

Isotope Effect Calculations in the Supramolecular Age

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Kinetic isotope effects (KIEs) are important experimental probes of mechanism for chemical reactions, the vast majority of which occur in condensed phases. Traditional methods for their calculation are molecular in nature, which is fine for gas-phase reactions but generally inadequate for systems in which coupling between a substrate and its environment is significant. However, atomic subsets of supramolecular systems, whose isotopically sensitive vibrational frequencies are explicitly considered, may be (surprisingly) small without significant error for KIEs provided that all their degrees of freedom are considered, but their Hessian elements must be evaluated within an adequately large environment whose electrostatic properties are accurately described.¹ KIEs should be evaluated as simple quotients of isotopic partition function ratios determined independently for the reactant state and the transition state averaged over thermally accessible configurations.²

Enzyme-catalyzed methyl transfer will be discussed in the light of experimental results for mutants of catechol-O-methyltransferase. Possible reasons for a discrepancy between calculation (so far) and experiment will be examined, including the role of the dielectric environment of the methyl group. EIE and KIE calculations for CH_3^+ vs. CD_3^+ and $^{14}\text{CH}_3^+$ within highly constrained cages comprising “axial” interactions (normal to the plane of the methyl moiety) and “equatorial” interactions (within the plane of the methyl moiety) will be discussed. Determination of isotope effects on the basis of a “cutoff” model which considers vibrational frequencies only for the 12 degrees of freedom of the methyl group (6 internal and 6 external) within the larger environment of aqueous solution, or a cage, or an enzyme active site, yields results that do not differ significantly from those obtained from “full-size” Hessians involving much larger numbers of atoms.

1. Williams, I. H. *J. Chem. Theory Comput.* **2012**, *8*, 542-553.
2. Ruiz-Pernía, J. J.; Williams, I. H. *Chem. Eur. J.* **2012**, *18*, 9405-9414.