

COMPUTATIONAL SIMULATION OF ENERGY LANDSCAPES AND ISOTOPE EFFECTS FOR GLYCOSIDIC REACTIVITY

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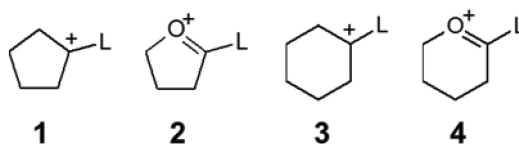
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Kinetic isotope effects (KIEs) offer powerful probes for mechanism and transition-state (TS) structure in enzyme-catalyzed reactions, as long as their experimentally determined values and variations can be correctly interpreted. It is common for analyses of TS structure, based upon KIEs for multiple isotopic substitutions, to consider force-constant changes only as functions of molecular geometry. However, work in our group suggests that consideration of the electrostatic environment is also necessary, as force-constant changes can depend on the relative permittivity of the medium. If so, there would be important implications for the interpretation of experimental KIEs in mechanistic enzymology.^[1,2]

The use of both implicit (polarized continuum model) and explicit (hybrid QM/MM) treatments of solvation with DFT calculations is considered critically for equilibrium isotope effects upon transfer of some carbocations (cyclopentyl **1**, tetrahydrofuranlyl **2**, cyclohexyl **3** and tetrahydropyranyl **4**) from water to cyclohexane, mimicking the change from a polar aqueous environment to an extreme non-polar enzyme active site.

1D scans of potential and free energy for cleavage of the glycosidic bond in 2-(p-nitrophenoxy)tetrahydropyran do not show a TS. A 2D free-energy surface that considers also the distance between C_α and a nucleophilic water indicates a pre-association D_N*A_{Nint}[‡]



(S_N2 intermediate) mechanism with a TS involving nucleophilic attack upon an ion-pair intermediate, and this is supported by good agreement between the mean values of the calculated and experimental α-D KIEs. This work outlines our efforts to accurately calculate the isotope effects, including the effects of the electrostatic environment on the reactant and transition states, for the hydrolysis of. Both QM and QM/MM molecular dynamics techniques have been used.

REFERENCES

- [1] P. B. Wilson, P. J. Weaver, I. R. Greig, I. H. Williams, *J. Phys. Chem. B* **2015**, *119*, 802–809.
[2] P. B. Wilson, I. H. Williams, *Angew. Chemie - Int. Ed.* **2016**, *55*, 3192–3195.