Ten years on for the Houk-List Transition states for organocatalysis and NCI analysis.

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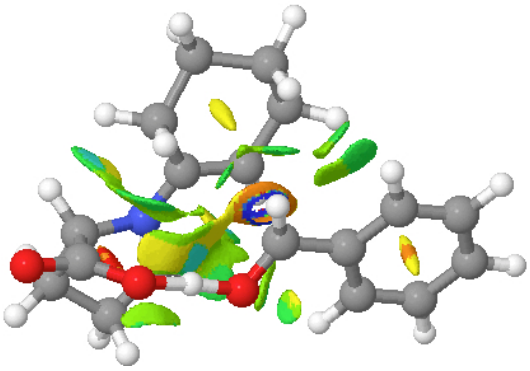
Abstract

The ten-year-old Houk–List transition state model for organocatalysed intermolecular aldol addition represents a keystone example of the use of quantum chemical methods for rationalising the origins of stereoselective control. [1] Here we review five key aspects where significant advances have been made since the original study. 1. DFT functionals now include empirical corrections for dispersion terms, which even for such a relatively small system are shown to be of crucial importance. 2. The essential use of basis sets where the superposition errors are shown to be low. 3. A more complete exploration of conformational space. 4. The routine use of continuum solvent models using smoothed solvent cavities for computing the relative free energies and intrinsic reaction coordinates (IRCs) of transition states. 5. Adoption of a new style of journal publication, where full data and describing metadata is held in a modern digital repository, and where interactive figures can be dynamically constructed by query of the repository. [2]

An NCI (non-covalent interaction) analysis of the transition states and presentation *via* visual inspection using such an interactive figure (below) can be used to rapidly identify the noncovalent interactions that may influence the selectivity of the reaction. These expose the role of the electrostatic NCH$\delta^{+}\cdots O\delta^{-}$ and π-stacking interactions. Such inspection of the NCI surfaces is shown to be a useful tool for the design of other reactants. Alternative mechanisms, such as the Hajos–Parrish or proton-relays involving a water molecule are shown to be higher in free energy. Computed kinetic isotope effects for the Houk–List transition state match experiment closely, unlike alternative mechanisms. The NCI technique is also illustrated for several other reaction transition states. [3]



References:

[1] A. Armstrong, R. A. Boto, P. Dingwall, J. Contreras-García, M. J. Harvey, N. Mason and H. S. Rzepa, *Chem. Sci.*, 2014, DOI: http://doi.org/10.1039/C3SC53416B
[2] A talk on this aspect can be found at DOI: http://doi.org/10042/a3v08
[3] The slides for this talk are available at DOI: http://doi.org/10042/a3v14