

Reaction Coordinate

Beyond the transition state:

Textbook analysis of reaction mechanisms typically involves static structures and ends at the transition state, but modern mechanistic research shows that this isn't always a complete picture. This talk will examine several cases where the dynamic nature of the various species in a reaction require a more detailed look in order to accurately explain real world observations.

Goals:

1) Reach a more complete understanding of how reaction mechanisms actually occur.

2) Examine where and to what extent the assumptions in standard theories of reactivity break down.

3) Showcase explanatory power of new models in cases where reactivity is otherwise hard to rationalize.

Scope:

The effects considered here are fundamentally non-equilibrium in nature, so reactions considered will generally be under kinetic control.

Much of the work in this area has large computational components: I will make no attempt to explain the specifics of the computational approaches used, and priority was given to examples that have some experimental observables.

Effort was made to cover broader classes of phenomena, and several specific examples are missed for the sake of time.



Carpenter, B. K. Chem. Rev. 2013, 113, 7265.

Hypersurface Dimensionality and Vibrational Modes:

A system with N many atoms and a non-linear geometry will have 3N-6 degrees of freedom, which will correspond to the relative positioning of all atoms in 3-d space. Each configuration will have an associated potential energy, which results in a potential energy surface of dimensionality 3N-6 in a 3N-5 dimension vector space.

A useful way of considering these degrees of freedom is in terms of a molecule's vibrational normal modes, making the potential energy surface simply a composite of the whole set of available vibrations.

Reaction Coordinates:

The path from reactant to product on the PES can be simplified into a single reaction coordinate, which is a (potentially extremely complicated) composite function of relevant vibrational modes. A trajectory along the reaction coordinate can involve many twists and turns with respect to vibrational modes and may in principle require energy transfer between modes to overcome energy barriers.

Intermediates:

An intermediate is a structure defining a local minimum on the potential energy surface lying on the reaction coordinate between the reactant and the product.

Transition States:

A transition state is a saddle point in the PES that defines the potential energy maximum between two minima on a reaction coordinate.



Goldman, L. M. et. al. J. Am. Chem. Soc. 2011, 133, 5312.

Thermal Relaxation:

As a system moves from a transition state to an intermediate or product, the decrease in potential energy will cause an increase in translational, rotational, and/or vibrational energy depending on the composite nature of the specific reaction coordinate in question. This energy will then be equilibrated, first through intramolecular vibrational energy redistribution (IVR) and then through energy loss to the surroundings (e.g. solvent).

The effects considered here are largely related to this thermal relaxation. The nature and magnitude of the effects will depend on the extent to which reactive species have undergone IVR and/or energy loss prior to subsequent processes.

Canonical Transition State Theory (TST):

Traditional theory wherein the rate of any process is determined by the energy barrier to reach the transition state. Relative rates between competing processes determined by relative energies of transition states.

Pros:

- 1) Works well in most reactions
- 2) Easiest to form intuitive understanding of relevant chemistry
- 3) Only requires relative energy of starting state and transition state

Cons:

1) Assumes complete thermal equilibrium of every species

2) Assumes any competing processes will have distinct transition states

Variational Transition State Theory:

Method developed by Truhlar that uses a variational criterion to define the dividing line between starting species and product rather than searching for a saddle point in the potential energy surface.

Pros:

1) Maintains statistical framework for understanding reactivity

2) Allows identifying dynamical bottleneck in cases where no apparent energy maximum exists in the potential energy surface

Cons:

- 1) Retains fundamental assumptions of equilibration behind TST
- 2) Harder to rationalize when transition state isn't defined in potential energy

Truhlar, D. G. et. al. Acc. Chem. Res. 1980, 13, 440.

Rice-Ramsperger-Kassel-Marcus (RRKM) Theory:

Microcanonical theory in which energy available to a molecule is treated explicitly by dividing it statistically into available vibrational modes. Rate is calculated by examining energy in mode corresponding to the reaction coordinate.

Pros:

1) Works in cases where intermediates aren't in thermal equilibrium with the bath (e.g. solvent)

Cons:

- 1) Assumes vibrational energy is evenly distributed intramolecularly
- 2) Still relies on identification of a transition state, as in above theories

Direct Dynamics:

Model wherein simulations are run on calculated energy surfaces and trajectories are calculated over small time increments (e.g. 1 fs). Starting structures are usually provided with random Boltzmann-weighted energies and random phase in all nodes except for the "forward" reaction coordinate.

Pros:

- 1) Doesn't assume any levels of thermal equilibration
- 2) Most reliable in replicating experimental results
- 3) Allows analysis of time dependent behavior

Cons:

- 1) Computationally demanding
- 2) Harder to form intuitive understanding from results



Patel, A. et. al. J. Am. Chem. Soc. 2016, 138, 3631.

Example of a set of trajectories from a direct dynamics calculation with canonical transition state shown and a second transition state found using variational TST.

Shenvi Lab Group Meeting February 12th, 2018	Hydroboration	Tucker Huffman
$\mathbf{D}_{3}\mathbf{C} \xrightarrow{\mathbf{D}}_{\mathbf{D}} \xrightarrow{\mathbf{1. BH}_{3} (100 \text{ eq})} \begin{bmatrix} \mathbf{H}, \mathbf{H}_{\mathbf{B}}, \mathbf{H} \\ \mathbf{D}_{\mathbf{A}}, \mathbf{C}, \mathbf{H} \\ \mathbf{D}_{\mathbf{A}}, \mathbf{C}, \mathbf{H} \\ \mathbf{D}_{\mathbf{A}}, \mathbf{C}, \mathbf{H} \\ \mathbf{D}_{\mathbf{A}}, \mathbf{C}, \mathbf{H} \end{bmatrix}$	Product Determining Step $ \begin{bmatrix} H_2B & D \\ D_3C & H \\ D_D & H \end{bmatrix} $ $ \begin{array}{c} H_2B & D \\ D_3C & H \\ D_D & H \end{array} $ $ \begin{array}{c} H_2B & D \\ D_3C & H \\ D_D & H \\ D_3C & H \\ D_0 & $	2. H_2O_2 , NaOH D_3C D_3C H_0 H_0 H_1 H_2 H_3C H_2 H_3C H_2 H_3C H
	largely overestimate the observed selectivity under canonical TS	<u> </u>
 Dynamic Trajectory Modelling: Singleton and coworkers ran classical trajectory simulations over a calculated potential energy surface. Starting trajectories prior to complex formation resulted in 10-12% of Markovnikov product. Analysis of trajectories showed that the subset of material reacting within 800 fs had reduced selectivity versus that which took longer to proceed to products. The authors propose that sub-populations react in 3 stages at varying levels of relaxation: 1. Pre-IVR, direct-trajectory and low selectivity 2. Post-IVR, RRKM control and moderate selectivity 3. Post-thermal equilibration, canonical TST control and high selectivity 	Canonical Competititve Nonstatistical Model: Truhlar and coworkers developed a model that divides the reaction into so-called direct and indirect mechanisms, where some fraction of reacting molecules is divided into each. The indirect sub-population is treated under TST, whereas the direct sub-population is treated with a nonstatistical phase space theory. In essence, this approach takes the qualitative conclusions from Singleton's work and fits them into a quantitative model that doesn't rely on computationally demanding trajectory calculations.	RRKM-Master Equation: Pilling and coworkers utilized a master equation model that considers interconversion of reactants, intermediates, and products and collisional energy loss to solvent under a statistical framework using RRKM theory. This model doesn't invoke nonstatistical effects, nor does it rely on trajectory calculations to determine reaction selectivity.
Oyola, Y. et. al. J. Am. Chem. Soc. 2009, 131, 3130.	Zheng, J. et. al. J. Am. Chem. Soc. 2009, 131, 15754.	Glowacki, D. R. et. al. J. Am. Chem. Soc. 2010, 132, 13621.

Alkene	Experimental Markovnikov (M)	TST ^{a,b}	CVT/SCT ^{c,b}	statistical CCNM ^d	nonstatistical CCNM ^d	best-fit RRKM-ME	localized RRKM-ME	competitive local- ized noncanonical
propene	$10.0\pm0.3\%^{\rm e}$	1.4%	2.2%	4.2%	3.3%	13.0%	8.7%	10.0%
propene at 70 °C	$11.2\pm0.3\%^{\rm e}$	2.4%	3.5%	6.4%	5.2%	13.7%	10.3%	11.1%
1-butene (2)	-	1.9%	2.8%	5.6%	4.4%	11.7%	10.9%	12.3%
1-hexene (3)	$10.7\pm0.5\%^{\rm f}$	2.0%	2.8%	6.2%	4.1%	9.5%	10.9%	11.6%
1-octene (4)	$9.8\pm0.4\%^{\rm f}$	2.1% ^g	2.9% ^g	6.1% ^g	4.5% ^g	6.8%	10.6% ^g	10.8%
1-dodecene (5)	$9.2\pm0.2\%^{\rm f}$	2.2% ^g	2.9% ^g	6.2% ^g	4.5% ^g	5.7%	10.1% ^g	10.3%
(CH ₃) ₃ C (6)	$11.2\pm0.4\%^{\rm f}$	1.8%	2.6%	1.9%	1.7%	8.6%	11.4%	11.3%

Singleton's group re-examined the problem with a combination of new experiments and detailed comparision of various models. The trend of increasing selectivity with alkyl chain length and the surprising low selectivity of the tert-butyl substituted olefin served as key tests of each model's success.

Main Takeaway:

Trends in selectivity for Markovnikov vs. Anti-Markovnikov regiochemistry are dominated by the ability of the borane-olefin complex to disipate energy and thus select between the possible pathway.



	predicted A/B ^{d,e}		
alkyl group	$\operatorname{exptl} A/B^{a,b,c}\left(n\right)$	TST	RRKM
methyl	$25.9 \pm 1.2 (12)$	43×10^5	10.0
ethyl	$36.3 \pm 1.0 (33)$	9.8×10^{5}	10.9
butyl	$47.2 \pm 2.0(14)$	$8.5 imes 10^5$	18.5
octyl	$54.8 \pm 1.8 (16)$	9.6×10^{5}	47.8
3,7-dimethyloctyl	63.2 ± 2.0 (7)	5.7×10^{5}	61
3,7,11,15-tetramethylhexadecyl	$74.5 \pm 1.9(9)$	9.6×10^{5}	343
ethyl $(-31 ^{\circ}C)$	$33.7 \pm 1.3(10)$	2.4×10^5	10.9
ethyl (8 °C)	$24.7 \pm 1.4(10)$	0.45×10^5	10.9
ethyl (23 °C)	23.6 ± 2.1 (14)	0.26×10^{5}	10.8
octyl (-31 °C)	$51.5 \pm 1.0(5)$	2.5×10^{5}	47.9
octyl (8 °C)	$43.1 \pm 0.6(7)$	0.44×10^{5}	48.0
octyl (23 °C)	$40.0 \pm 0.7 (8)$	0.26×10^{5}	48.1

TST based predictions are off by several orders of magnitude. RRKM predictions are much closer and qualitatively predict the improved selectivity observed with increased alkyl group size, yet err in accurately quantifying the magnitude of the trend.

Direct-dynamics trajectory calculations much more reliably matched the experimental results. Analysis of the trajectories showed that the alkyl group takes up kinetic energy at a rate of ~20 kcal/mol/ps with the rate increasing slightly as the group becomes larger. The long delay time between primary ozonide formation (~70 fs) and ozonide cleavage (>200 fs) was interpreted to mean that dynamic matching isn't involved.

Hydroboration and ozonolysis both show improvements in selectivities with increased alkyl group size, even fairly remote from the reaction site. These molecular heat sinks help spread out the thermal energy deposited into the reactive intermediates, effectively cooling the vibrationally hot state that is initially formed.

RRKM

Prediction

1.043

1.053

1.053

1.060

1.030

1.037



Different conditions for fragmentation showed distinct KIE's that tracked well with the different energy release expected from each condition. This "energy" labelling" allowed calculation of the E_{vib} in the radical from the observed KIE and prediction of the KIE from estimated Evib values.

Using these calculated vibrational energies, application of RRKM theory produced KIE's close to experimental values. A localized RRKM model that assumes IVR only in close proximity to the cyclobutane reduced the error for the octyl substituted substrate.

Experimental

KIE

1.044(1)

1.051(2)

1.051(2)

1.058(1)

1.027(2)

1.067(2)



Carpenter, B. K. J. Am. Chem. Soc. 1995, 117, 6336.



In the study of a formal [1,3]-sigmatropic rearrangement, the stereochemical outcome of the reaction was found to be hard to consistently rationalize using existing theories of reactivity.

High levels of apparent stereospecificity in accordance with Woodward-Hoffmann rules suggest a concerted pericyclic mechanism.

Change between inversion and retention of stereochemistry go against Woodward-Hoffmann rules, making pericyclic mechanism unlikely.

Inverse relationship between temperature and selectivity is opposite of what is predicted by 7 TST/ any thermal statistical model.



Carpenter, B. K. J. Am. Chem. Soc. 1996, 118, 10329.

Direct-dynamics calculations showed a bimodal distribution in intermediate lifetime, wherein molecules that didn't quickly turn over into product remained in the intermediate for extended times. Reversing the phase of the vibrational mode corresponding to the critical C-C bond rotation had to effect of drastically increasing the intermediate lifetime.

Dynamic Matching Model:

C-C bond homolysis is strongly coupled to a specific bond rotation that aligns well with the exit-channel for the biradical intermediate, leading to the observed tendency for inversion of stereochemistry.



Preference for ring inversion in the shown thermal deazetization has been justified using a dynamic matching argument. The decrease in selectivity in high pressure reactions in supercritical propane and was suggested to provide evidence for the dynamic effect. The lack temperature dependence in various solvents provides further evidence over a traditional explanation of two competing mechanisms.







Baldwin, J. E. et. al. J. Am. Chem. Soc. 2002, 124, 380.

Careful kinetic analysis of the thermal rearrangement of bicyclo[3.1.0] hexenes show unequal rate constants in the formation of the isomeric products.

Similar results have been found by Doering in studying the thermal rearrangement kinetics of thujene. Doering, W. v. E., *et. al. Tetrahedron*, **1963**, *19*, 1989. Doering, W. v. E. *et. al. J. Org. Chem.* **2006**, *71*, 5688.



Doubleday, C. et. al. J. Am. Chem. Soc. 2006, 128, 90.

Houk and Doubleday investigated this system computationally, running dynamic simulations across the "caldera" potential surface. The agreement with Baldwin's experimental results were excellent (within sampling error \sim 1.5%), and a simple vectorial decomposition model is sufficient to qualitatively agree with the results.



Behavior at bifurcations in the reaction coordinate are fundamentally outside of the scope of traditional TST to predict. With a single transition state leading to two (or possibly more) potential products, additional criteria must be used in order to model reaction outcome.

Some factors to consider:

- 1) The steepest decent path in the potential energy surface, which defines the intrinsic reaction coordinate (IRC)
- 2) Asymmetry in the transition state which causes it to resemble one product over the other
- 3) Dynamic matching between the reaction coordinate leading over the transition state and one of the two products

Degenerate Symmetric Bifurcations:



When a product is formed from a transition state of a higher level of symmetry, the potential energy surface will inevitably bifurcate into enantiomers or equivalent structures. While these degenerate cases are trivial with respect to observable, experimental outcomes, they do serve as simple theoretical platforms for computational study.

Important features:

Because of the symmetry of the potential energy surface, 1) no unique IRC can be defined,

2) the true transition state will equally resemble both products,3) dynamic matching cannot favor one product over another.

Product determination can be thought of in the classic Newtonian sense as falling out of the position and momentum of relevant atoms as the transition state is passed, or quantum mechanically as coming from the time-dependent phase information in the vibrational mode that defines the coordinate separating the two products.



Cyclopentadiene dimerization:

Early work by Caramella proposed that the dimerization of cyclopentadiene passes through a so called bispericyclic transition state, wherein each monomer is aligned to act as the diene or the dienophile.





Caramella, P. et. al. J. Am. Chem. Soc., 2002, 124, 1130.

Divergent dienone cycloadditions:



Singleton and coworkers examined the relative preference of dienones to react as 2π or 4π components in cycloaddition reactions with dienes. Calculated transition states were bispericyclic in nature but had geometry most closely resembling the favored product. Experimental KIE's supported the asynchronous nature of the reaction.



Thomas, J. B. et. al. J. Am. Chem. Soc. 2008, 130, 14544.

Hetero Diels-Alder:



Greater than 50% of trajectories recross the transition state and return to starting material without forming product. Selectivity in simulations was strongly correlated to an internal vibrational mode in the transition state and the random phase that was applied to it.

Spinosyn A Biosynthesis:



[6+4] Cycloaddition of Tropone and Dimethylfulvene:

Houk and coworkers computationally analyzed the formation of the 2:1 adduct of tropone and dimethylfulvene, finding that the initial [6+4] cycloaddition passes through an ambimodal transition state. Trajectory simulations showed that both [6+4] pathways are apparently operative, with a subsequent Cope rearrangement interchanging the two intermediates which are then funneled to the ultimate product. The calculations suggest that the higher energy intermediate is formed preferentially, and methyl substitution had little impact on transition state structure but negatively impacted bond formation at the substituted carbon.



Nitration of Toluene

Classic textbook organic chemistry reaction, with known ortho/para regioselectivity regularly rationalized on the basis of carbocation stability or FMO theory alongside general electrophilic aromatic substitution chemistry. Olah and coworkers discovered apparent discrepancy between intra- and intermolecular selectivites in the reaction of nitronium salts and toluene, and they provided a TST consistent rationalization; however, Singleton and coworkers recently evaluated this reaction computationally and found that the mechanistic details deviate significantly from TST.



Only small variations in regioselectivity over diverse nitration conditions.

Mechanistic Proposal under TST:



Singleton's group extensively explored the reaction of $NO_2^+BF_4^-$ with toluene in DCM, and found that a diverse array of calculations using implicit solvent utterly failed to reproduce the observed selectivities. Only when solvent was explicitly calculated could matching results be found.

•	•	-
Model:	# of TS's Identified:	Selectivity (ipso/ortho/meta/para):
Experiment	-	(3) / 57 / 2 / 41
Implicit Solvent, w/o BF4 ⁻ , IRC analysis	5	26 / 20 / 0 / 54
Implicit Solvent, w/o BF ₄ ⁻ , trajectory	"	21 / 20 / 11 / 48
Implicit Solvent, w/ BF ₄ , IRC analysis	38	79 / 19 / 0.1 / 3
ONIOM Surface, w/ BF ₄ , trajectory	42	12 / 20 / 27 / 29
Implicit Solvent, w/ H ₂ SO ₄ , IRC analysis	28	11 / 76 / 0 / 13
Implicit Solvent, w/ H ₂ SO ₄ , trajectory	"	24 / 63 / 1 / 12
 105 out of 115 TSs identified show nitron heavy multifurcation of the potential energy	ium approach betwee gy surface under the i	n carbon atoms, demonstrating
Explicit Solvent, w/ BF4, trajectory	0	3 / ~50 / 2 / 45



regioselectivity would suggest.



Potential of mean force curves in explicit solvent calculations.

Representative trajectory showing nitrogen movement in explicit solvent calculation.

Explicit solvent calculation allowed exploration of a free-energy surface that notably features no free-energy barrier to C-N bond formation. Trajectory calculations have significantly improved correspondence to the experimental results, and have notably long trajectory times with a median length of 3100 fs (implicit solvent trajectories had a median 75 fs trajectory time).

Origin of Selectivity:

The authors state selectivity arises from which path intrinsically has the steepest descent and thus requires the least solvent rearrangement to stabilize the changing charge distribution.

1) A reaction under kinetic control is not necessarily under transition state control. Selectivity trends may be determined by dynamic factors rather than changes in energy barriers.

2) In evaluating mechanistic evidence, care should be taken to consider all possible explanations. The retention of stereochemical information does not necessarily rule out a step-wise process through formally symmetrized intermediates if dynamic matching is a possibility.

3) It is incredibly difficult to assess for a given reaction whether or not dynamic effects will be in play and, if they are, the nature and magnitude of these effects if they are present.

"...the applicability of any rate theory assuming a canonical ensemble will depend on the relative rates of hot intermediates versus their rate of thermal equilibration. The latter in particular is sufficiently nebulous that chemistry has no clear criteria for recognizing when TST will not work."

Bailey, J. O. et. al. J. Am. Chem. Soc. 2017, 139, 15710.