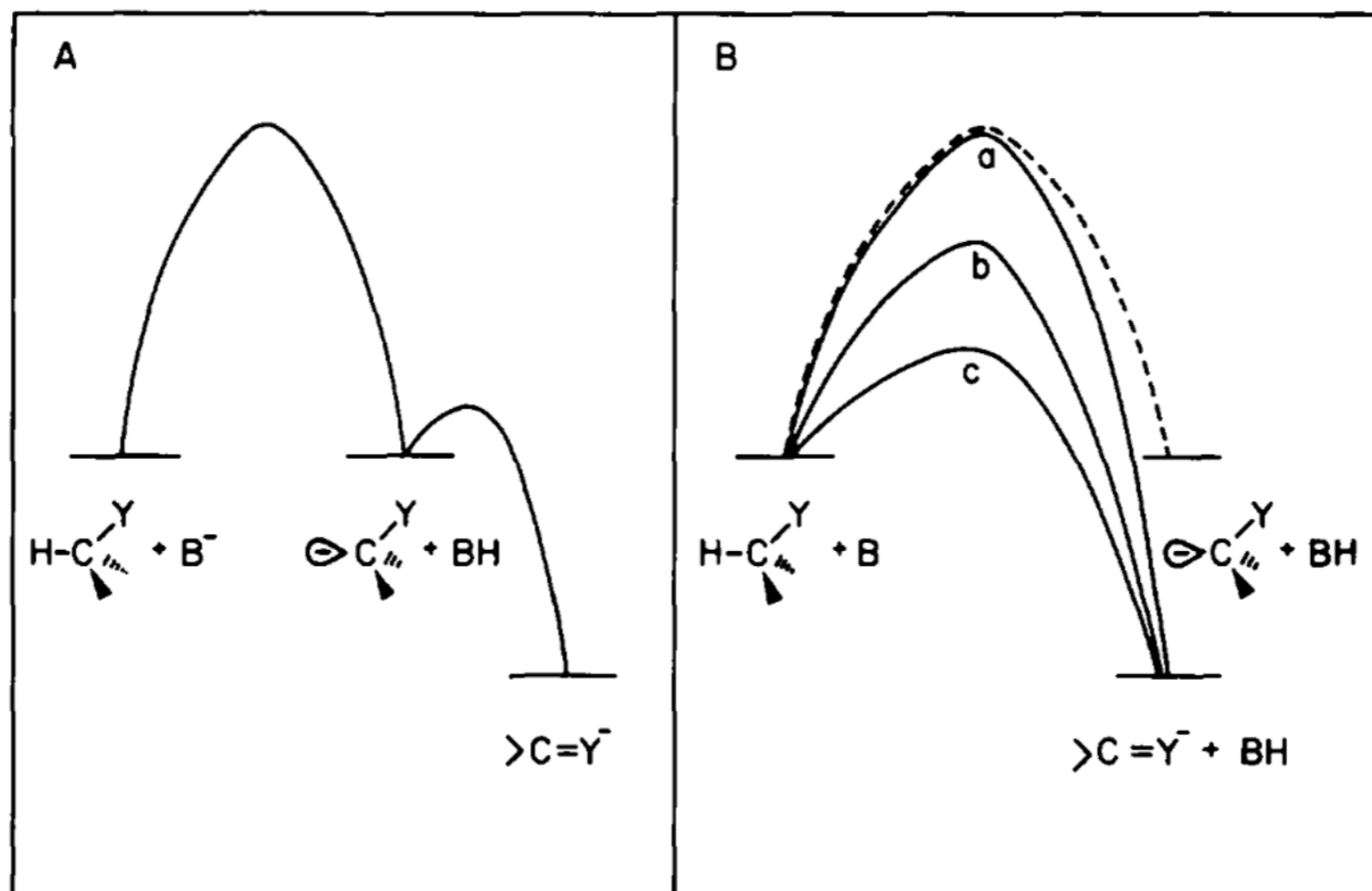
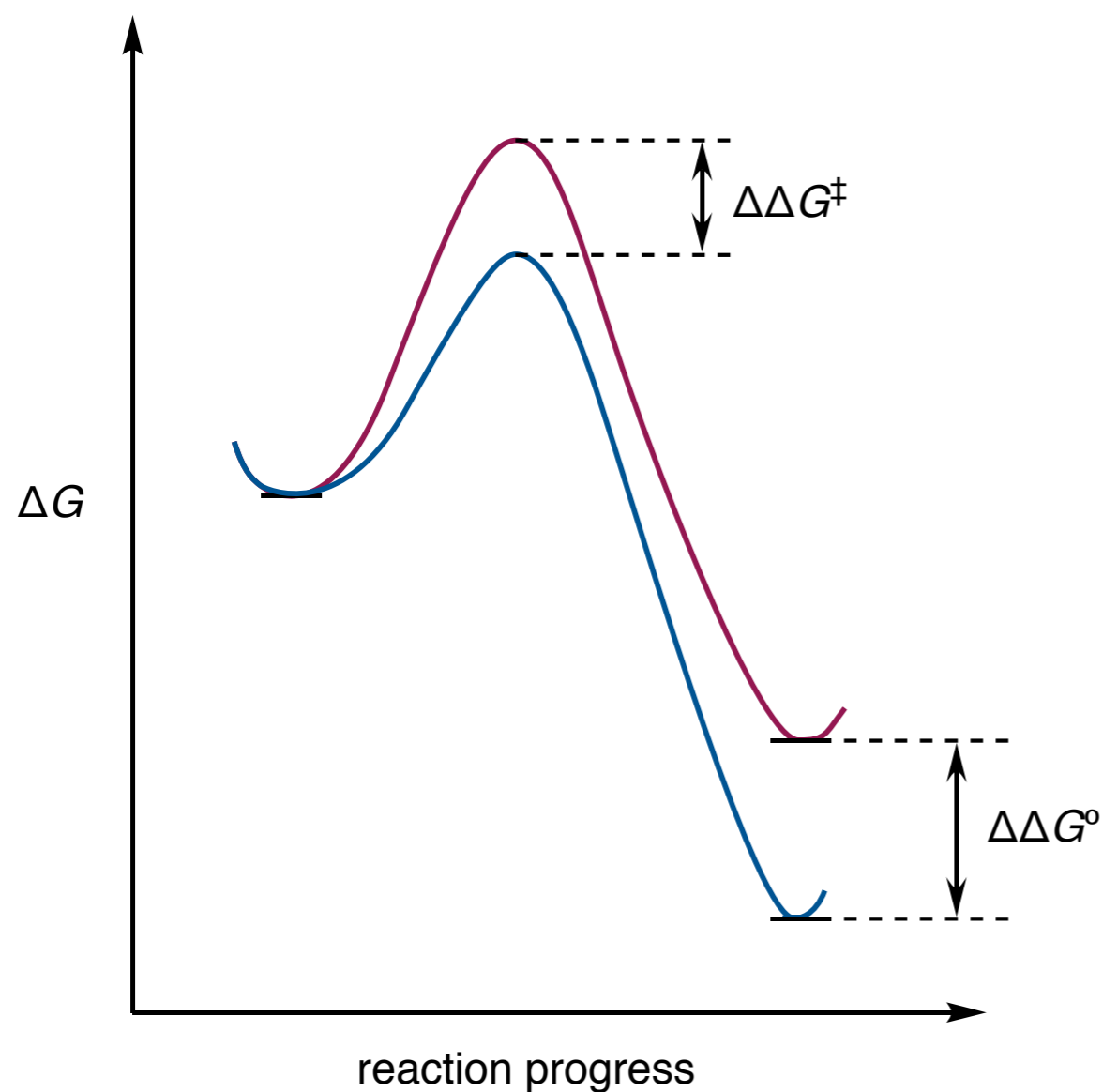


The Principle of Nonperfect Synchronization

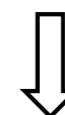


Patrick Sarver
MacMillan Group Meeting
27 June 2019

Rate-Equilibrium Relationships



a transition state has a structure that is intermediate between reactants and products



a change to the reactants should have an effect on the transition state which is intermediate between its effect on the reactants and products



in general, changes in equilibria are only partially reflected in reaction rates

$$\Delta\Delta G^\ddagger = \alpha \cdot \Delta\Delta G^\circ$$

$$0 < \alpha < 1$$

What causes these relationships to fail?

Outline

The **Principle of Nonperfect Synchronization (PNS)** describes the relationship between the intrinsic rate of a reaction and where along the reaction coordinate stabilizing (or destabilizing) effects develop

■ Physical organic background

- *Intrinsic rate constants and Brønsted relationships*
- *The nitroalkane anomaly*

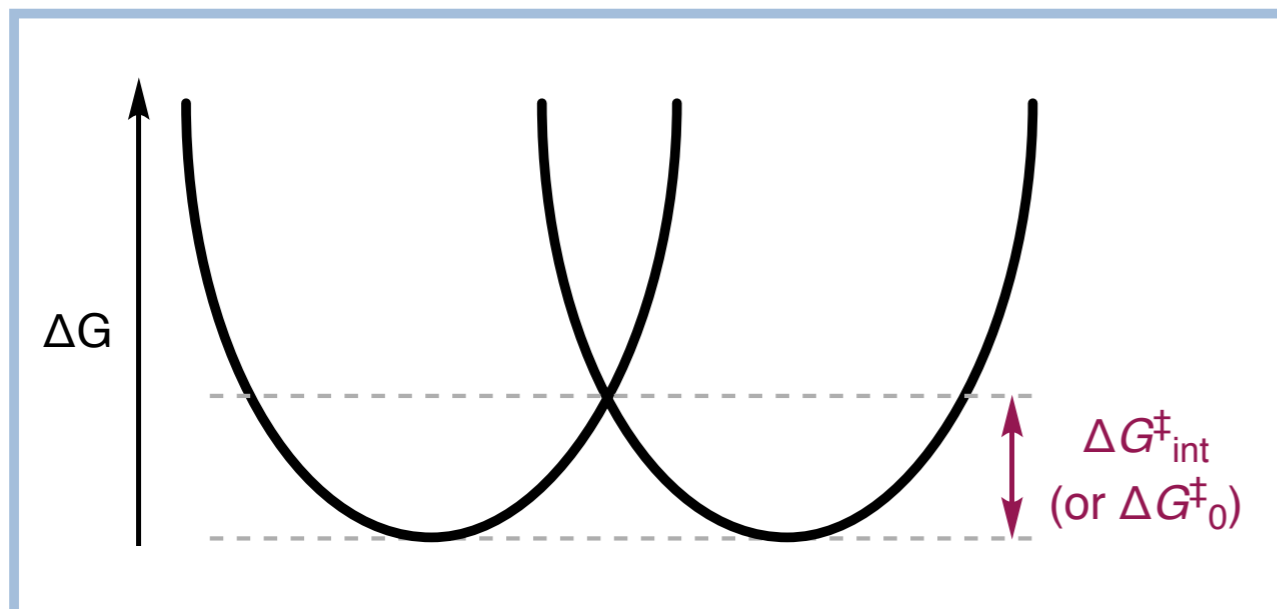
■ The Principle of Nonperfect Synchronization (PNS)

- *Proton transfer of resonance-stabilized anions*
- *Other causes*
- *Carbocations and free radicals*

■ Recent case studies

- *Predicting selectivity of C(sp³)-H DMDO oxidation*
- *Rate-driving force relationships in PCET activation of ketones*
- *Transition state asymmetry in PCET activation of C-H bonds*

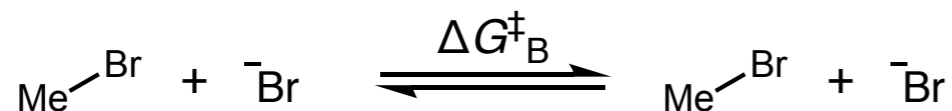
Physical Organic Background I: Intrinsic Rate Constants



The **intrinsic barrier** ($\Delta G^\ddagger_{\text{int}}$ or ΔG^\ddagger_0) of a reaction is the activation energy when $\Delta G^\circ = 0$.

The **intrinsic rate** (k_{int} or k_0) of a reaction is the rate when $\Delta G^\circ = 0$.

intrinsic rates enable kinetic comparisons between reactions of different driving forces

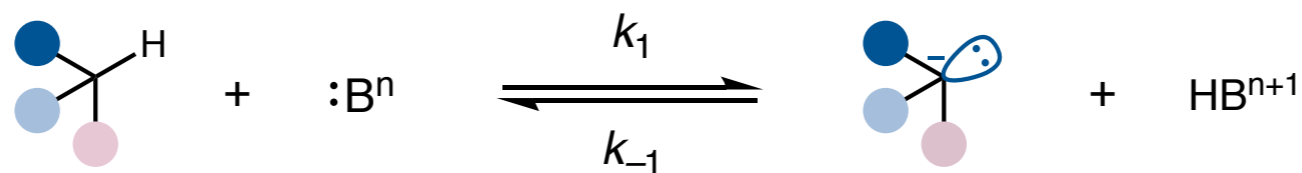


$$\Delta G^\ddagger = \Delta G^\ddagger_0 \cdot [1 + \Delta G^\circ / 4\Delta G^\ddagger_0]^2$$

solve using experimental ΔG° , ΔG^\ddagger

$$\Delta G^\ddagger_0 = (\Delta G^\ddagger_A + \Delta G^\ddagger_B) / 2$$

Physical Organic Background II: Brønsted-type Plots



for a single base, varying acid pK_a

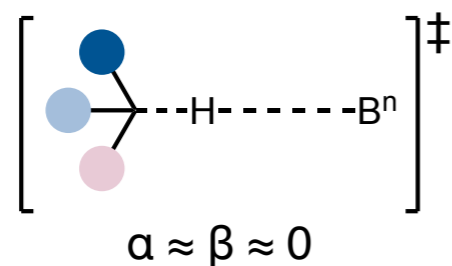
$$\log(k_1) = -\alpha \cdot pK_a + c$$

for a single acid, varying base pK_a

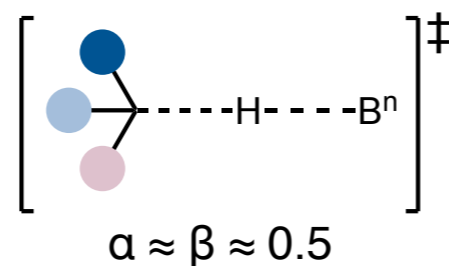
$$\log(k_1) = \beta \cdot pK_a + c$$

α , β give sensitivity of proton transfer rate to pK_a of acid, base

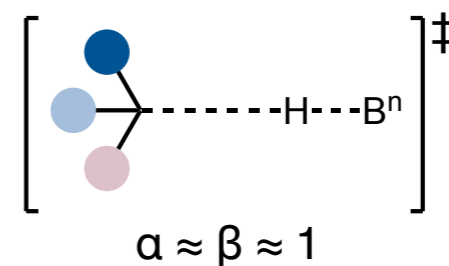
reactant-like TS



intermediate TS

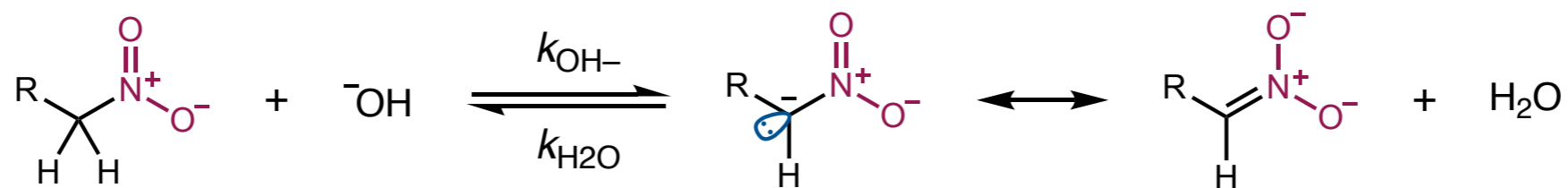


product-like TS



$\alpha \neq \beta$, $\alpha > 1.0$, or $\alpha < 0$ precluded in "normal" proton transfers

The Nitroalkane Anomaly I



substrate	pKa	k_{OH^-} ($\text{M}^{-1} \text{s}^{-1}$)
	10.22	27.6
	8.60	5.19
	7.74	0.316

acidity increases

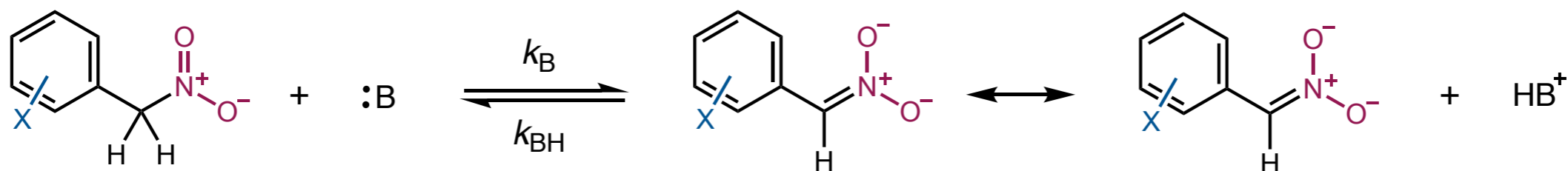
rate decreases?

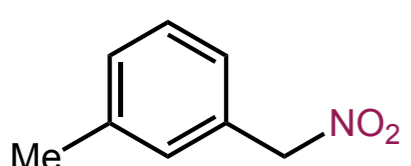
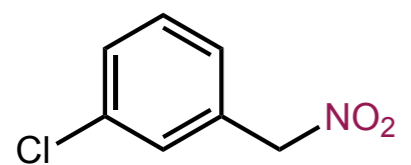
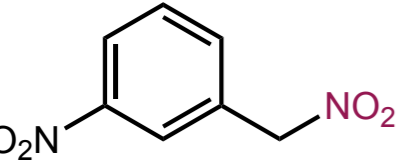
$$\alpha = -0.5 \pm 0.1$$

$$\log(k_{\text{OH}^-}) = -0.5 \cdot \text{pKa} + c$$

methyl substitution increases acidity, but reduces deprotonation rate

The Nitroalkane Anomaly II



substrate	$\text{p}K_a$	k_{OH^-} ($10^2 \text{ M}^{-1} \text{ s}^{-1}$)
	6.97	1.24
	6.63	4.78
	6.30	12.5

base	$\alpha_{\text{C-H}}$	β_B
OH^-	1.54	nd
morpholine	1.29	0.55
2,4-lutidine	1.30	nd

$$\log(k_B) = -\alpha_{\text{C-H}} \cdot \text{p}K_a + c \quad \text{effect of acid p}K_a \text{ on rate}$$

$$\log(k_B) = -\beta_B \cdot \text{p}K_a + c \quad \text{effect of base p}K_a \text{ on rate}$$

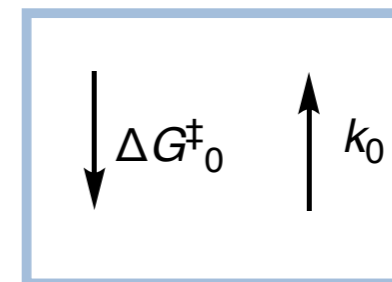
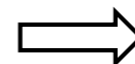
$\text{p}K_a$ decreases by 0.67, $\log(k_{\text{OH}^-})$ increases by 1.00

$\alpha \neq \beta$, $\alpha > 1$

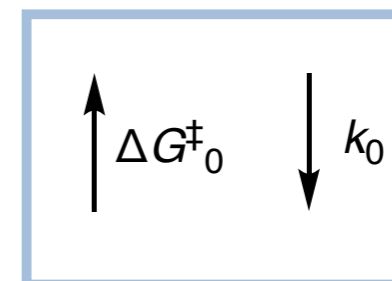
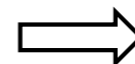
deprotonation rate more sensitive to changes in $\text{p}K_a$ than $\text{p}K_a$ itself!

The Principle of Nonperfect Synchronization

if a product-stabilizing factor develops early along the reaction coordinate



if a product-stabilizing factor develops late along the reaction coordinate



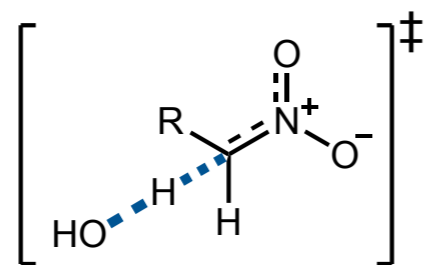
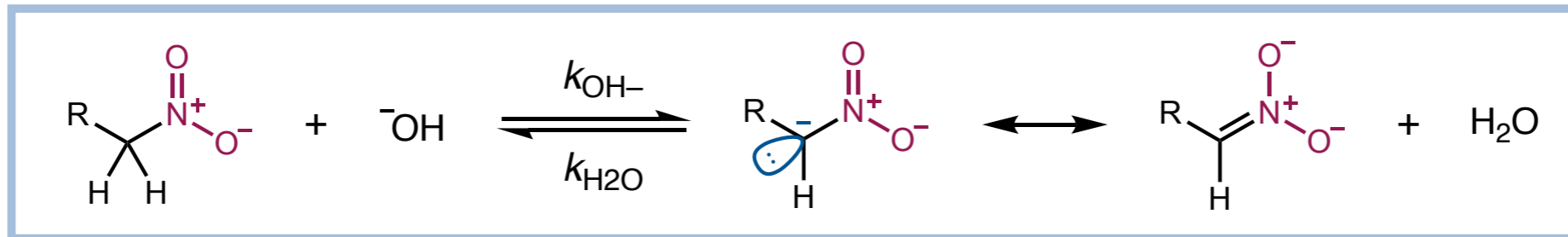
resonance stabilization, solvation, and hyperconjugation
develop late or are lost early

**reactions that generate resonance-stabilized products
have low intrinsic rate constants**

Why the unusual name?

“...it was introduced in 1985 as the principle of imperfect synchronization (PIS) but in later papers and reviews the name was changed due to the awkwardness of the acronym PIS.”

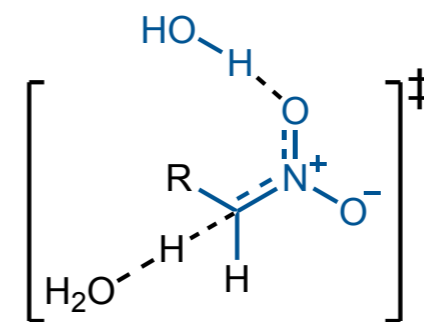
The Principle of Nonperfect Synchronization



primary processes

cleavage of C–H bond

formation of O–H bond



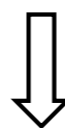
secondary processes

*resonance delocalization
(formation of C–N π -bond,
weakening of C–O π bond)*

*geometric distortion of C–H
and R–H bonds*

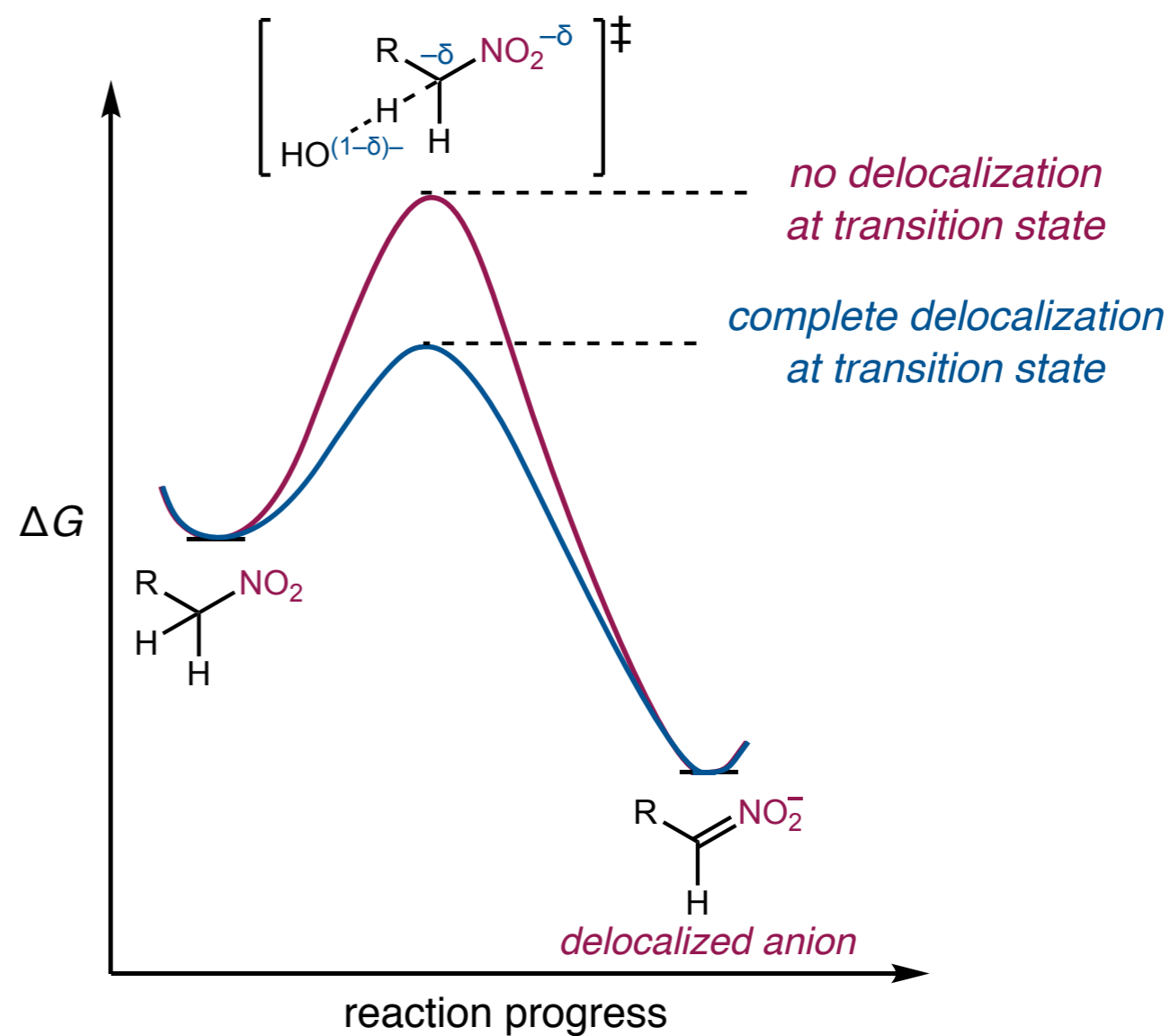
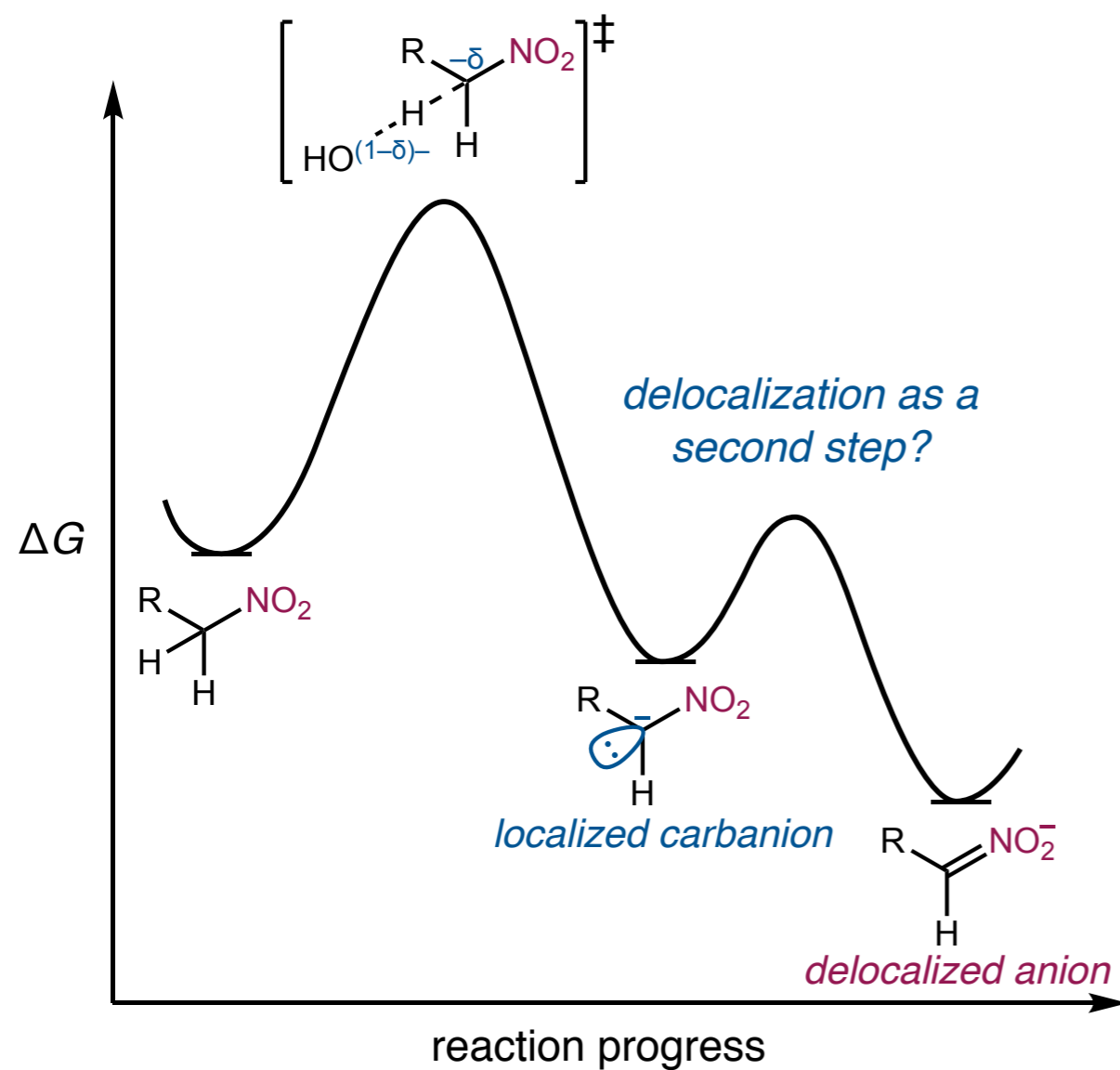
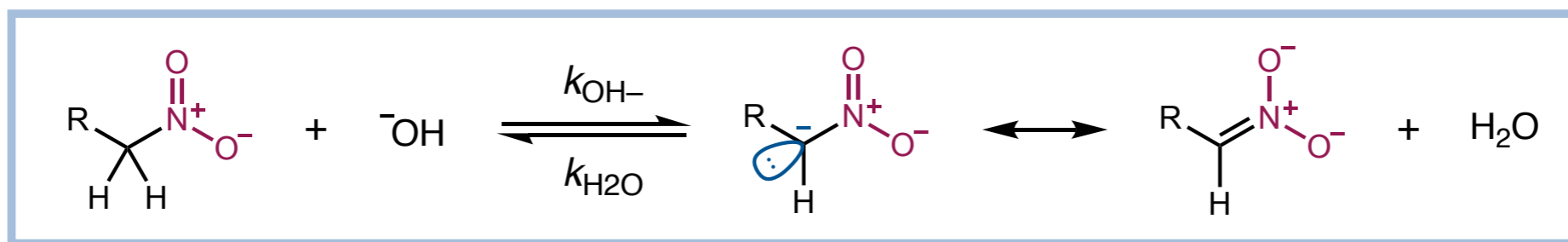
solvent reorganization

secondary processes may progress to different extents at the transition state



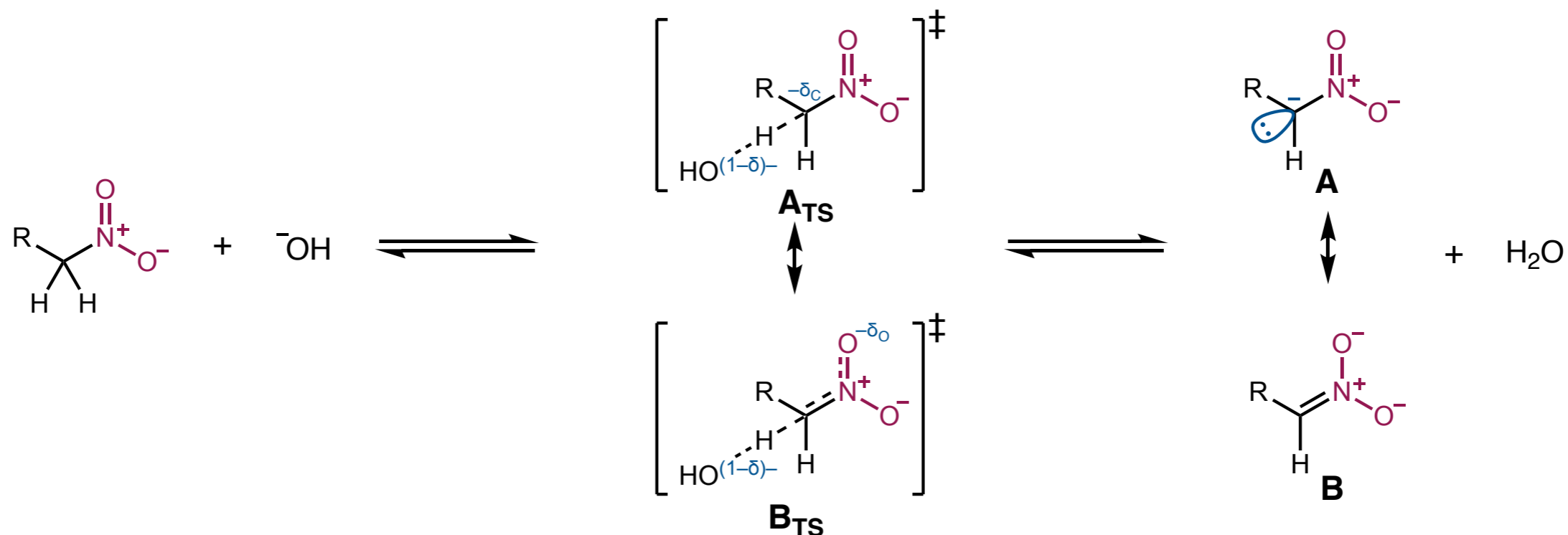
this can alter the relative energy of the transition state and product

The Principle of Nonperfect Synchronization



late development of resonance stabilization increases ΔG^\ddagger_0 , reduces k_0

The Nitroalkane Anomaly, Revisited



resonance develops late



mostly carbanion (**A_{TS}**) character in the transition state

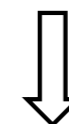


substituents that stabilize negative charge on carbon reduce ΔG^\ddagger_0 (increase k_0)

nitronate (**B**) is more stable than (**A**)

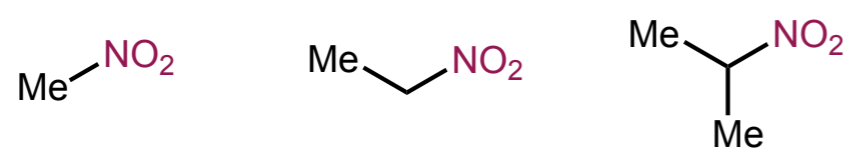
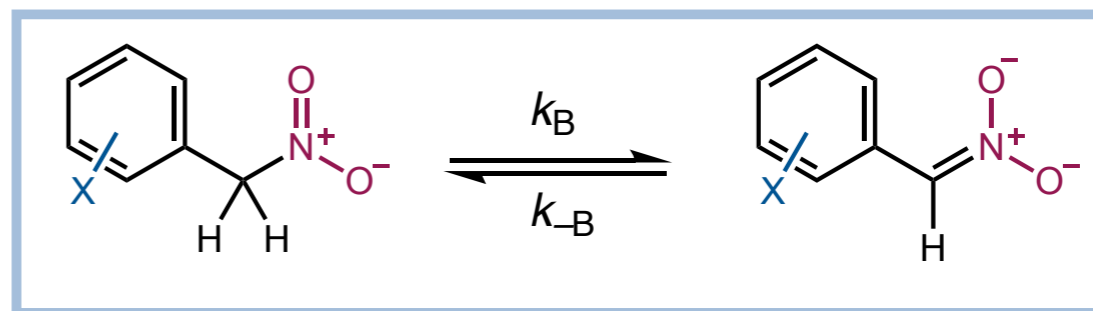
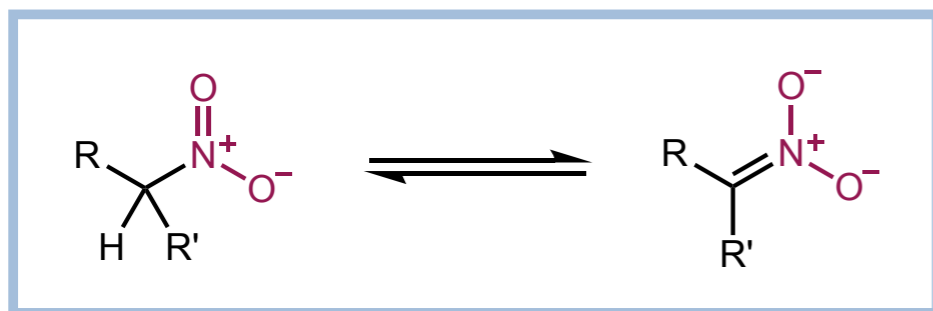


mostly nitronate (**B**) character in the product

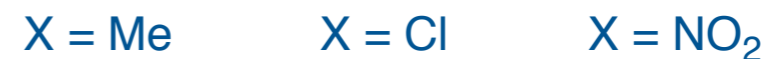


substituents that stabilize nitronate increase ΔG° (reduce pKa)

PNS Rationalizes Unusual Brønsted Coefficients



increasing acidity
 decreasing deprotonation rate

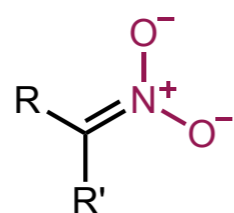
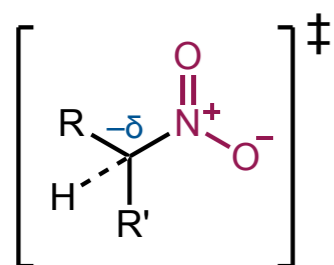


$$\alpha_{\text{C-H}} \approx 1.4$$

rate increase > pK_a increase!

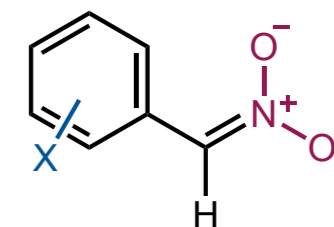
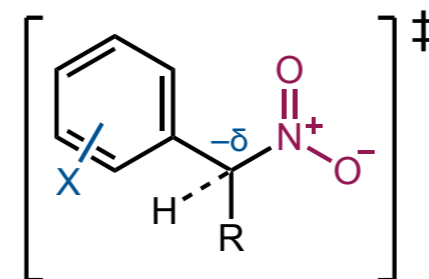
..... for R or R' = Me

..... for X = EWG



destabilizes carbanion
(electron-donating Me)

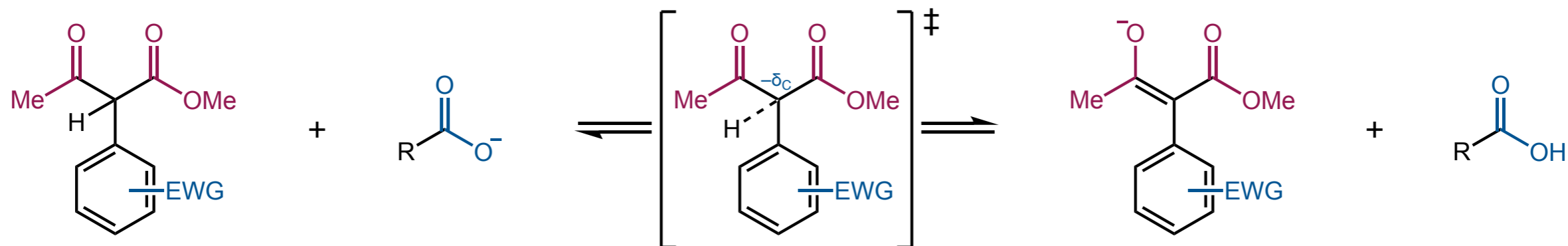
stabilizes nitronate
(hyperconjugation)



strongly stabilizes carbanion
(charge adjacent to aryl group)

weakly stabilizes nitronate
(charge distal to aryl group)

PNS Applied to Other Proton Transfers

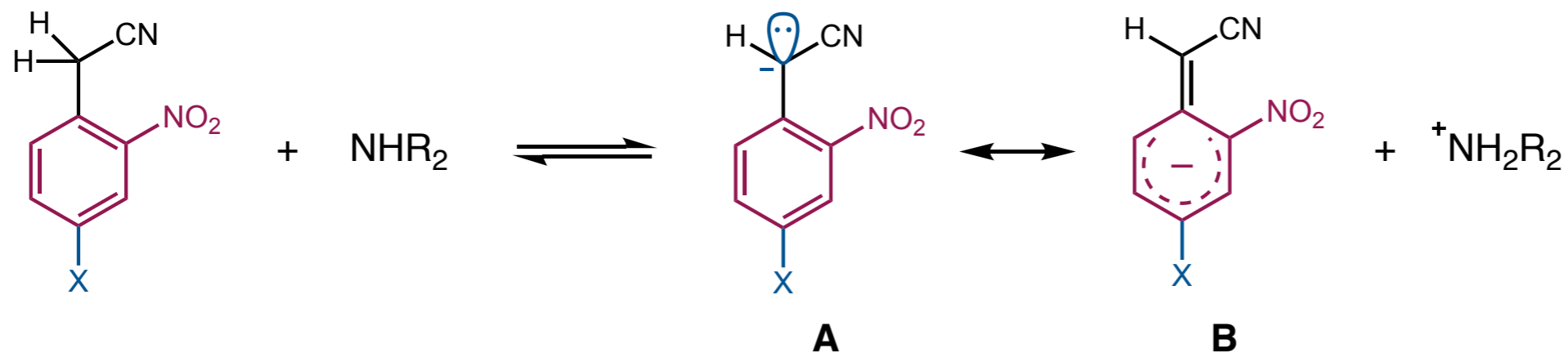


$$\alpha = 0.76$$

$$\beta = 0.44$$

$$\alpha - \beta = 0.32$$

increase in acidity disproportionately increases rate
(EWG stabilizes TS carbanion)



$$\alpha = 0.46$$

$$\beta = 0.64$$

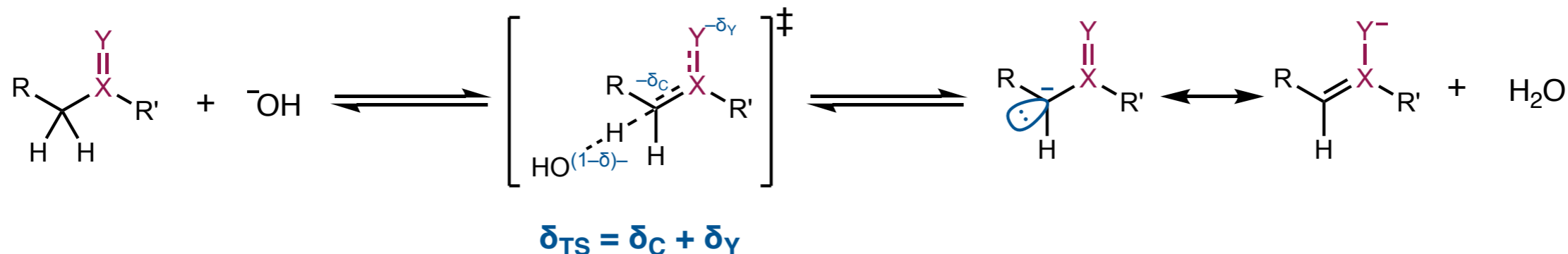
$$\alpha - \beta = -0.18$$

increase in acidity subproportionately increases rate
(EWG stabilizes product)

TS resembles **A**
(anion **distal** to X)

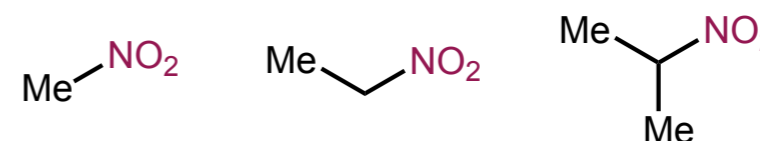
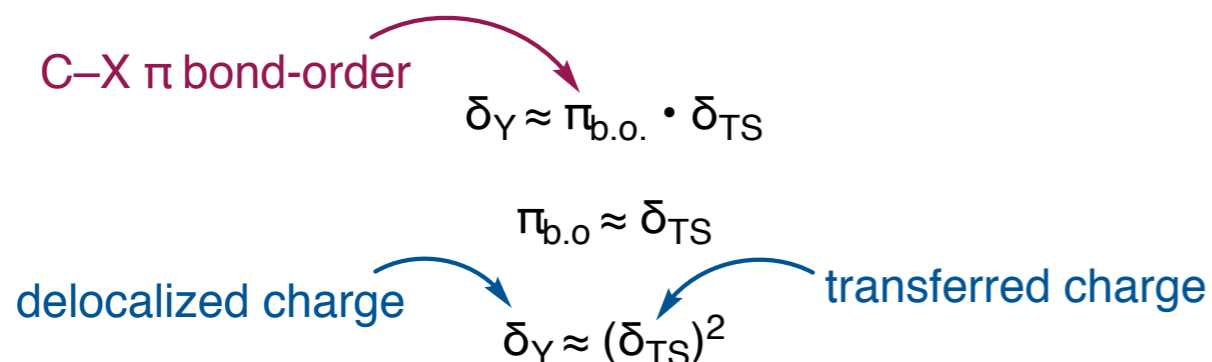
product resembles **B**
(anion **proximal** to X)

Why Does Delocalization Occur Late? Kresge's Approach



in the transition state

for nitroalkane deprotonation



$$a_{\text{exp}} \approx -0.5 \quad \delta_{\text{TS}} = 0.4$$

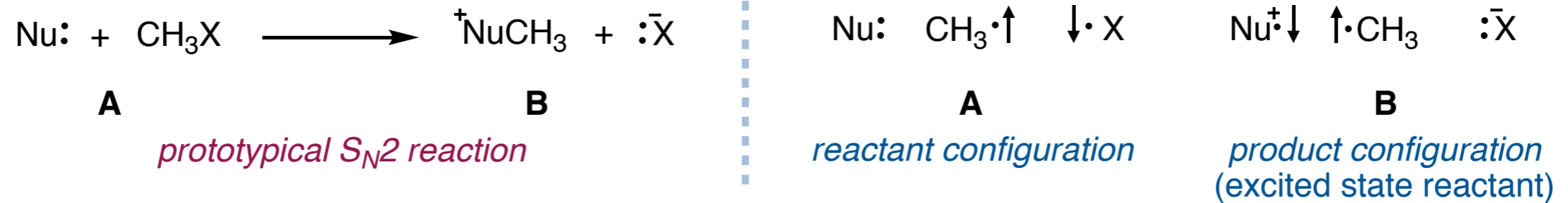
$\pi_{\text{b.o.}}$	δ_{Y}	a_{calc}
δ_{TS}	$(\delta_{\text{TS}})^2 = 0.16$	-0.23
$(\delta_{\text{TS}})^2$	$(\delta_{\text{TS}})^3 = 0.064$	-0.75

Suggests $\delta_{\text{Y}} \approx (\delta_{\text{TS}})^{\sim 2.5}$?

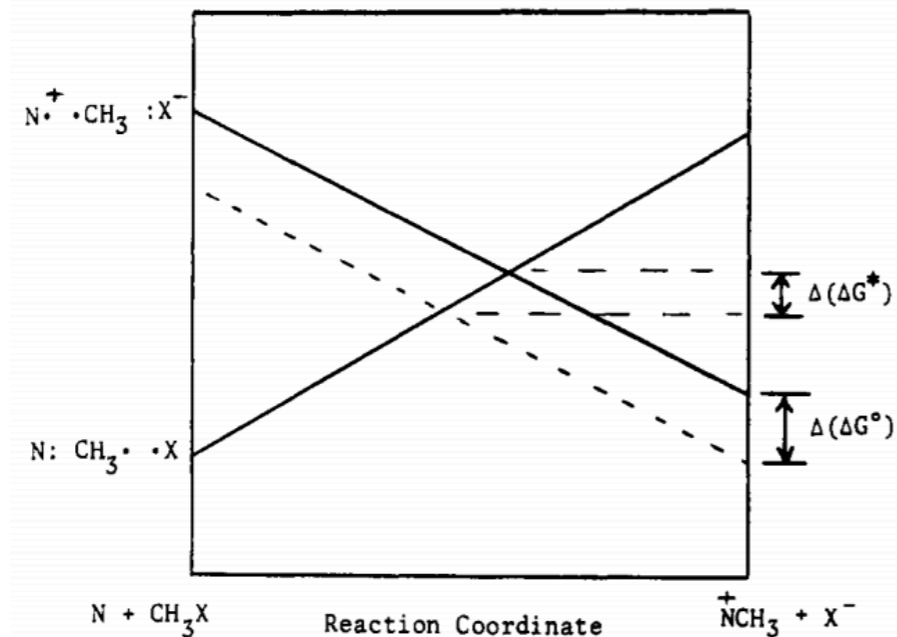
This agreement, however, must be regarded as fortuitous, for the calculations contain a number of arbitrary features. Their significance lies not so much in their ability to reproduce experimental fact, but rather in the insight they provide into Brønsted relations, especially the demonstration that Brønsted exponents outside the range zero to one can be the natural result of reasonable combinations of quite ordinary substituent effects.

Why Does Delocalization Occur Late? A VB Approach

1. Any reaction profile may be built up from a linear combination of valence bond configurations.



2. The character of the transition state depends on the weight of each valence bond structure in the linear combination at the transition state.

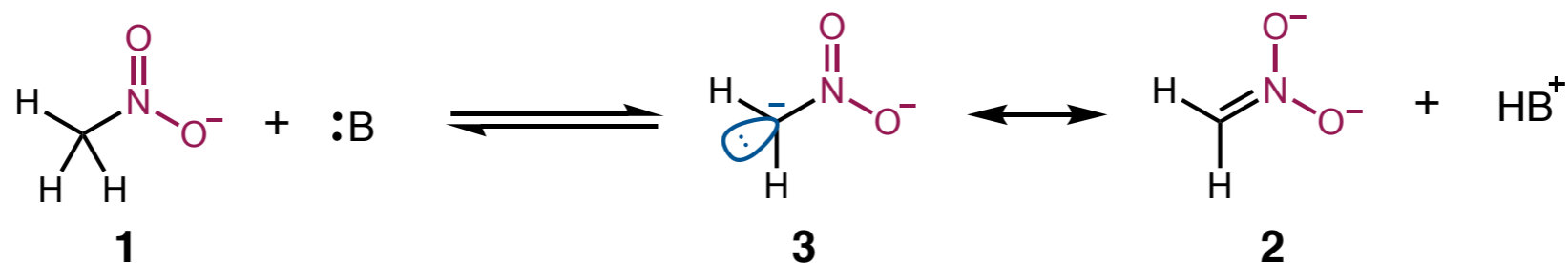


reactions which can be described by just two configurations (reactant and product) follow "normal" rate-equilibrium equations

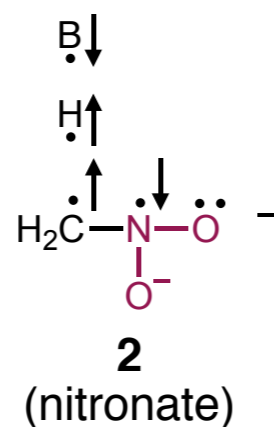
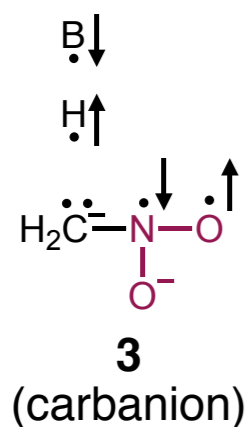
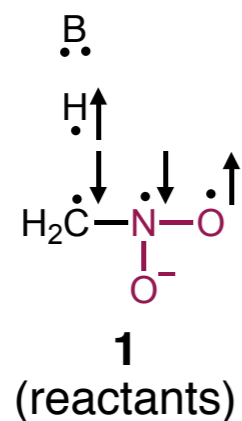
$$\Delta(\Delta G^{\ddagger}) = \alpha \cdot \Delta(\Delta G^{\circ}) \quad 0 < \alpha < 1$$

What if more than two configurations contribute to the transition state?

Why Does Delocalization Occur Late? A VB Approach

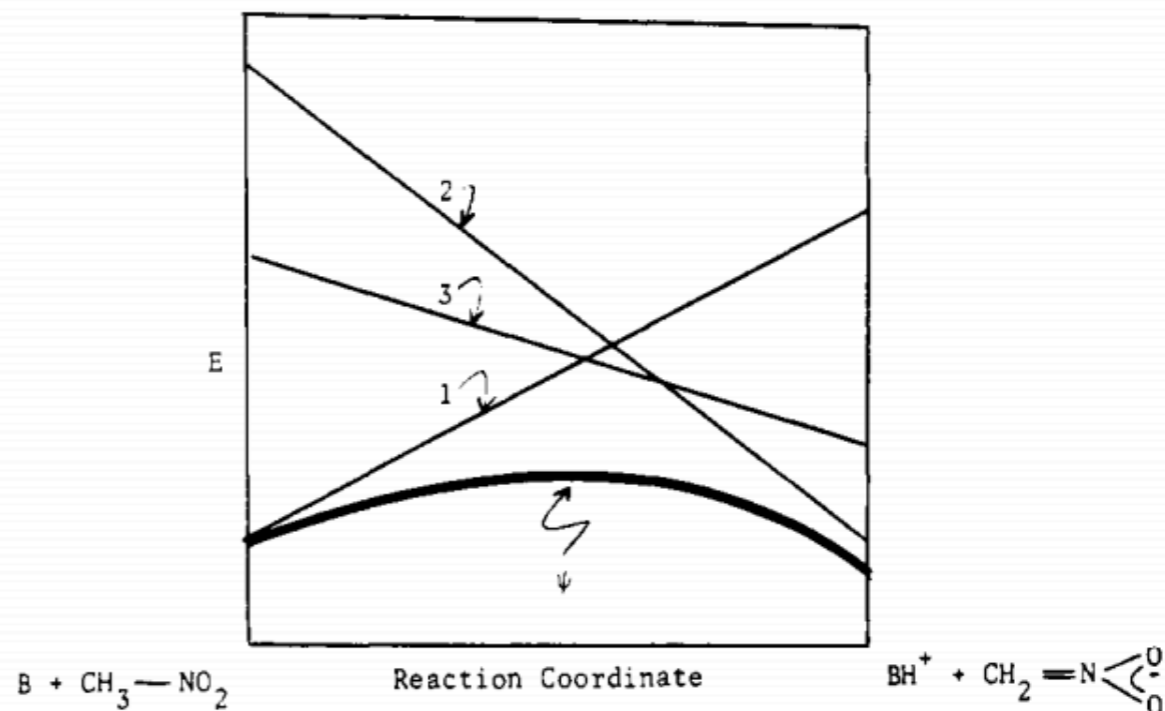


valence bond configurations



singly-excited 1

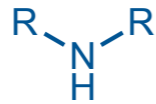
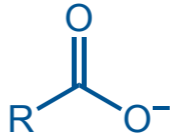
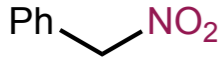
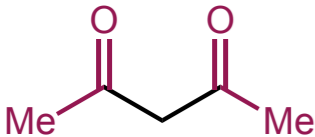
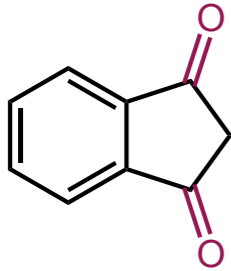
doubly-excited 1



2 is higher in energy than **3** at the end of the reaction (carbanion vs. oxyanion), but lower in energy at the transition state (singly-excited vs. doubly excited)

stabilization of 3 lowers ΔG^\ddagger more than ΔG°

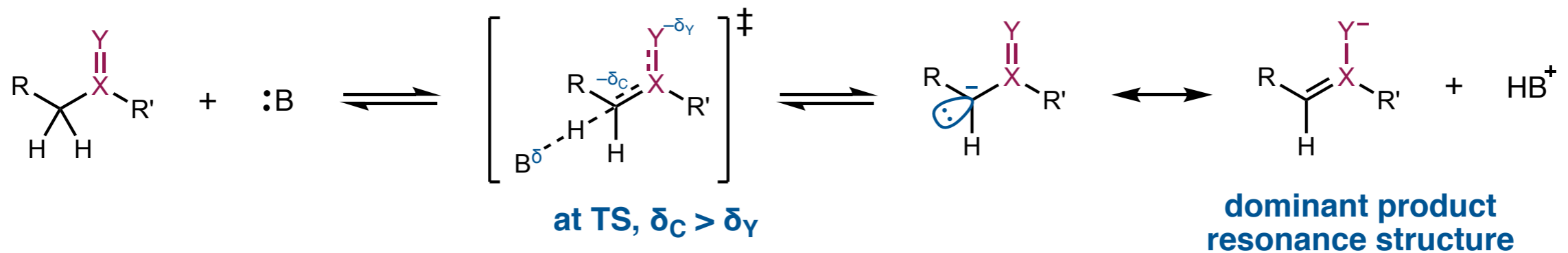
Nonperfect Synchronization of Solvent Effects

C-H acid	 $\log(k_0)$ ($M^{-1} s^{-1}$)			 $\log(k_0)$ ($M^{-1} s^{-1}$)		
	H ₂ O	1:1 DMSO:H ₂ O	9:1 DMSO:H ₂ O	H ₂ O	1:1 DMSO:H ₂ O	9:1 DMSO:H ₂ O
	-0.86	-0.25	1.75	-0.86	-0.25	1.75
	2.60	2.75	3.64	2.89	3.80	~5.3
	nd	3.13	3.85	nd	3.18	4.53

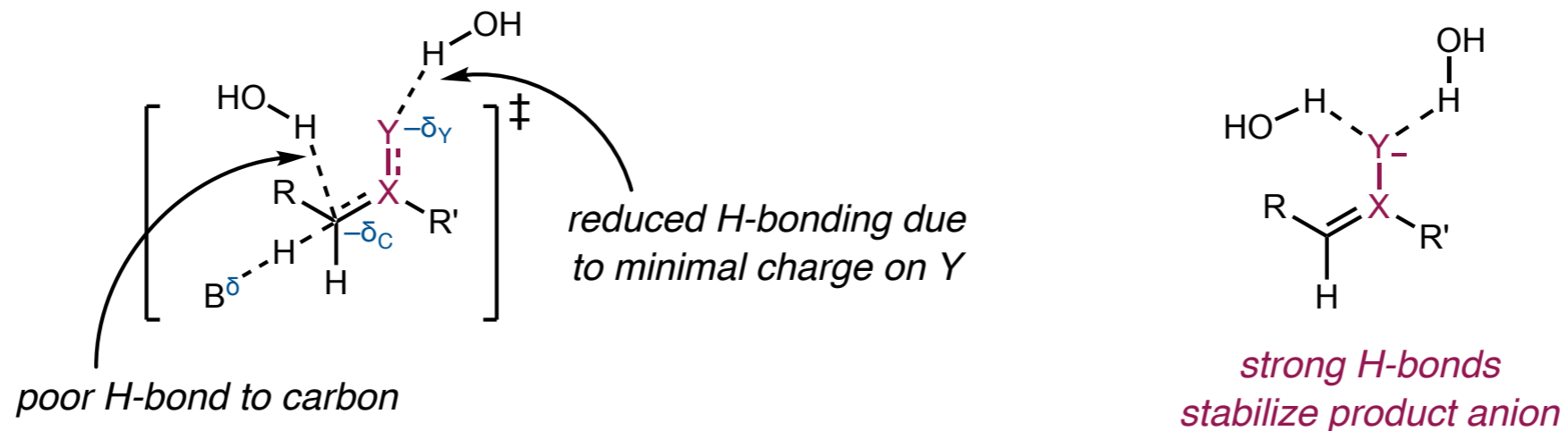
$\xrightarrow[\text{(smaller effect)}]{k_0 \text{ increases}}$
 $\xrightarrow[\text{(larger effect)}]{k_0 \text{ increases}}$

**Why does hydrogen-bonding solvent reduce k_0 ?
Why is this effect more pronounced with carboxylate bases?**

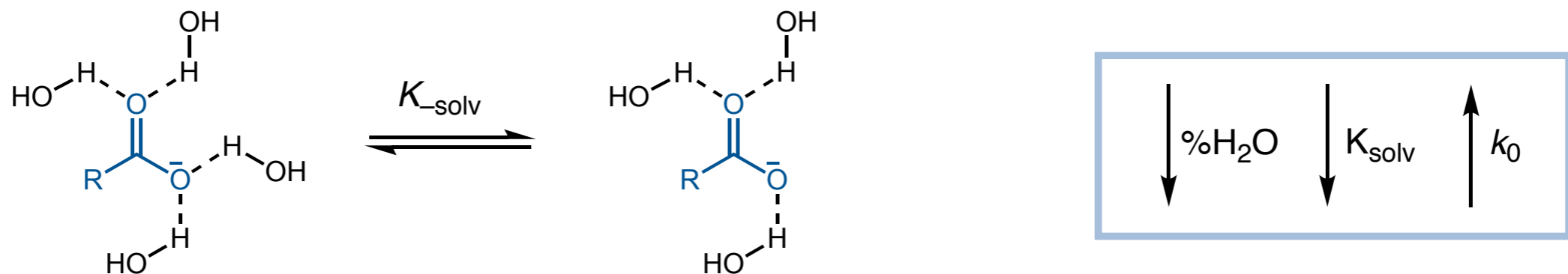
Nonperfect Synchronization of Solvent Effects



- transition state less stabilized by hydrogen bonding than product



- early desolvation must precede deprotonation by carboxylate base

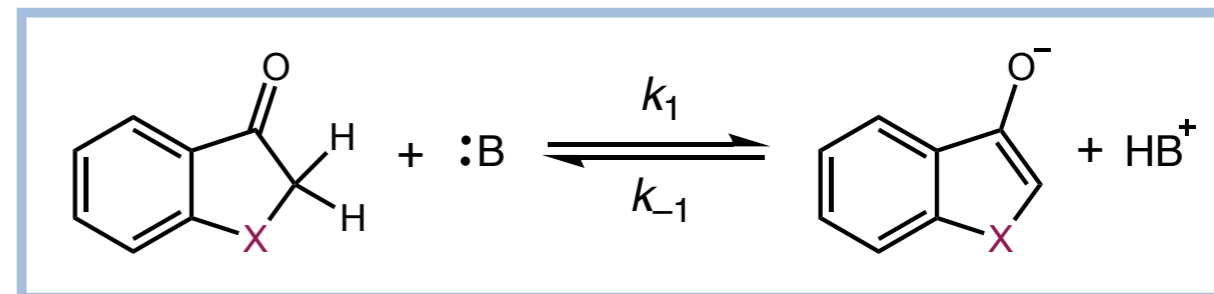
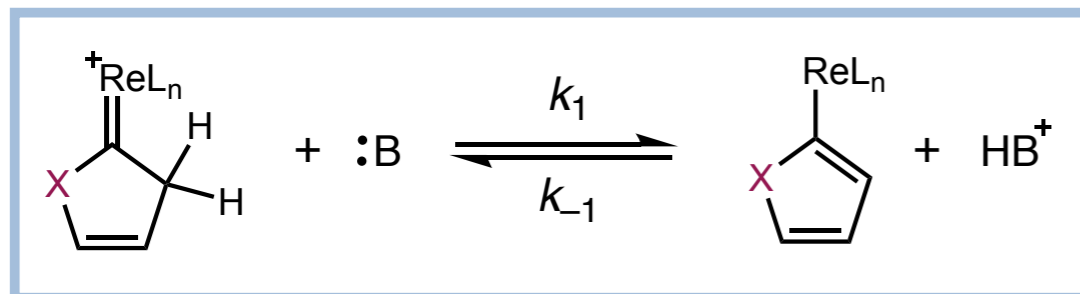


Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045–7051.

Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119–238, pp. 184–205.

Bernasconi, C. F. *Adv. Phys. Org. Chem.* **2010**, *44*, 223–324, pp. 238–242.

Development of Aromaticity: Stabilization Occurs Early?



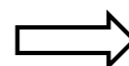
	pK _a	log(k ₀) (M ⁻¹ s ⁻¹)		
		R ₂ NH	RNH ₂	RCO ₂ ⁻
	2.50	1.05	0.27	1.21
	4.18	0.92	0.14	0.72
	5.78	-0.46	-0.88	-0.01

	pK _a	log(k ₀) (M ⁻¹ s ⁻¹)	
		R ₂ NH	RNH ₂
	9.45	2.64	1.72
	11.72	1.64	1.16

relative aromaticity:



k₀ increases with increasing aromaticity



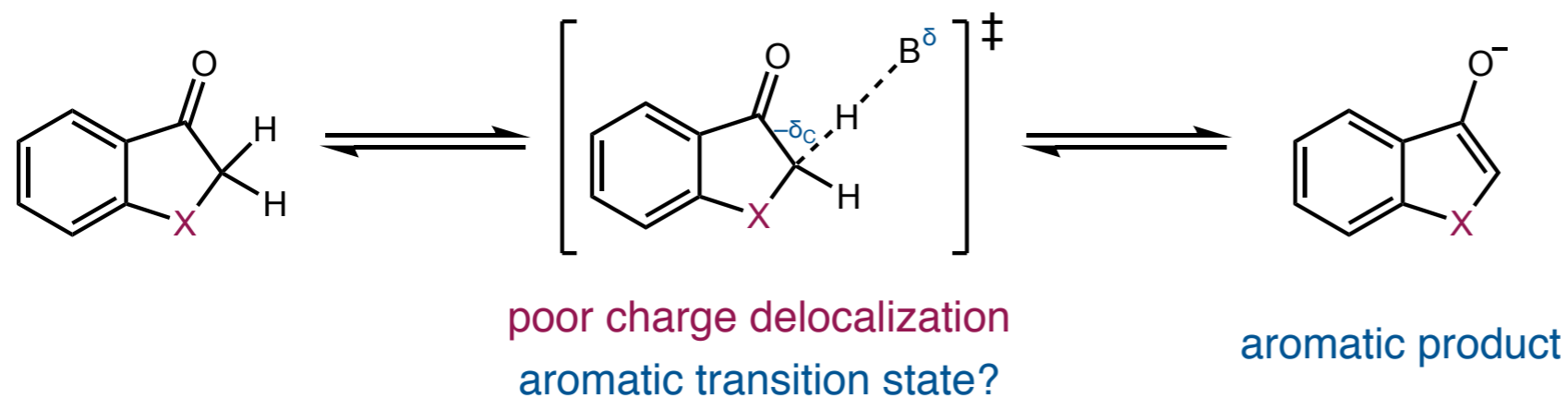
unlike resonance, aromaticity develops early?

Bernasconi, C. F.; Ragains, M. L.; Bhattacharya, S. *J. Am. Chem. Soc.* **2003**, *125*, 12328–12336.

Bernasconi, C. F.; Pérez-Lorenzo, M. *J. Am. Chem. Soc.* **2007**, *129*, 2704–2712.

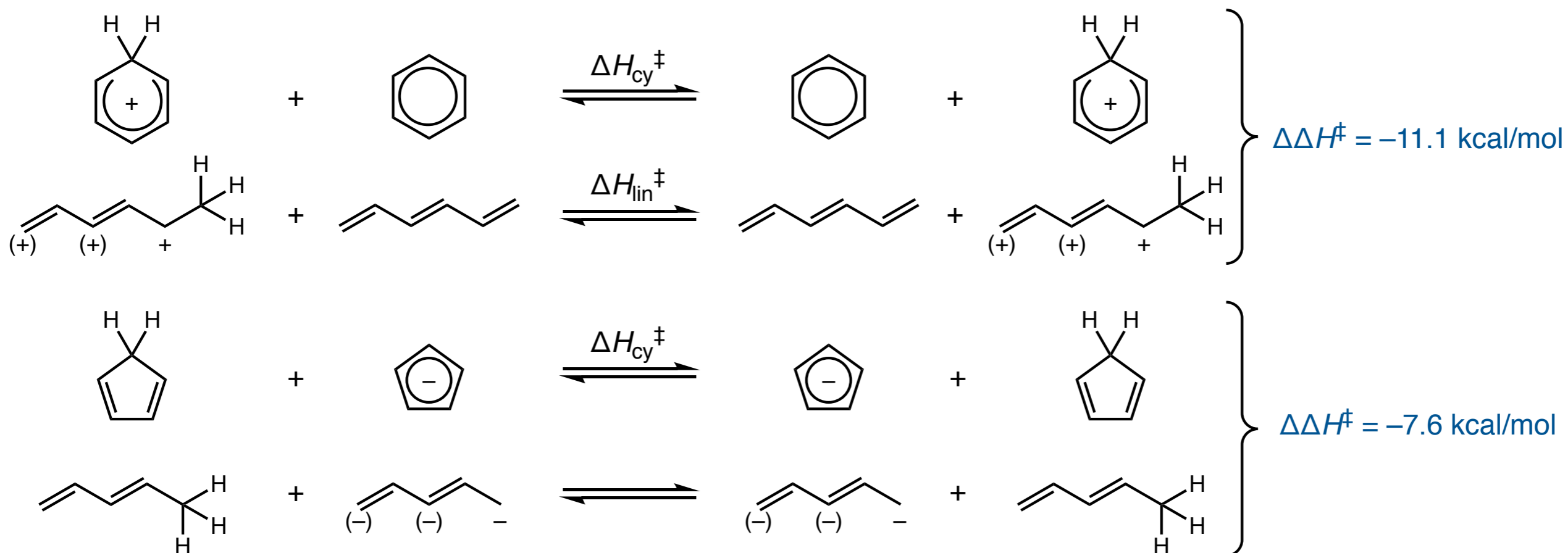
Bernasconi, C. F. *Adv. Phys. Org. Chem.* **2010**, *44*, 223–324, pp. 258–261.

Can a Poorly Delocalized Transition State Be Aromatic?

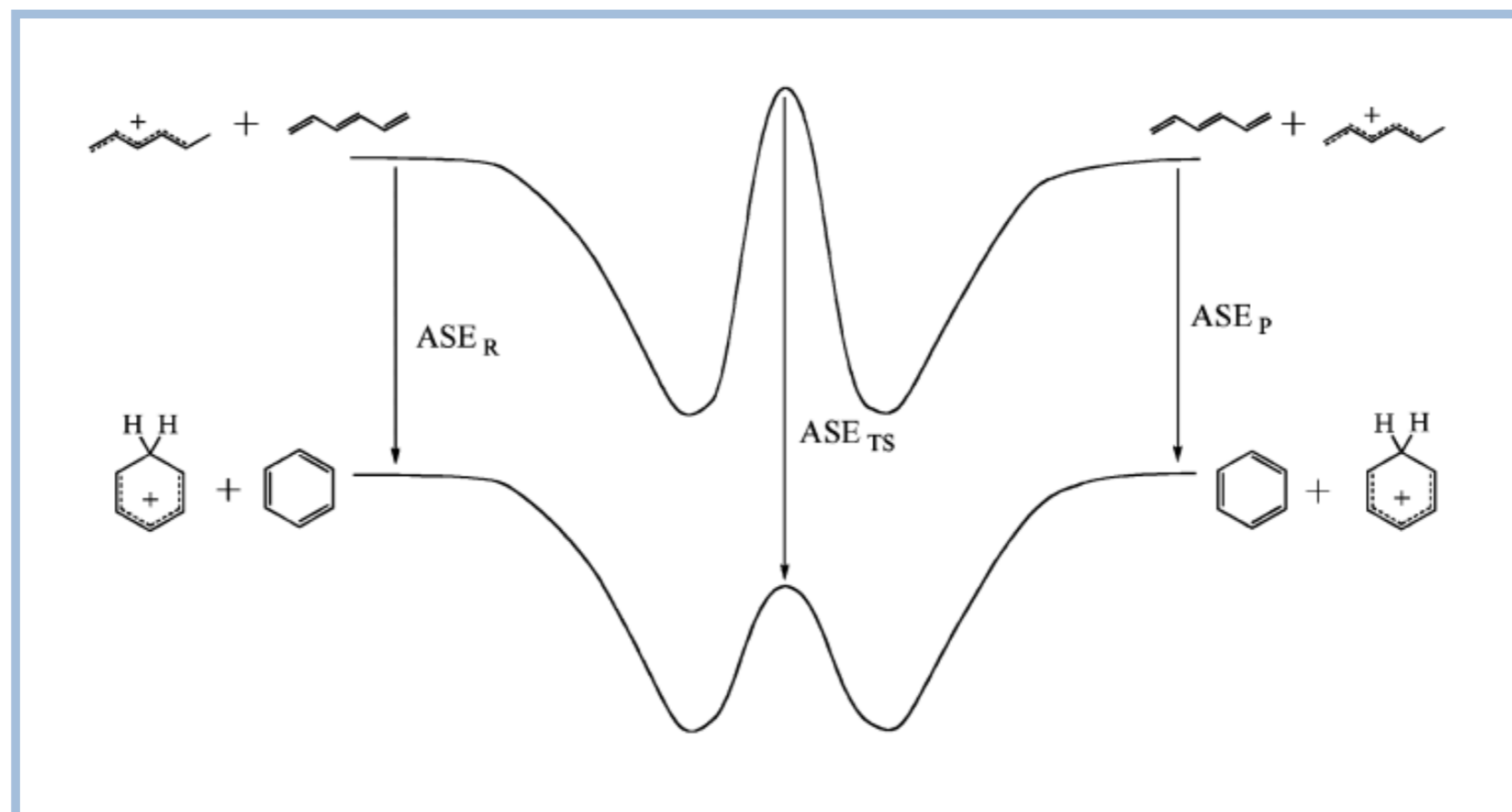


can aromaticity develop
without charge delocalization?

■ from gas-phase calculations (MP2//6-311+G(d,p))



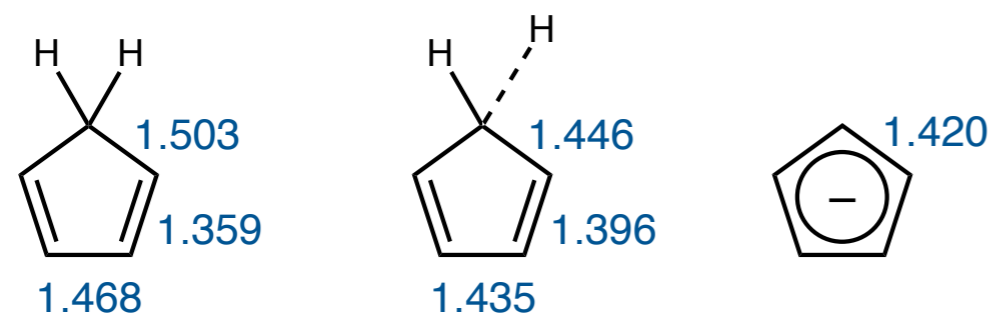
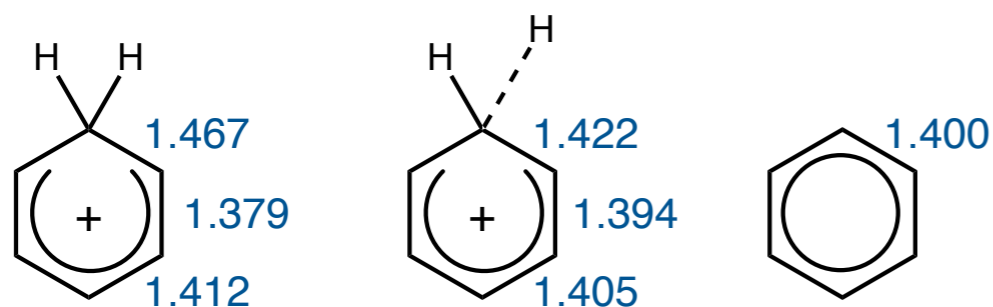
Support for Highly Aromatic Transition State



				% progress at TS	
measures of aromaticity	pyramidal angle (α)	50.1	14.5	0.0	71.0
	HOMA	0.415	0.874	0.963	83.8
	NICS(1)	-6.05	-9.26	-10.20	77.3

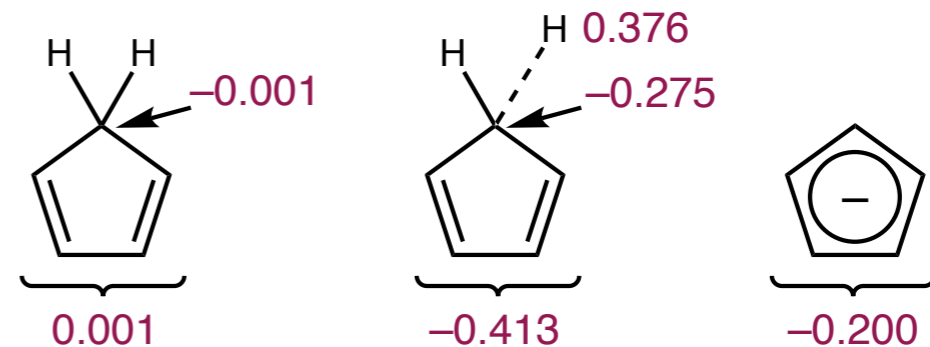
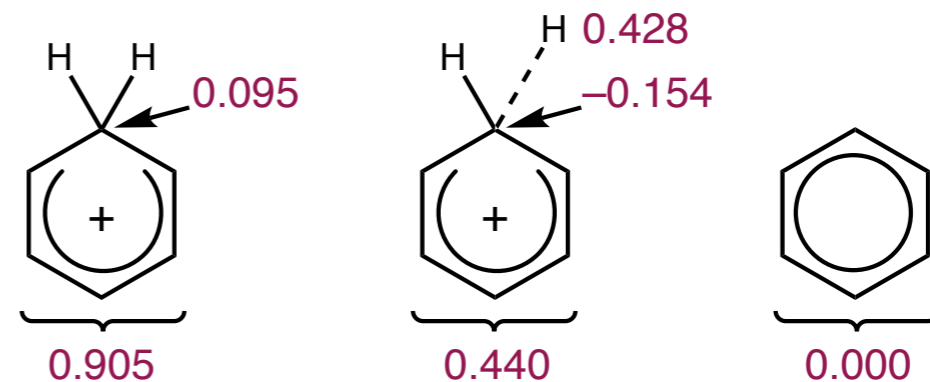
Support for Highly Aromatic Transition State

bond lengths (Å)

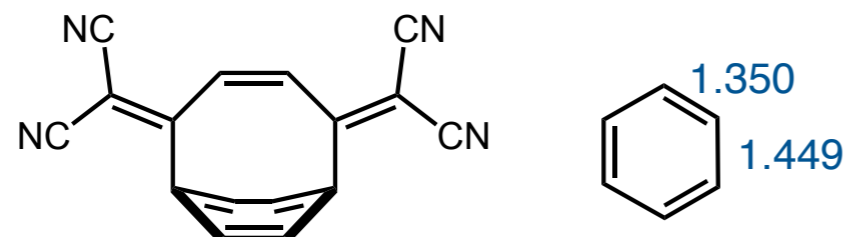


TS bond lengths resemble aromatic product

charge distribution



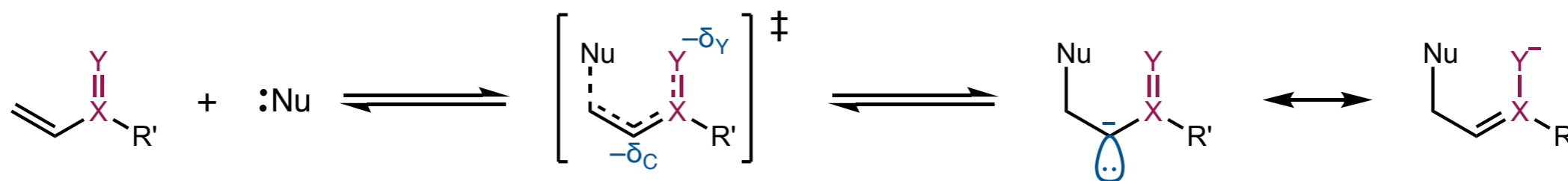
significant delay in delocalization of charge



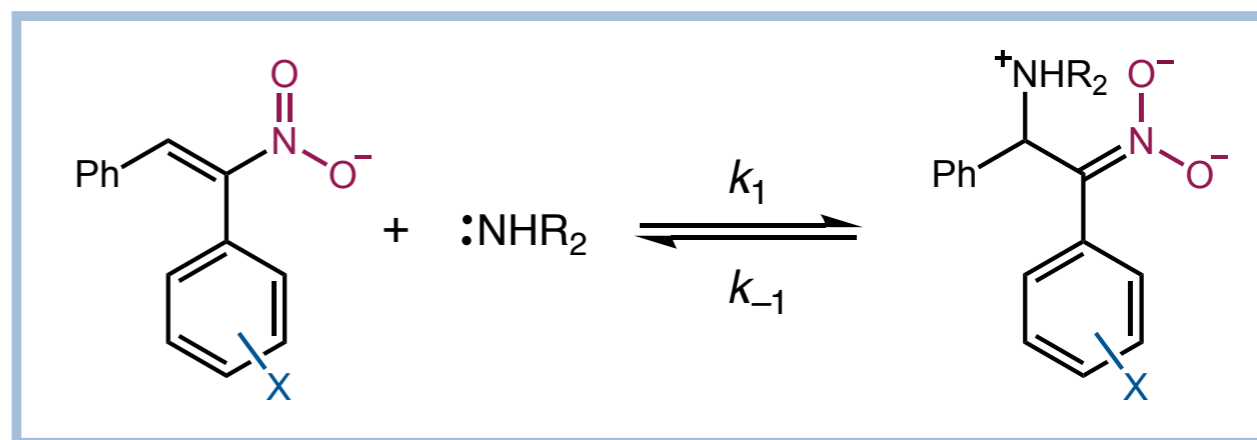
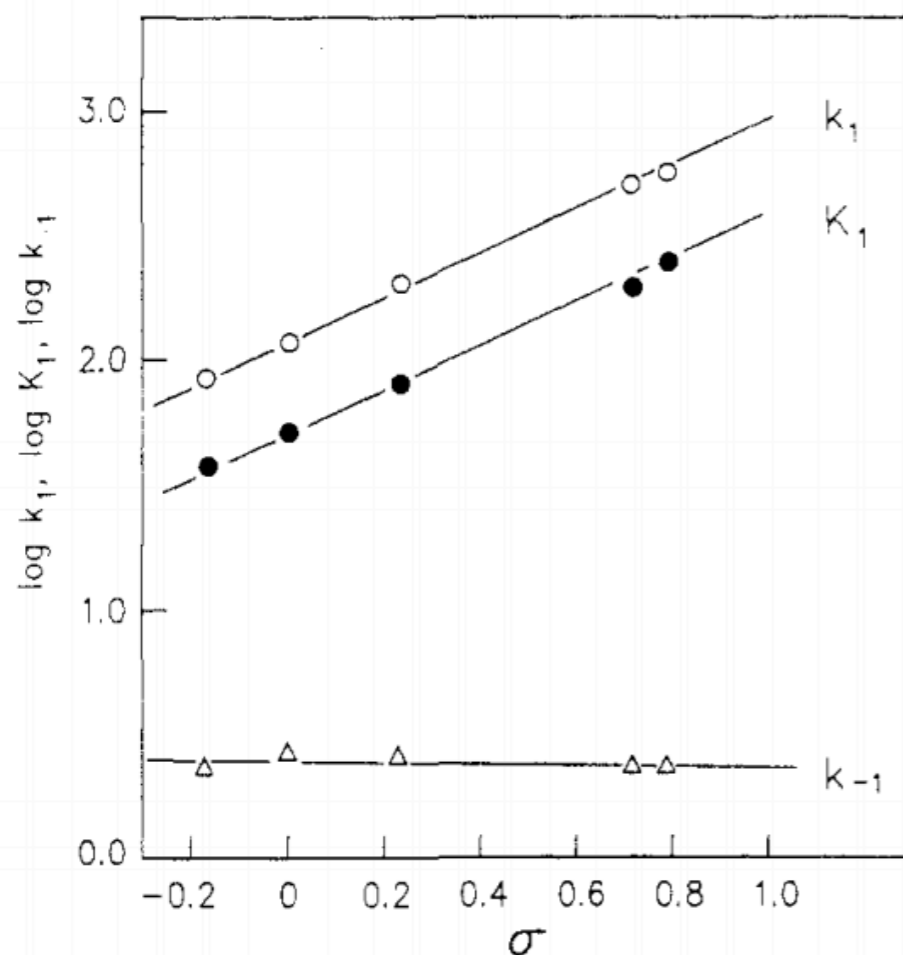
both show significant aromatic character

The disproportionately high aromaticity of the transition states in the reactions involving aromatic systems suggests that only relatively minor progress in the creation of the appropriate orbitals or their optimal alignment is required for aromatic stabilization to become effective.

Nonperfect Synchronization in Conjugate Additions



Is $\delta_C > \delta_Y$ as PNS would predict?



$$\alpha_{\text{nuc}} = \rho(k_1)/\rho(K_1) \approx 1$$

$$\beta_{\text{nuc}} = d[\log(k_1)] / d[\text{p}K_a(\text{NHR}_2)] \approx 0.34$$

sensitivity to electrophile

sensitivity to nucleophile

$$\alpha_{\text{nuc}}(\text{corr.}) - \beta_{\text{nuc}} = 0.67 - 0.34 = 0.33$$

(corrected for electrostatic effects)

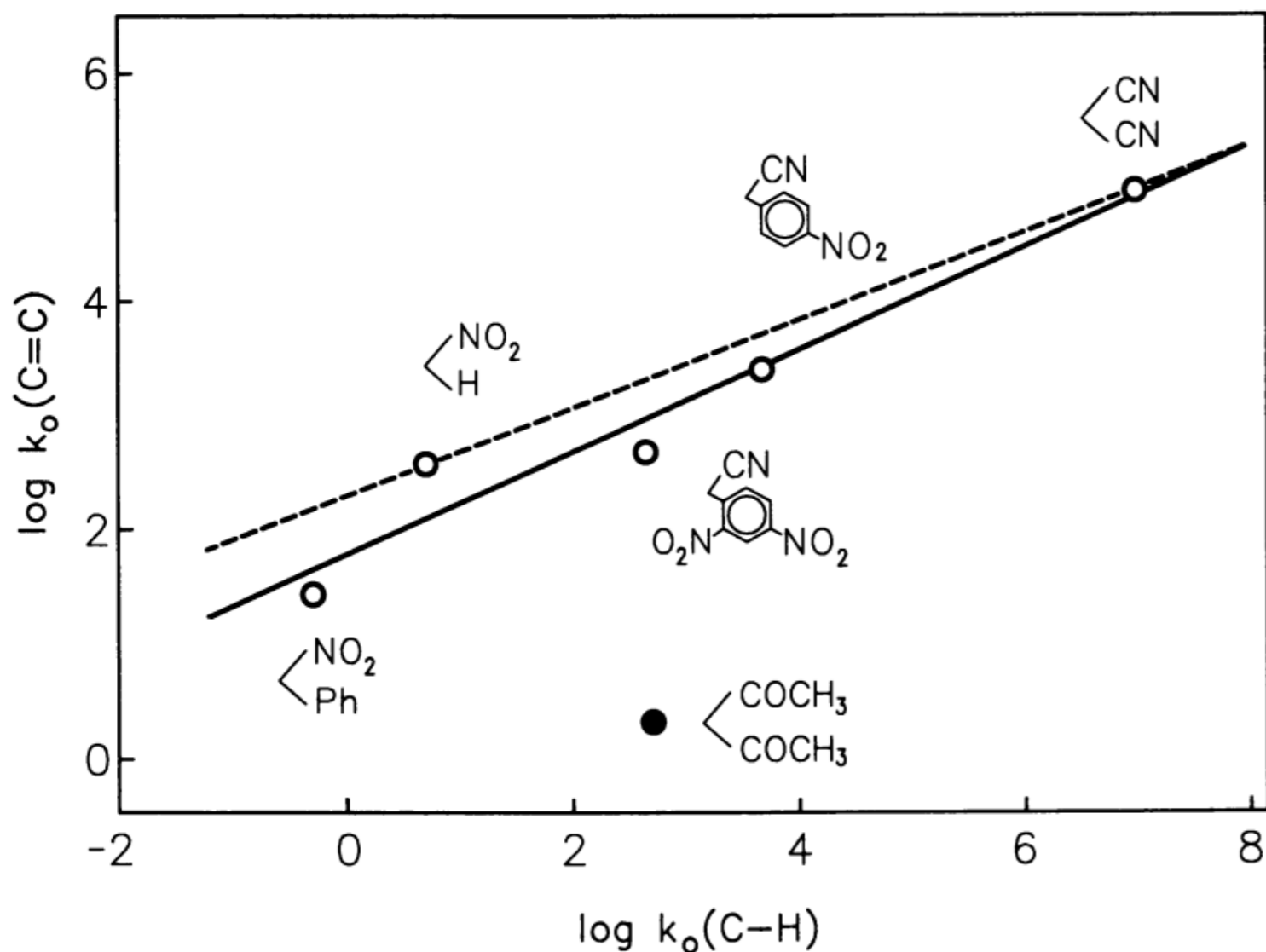
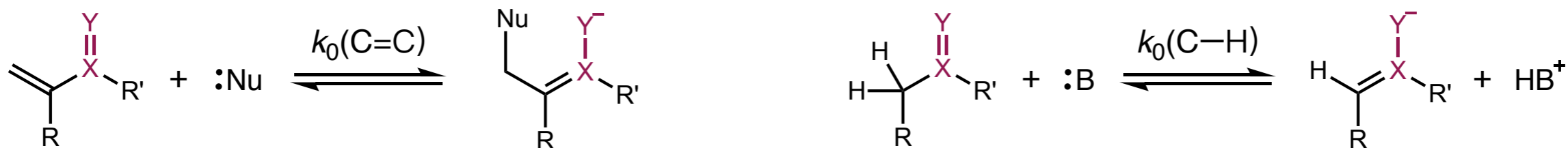
asynchronous, but less so than deprotonation

Bernasconi, C. F.; Renfrow, R. A. *J. Org. Chem.* **1987**, *52*, 3035–3041.

Bernasconi, C. F. in *Nucleophilicity* (Harris, J. M.; McManus, S. P., eds.), *Adv. Chem. Ser.* **1987**, *215*, 115–133.

Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119–238, pp. 205–212.

Comparing Proton Transfer and Conjugate Addition



$$\log[k_0(\text{C}=\text{C})] \approx 0.45 \cdot \log[k_0(\text{C}-\text{H})]$$

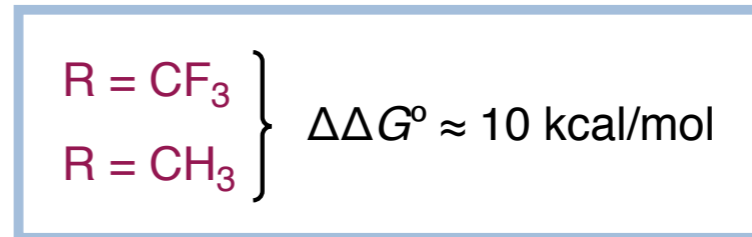
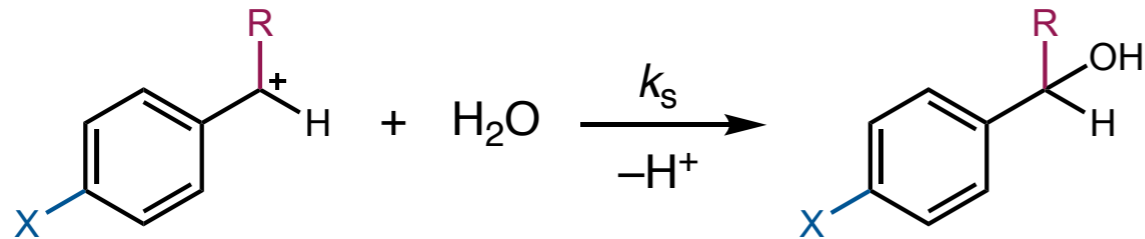


PNS applies to conjugate additions, but the effect is significantly reduced

better charge delocalization from sp^2 carbon?

lack of hydrogen bond to departing H^+ ?

Nonperfect Synchronization in Reactions of Carbocations

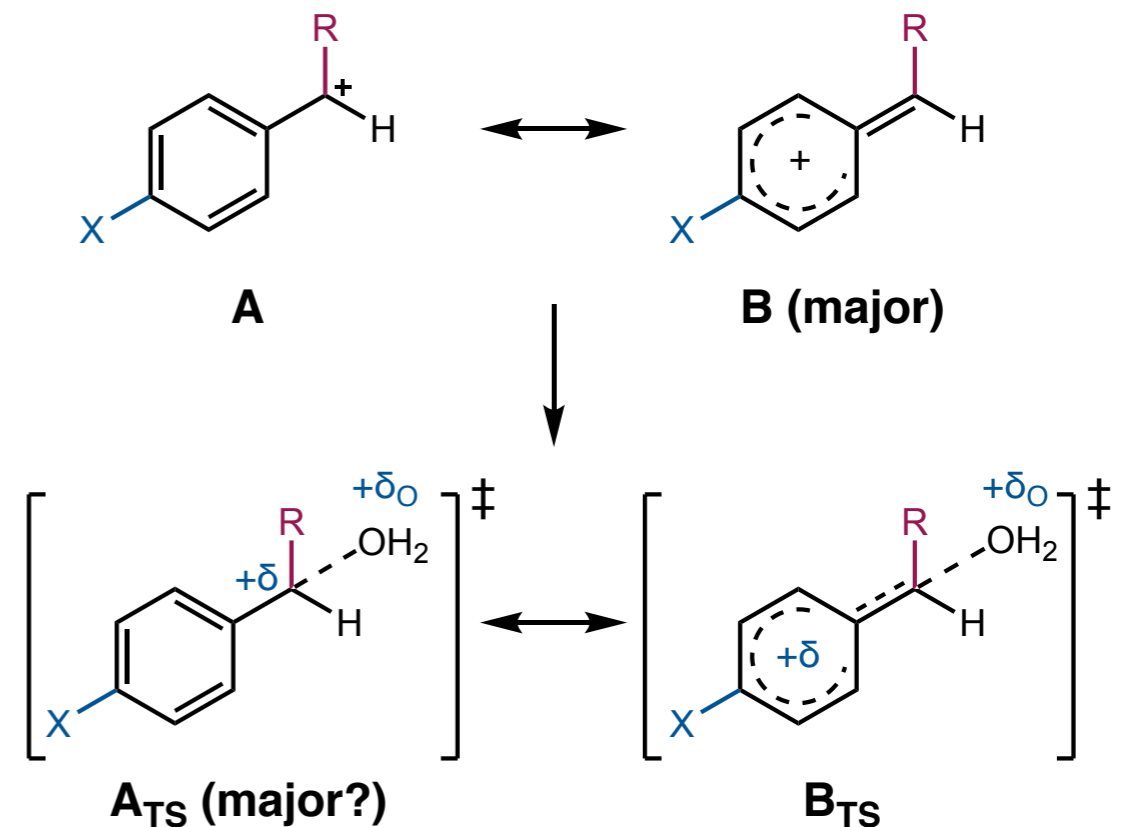


X	R = CF ₃	R = Me	
	k _s (s ⁻¹)	k _s (s ⁻¹)	
N(Me) ₂	8 · 10 ²	2 · 10 ³	<div style="display: flex; align-items: center;"> <div style="border-left: 1px solid black; height: 100px; margin-right: 10px;"></div> <div style="text-align: center;"> <p>large effect on rate</p> </div> </div>
SMe	1 · 10 ⁷	4 · 10 ⁷	
OMe	5 · 10 ⁷	5 · 10 ⁷	
Me	6 · 10 ⁹	6 · 10 ⁹	

$k_s(\text{CF}_3) \approx k_s(\text{Me}) \quad \Rightarrow \quad k_0(\text{CF}_3) \ll k_0(\text{Me})$

small effect on rate

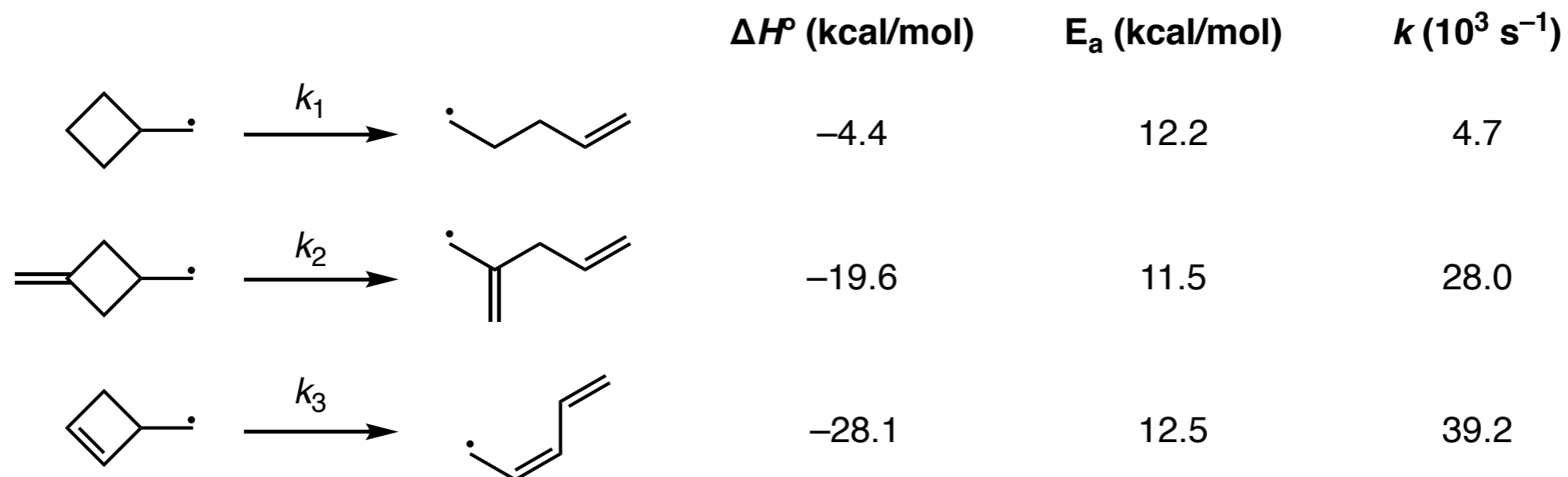
for R = CF₃, **B** is much more stable than **A**



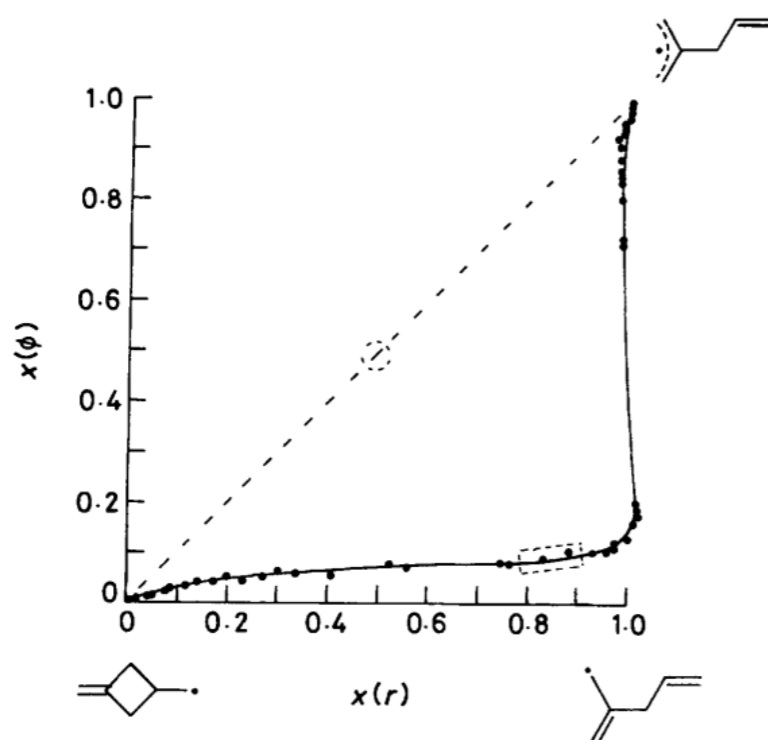
early loss of resonance increases benzylic δ^+ at the transition state, increasing ΔG^\ddagger_0

by PNS, the transition state resembles **A_{TS}** more than **B_{TS}** (resonance develops late, is lost early)

Nonperfect Synchronization in Radical Rearrangements



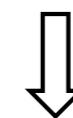
modest increase in rate with large increase in driving force



from MNDO calculations:

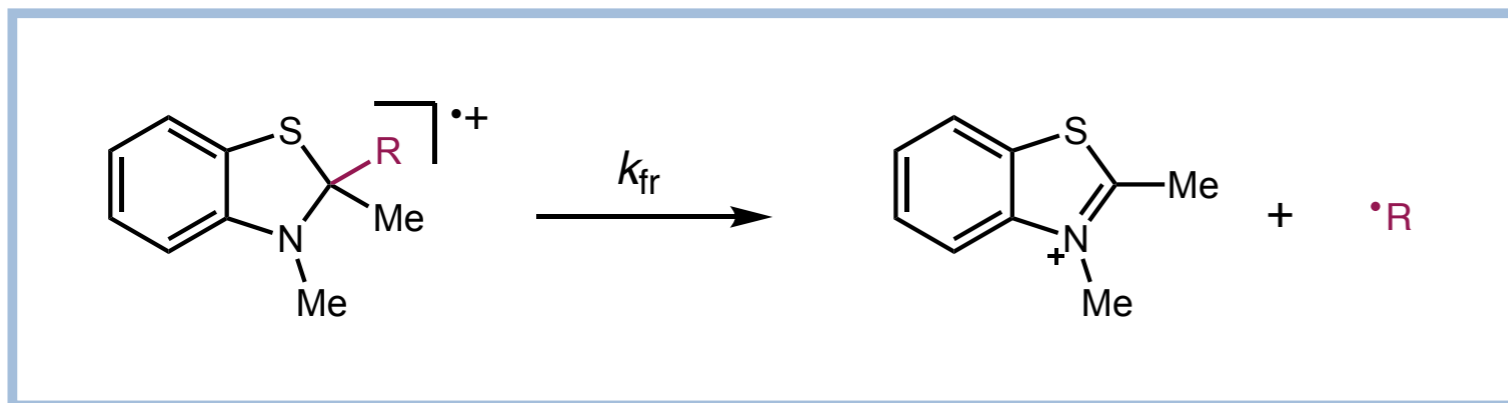
85% β -scission at TS

10% resonance stabilization at TS



much greater asynchronicity than proton transfer

Nonperfect Synchronization in Radical Rearrangements



how does R affect k_{fr} ?

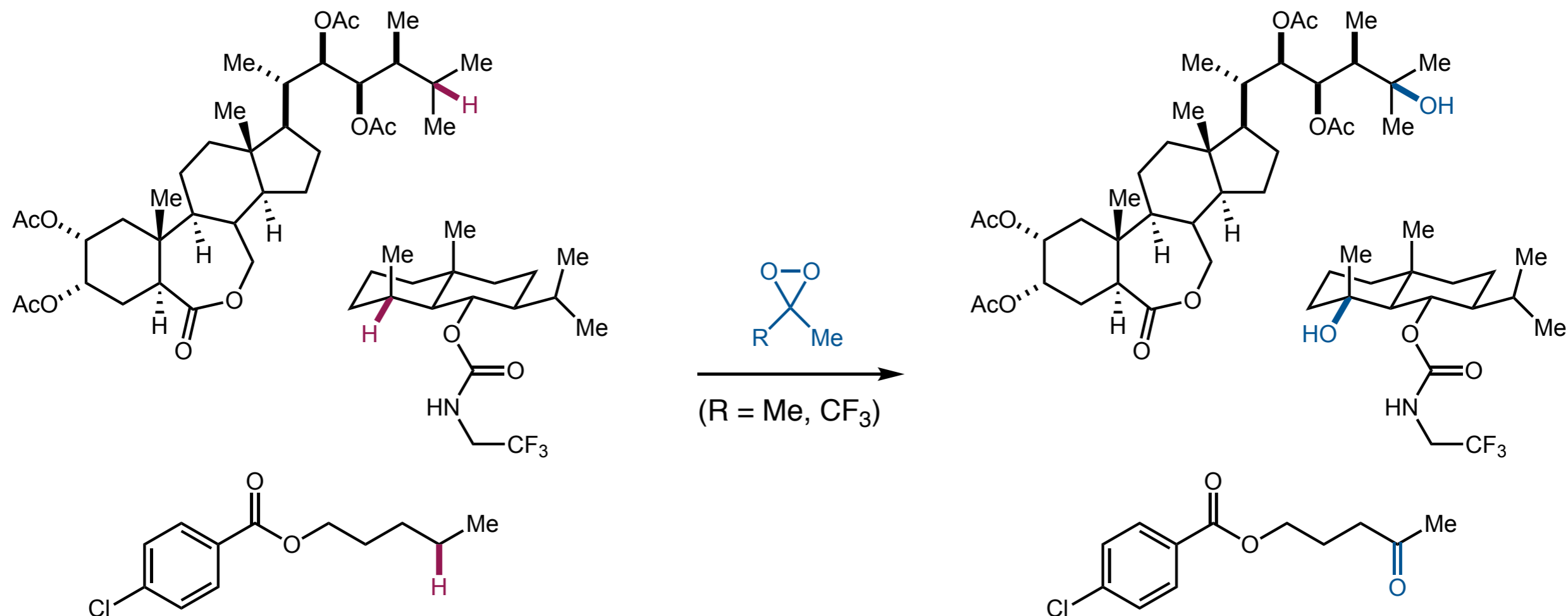
R	k_0 (10^4 s^{-1})	$\Delta H^\ddagger_{\text{exp}}$ (kcal/mol)	$\text{BDE}_{\text{calc}} (\text{BT}-\text{R}^{\bullet+})$ (kcal/mol)
	9.8	9.6	-10
	19	9.6	-9
	500	3.9	-16
	610	4.3	-19

modest effect of BDE on ΔH^\ddagger attributed to resonance delocalization of product radical

$$\Delta G^\ddagger_0 \approx 10 \text{ kcal/mol}$$

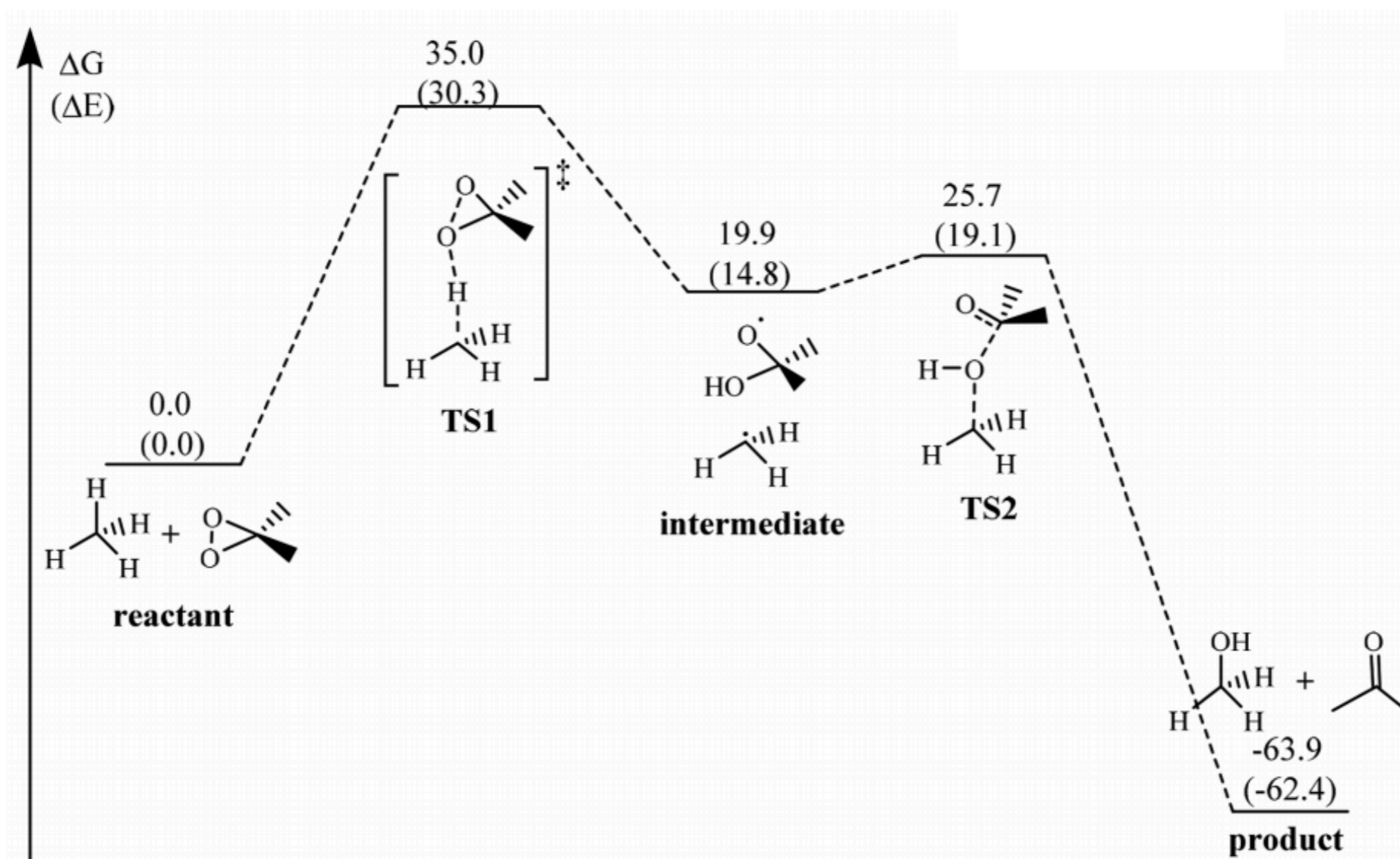
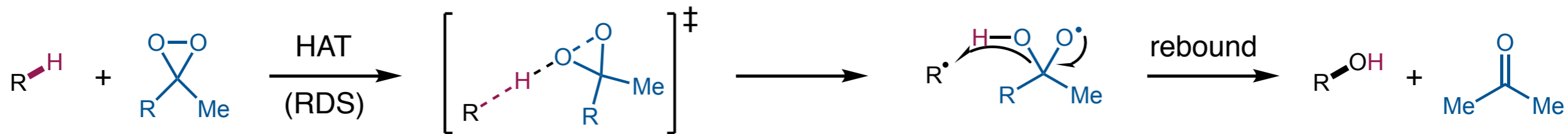
“...the same factors that lead to the thermodynamic driving force for the fragmentations – the stabilities of the benzothiazolium cation and the resonance-delocalized radicals – simultaneously result in large intrinsic barriers.”

Late-Stage C–H Oxidation with Dioxiranes

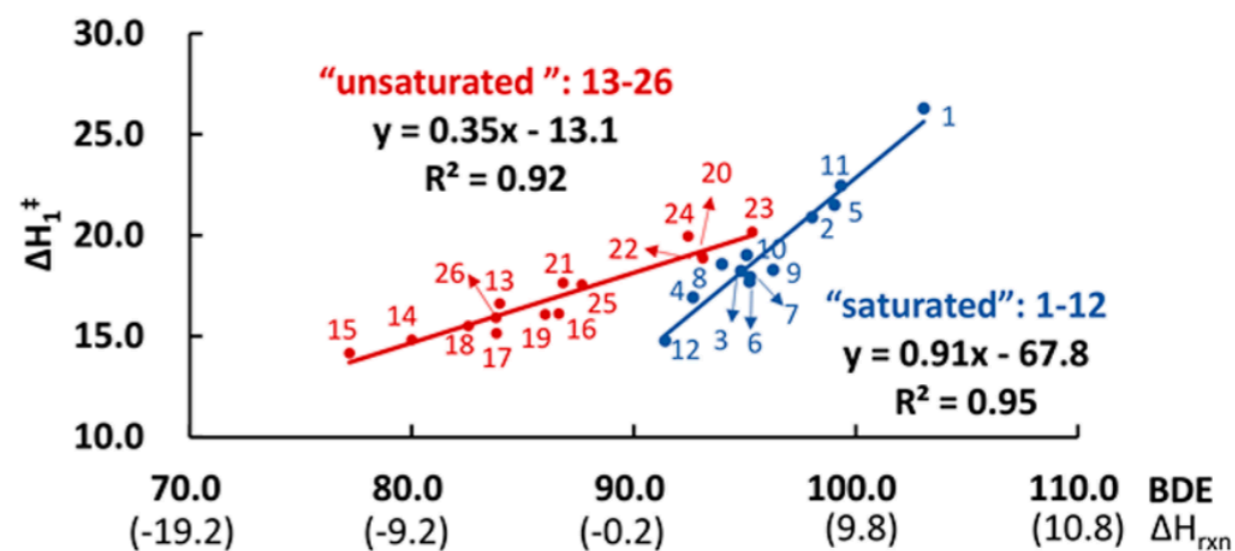
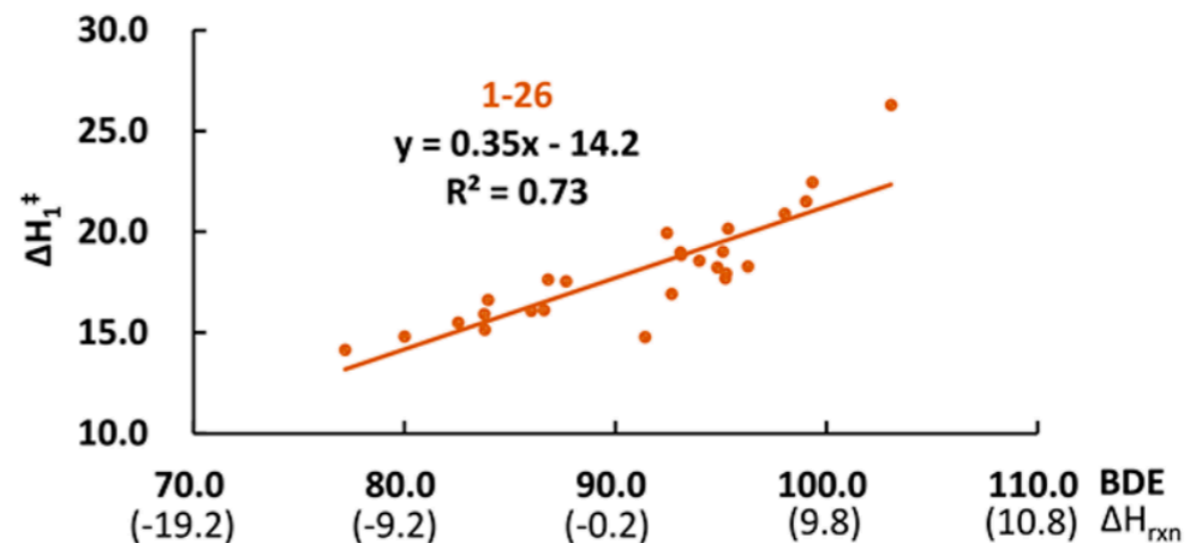
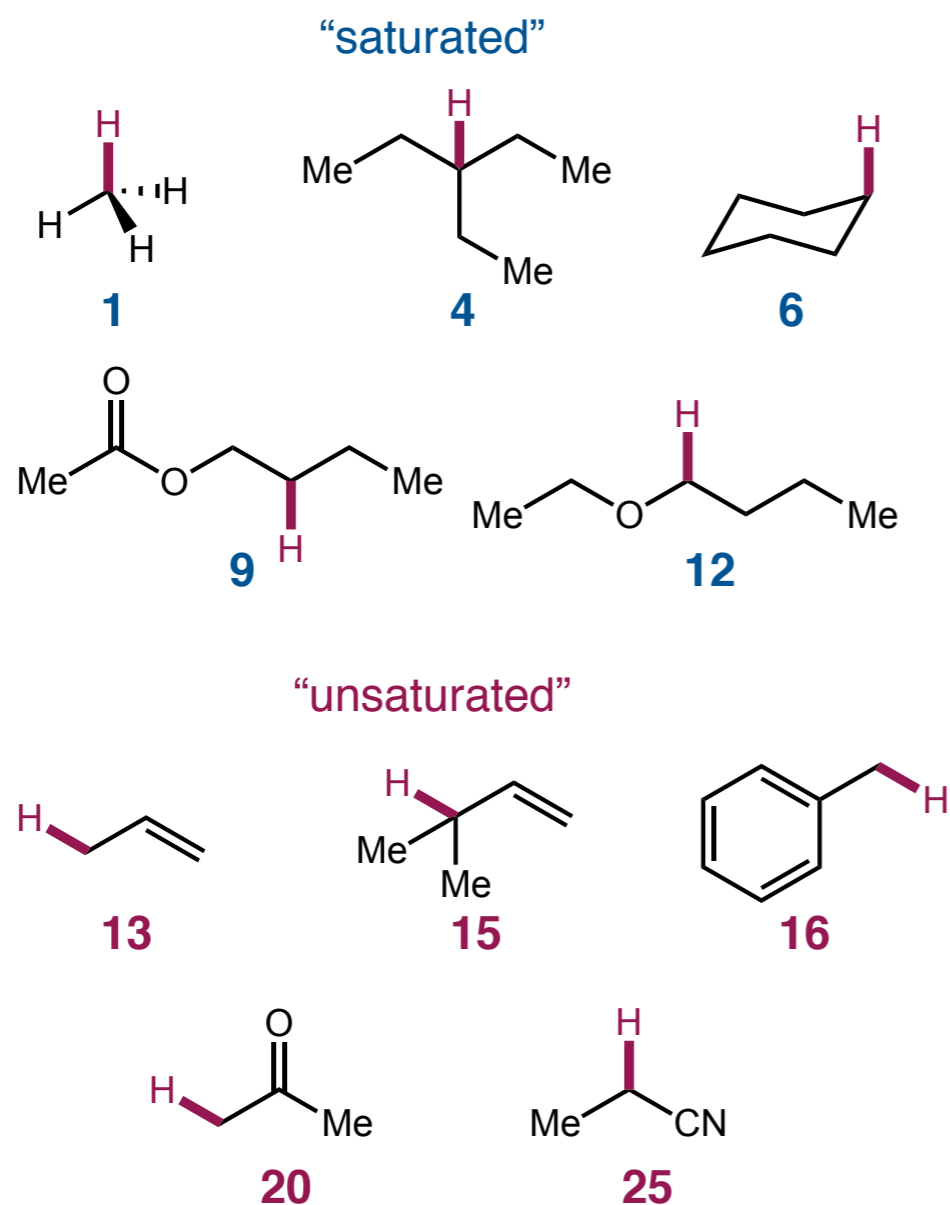
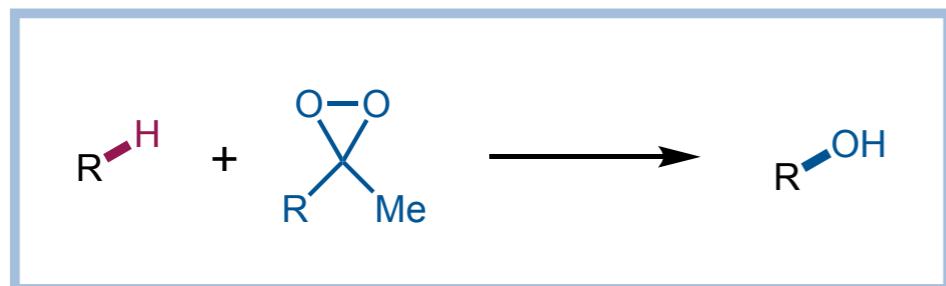


what governs the selectivity of dioxirane-mediate oxidation?

Mechanism of Dioxirane Oxidation


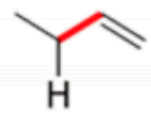
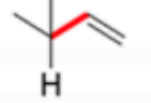
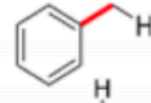
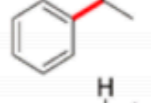
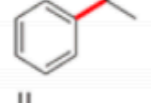



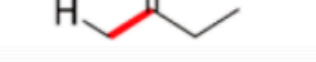




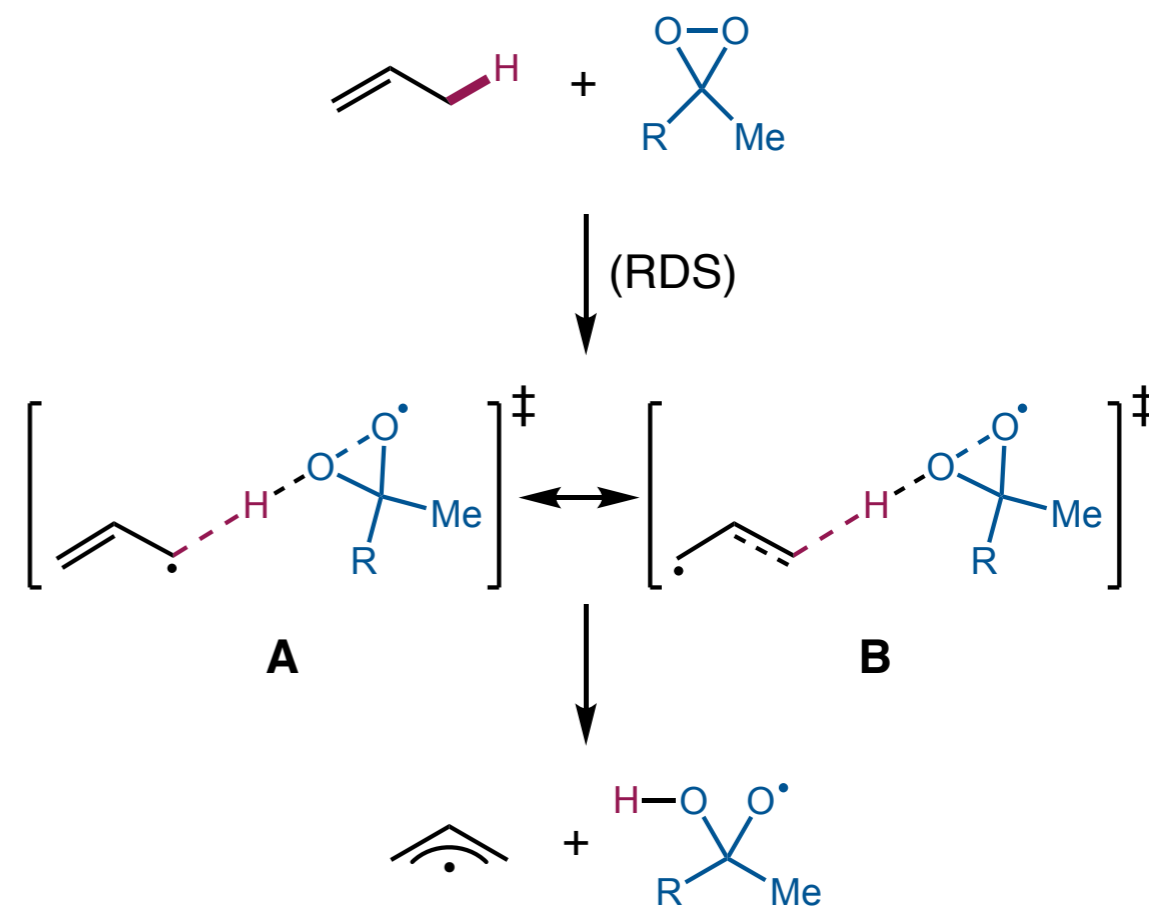
Bell-Evans-Polanyi-Type Relationship for Dioxirane-Mediated Oxidation



ΔH^\ddagger vs. ΔH_{rxn} only provides linear relationship if saturated and unsaturated compounds are treated independently

Transition State Analysis

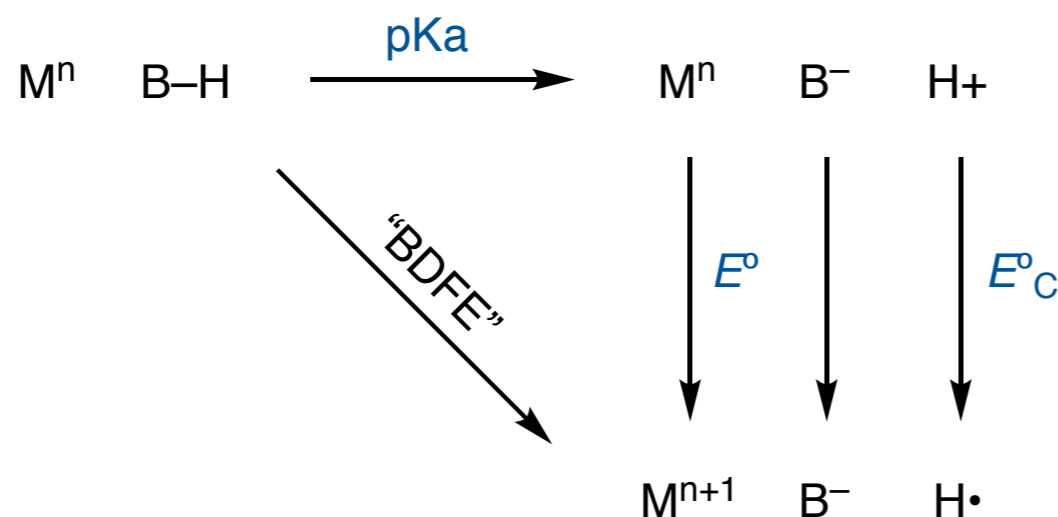
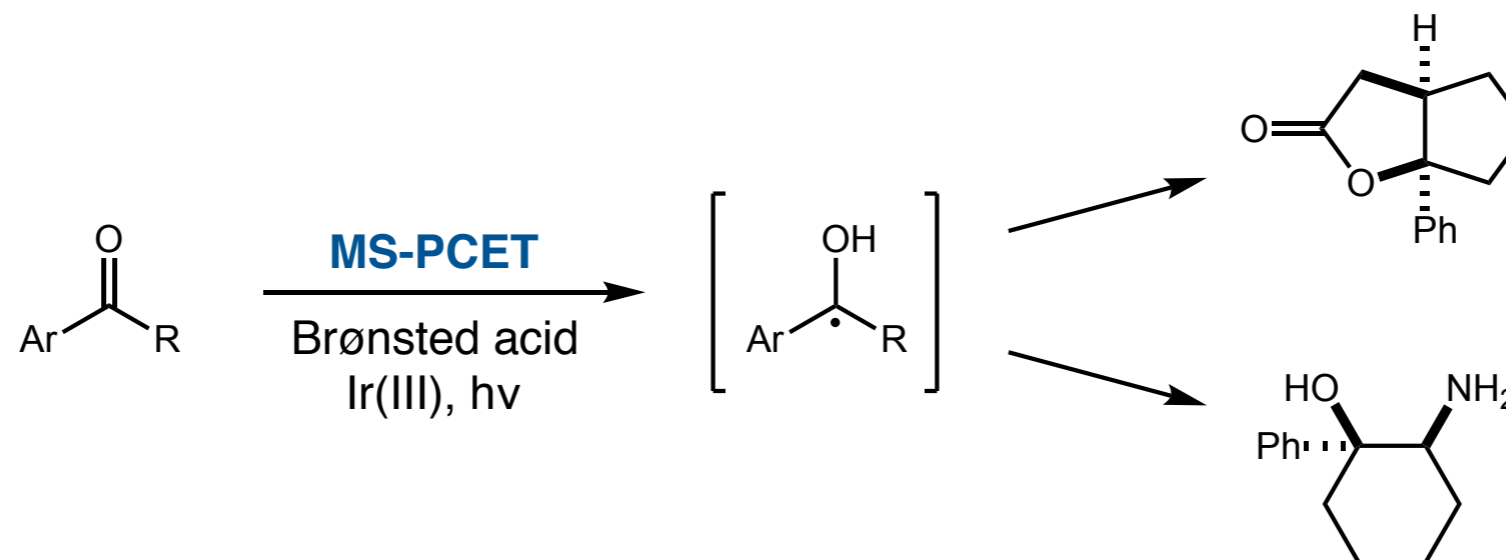
compounds	r_{C-C} (RH)	r_{C-C} (TS)	r_{C-C} (R·)
13 	1.50	1.47	1.39
14 	1.50	1.47	1.39
15 	1.51	1.49	1.40
16 	1.51	1.47	1.41
17 	1.51	1.49	1.42
18 	1.52	1.50	1.43
19 	1.51	1.47	1.40
20 	1.52	1.49	1.44
21 	1.52	1.49	1.44
22 	1.53	1.50	1.44
23 	1.51	1.49	1.45
24 	1.46	1.43	1.38



computation shows much stronger resonance delocalization in product than transition state

product stabilization due to resonance is not proportionally felt in the transition state, so $d\Delta H^\ddagger/d\Delta H^\circ$ (α) is small

Proton-Coupled Electron Transfer Activation of Ketones

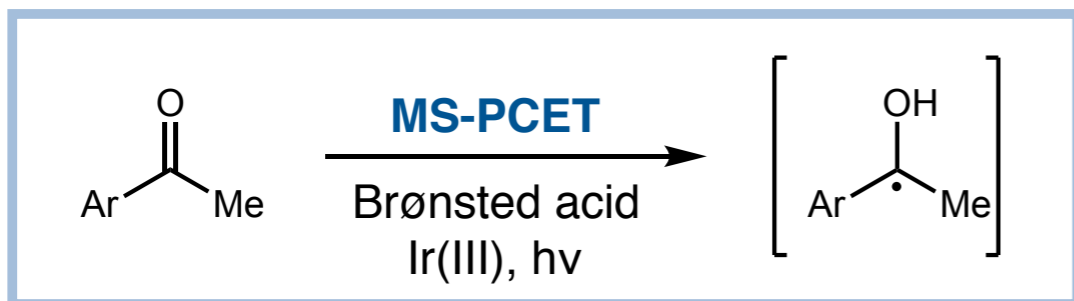


$E_0(\text{M}^n/\text{M}^{n+1})$ and $\text{pK}_a(\text{B-H})$ provide decoupled, modular tuning of reaction driving force

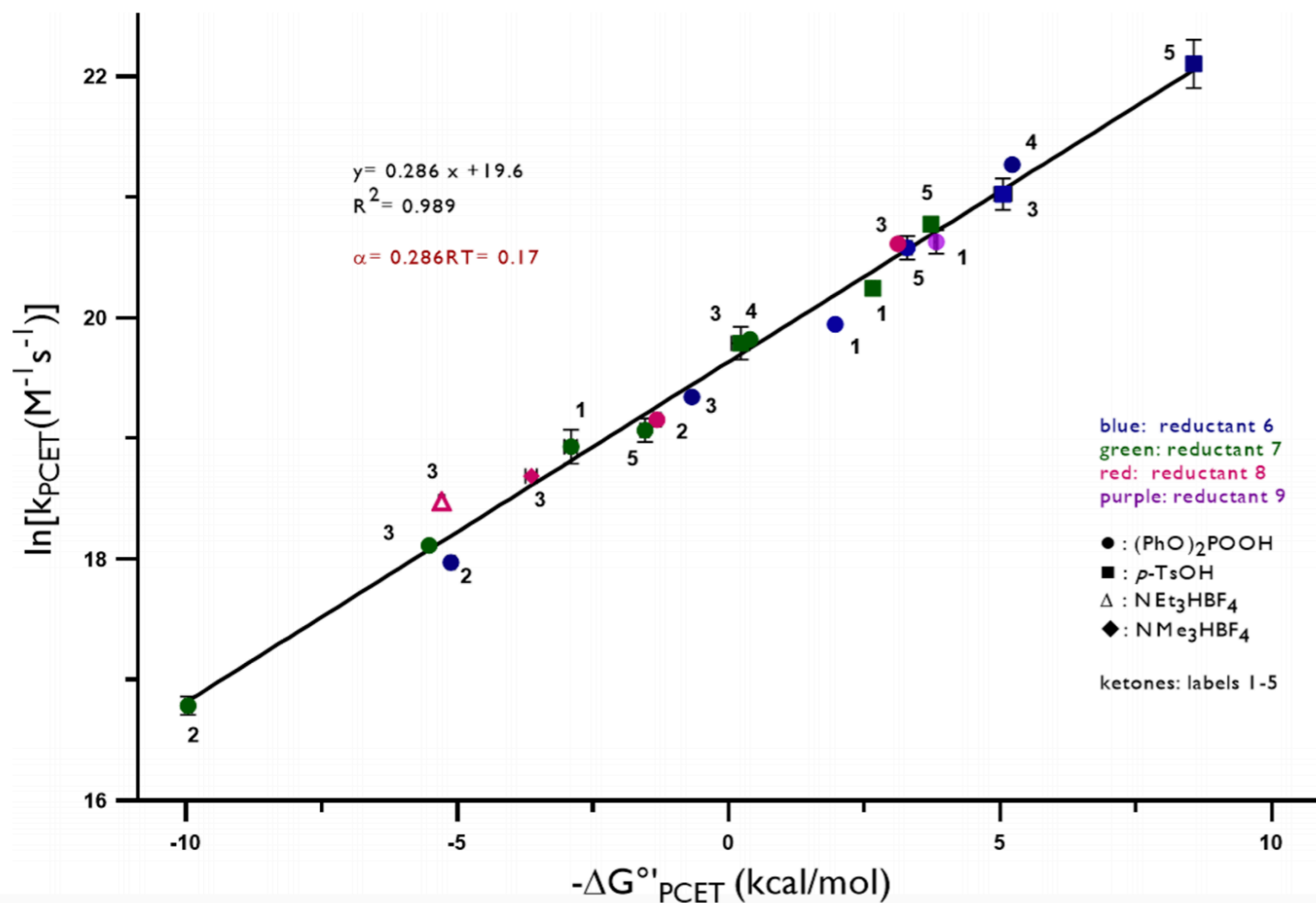
any effective BDFE can be accomplished with a broad range of reductant/proton donor pairs

$$\text{“BDFE”} = 1.37 \text{ pK}_a(\text{B-H}) + 23.06 E^\circ(\text{M}^n/\text{M}^{n+1}) + 23.06 E^\circ(\text{H}^+/\text{H}^\bullet)$$

Correlation Between Rate and Driving Force



linear correlation between effective BDFE and rate



from Marcus Theory:

$$\Delta G^\ddagger = \frac{(\lambda + \Delta G^\circ)^2}{4\lambda}$$

$$\alpha = \frac{\partial \Delta G^\ddagger}{\partial \Delta G^\circ} = \frac{1}{2} + \frac{\Delta G^\circ}{2\lambda}$$

if $\Delta G^\circ \ll \lambda$:

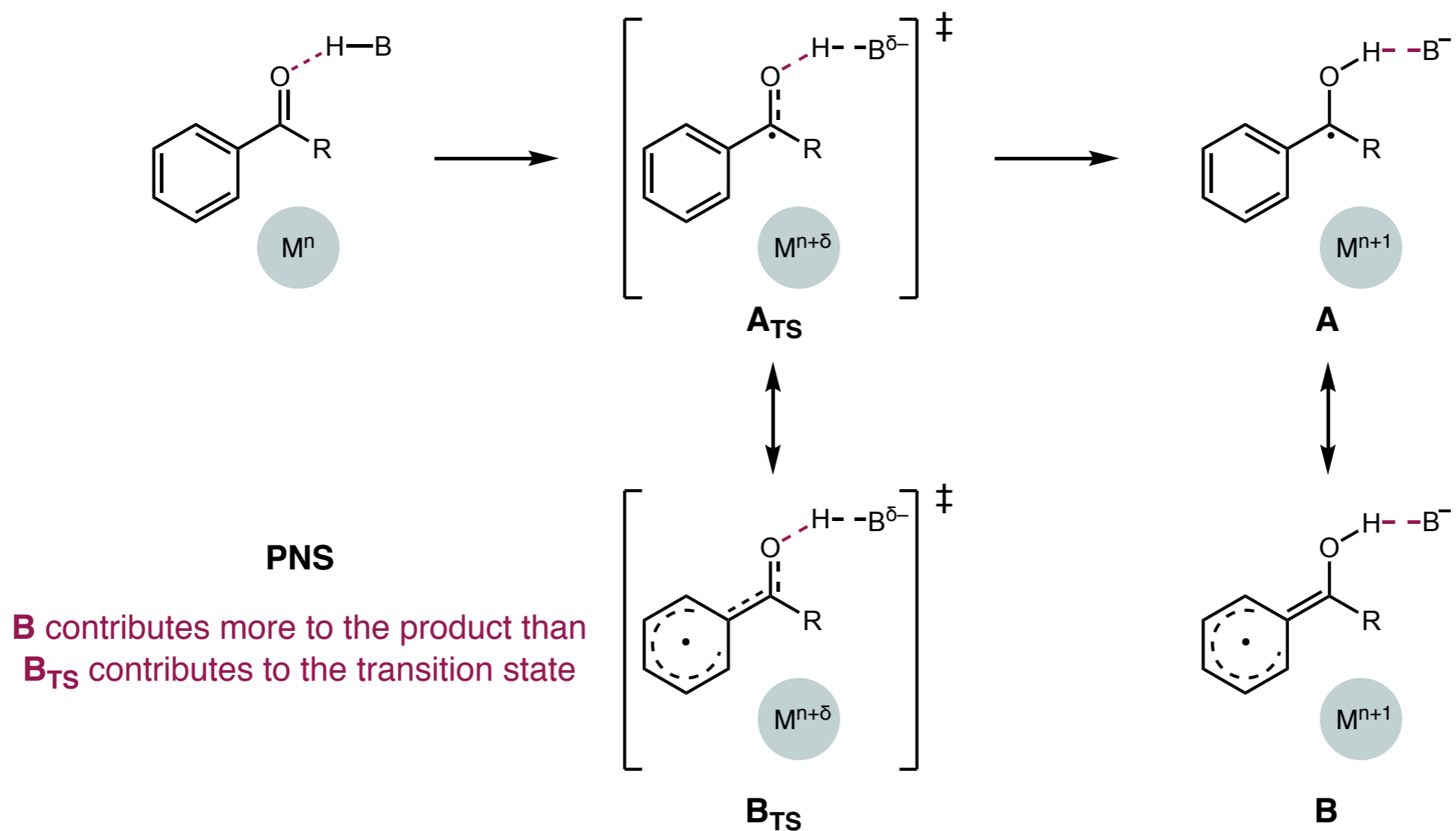
$$\alpha = 0.5$$

from analysis of 20 MS-PCET reactions:

$$\alpha = 0.17$$

why is α so low for ketone PCET?

MS-PCET of Ketones Generates Resonance-Stabilized Radical

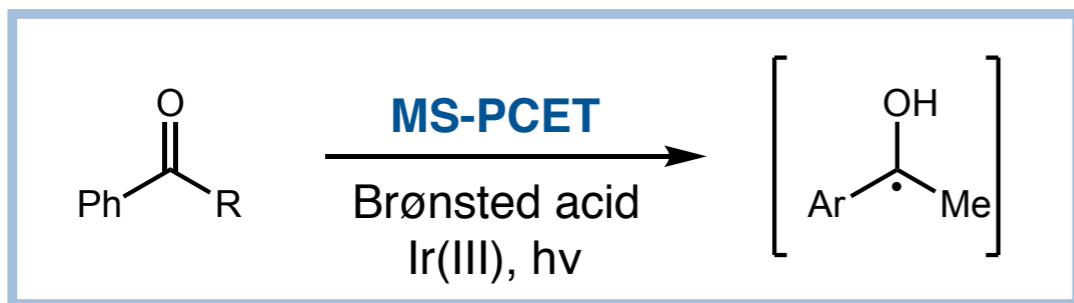


product-stabilizing factors are poorly developed in the transition state

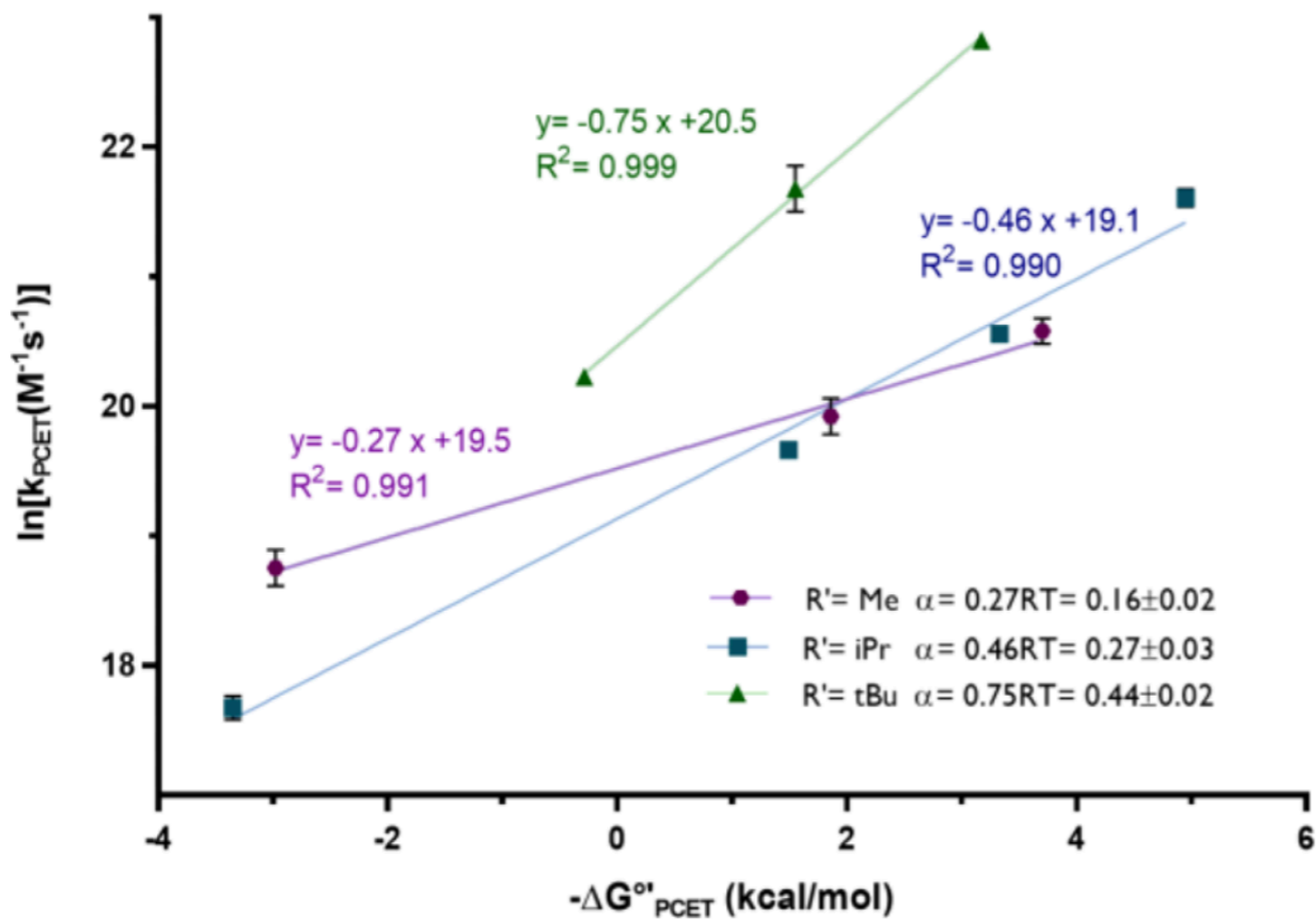


$\Delta\Delta G^\circ$ has a comparatively small effect on $\Delta\Delta G^\ddagger$ (α is small)

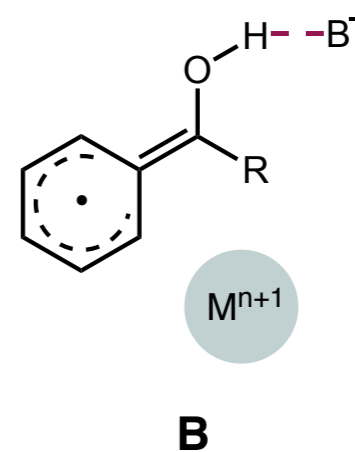
Probing Effects of Ketone Sterics



large R moves transition state later
increasing impact of product-stabilizing factors

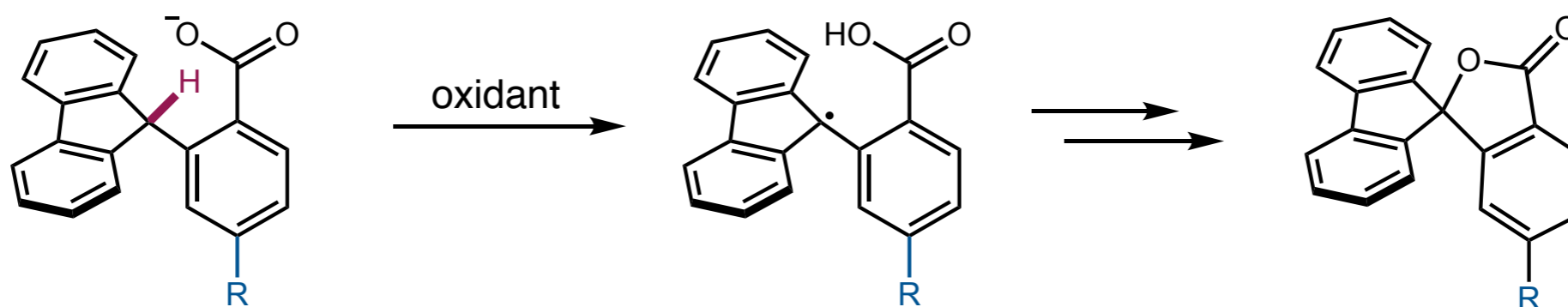


R	α	later TS
Me	0.16	↓ larger α
i-Pr	0.27	
t-Bu	0.44	



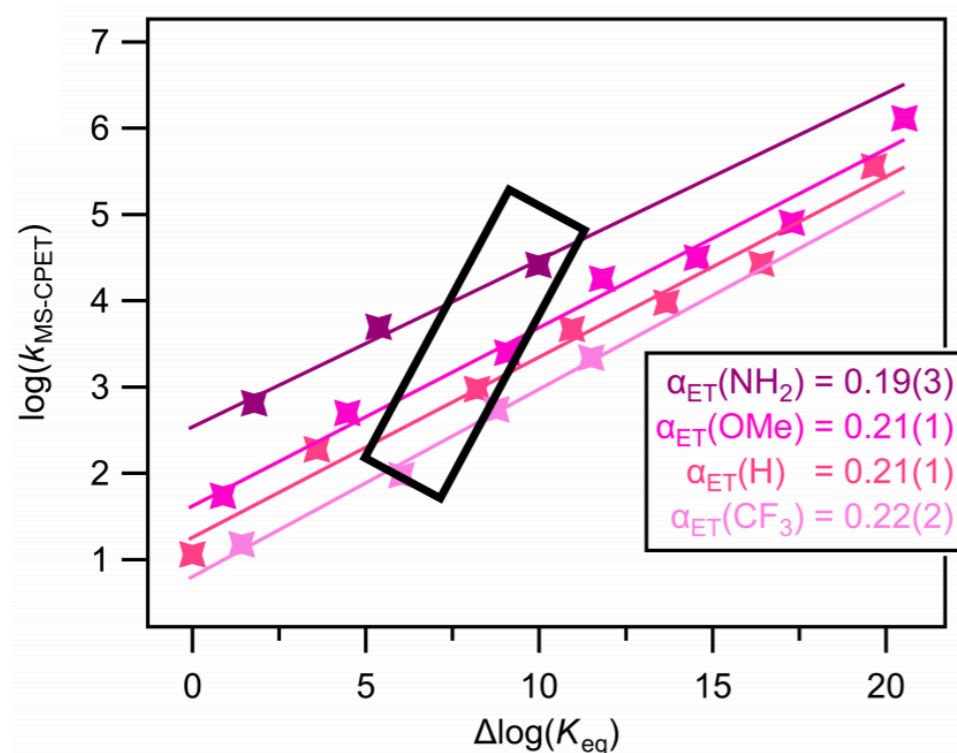
does large R destabilize **B**, reducing importance of resonance to product stability?

Proton-Coupled Electron Transfer Activation of C–H Bonds



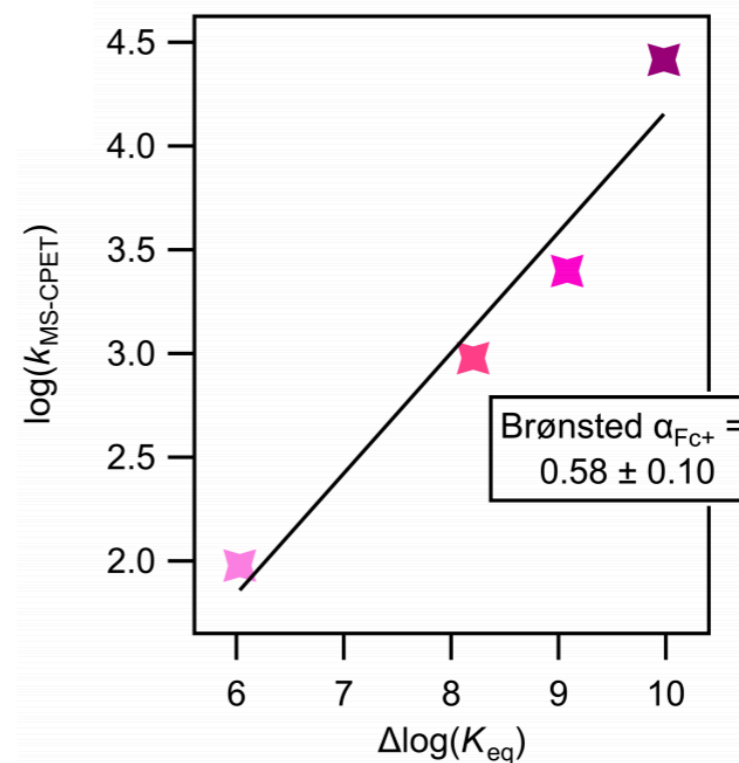
enables PCET functionalization of bonds that do not form H-bonded complexes

effect of oxidant on rate



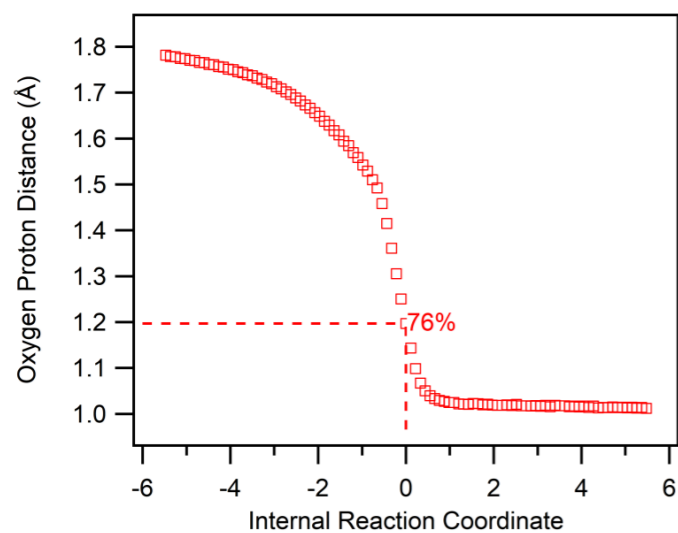
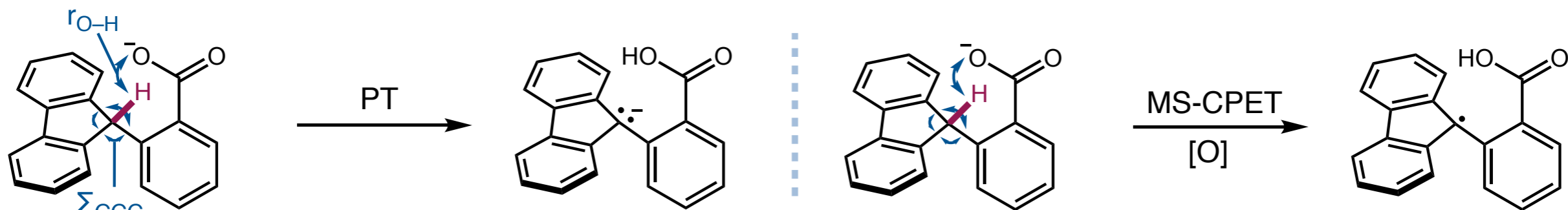
$\alpha_{\text{ox}} = 0.21$

effect of substituent on rate

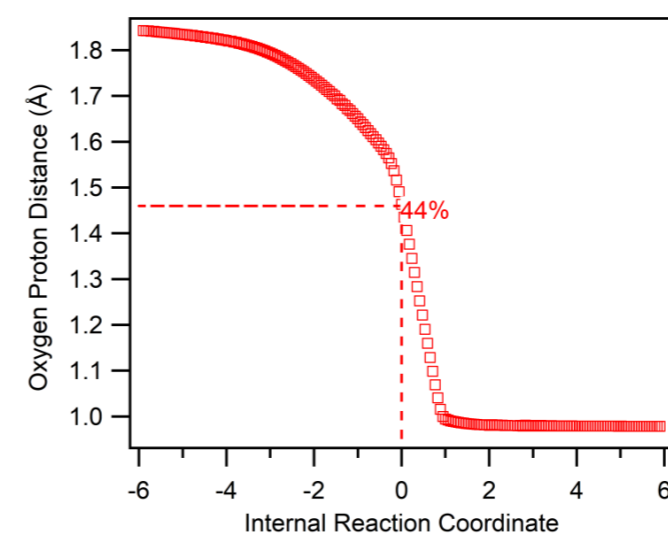


$\alpha_{\text{R}} = 0.58$

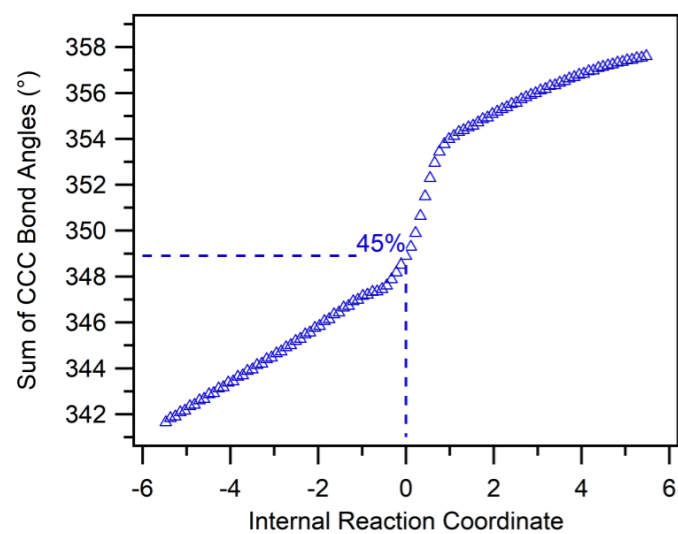
Computational Investigation of MS-CPET Transition States



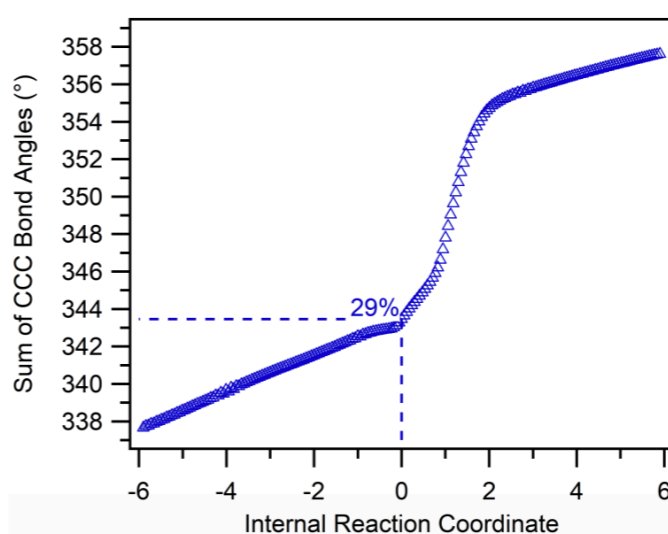
76% of product
O–H distance



44% of product
O–H distance



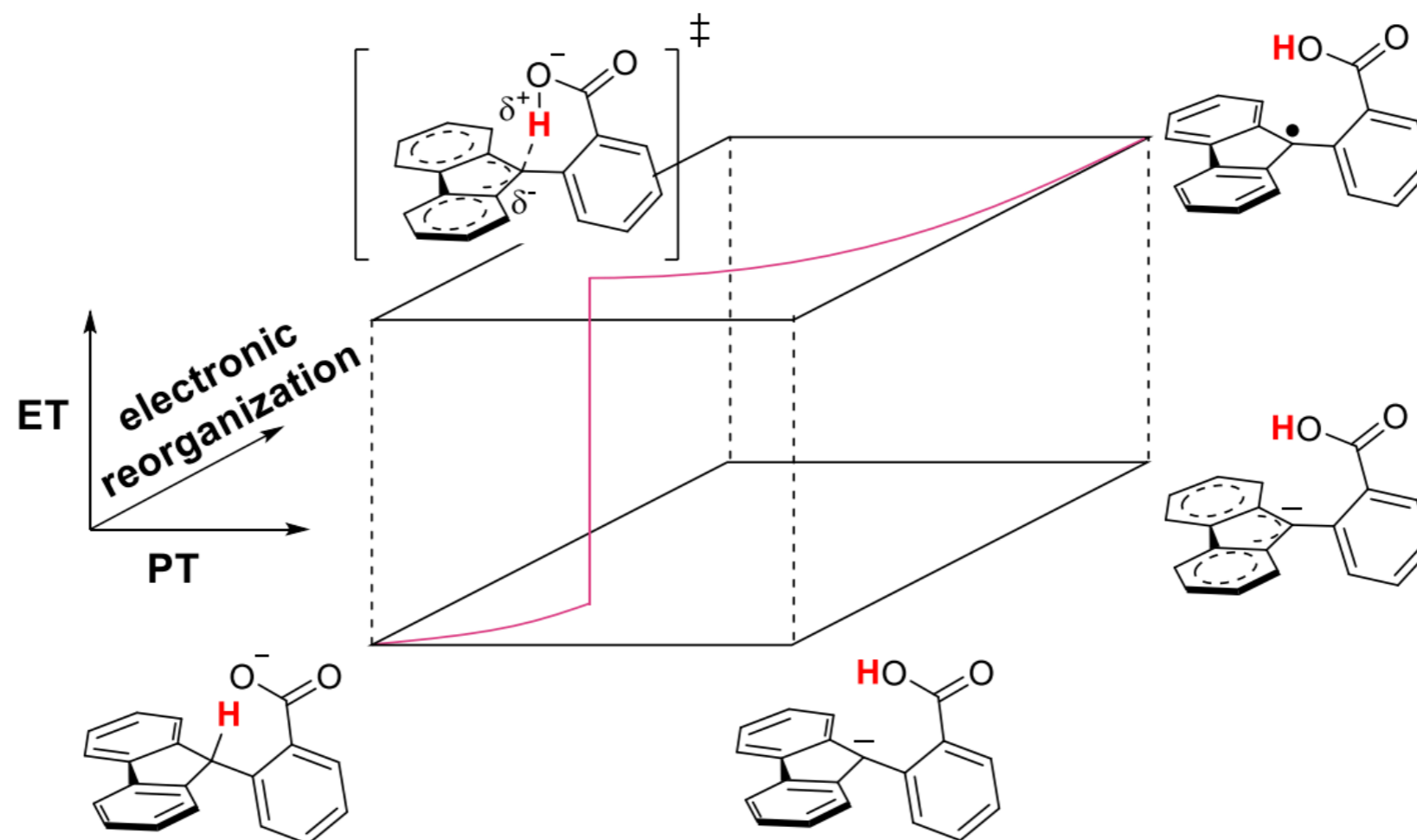
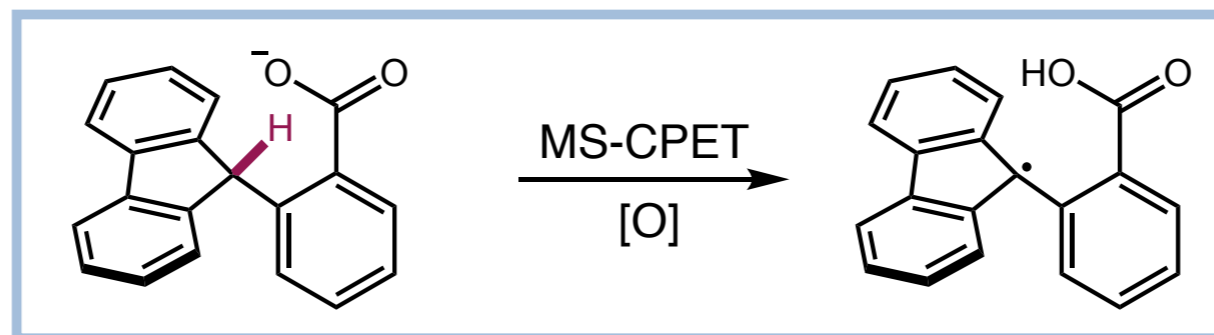
45% of product
sum of CCC angles



29% of product
sum of CCC angles

in both cases, O–H bond formation appears to precede electronic rearrangement

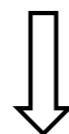
More O'Ferrall-Jencks Analysis



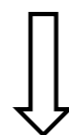
Brønsted coefficient, calculations support early proton transfer followed by late delocalization

The Principle of Nonperfect Synchronization

A product-stabilizing factor will lower the intrinsic rate of a reaction if it develops late, but increase the intrinsic rate if the factor develops early

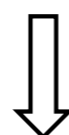


In general, **resonance stabilization**, **solvation**, and **hyperconjugation** develop late or are lost early



Reactions that generate resonance-stabilized products tend to show a smaller increase in rate with increasing driving force

$$\alpha = \frac{\partial \Delta G^\ddagger}{\partial \Delta G^\circ} \text{ is small}$$



These effects are relevant to a broad range of reactions, including photoredox PCET and C(sp³)-H functionalizations