molecules of **1** connected by two Se···N interactions and two **ipf** units halogen bonded to the nitrogen atoms (Fig. 1). The tetramers are further assembled into infinite stacks with the alternating aryl and perfluoroaryl rings. The structure of **1·pfp** also contains tetramers, where two molecules of **pfp** are bonded two the dimers of **1** by the O–H···N hydrogen bonds. Again the tetramers form π-stacks stabilized by aryl–perfluoroaryl interactions. In contrast, the co-crystals of **2·pfp** in absence of SBIs reveal a layered structure with the component molecules held together by the O–H···N hydrogen bonds and aryl–perfluoroaryl π–π stackings.

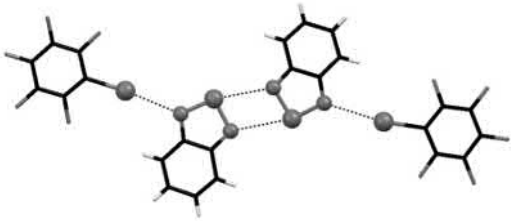


**Fig. 1.** Crystal structure of **1·ipf**

***References***

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*Acknowledgements*: Financial support from Ministry of Science and Computerisation (project no. 3 T09A 030 29) is gratefully acknowledged.

# Pure Steric Effects in Reactions of Aliphatic Carboxylic Acids

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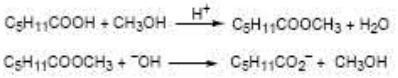
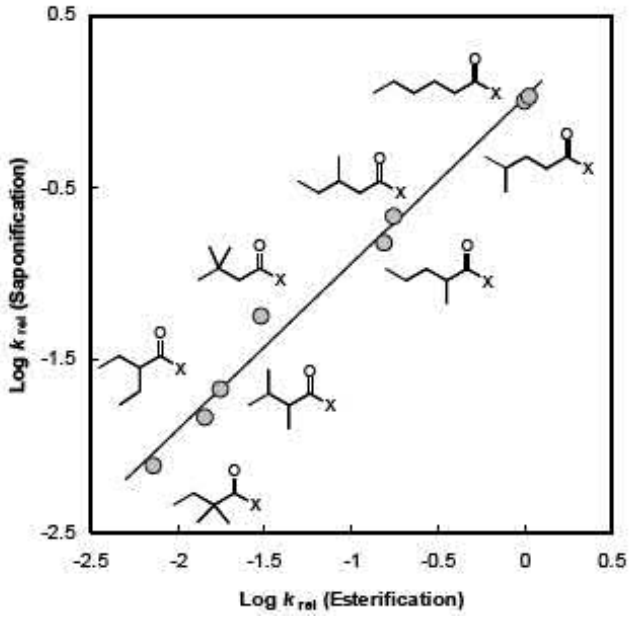
The merits of comparing the behaviour of isomers in assessing contributions to reactivity from saturated hydrocarbon residues will be discussed. Reactivities of the hexanoic acid and its seven isomers in acid-catalysed methyl ester formation, and in saponification will be compared and shown to be consistent with the Taft-Ingold proposal that steric effects in these ($A_N + D_N$) reactions are closely comparable, and that electronic effects associated with the structural variation within the set are small.




Relative reactivities for other carboxylic acid derivatives, including acid chloride hydrolysis and saponification of reactive phenolic esters will be presented and shown to be inconsistent with $A_N + D_N$ mechanisms.

# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## Sponsors

The Organising Committee is very grateful for assistance and donations from the following institutions:

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| FCT<br>Fundação para a Ciência e a Tecnologia | Dept. de Química, Bioquímica e Farmácia Universidade do Algarve | Caixa Geral de Depósitos | Dias de Sousa Instrumentação Analítica e Científica S.A. |
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# ESOR XI

11TH EUROPEAN SYMPOSIUM ON ORGANIC REACTIVITY

## Maps

# Faro Map

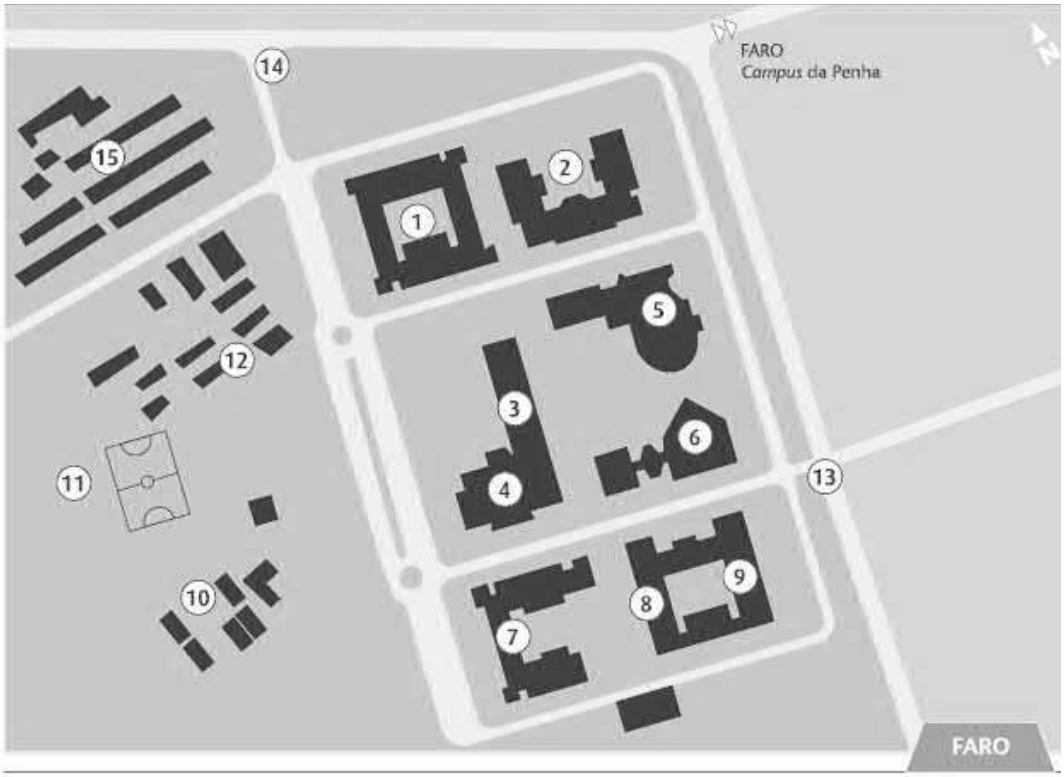

## Legenda | Legend

1. **Arco da Vila** / Town Arch
2. **Ermida da Senhora do Ó** / Chapel of Senhora do O
3. **Governo Civil** / Civil Government
4. **Paços do Concelho** / Town Hall
5. **Sé Catedral** / Cathedral
6. **Paço Episcopal** / Bishop's Palace
7. **Seminário Episcopal** / Seminary
8. **Galerias Municipais Trem e Arco** / Trem and Arco Municipal Galleries
9. **Muralhas e Castelo** / Walls and Castle
10. **Museu Arqueológico Infante D. Henrique - Convento de Nª Senhora da Assunção** / Infante D. Henrique Archaeological Museum - Convent of Nossa Senhora da Assunção
11. **Ermida de Nossa Senhora do Repouso** / Chapel of Nossa Senhora do Repouso
12. **Igreja da Misericórdia** / Church of the Misericórdia
13. **Museu Etnográfico** / Ethnographic Museum
14. **Ermida de Nossa Senhora do Pé da Cruz** / Chapel of Nossa Senhora do Pé da Cruz
15. **Cerca de Muralhas** / Wall enclosure
16. **Celeiro de São Francisco** / São Francisco Barn
17. **Igreja de São Pedro** / Church of São Pedro
18. **Igreja do Carmo** / Church of Carmo
19. **Igreja e Convento dos Capuchos** / Church and Convent of Capuchos
20. **Casa do Compromisso Marítimo** / Compromisso Marítimo House
21. **Alfândega** / Customs
22. **Ermida da Madalena** / Chapel of Madalena
23. **Ermida de São Sebastião** / Chapel of São Sebastião
24. **Ermida de Nossa Senhora da Esperança** / Chapel of Nossa Senhora da Esperança
25. **Museu Antonino - Ermida de Santo António do Alto** / Antonino Museum - Chapel of Santo António do Alto
26. **Ermida de São Luís** / Chapel of São Luís
27. **Ermida de São Miguel** / Chapel of São Miguel
28. **Cemitério dos Judeus** / Jewish Cemetery
29. **Teatro Lethes** / Lethes Theatre
30. **Horta do Ourives** / Ourives Garden
31. **Igreja e Convento de São Francisco** / São Francisco Church and Convent
32. **Museu da Marinha** / Navy Museum

- A **Câmara Municipal** / County Council
- B **Terminal Rodoviário** / Bus Terminal
- C **Estação Ferroviária** / Railway Station
- D **Correios** / Post Office
- E **Mercado Municipal** / Municipal Market
- F **Cortes de Ténis** / Tennis Courts
- G **Polícia de Segurança Pública** / Police Station
- H **Serviços de Estrangeiros** / Foreign Division
- I **Polícia Judiciária** / Criminal Investigation Department
- J **Hospital** / Hospital
- K **Guarda Nacional Republicana** / National Guard
- L **Jardim** / Garden

- **Região de Turismo do Algarve** / Algarve Tourism Board
- **Posto de Turismo** / Tourist Information Point
- **Áreas pedonais** / Pedestrian areas

# Gambelas Campus Map




1 - FCHS (Faculty of Human and Social Sciences)
2 - FCT (Faculty of Sciences and Technology)
3 – Complexo Pedagógico (Lecture Hall)
4 – Grande Auditório (Auditorium)
5 - University Library
6 – University Restaurant
7 – FCMA (Faculty of Environment and Sea Sciences)
8 – FERN (Faculty of Natural Resources Engineering)
9 – FE (Faculty of Economical Sciences)
13 – Main Entrance (East)
14 – Northern Entrance