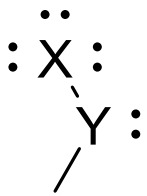
The alpha effect

Andrew Zahrt
Denmark Group Meeting
4.28.15

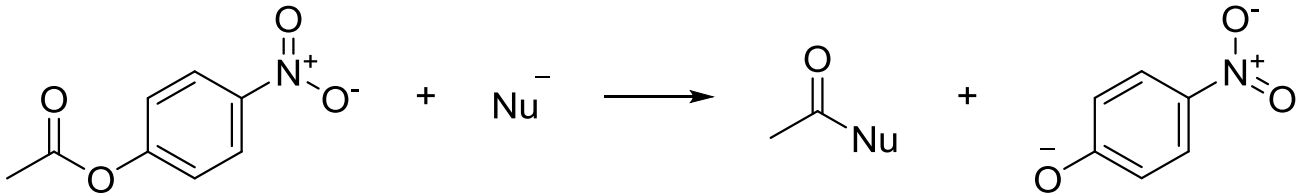
Overview

- Introduction
- Early Publications/Hypotheses:
  - Thermodynamic Product Stability
  - Ground State Destabilization
  - Transition State Stabilization
- Solvent Effects
- Gas Phase Experiments
- Conclusions

Introduction



- The alpha effect:
  - Refers to the increased reactivity of a nucleophile due to the presence of an adjacent (α) atom with a lone pair of electrons.
  - Frequently referenced with basicity
- Seminal Investigation: Jencks and Carriuolo



  - First to attribute enhanced nucleophilicity to the presence of an atom with a lone pair α to the nucleophilic center

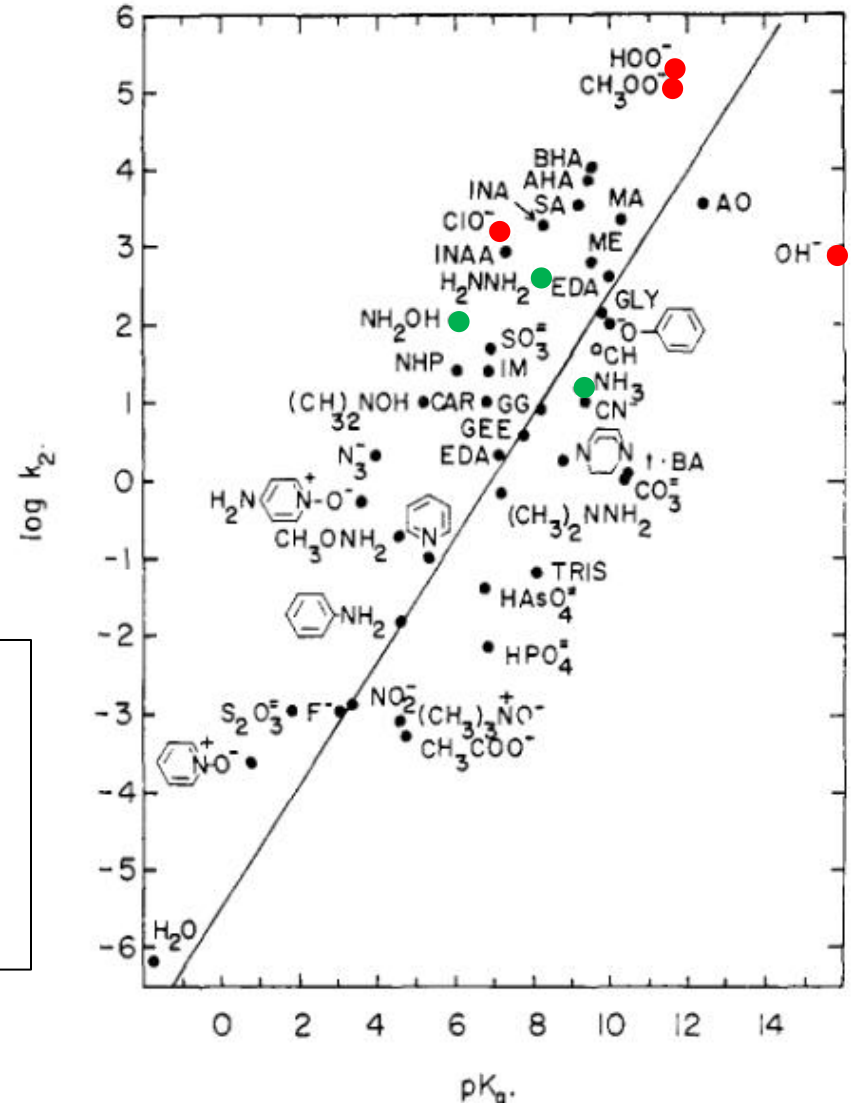
$HO-O^-$

Jencks *et* al. JACS, 1960, **82**, 675

Jencks and Carriuolo

- Relative rates of substitution
- Attributed the abnormal reactivity to increased polarizability of nucleophiles

The presence of an α-atom with lone pairs leads to greater nucleophilicity than the basicity would suggest



The α-effect

- The term "the α-effect" was first used by Edwards and Pearson.
  - Described it as an additional factor influencing nucleophilicity, separate from polarizability.
  - Their hypothesis:
    - Stabilization of the relative electron deficiency in the transition state via π-bonding (conceptually similar to carbocation stabilization by a neighboring heteroatom)

$$N^{m} \longrightarrow N^{m+2} + 2e^{-}$$

    - Extent of π-donation is greater in nucleophilic addition products than in the conjugate acid, resulting in enhanced stability of the former

Edwards *et* al. JACS, 1962, **84**, 16

What is the origin of the α-effect?

- Hypotheses:
  - Increased Polarization of Nucleophiles[1]
  - Transition State Stabilization by lone pair at α-position[2]
  - Relative stability of products[2]
  - Diminished Solvation of α-nucleophiles[3]
  - Ground State Destabilization due to electron-electron repulsion[4]

[1] Jencks *et* al. JACS, 1960, **82**, 675
[2] Edwards *et* al. JACS, 1962, **84**, 16
[3] C.A. Bunton in "Peroxide Reaction Mechanisms," J.O. Edwards, Ed., Intersience Publishers, Inc., New York, N.Y., 1962, p25
[4] Edwards, JACS, 1962, **84**, 763

Product Stability

- Overlap of α-electrons should lower the transition state energy *and* increase the pK_a, which would result in no deviation from Brønsted plot

- pK_a may not be the best reference by which to compare nucleophilicity

$$H_2O + A^- \rightleftharpoons OH^- + AH \qquad K_A$$

$$ROH + A^- \rightleftharpoons OH^- + AR \qquad K_A^R$$

$$ROH + AH \rightleftharpoons H_2O + AR \qquad K_{HA}^{RA}$$

$$K_{HA}^{RA} = \frac{K_A^R}{K_A}$$

Bruice *et al.* JACS, 1967, **89**, 1967
Hine *et al.* JACS, 1965, **87**, 3387

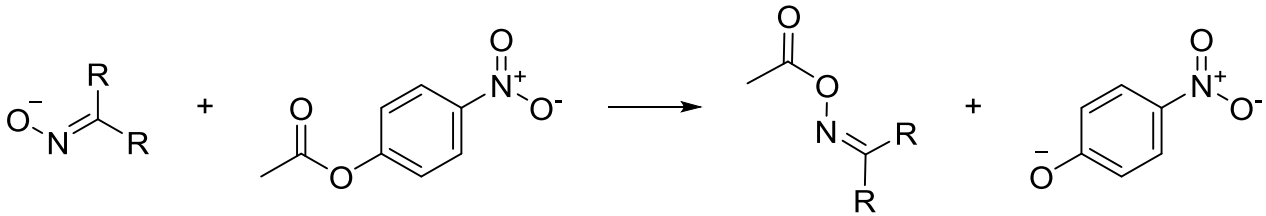
Product Stability

Table IV. Values of K_{HA}^{RA}, K_A, and K_A^R in Water at 25°[a]

R	A	K_{HA}^{RA}
Me	OMe	1.1×10^2
Me	OPh	1.4×10
Me	SH	8×10^8
Me	SMe	2×10^{10}
Me	SPh	7×10^9
Me	CN	7×10^{15}
Me	CH_2Ac	4×10^{12}

- K_A^R or K_{HA}^{RA} could be a better reference for stability
- The factors that stabilize the products of α-nucleophilic reactions also stabilize the transition state

Reactions of Oximes



Rate enhancements in reactions of oximate anions with p-*nitro-phenyl acetate in water at* 25°

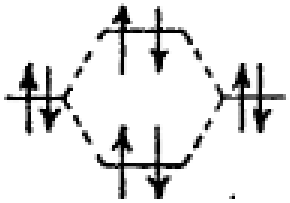
Oxime	pK_a	Rate enhancement[a]
H_2N, Me, C=N–OH	12·9	1·2
Et, Et, C=N–OH	12·60	1·0
Me, Me, C=N–OH	12·42	1·0
Ph, Me, C=N–OH	11·48	2·7
Ac, Me, C=N–OH	9·38	100
Ac, Ac, C=N–OH	7·38	933

[a] Defined as the ratio (bimolecular rate constant for oximate anion/bimolecular rate constant for a phenoxide or alkoxide anion of the same basicity).

[7] Hudson *et al.* J. Chem. Soc. D, 1970, 937

A MO Explanation of Increased Nucleophilicity

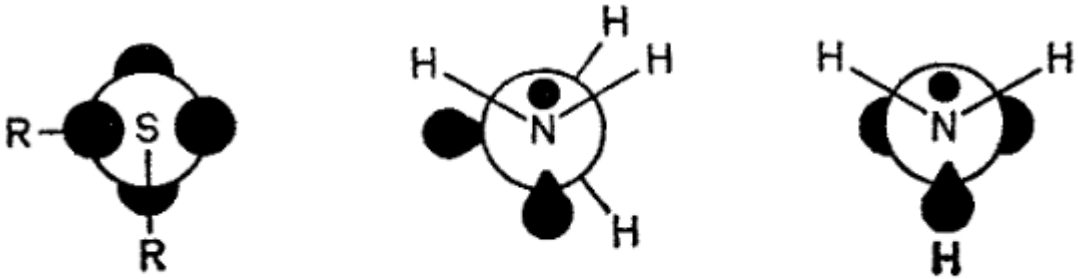
- Hudson proposed that overlap of doubly occupied p_π orbitals leads to an increase in the HOMO energy
- A reaction of such a nucleophile will have decreased p_π–p_π interaction in the transition state
- The combination of these factors results in the increased reactivity
- Some α-nucleophiles might not have the proper orbital symmetry for this interaction



[7] Hudson *et al.* J. Chem. Soc. D, 1970, 937

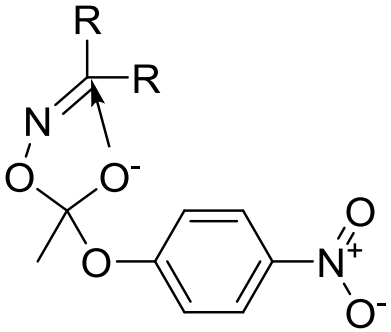
“Intramolecular Catalysis”

- Some molecules have conformers that minimize p_π–p_π overlap:



III(a) R–S–S–R $\theta = 90°$ III(b) NH_2–NH_2 $\theta \cong 90°$ III(c) NH_2–OH $\theta = 180°$ (or 0°)

- α–effect attributed to “intramolecular catalysis”



Unanswered Questions

- Why does higher HOMO not result in enhanced proton affinity?
- Why do some α-nucleophiles show enhanced reactivity, while similar α-nucleophiles do not?

Charge vs Frontier Orbitals

- Derived perturbation for all interacting orbitals:

$$\Delta E = -q_s q_r \Gamma_{rs} + \Sigma_m \Sigma_n (v_m - v_n + \chi_{mn}) \left[\frac{2(c_r^m c_s^n \beta_{rs})^2 \varepsilon_{mn}}{E_m^* - E_n^*} + c_r^m c_s^n \beta_{rs}(1 - \varepsilon_{mn}) + \frac{\chi_{mn}(EA_m - IP_n)}{4} \right]$$

q = charge

Γ_{rs} = Coulomb term $\left(\frac{e^2}{\sqrt{R^2+(\partial_n+\partial_m)^2}}\right)$

v = orbital occupancy

X = constant (2 if both ν_n and ν_m = 1, 0 otherwise)

ϵ_{mn} = 0 if orbitals are degenerate, 1 otherwise

c = orbital coefficients

β = resonance integral

Ea_m = Energy lost by removing 1 electron

Ip_n = Energy gained by adding one electron

E_m^* = Energy of electron in orbital m

E_n^* = Energy of electron if it was in orbital n

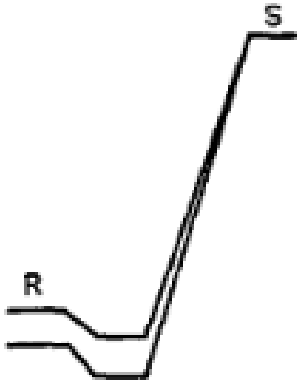
Limiting Cases

$$\Delta E = -q_s q_r \Gamma_{rs} + \Sigma_m \Sigma_n (v_m - v_n + \chi_{mn}) \left[\frac{2(c_r^m c_s^n \beta_{rs})^2 \varepsilon_{mn}}{E_m^* - E_n^*} + c_r^m c_s^n \beta_{rs}(1 - \varepsilon_{mn}) + \frac{\chi_{mn}(EA_m - IP_n)}{4} \right]$$

- If $E_m^* - E_n^*$ is large, the value in the summation is small – charge difference is most important.
  - Also possible if β is small (poor orbital overlap)

- Γ_{rs} is also largest at with smaller radii, corresponding to low polarizability

$$\Gamma_{rs} = \frac{e^2}{\sqrt{R^2 + (\partial_n + \partial_m)^2}}$$



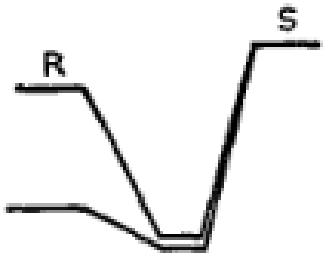
Large $E_m^* - E_n^*$

Small Perturbation

Limiting Cases

$$\Delta E = -q_s q_r \Gamma_{rs} + \Sigma_m \Sigma_n (v_m - v_n + \chi_{mn}) \left[\frac{2(c_r^m c_s^n \beta_{rs})^2 \varepsilon_{mn}}{E_m^* - E_n^*} + c_r^m c_s^n \beta_{rs}(1 - \varepsilon_{mn}) + \frac{\chi_{mn}(EA_m - IP_n)}{4} \right]$$

- If $E_m^* - E_n^*$ is small, the value in the summation is large:
  - Corresponds to frontier orbital control
- Charge term also decreases as radii increases



Small $E_m^* - E_n^*$

Large Perturbation

Unanswered Questions

- ~~Why does higher HOMO not result in enhanced proton affinity?~~
  - Because an interaction with a proton is less dependent on frontier orbital interactions, the perturbation will be smaller in a reaction with a proton
    - Frontier orbitals are changed less. Therefore, we have relieved less of the destabilizing interaction.
- Why do some α-nucleophiles show enhanced reactivity, while similar α-nucleophiles do not?

Hudson's Equation for α-nucleophiles

$$\Delta\Delta log k = \frac{\beta c_2^H (m-1)\alpha_j'}{\alpha_j^2} \quad where\ m \equiv c_1^H c_2 / c_2^H c_1$$

Brønsted value

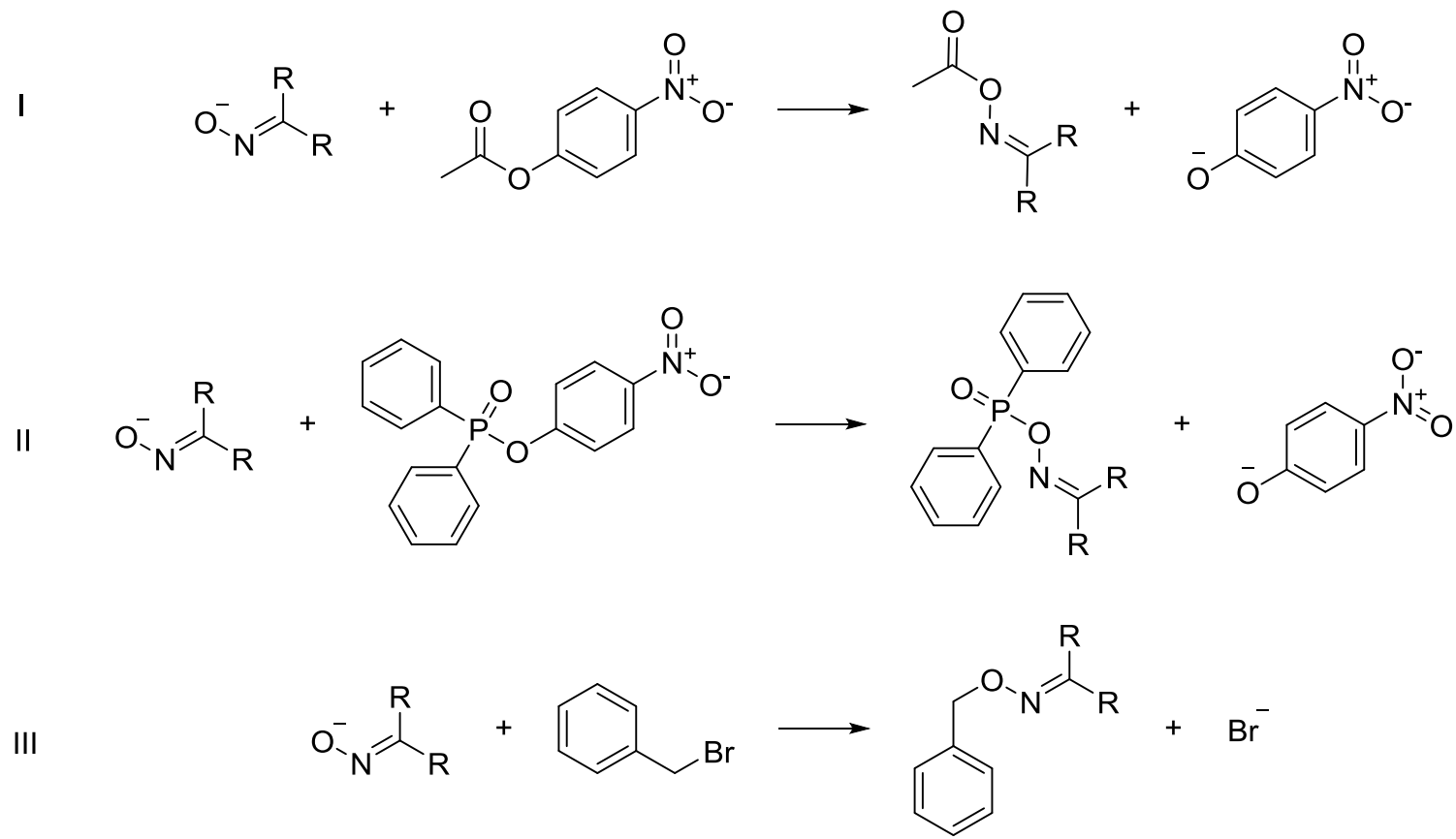
Unperturbed nucleophilic orbital energy

Perturbed nucleophilic orbital energy

- The magnitude of the α-effect should:
  - Increase as β increases
  - Show a dependence on orbital symmetry
  - Decrease with the magnitude of α_j

Filippini, F.; Hudson, R. J.C.S. Chem. Comm. 1972, 522

Oximes Revisited



Aubort, J.D.; Hudson, R.F.; Woodcock, R.C. *Tet. Lett.* 1973, **24,** 2229

Oximes Revisited

Cannot be "intramolecular catalysis" as proposed in first publication

	pKa	I	II	III
$NH_2(Me)C{=}N{-}OH$	12.9	1.2	-	-
$Et_2C{=}N{-}OH$	12.6	1.0	0.6	-
$Me_2C{=}N{-}OH$	12.42	1.0	1.0	1.0
$Ph(Me)C{=}N{-}OH$	11.48	2.7	1.0	-
$(MeCO)(Me)C{=}N{-}OH$	9.38	100	16.5	4.0
$(MeCO)_2C{=}N{-}OH$	7.38	933	25.0	-
Brönsted β		0.8	0.38	0.29

Aubort, J.D.; Hudson, R.F.; Woodcock, R.C. *Tet. Lett.* 1973, **24,** 2229

Oximes Revisited (3)

- Oxygen has two potentially reactive lone pairs:
  - One in conjugation (π-orbital)
  - One interacting with lone-pair on nitrogen (n*)

Electron withdrawing substituents lower the energy of the π orbital below n*. When this is the case, an α-effect is observed.

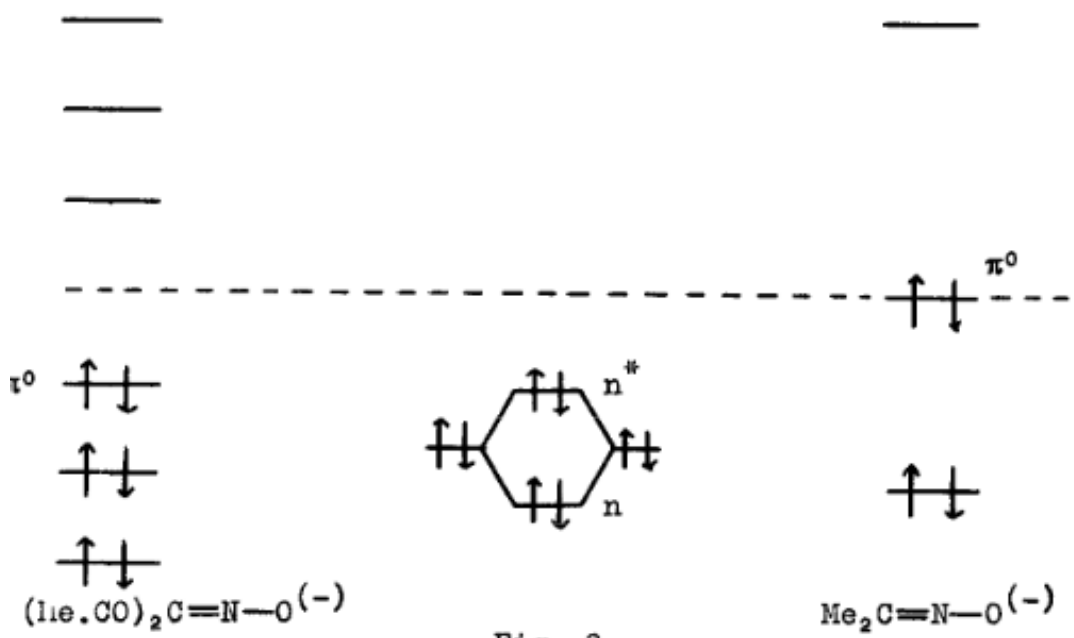


Fig. 2

Aubort, J.D.; Hudson, R.F.; Woodcock, R.C. *Tet. Lett.* 1973, **24,** 2229

Polarization Revisited

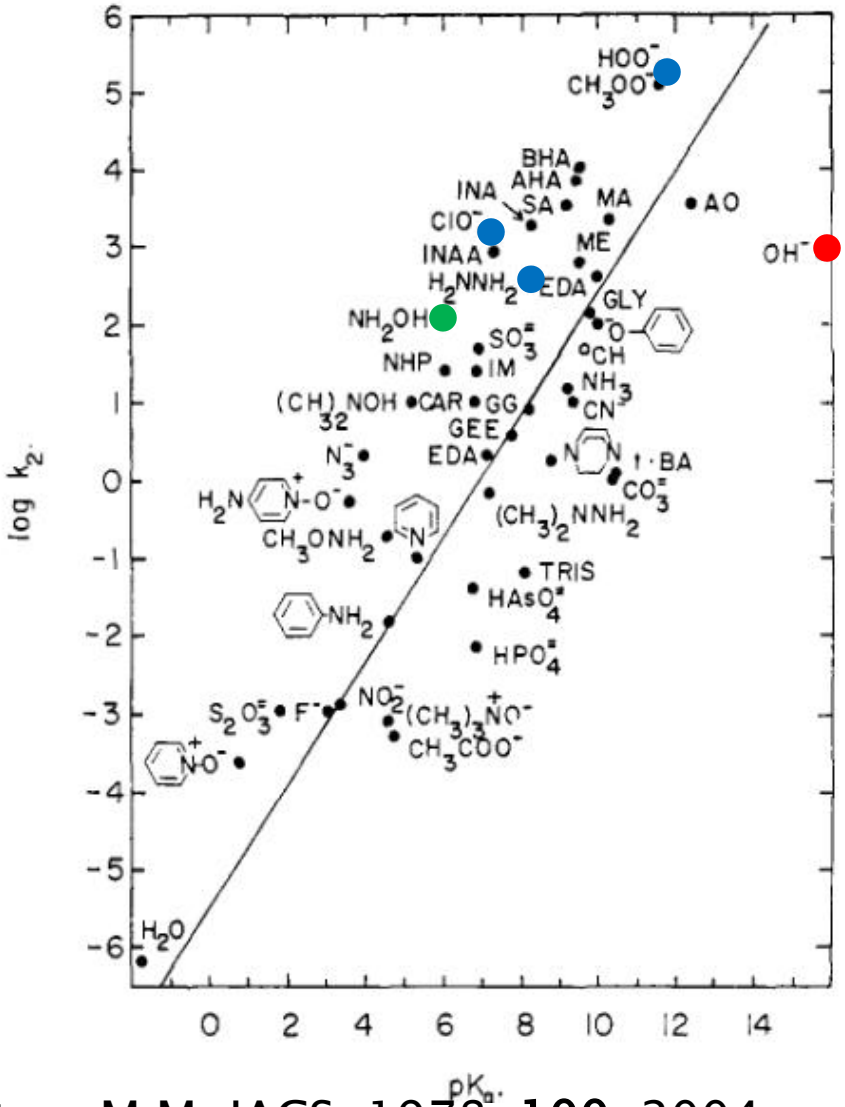
- Ingold suggested increased reactivity of α-nucleophiles could result from an antibonding HOMO, with a node between the nucleophile and α-atom
  - Results in inhomogeneous polarizability, facilitating interaction with electrophile
  - Antibonding interaction is decreased as interaction with an electrophile progresses, hence lowering transition state energy

Ingold, K.C. "Structure and Mechanism in Organic Chemistry", 2nd ed. Cornell University Press, Ithaca, N.Y., 1969, pp 452-453

Electronic Structure Analysis

- Ab initio calculations on Cl^-, OH^-, NH_3, CH_3NH_2, NH_2OH, NH_2NH_2, ClO^-, and OOH^-:
  - HOMO energies: $NH_2OH < NH_3 < NH_2NH_2 < CH_3NH_2 < ClO^- < Cl^- < OH^- < OOH^-$

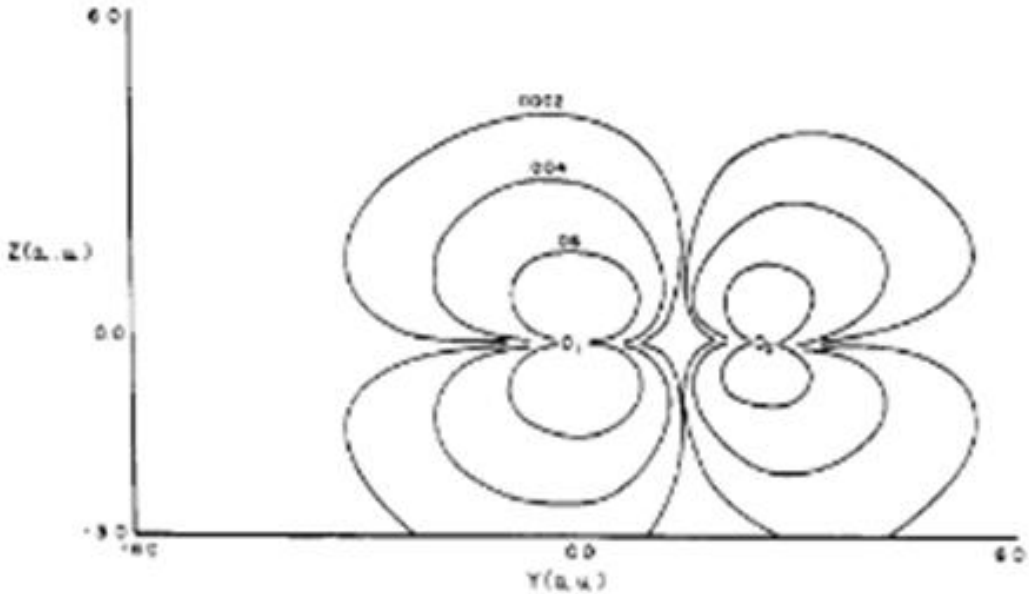
- OH^- and Cl^- HOMOs are lone pairs
- HOMOs of CH_3NH_2 and NH_2OH have some antibonding character
- NH_2NH_2, OOH^-, and OCl^- have strong antibonding character in HOMOs



[12]Heaton, M.M. JACS, 1978, **100**, 2004

The case of OOH^-

Figure 1.



Probability Distribution of OOH^-

1. Of the anionic nucleophiles, OOH^- has the least excess negative charge on the nucleophilic center

2. HOMO is an asymmetric antibonding combination of p_z orbitals, with the nucleophilic orbital being more diffuse.

Table III. Net Atomic Charges on Nucleophiles[a]

OH^-	ClO^-	OOH^-	NH_3	NH_2OH	NH_2NH_2	CH_3NH_2
O −1.2	O −0.78	O_1 −0.73	N −0.88	N −0.50	N −0.59	N −0.70
H +0.2	Cl −0.22	O_2 −0.55	H +0.29	O −0.53	$H_{1,3}$ +0.27	C −0.42
		H +0.28		$H_{1,2}$ +0.31	$H_{2,4}$ +0.31	$H_{1,2}$ +0.17
				H_3 +0.41		H_3 +0.21
						$H_{4,5}$ +0.29

Analysis of OOH^-

- High HOMO and charge considerations are consistent with Hudson's analysis
  - High HOMO suggests ground-state destabilization
  - Low charge and nucleophilic oxygen suggests the Coulomb term is relatively small for OOH^-

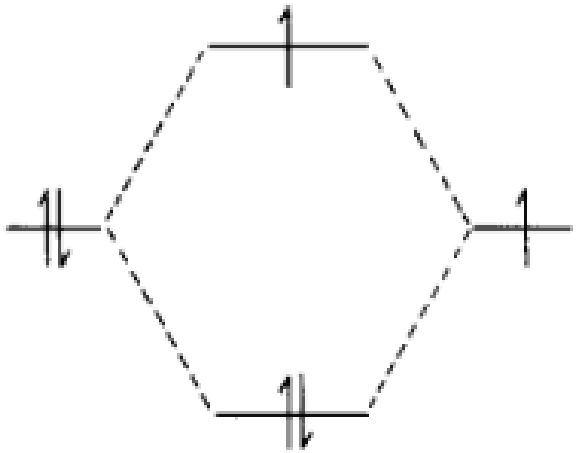
- Antibonding combination of orbitals supports Ingold's hypothesis on α-nucleophilicity:
  - Diffuse nucleophilic is more easily polarized by approach of electrophile
  - Donation of antibonding electrons to electrophile has a stabilizing effect on the system

Transition State Stabilization

- Some nucleophilic reactions involve a partial electron transfer event:[13]

$$N: + S \rightarrow [N\cdot + S\cdot] \rightarrow N\text{–}S$$

- Because of diradical character, α–lone pair stabilizes the transition state:



[13]Hoz, S. J. Org. Chem. 1982, **47**, 3545

Transition State Stabilization

- Extent of stabilization will be proportionate to contribution of diradicaloid character:
  - Substrates with high electron affinity (lower LUMO) are more likely to undergo an ET event
    - Explains observation of smaller α-effects in Sn2 reactions relative to addition to unsaturated compounds
  - Large β-values associated with ET reactions
    - Dependence of magnitude of α-effect on β agrees with Hudson's work

Intermission

Studying Solvent Effects: Gas Phase Reactions

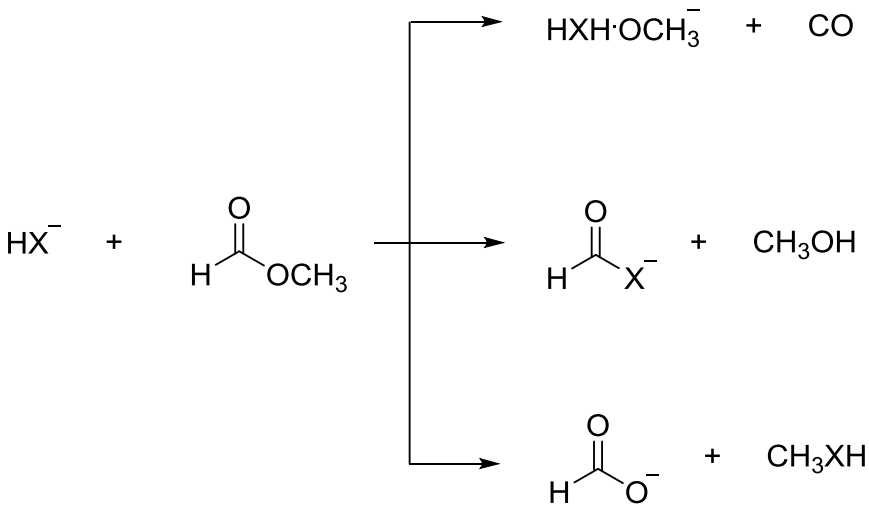


Table I. Reaction Pathways with Methyl Formate[a]

	proton abstraction, %	carbonyl addition, %	S_N2 displacement, %
$H^{18}O^-$	61	34	5
HOO^-	64	28	8

"HOO^- shows no enhanced nucleophilic reactivity compared to HO^- in the gas phase, and we conclude that the α-effect is most likely a manifestation of solvent effects."

DePuy *et al.* JACS. 1983, 105, 2481

Solvent Effects?

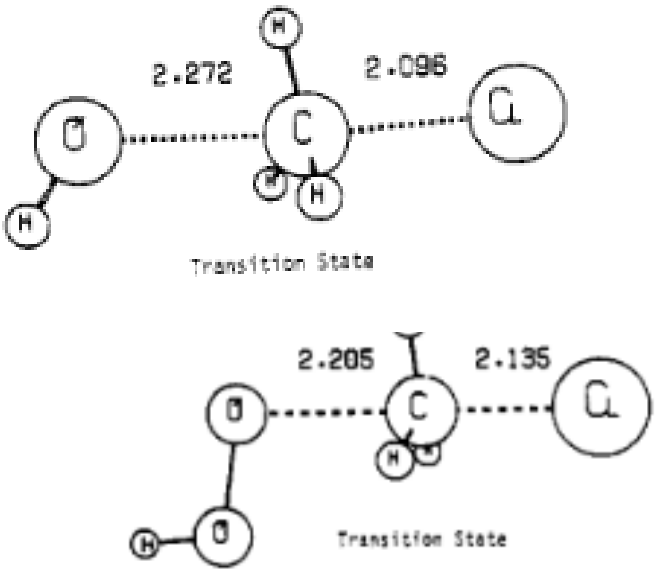
- The magnitude of the α-effect is dependent on β
- Prior reactions have low selectivity
  - Evident by 20kcal/mol difference in proton affinities
- It is likely that β approaches 0, so we would expect to observe no α-effect
- "Determination of β_{nuc} is essential in order to obtain a meaningful conclusion."

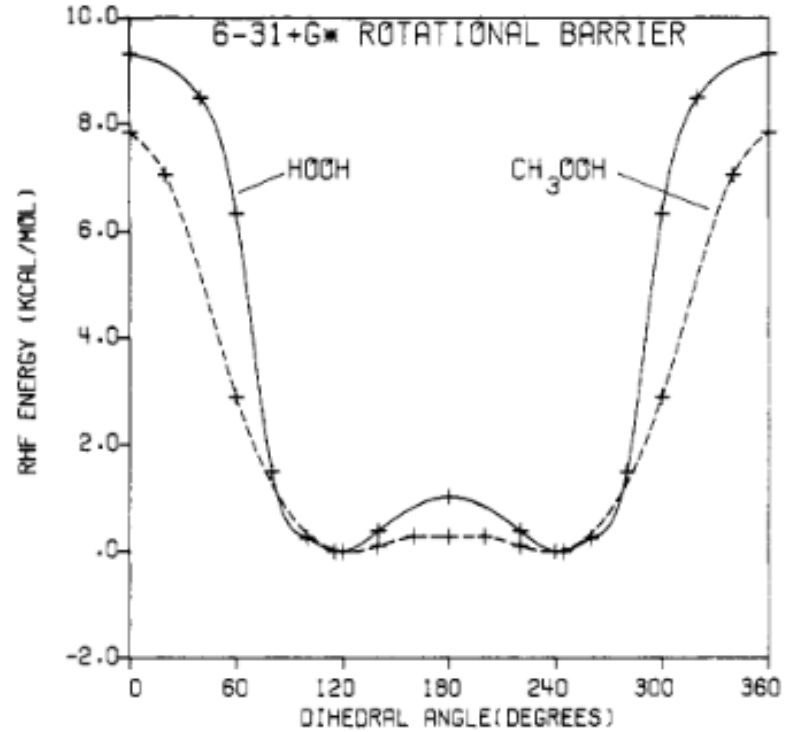
Hoz, S.; Bunce., E. Tet. Lett. 1984, 25, 3411

Solvent Effects: A Theoretical Study

$$HO{-}O^{-} + {-}Cl \longrightarrow CH_3OOH + Cl^{-}$$

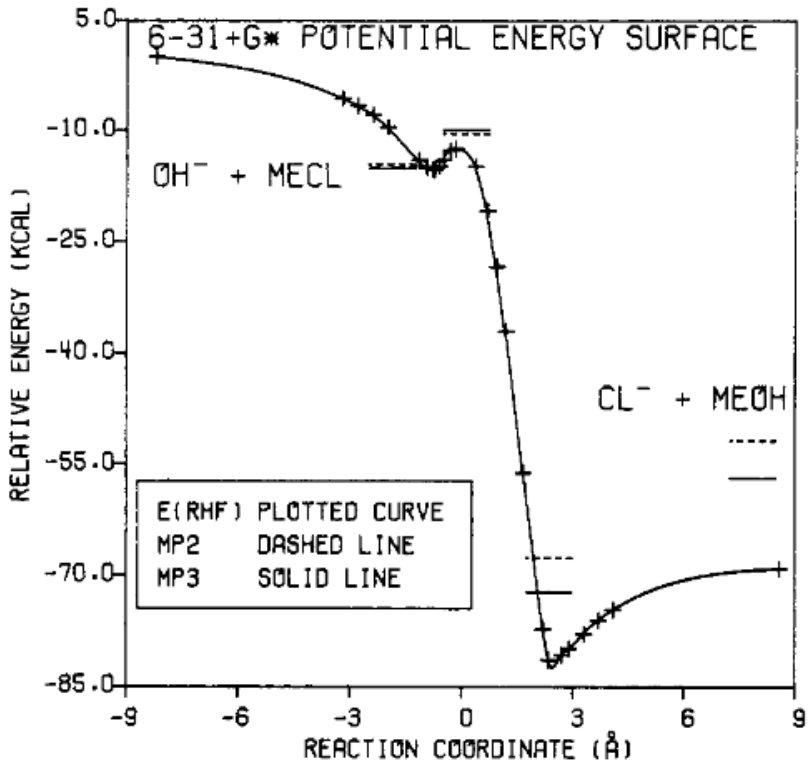
$$OH^{-} + {-}Cl \longrightarrow CH_3OH + Cl^{-}$$

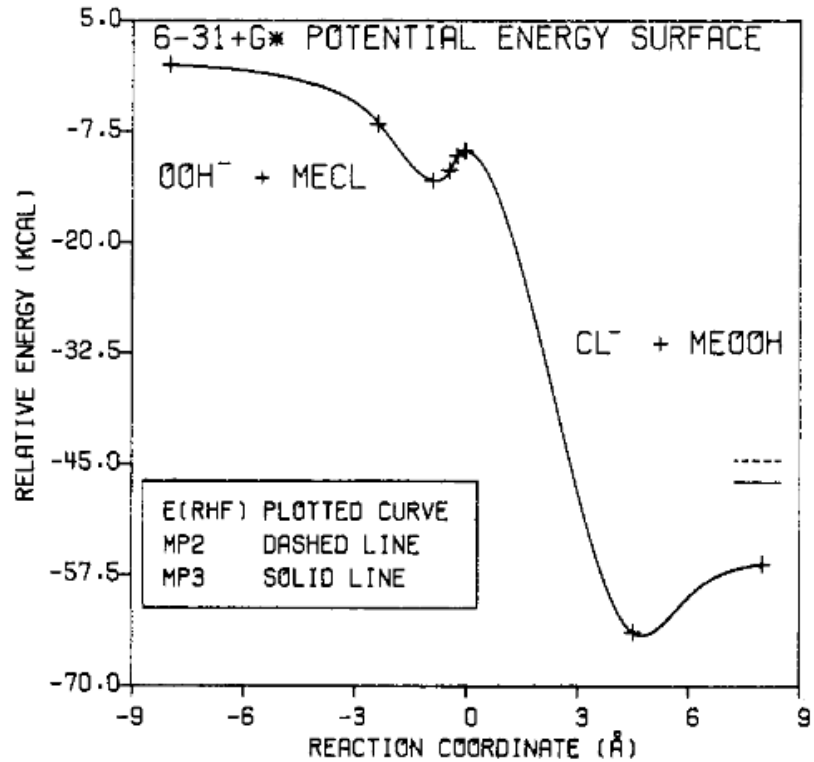




Jorgensen *et al.* JACS. 1987, 109, 2349

Solvent Effects: A Theoretical Study

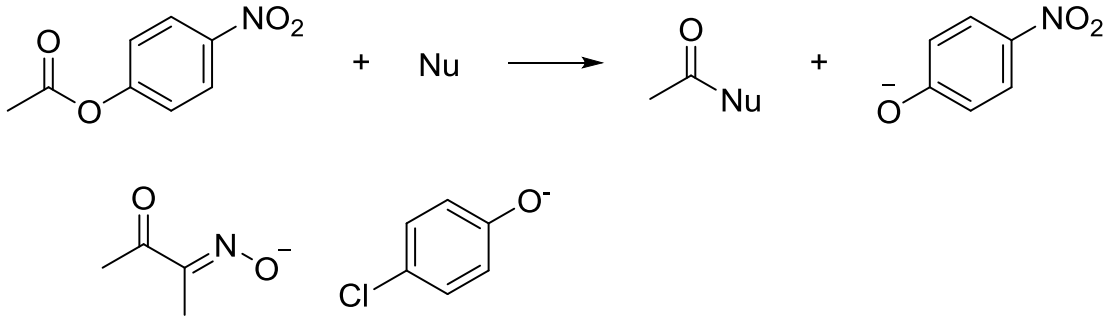




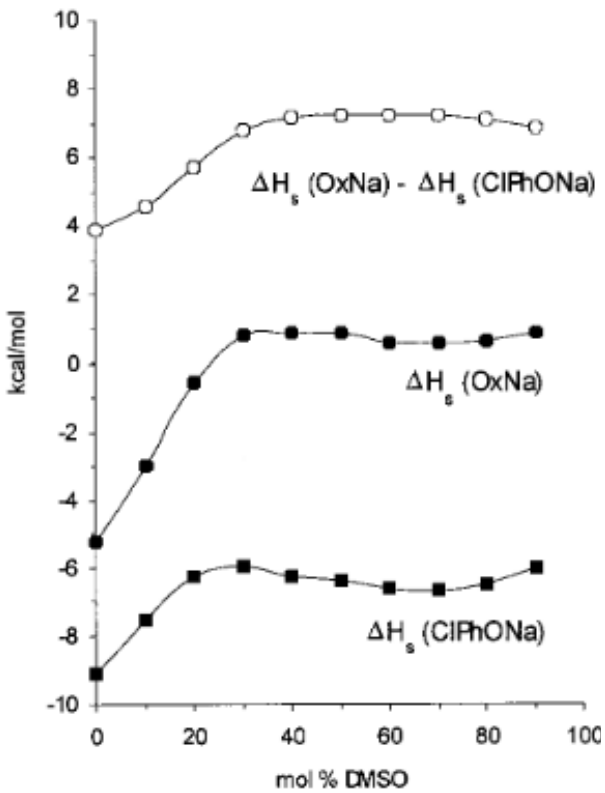
species	6-31+G(d)	MP2[a]	MP3[a]
reactants	0.0	0.0	0.0
$HO^-\cdots CH_3Cl$	−15.3	−14.9	−15.1
transition state	−12.4	−10.4	−10.1
$CH_3OH\cdots Cl^-$	−81.4	−67.6	−72.3
products	−69.1	−51.8	−56.8

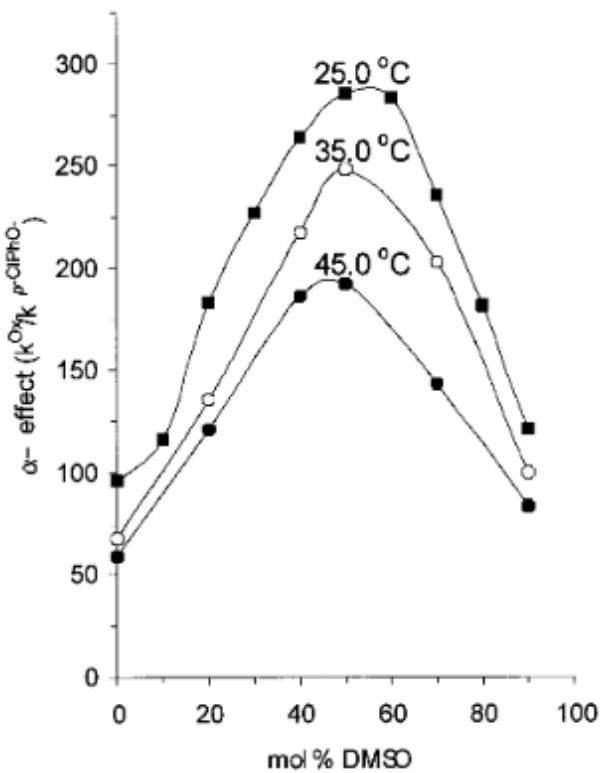
species	6-31+G(d)	MP2[a]	MP3[a]
reactants	0.0	0.0	0.0
$HOO^-\cdots CH_3Cl$	−13.8		
transition state	−9.7		
$CH_3OOH\cdots Cl^-$	−68.0		
products	−56.3	−44.5	−47.0

Jorgensen *et al.* JACS. 1987, 109, 2349



Um and Buncel: Effects of Solvation GS





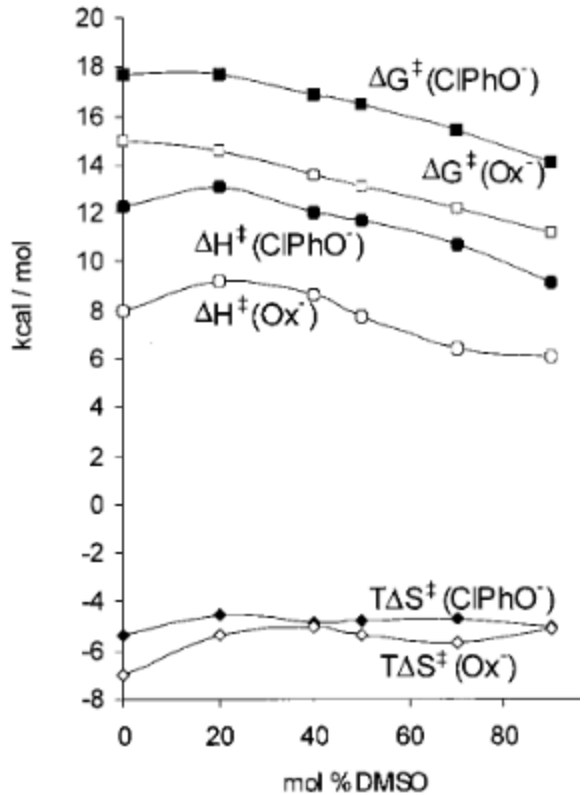
- Trend in desolvation parallels α-effect up to ~40% DMSO in water.
- Difference in GS desolvation does not explain the changes in the α-effect at higher mol% DMSO

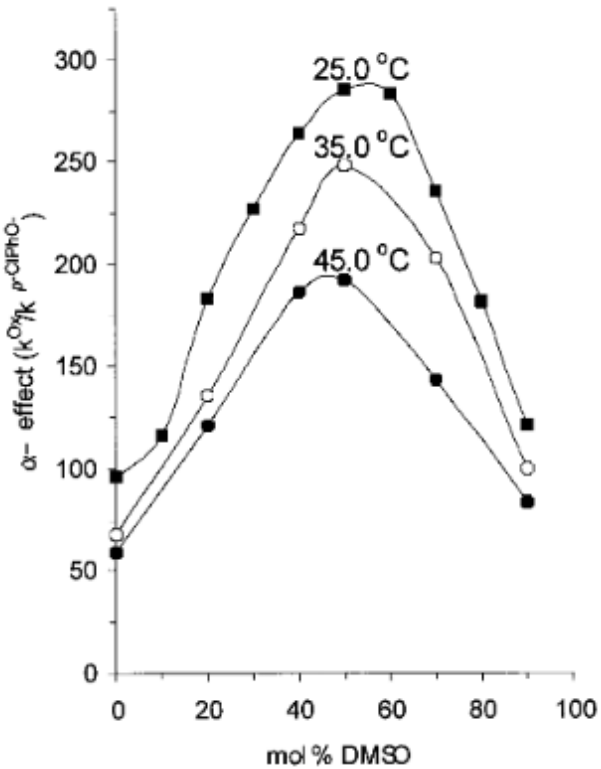
Um, I.-H.; Buncel, E. J. Org. Chem. 2000, 65, 577-582

TS Stabilization

$\Delta G^{\ddagger}$ ($ClPhO^-$) decreases more rapidly than $\Delta G^{\ddagger}$ (Ox^-) at high mol% DMSO

The extent of asynchronicity in the $\Delta G^{\ddagger}$ (Ox^-) transition state is more variable with respect to solvent , where asynchronicity in $\Delta G^{\ddagger}$ ($ClPhO^-$) remains constant

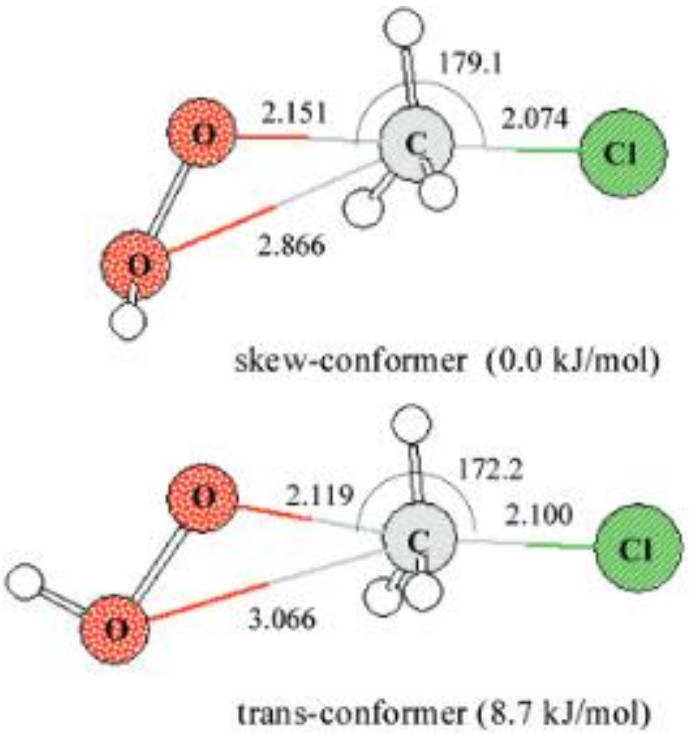




Um, I.-H.; Buncel, E. J. Org. Chem. 2000, 65, 577-582

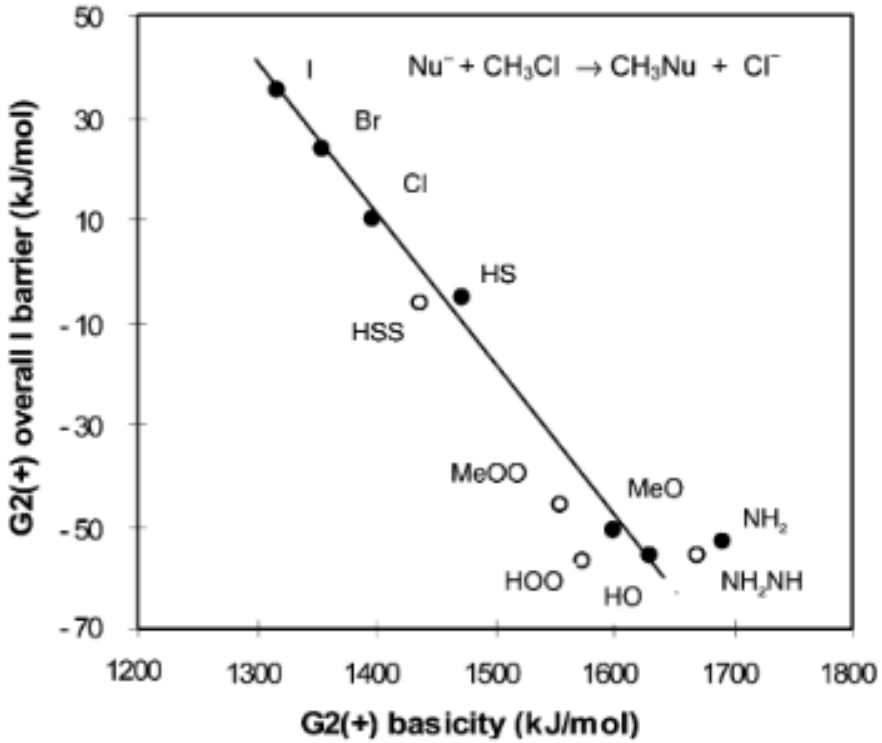
Gas Phase α-effect

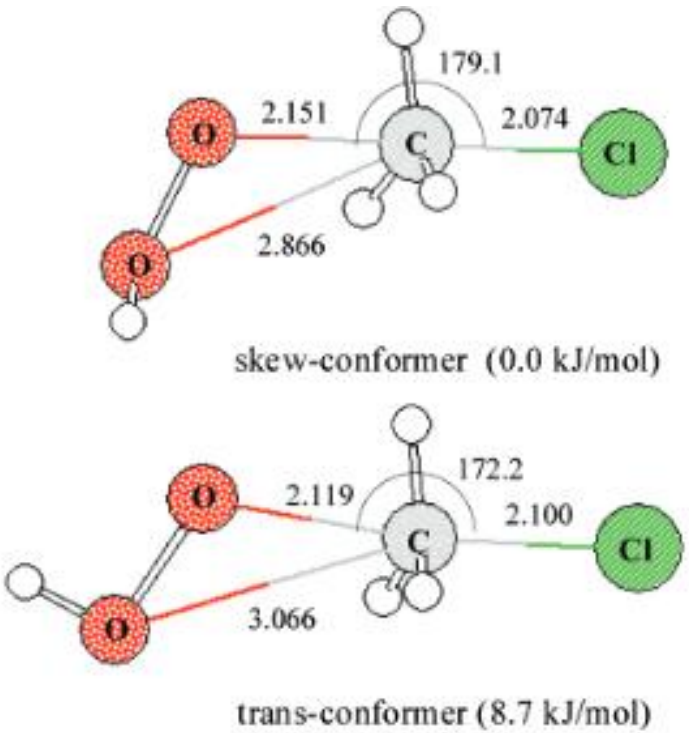
- Most evidence pointed to the absence of a solvent effect in the gas phase
- New study found lower energy transition state at higher level of theory



Jorgensen *et al.* JACS. 1987, 109, 2349
Ren, Y.; Yamataka, H. Org. Lett. 2006, 8, 119-121

Gas Phase α-effect





Ren, Y.; Yamataka, H. Org. Lett. 2006, 8, 119-121

Gas Phase S_N2

Nucleophilicity of "normal" nucleophiles correlates well to proton affinity, while α-nucleophiles show negative deviation

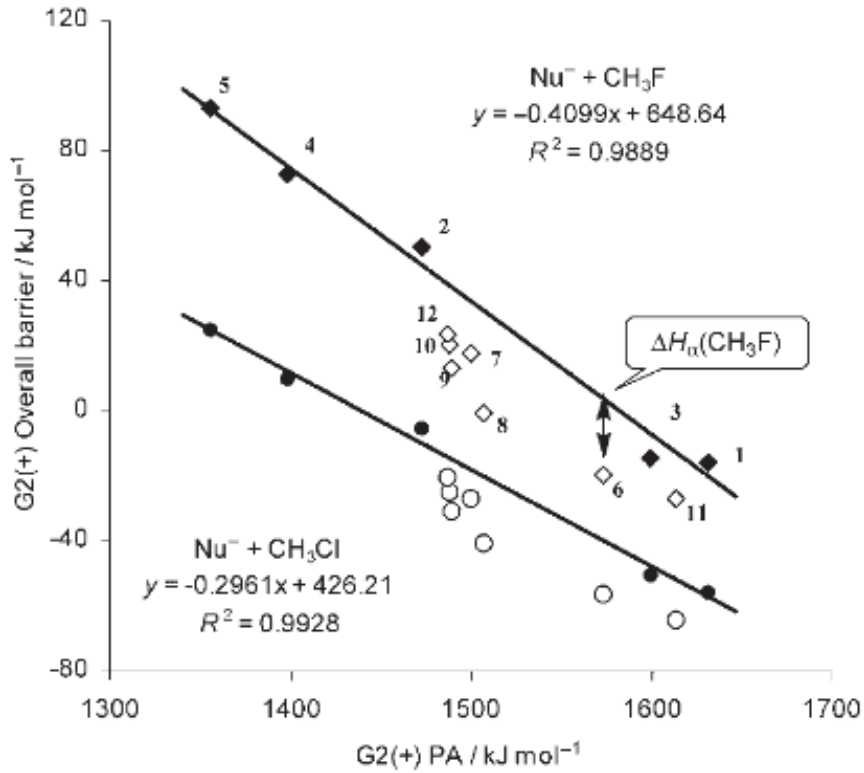


Figure 1. Plot of the G2(+) overall barriers versus the PA's of normal nucleophiles (◆ and ●) and α-nucleophiles (◇ and ○) for the reactions given in Equations (1) (upper) and (2) (below) at 298.15 K. The numbers in bold represent the nucleophiles: **1**: HO^-; **2**: HS^-; **3**: CH_3O^-; **4**: Cl^- **5**: Br^-; **6**:HOO^-; **7**:HSO^-; **8**: FO^-; **9**: ClO^-; **10**:BrO^-; **11**: NH_2O^-; **12**: $HC(=O)OO^-$.

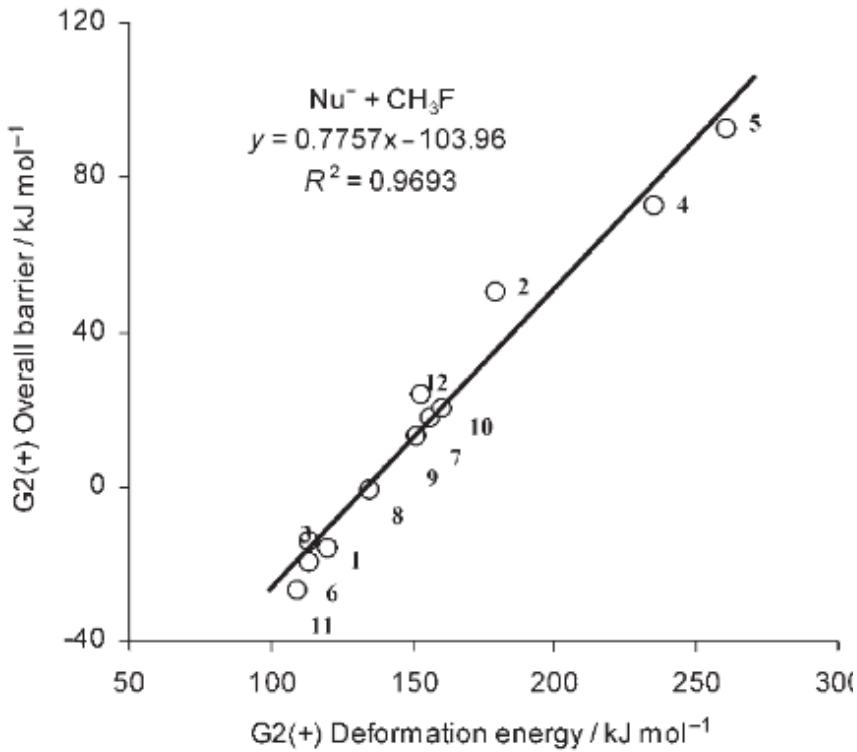
Ren, Y.; Yamataka, H. Chem. Eur. J. 2007, 13, 677

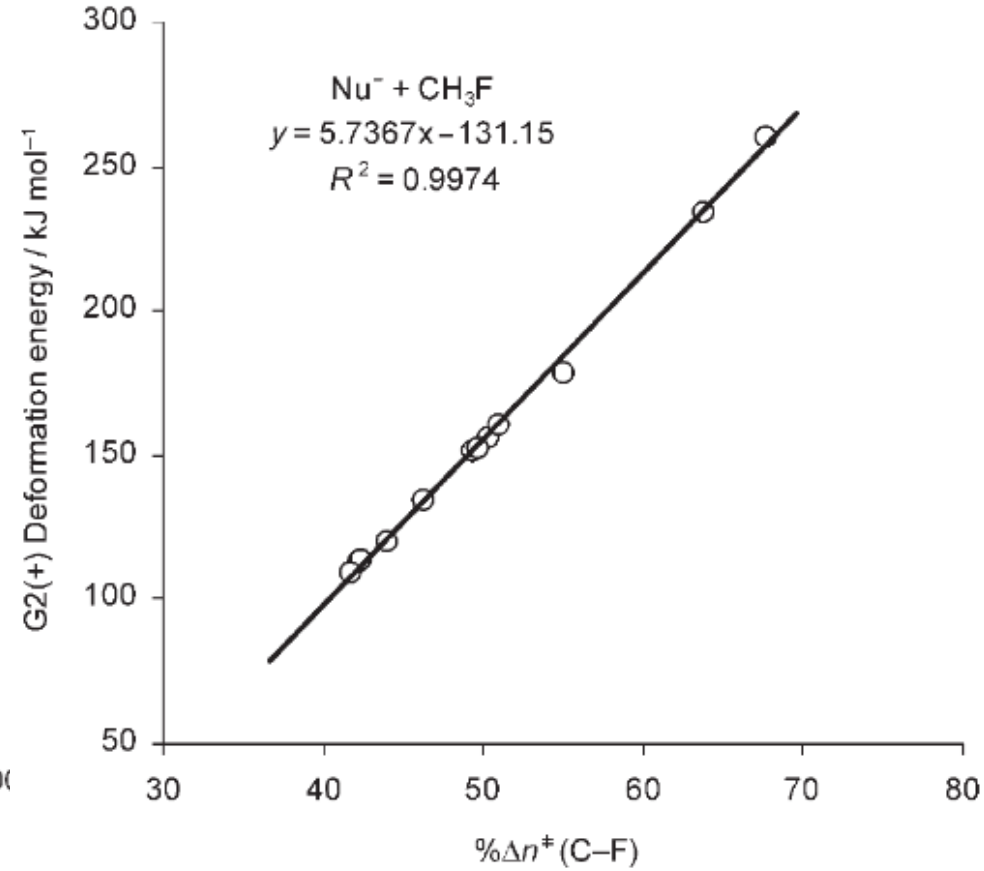
Gas Phase S_N2

	Nu⁻	G2(+) PA	$\Delta H^{\ddagger}$ (CH_3F)	$\Delta H^{\ddagger}$ (CH_3Cl)	ΔH (CH_3F)	ΔH (CH_3Cl)	ΔE_{def} (CH_3F)	ΔE_{def} (CH_3Cl)
1	HO^-	1631.8	−15.6	−55.5	−77.6	−205.6	119.9	56.9
2	HS^-	1473.1	50.4	−5.6	42.7	−85.3	178.7	98.3
3	CH_3O^-	1599.0	−14.1	−50.6	−66.8	−194.8	113.1	50.1
4	Cl^-	1398.4	73.1	9.9	128.0	0.0	234.7	135.0
5	Br^-	1355.3	92.9	24.7	162.0	34.0	260.4	142.4
6	HOO^-	1573.1	−19.4	−56.6	−53.0	−180.9	113.6	55.7
7	HSO^-	1500.2	17.9	−26.7	32.7	−95.3	156.2	81.8
8	FO^-	1507.2	−0.7	−40.8	2.5	−125.5	134.6	71.3
9	ClO^-	1489.6	13.2	−31.0	35.3	−92.6	151.3	75.5
10	BrO^-	1488.0	20.4	−24.9	42.6	−85.4	160.4	82.8
11	NH_2O^-	1614.1	−26.8	−64.2	−83.5	−211.4	109.4	48.8
12	$HCOOO^-$	1486.9	23.7	−20.4	43.0	−84.8	152.8	82.9

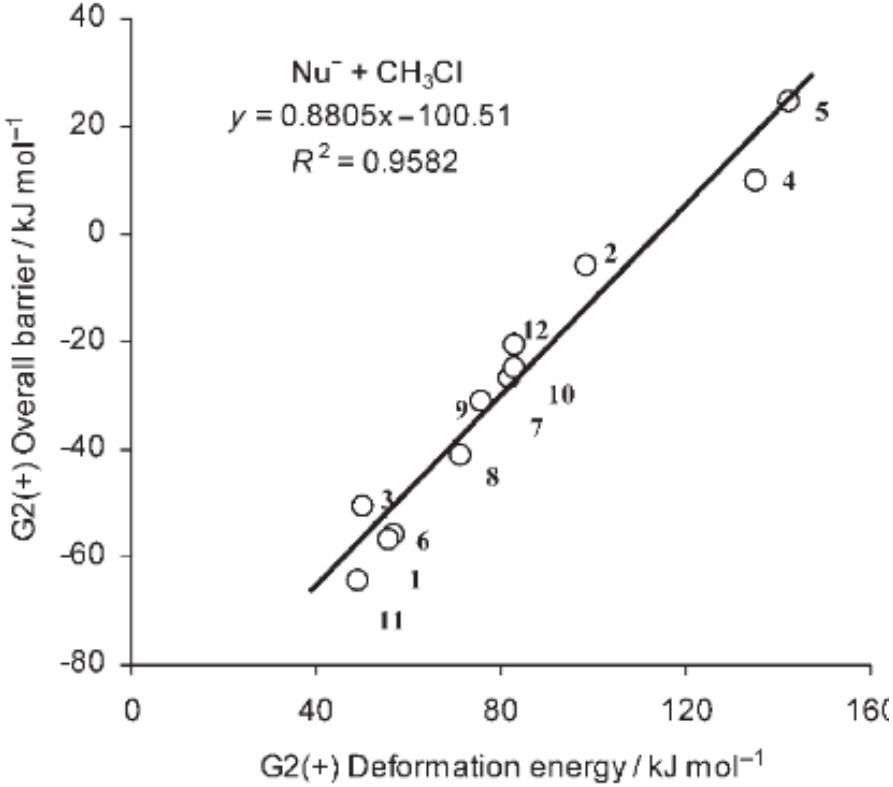
Strong correlation between deformation energy and overall barrier indicates that the transition states for α-nucleophiles have less C–X bond cleavage in the transition state than expected from their proton affinity

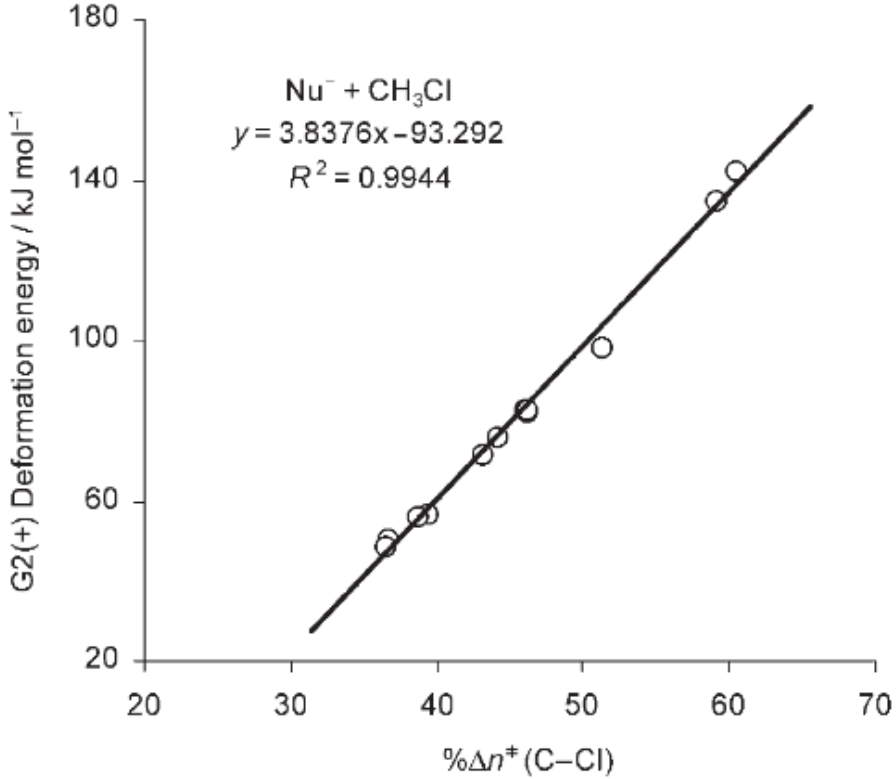
Ren, Y.; Yamataka, H. Chem. Eur. J. 2007, 13, 677





Top: **1**: HO^-; **2**: HS^-; **3**: CH_3O^-; **4**: Cl^- **5**: Br^-; **6**:HOO^-; **7**:HSO^-; **8**: FO^-; **9**: ClO^-; **10**:BrO^-; **11**: NH_2O^-; **12**: $HC(=O)OO^-$

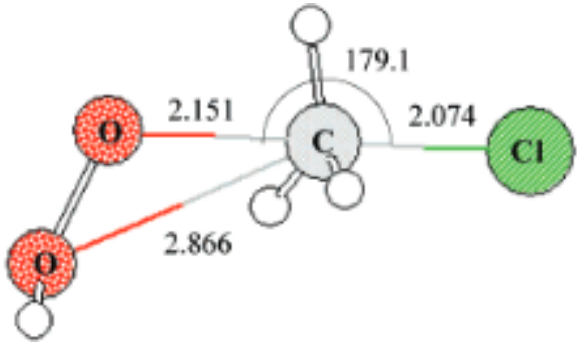




Bottom: **1**: HO^-; **2**: HS^-; **3**: CH_3O^-; **4**: Cl^- **5**: Br^-; **6**:HOO^-; **7**:HSO^-; **8**: FO^-; **9**: ClO^-; **10**:BrO^-; **11**: NH_2O^-; **12**: $HC(=O)OO^-$.

The magnitude of the α-effect

- More electronegative α-atoms lead to larger α-effects (FO^- vs ClO^-)
- Electron withdrawing groups diminish the alpha effect
- Higher electron density at the α-atom and greater positive charge at the electrophile lead to a greater α-effect



Old and New Hypotheses

- Thermodynamic Product Stability
- Transition State Stability
  - TS tightness
  - Polarizability
  - Deformation Energy

[20]Ren, Y.; Yamataka, H. J. Org. Chem. 2007, 72, 5660

Thermodynamic Product Stability

- α-nucleophiles have negative deviation $\Delta H^{\ddagger}$ vs ΔH_{rxn} plot
- Thermodynamic stability does not explain gas-phase α-effects

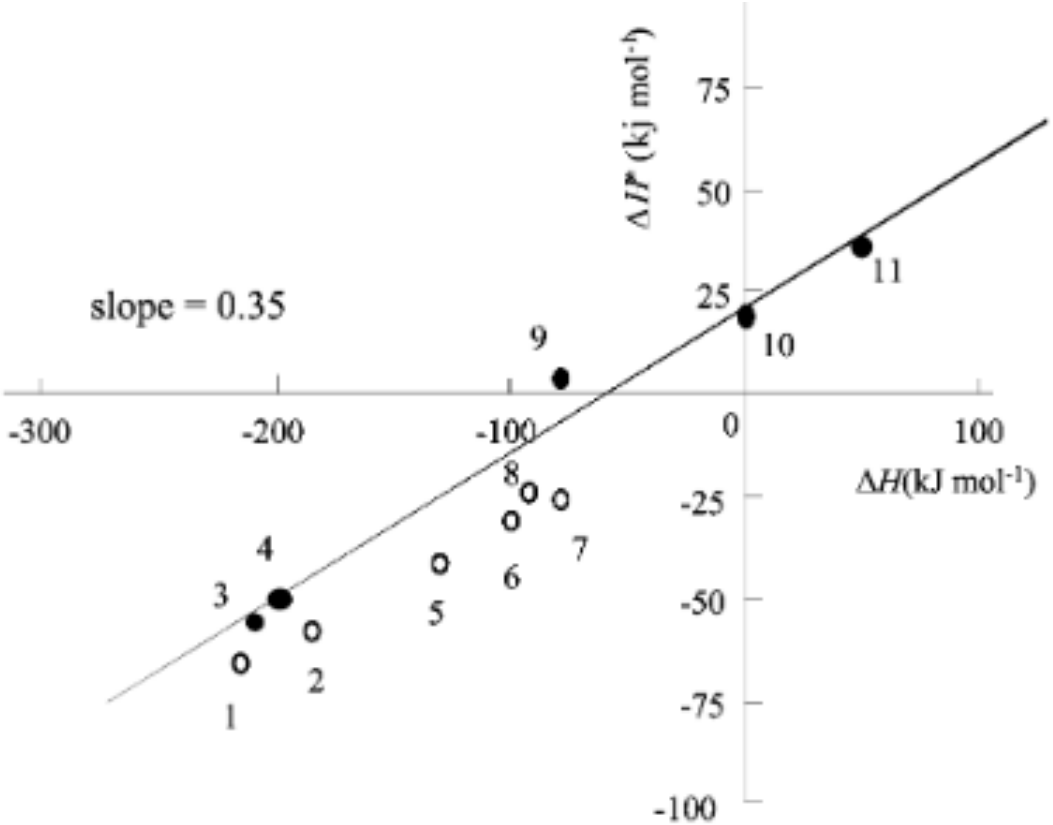


FIGURE 3. Plots of the G2(+) overall activation energy vs reaction energy for the reaction of EtCl. Filled circles for normal nucleophiles (3, HO^-: 4, CH_3O^-: 9, HS^-: 10, Cl^-: 11, Br^-) and open circles for α-nucleophiles (1, NH_2O^-: 2, HOO^-: 5, FO^-: 6, ClO^-: 7, HSO^-: 8, BrO^-).

Transition State Tightness

TABLE 1. Bond Lengths and Bond Orders of the Nu−C and C−Cl Bonds at the S_N2 TS Structures, $[Nu-Et-Cl]^{-\ddagger}$ (Nu = HO, HS, CH_3O, Cl, Br, HOO, HSO, FO, ClO, BrO, and NH_2O)[a]

Nu^-	r_{Nu-C}	r_{C-Cl}	$n^{\ddagger}_{Nu-C}$	$n^{\ddagger}_{C-Cl}$	$n^{\ddagger}_{Nu-C} + n^{\ddagger}_{C-Cl}$	$D_{Y-O-C\alpha-C\beta}$[b]
HO^-	2.201	2.155	0.279	0.547	0.826	
HS^-	2.540	2.264	0.304	0.456	0.760	
CH_3O^-	2.184	2.119	0.283	0.581	0.864	
Cl^-	2.354	2.381	0.393	0.375	0.768	
Br^-	2.456	2.404	0.440	0.361	0.802	
HOO^-	2.163	2.115	0.296	0.585	0.881	173.8
HSO^-	2.091	2.196	0.342	0.511	0.853	162.6
FO^-	2.099	2.163	0.328	0.540	0.868	180.0
ClO^-	2.082	2.191	0.347	0.515	0.862	180.0
BrO^-	2.063	2.209	0.357	0.500	0.857	180.0
NH_2O^-	2.191	2.101	0.284	0.598	0.883	180.0

$1-n^{\ddagger}_{C-Cl} > n^{\ddagger}_{Nuc-C}$ in all cases: denotes bond breaking is ahead of bond forming in TS

1. Later Transition States have larger energy barriers
2. There is no difference between α-nucleophiles and "normal" nucleophiles. Therefore, transition state tightness cannot predict magnitude of α-effect

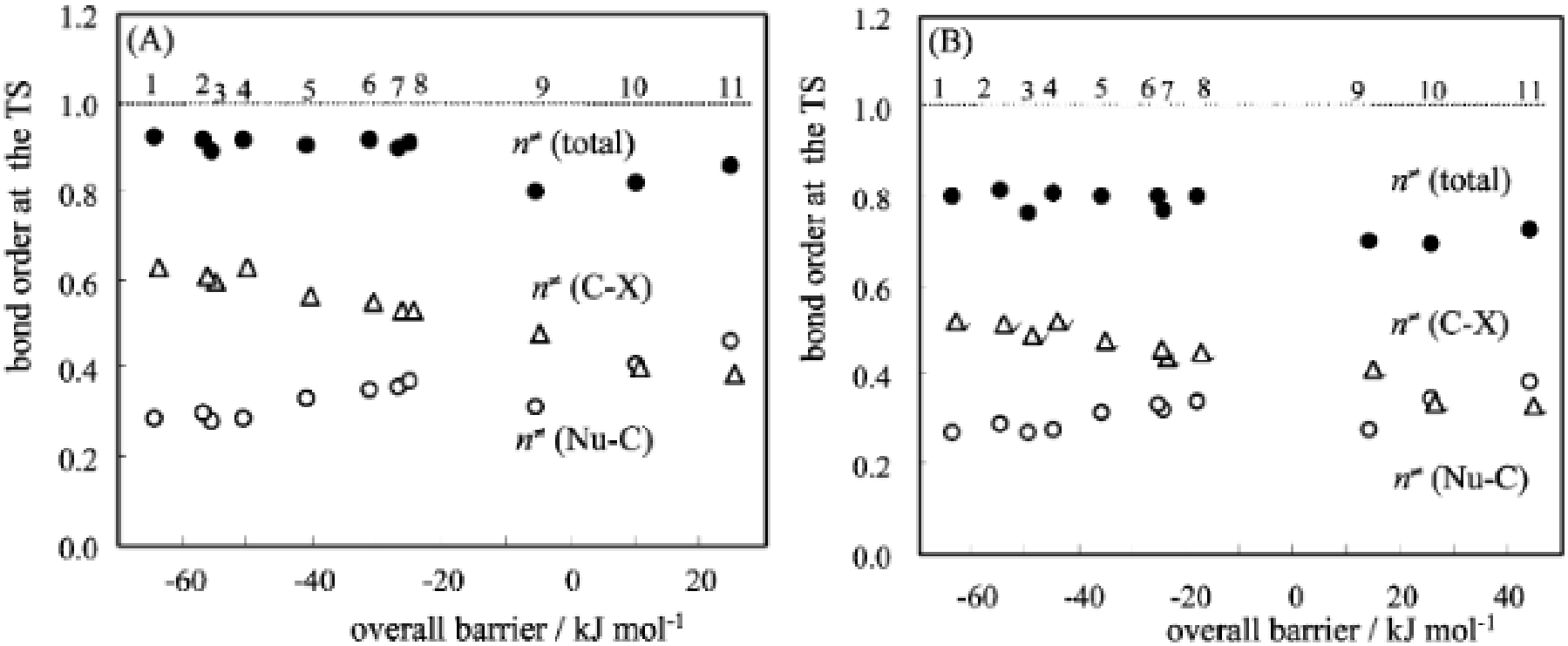


FIGURE 4. Variations of TS bond order with overall reaction barrier for (A) MeF and (B) *i*-PrCl. 1, NH_2O^-: 2, HOO^-: 3, HO^-: 4, MeO^-: 5, FO^-: 6, ClO^-: 7, HSO^-: 8, BrO^-: 9, HS^-: 10, Cl^-: 11, Br^-.

Polarizability and Deformation Energy

- Polarizability:
  - Hard α-atoms result in a larger α-effect
  - No immediate conclusion
- Deformation Energy:
  - α-nucleophiles have enhanced rates because of their smaller deformation energy

Is it possible that harder α-atoms perturb the nucleophilic orbital more than soft α-atoms?

Experimental Evidence: Gas Phase S_N2 Reactions

	thermodynamic data[a]		kinetic data[b]	branching fraction (Eff)[c]			α-effect
reaction (X^- + M)	PA (X^-)	ΔH_{rxn}	k_{expt} ($\times 10^{-10}$)	S_N2	PT	assoc	Eff_{HOO^-}/Eff_{X^-}
$HO^- + CH_3F$	1633	−91	0.120 ± 0.021	100 (0.0042)	–	–	0.62
$CH_3O^- + CH_3F$	1598 ± 2	−70	0.017 ± 0.001	100 (0.0007)	–	–	3.7
$C_2H_5O^- + CH_3F$	1585 ± 3	−60	<0.001	<0.00005	–	–	>50
$HOO^- + CH_3F$	1575 ± 4	−65	0.060 ± 0.002	100 (0.0026)	–	–	
$HO^- + CH_3OC_6H_5$	1633	−162	13.1 ± 0.2	28 (0.13)	51	20	0.69
$CH_3O^- + CH_3OC_6H_5$	1598 ± 2	−141	2.74 ± 0.01	32 (0.04)	–	68	2.3
$C_2H_5O^- + CH_3OC_6H_5$	1585 ± 3	−131	1.38 ± 0.10	10 (0.01)	–	90	9.0
$HOO^- + CH_3OC_6H_5$	1575 ± 4	−135	3.49 ± 0.05	54 (0.09)	–	46	
$i\text{-}C_3H_7O^- + CH_3OC_6H_5$	1576 ± 3	−121	–	–	–	100	
$HO^- + CH_3OC_6H_4F$	1633	−174	23.0 ± 0.6	–	100	–	
$CH_3O^- + CH_3OC_6H_4F$	1598 ± 2	−153	10.7 ± 0.4	32 (0.10)	10	58	2.3
$C_2H_5O^- + CH_3OC_6H_4F$	1585 ± 3	−143	6.88 ± 0.21	9 (0.02)	–	91	12
$HOO^- + CH_3OC_6H_4F$	1575 ± 4	−147	10.4 ± 0.5	70 (0.23)	–	30	
$i\text{-}C_3H_7O^- + CH_3OC_6H_4F$	1576 ± 3	−133	–	–	–	100	

Bierbaum, *et al.* JACS 2011, 113, 13897

Experimental Evidence

Relative rate enhancement of peroxide relative to nucleophiles with greater proton affinities provides evidence for an α-effect in the gas phase.

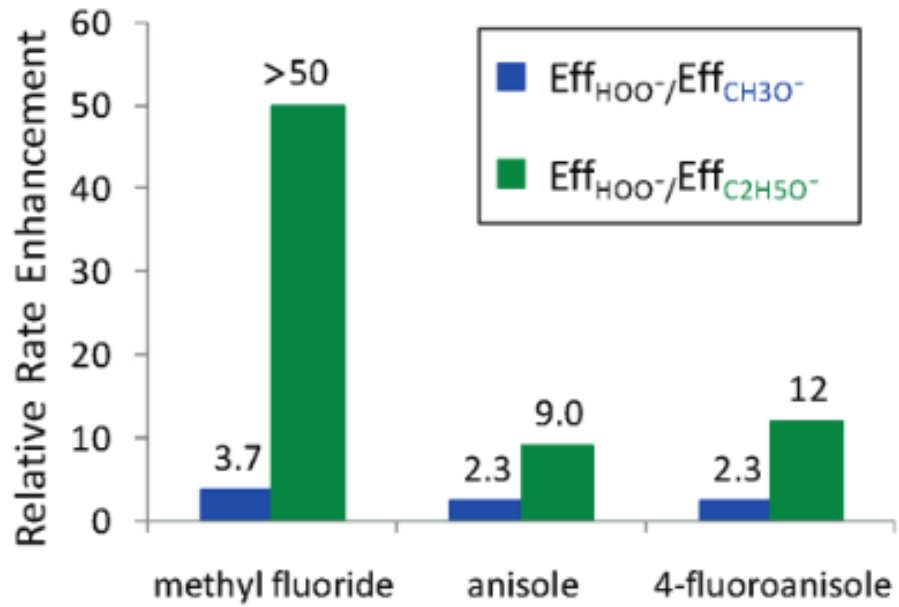
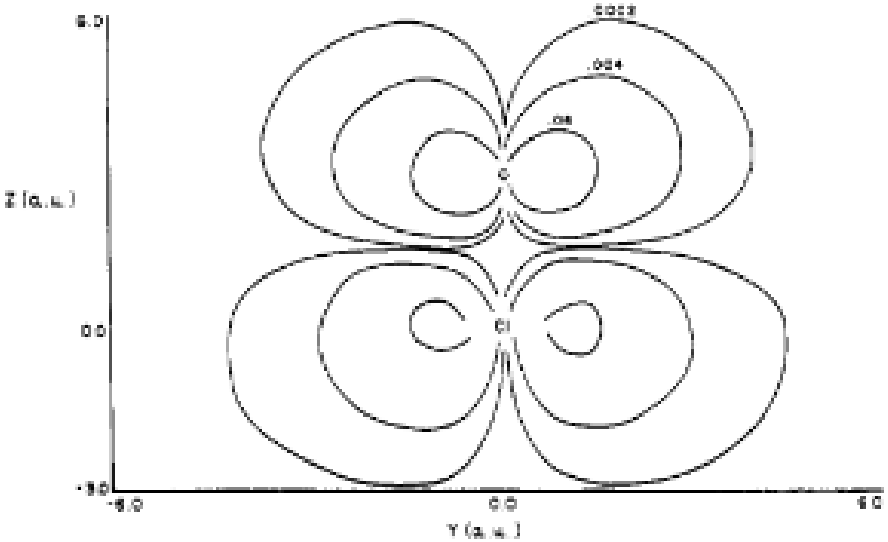


Figure 1. Magnitude of the α-effect for HOO^- (PA = 1575 kJ mol^{-1}) relative to CH_3O^- (PA = 1598 kJ mol^{-1}) and $C_2H_5O^-$ (PA = 1585 kJ mol^{-1}).

Conclusions

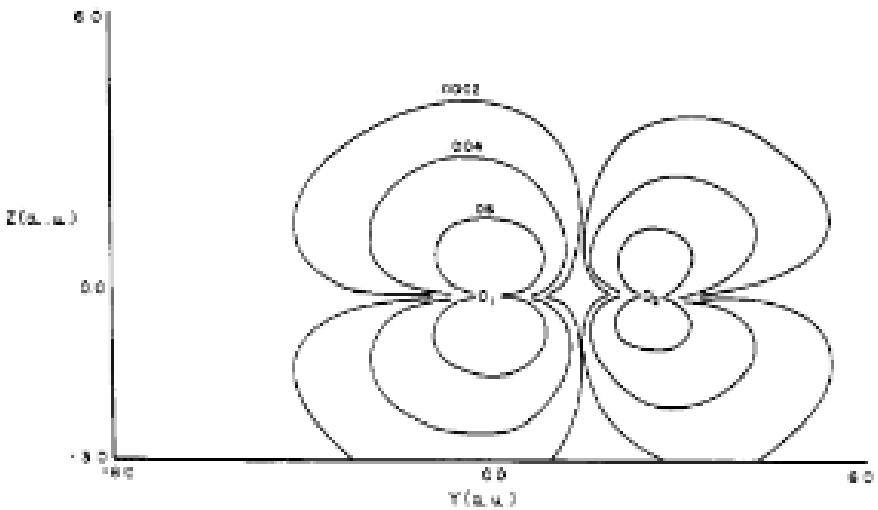
- Although the α-effect is heavily modulated by solvent, theoretical and experimental results that the α-effect is an intrinsic property and α-nucleophiles.

- The physical origin of the α-effect is related to similarities in the electronic structure of the products and the transition state. However, the precise origin of these similarities is still inconclusive.



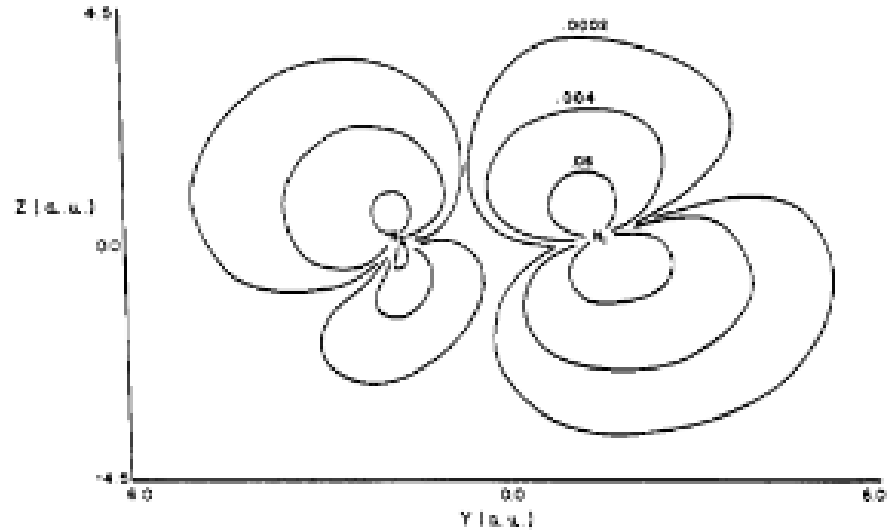
PROBABILITY DISTRIBUTION
ClO^- $^3\Pi_y$ M.O.

Figure 1.



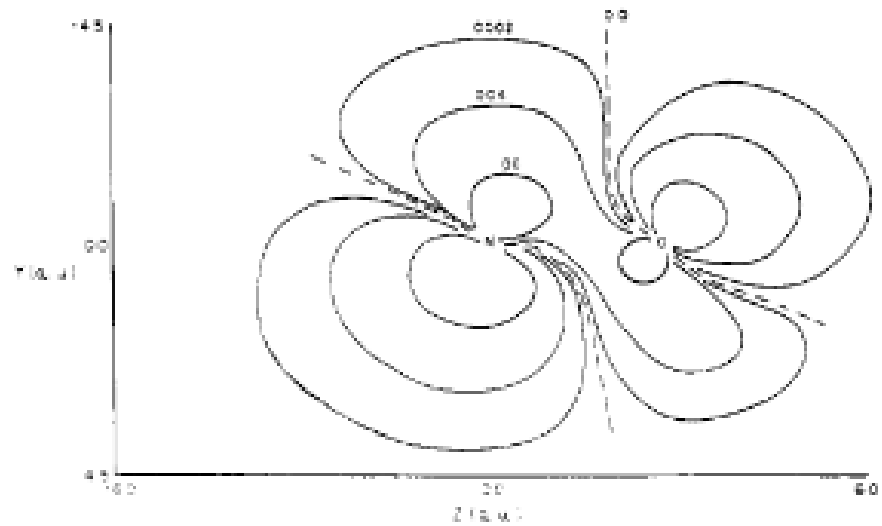
PROBABILITY DISTRIBUTION
OOH^- $2a_1''$ M.O.

Figure 2.



PROBABILITY DISTRIBUTION
N_2H_4 $9a_g$ M.O.

Figure 3.



PROBABILITY DISTRIBUTION
NH_2OH $7a''$ M.O.

Figure 4.