

An Electron Transfer Model (ETM) for Predicting Regioselectivity in Bimolecular Reactions

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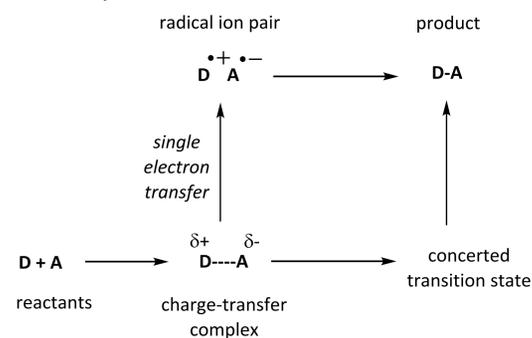
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Introduction and History

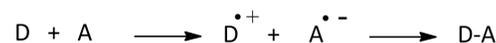
Polar bimolecular reaction mechanisms define a continuum that ranges from concerted through single electron transfer (SET). In some cases, there is experimental evidence for radical ion intermediates.¹ Most reactions probably have some degree of electron transfer. This is implicit in the frontier molecular orbital (FMO) description of reactions, which examines HOMO-LUMO interactions.² Polar and SET reactions may follow similar reaction coordinates.³



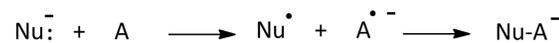
Many theories have been developed for the prediction of regio- and stereoselectivity in chemical reactions. Frontier molecular orbital (FMO) theory has held sway for the past four decades as one of the simplest approaches to predicting chemical reactivity and selectivity.² More recently, conceptual DFT and HSAB theories have also been described.⁴ Even slight differences in experimental bond lengths have been recognized as subtle augurs of reactivity.⁵ Unfortunately, as simple π electron wavefunctions were replaced by more advanced ab initio and DFT methods, the application of predictive models has become more complex.

We are exploring an **Electron Transfer Model (ETM)** for bimolecular reactions. In **ETM**, we *systematically* transfer an electron in the direction that is more likely based on reactant polarity. **Projecting along the mechanistic coordinate to a radical ion is expected to exaggerate and thereby clarify effects of polarization.** The basis for this model is the expected similarity of reaction coordinates for polar concerted and SET reactions.

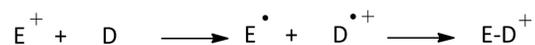
(1) Polar Addition



(2) Nucleophilic Addition



(3) Electrophilic Addition

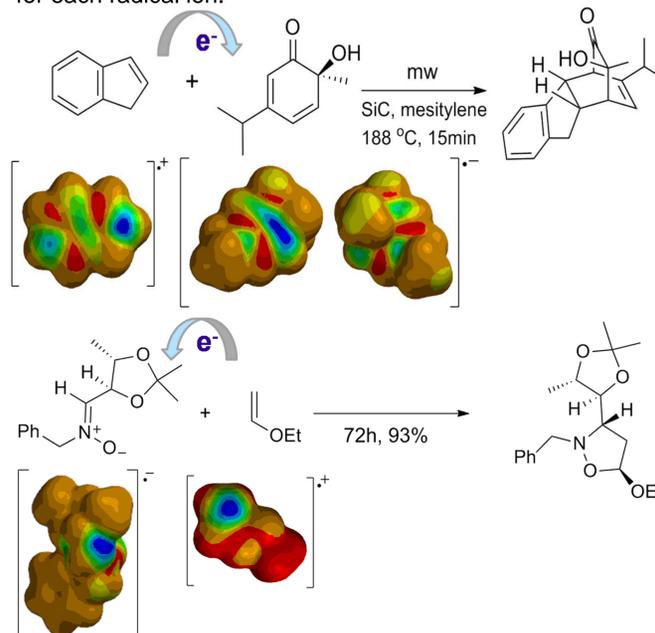


ETM Computational Details

For a polar bimolecular reaction, we choose the expected direction of electron transfer and optimize structures for the relevant radicals or radical ions using density functional methods (usually M052X) which are known to give an excellent account of radical ions. Sites of higher reactivity are then revealed by a **Spin Density Map** (odd electron character) on the electron density surface, assuming that a new two electron bond would occur at sites of highest spin density. *Spartan 10* and *Gaussian 03/09* were used for all calculations.

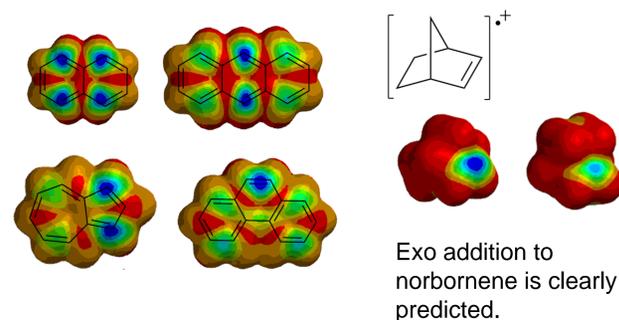
Polar Cycloaddition Reactions

Polar cycloadditions have been widely studied and it is usually easy to identify the expected direction of electron transfer. We find that the regiochemistry of both [2+4] and [3+2] cycloadditions is rationalized by optimizing the radical ion structures and visualizing the spin density map (SDM) for each radical ion.



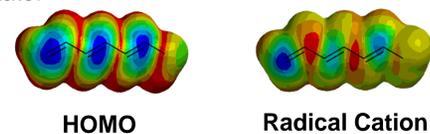
Electrophilic Additions

In electrophilic additions, ETM transfers an electron to make the electrophile radical and the **substrate radical cation**. In practice, visualization of the SDM for the reactant radical cation provides a clear prediction of reactive sites.



ETM vs. FMO – The effect of polarization

Visualization of the HOMO of 1,3,5-heptatriene does not clearly show where an electrophile will add. ETM is clearer because the SDM shows the effects of polarization at the transition state.

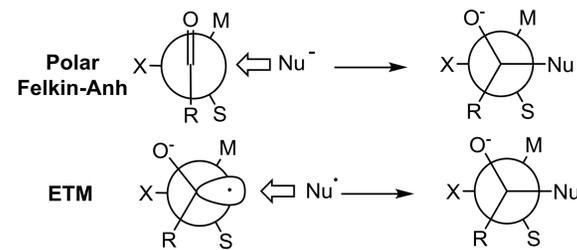


Acknowledgements

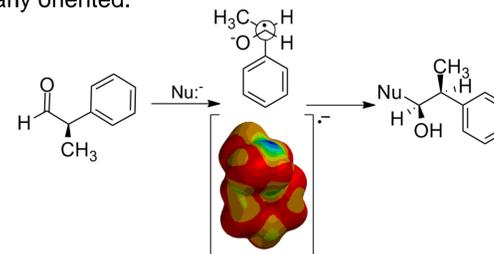
We are grateful for generous support from the National Science Foundation (CHE-0910826).



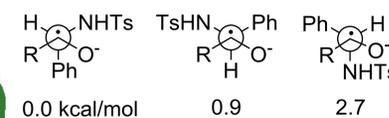
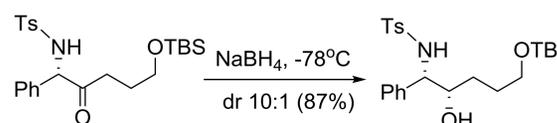
Nucleophilic Addition to Carbonyl



In the Polar Felkin-Anh model "X" is the substituent with the best acceptor antibonding orbital (σ^*C-X) which is oriented antiperiplanar to the forming C-Nu bond. In ETM, X is similarly oriented.

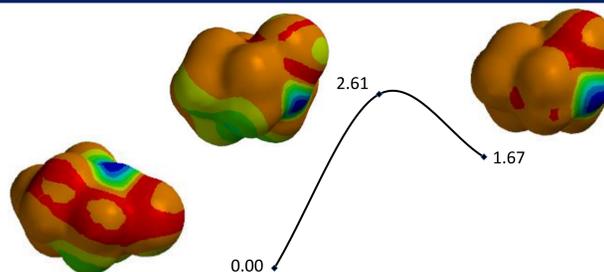


ETM easily predicts both regio- and stereoselectivity. For an acyclic structure, the lowest energy radical ion conformer predicts stereoselectivity. This is in agreement with the Felkin-Anh model.



This highly-selective example¹⁴ of a carbonyl reduction affords the Felkin-Anh product in good yield. ETM analysis of the radical anion models the correct diastereomer. The SDM shown is the lowest energy conformer of the radical anion including implicit solvation with acetonitrile.

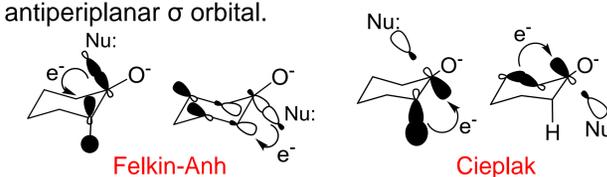
Cyclohexanone Radical Anions



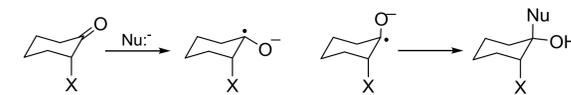
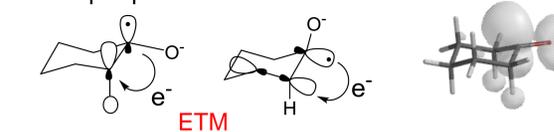
For the cyclohexanone radical anion, two chair conformers exist with a low energy barrier between them, as well as a twist-boat conformer at higher energy. The SDM for the lowest energy conformer reproduces the known preference for axial addition.

Hyperconjugation in Cyclohexanone Radical Anions

For cyclohexanone, the two most influential models¹² to explain axial vs. equatorial approach of a nucleophile are the Felkin-Anh model which describes the interaction of the σ orbital of the newly formed bond with the antiperiplanar σ^* orbitals; and the Cieplak model which invokes stabilizing interaction between the σ^* orbital associated with the newly formed bond and the antiperiplanar σ orbital.



ETM most closely resembles the Felkin model, the spin surface of the radical anion shows e^- density in the σ^* of the antiperiplanar C-H bond.



X	0.00 kcal/mol	1.7	In each case, the lower energy structure predicts addition stereochemistry. ¹⁵
X=H	0.00	1.7	
X=CH ₃	0.00	2.8	
X=OMe	0.00	3.7	

Conclusions

Our results¹⁶ show that ETM correctly predicts regiochemistry and stereochemistry in a broad array of reactions, including Diels-Alder and dipolar cycloadditions, many types of nucleophilic addition, and electrophilic addition to aromatic rings and polyenes. Carbonyl radical anions are pyramidalized; the preferred mode of pyramidalization is a reliable augur of reaction stereochemistry. This simple but powerful method presumably works because exaggerating the degree of electron transfer clarifies polar effects. We are continuing to explore the applications and limitations of this method.

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