Equilibrium Constants, Oxidation Potentials, and Nucleophilicity in S_N2 Displacements

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A comparison of recently available one-electron oxidation potentials, I', for a number of diverse nucleophiles shows that there is surprisingly little correlation with nucleophilic reactivity, n, toward methyl iodide. A plot of I' vs. n has a slope of only −0.11 and a correlation coefficient of only −0.66. Values of $\Delta G°$ for the reactions of these nucleophiles with CH_3I in water were calculated. A plot of $\Delta G°$ vs. n shows normal curvature for second-row donors (F, O, N, C). Limiting rates are reached for anions, determined by desolvation energies. Bases with donor atoms from the third, or higher, rows all show enhanced reactivity. Evidence is presented to show that this cannot be primarily a solvation effect but is due to soft acid–soft base stabilizing interactions. Thermodynamic leaving group abilities are presented covering a range of 10^{56}.

Introduction

The subject of nucleophilic reactivity in displacement reactions continues to be of great interest to organic chemists. While as many as 17 factors have been identified as influencing nucleophilic reactivity, there is still no general agreement on the factors that are most important, except for solvent effects. That is, we are still hard pressed to estimate the rate of an S_N2 reaction that involves a new combination of nucleophile and electrophile. The most common method seems to be to extrapolate from the known rates of related reactions.[2]

Recently two papers have appeared that suggest different properties of the nucleophile to be dominant. In the first, Ritchie has shown that there is a linear relationship between log k and the one-electron oxidation potential for a series of second row (period) nucleophiles for the reaction with the Pyronin cation.[3] Secondly, Streitwieser has shown that there is a linear relationship between log k and the (presumed) $\Delta G°$ for several anions reacting with CH_3I in dimethylformamide.[4] While no broad claims were made by these authors, it is reasonable to believe that oxidation potentials, and/or overall free energy changes, could be dominant factors in many displacement reactions.

The partial transfer of a pair of electrons from nucleophile to electrophile has long been thought to be an important part of the S_N2 reaction.[5] For a series of closely related bases, it has often been found that log k is linear with pK_a for the base, the Brønsted relation. Since it has also been shown that, for such bases, pK_a is a linear function of the irreversible half-wave potentials,[6] a linear relationship between log k and $E_{1/2}$ is inferred. Such a relationship was found by Dessy for a series of organometallic nucleophiles.[7]

The belief that log k is a linear function of $\Delta G°$ is also well-founded. It is, of course, an example of the linear free energy relationship (LFER).[8] It is fair to say that such a relationship is always to be expected, a priori, and that failure to observe it is a strong indication of a complexity in the mechanism. The fundamental equation may be written in the form

$$\Delta G^{\ddagger} = \alpha \Delta G° + \text{constant} \qquad (1)$$

where $\Delta G^{\ddagger}$ is the free energy of activation. There is no requirement that α remain constant over a wide range of $\Delta G°$, but it must change slowly and continuously.

Fortunately, recent developments make it possible to test both of the above conjectures with a much greater number of examples. For a series of anionic, X^-, and neutral, B, nucleophiles, the absolute, reversible one-electron oxidation potentials, I', in water at 25 °C have been calculated by thermodynamic cycles.[9] At the same time, free energies of hydration for the anions, X^-, and the cations, BH^+, have been calculated. This information, along with other data from the literature, enable $\Delta G°$ to be found for many of the nucleophiles.

The results will be tested on rate data for the reaction of CH_3I with the same nucleophiles. The rate data is for the reactions in methanol at 25 °C. The solvent methanol

$$CH_3I + X^- \xrightarrow{k} CH_3X + I^- \qquad (2)$$

$$CH_3I + B \xrightarrow{k} CH_3B^+ + I^- \qquad (3)$$

is selected because the greatest amount of rate data is available in this solvent.[10] The values of I' and $\Delta G°$ refer to water solvent. However, it is known that the same orders of nucleophilic reactivity are found in CH_3OH and in H_2O.[11]

The data is presented in the form

$$n = \log (k/k_s) \qquad (4)$$

where k refers to the nucleophile and k_s to the rate constant for the solvent, converted to units of $M^{-1}\ s^{-1}$. While k_s is twice as large for CH_3OH as for H_2O, n values in CH_3OH are about 1.4 units larger than in H_2O for anionic nucleophiles. For neutral nucleophiles, the data in water are less abundant but show similar increases in methanol.[12,13]

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(1) Bunnett, J. F. *Ann. Rev. Phys. Chem.* **1963**, *14*, 271.

(2) The well-known Swain–Scott equation is an example of this procedure.

(3) Ritchie, C. D. *J. Am. Chem. Soc.* **1983**, *105*, 7313.

(4) Streitwieser, A., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8288.

(5) Hudson, R. F. *Chimia (Aarau)* **1962**, *16*, 173. Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 2708. Note that complete transfer of one electron (SET) is not being considered.

(6) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314. Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1985 and references therein.

(7) Dessy, R. E.; Pohl, R. L.; King, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 5121.

(8) (a) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963. (b) *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1972.

(9) Pearson, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 6109.

(10) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

(11) Scott, J. M. W. *Can. J. Chem.* **1970**, *48*, 3807. Koskikallio, J. *Acta Chem. Scand.* **1972**, *26*, 1201.

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Table I. Some Properties of Selected Anions, X^-

X^-	I'[a]	n[b]	D_{CH_3X}[c]	D_{HX}[f]	$-\Delta G°$[i]
$C_6H_5CH_2^-$	3.40		72	88	69
CH_3^-	3.73		88	105	77
PH_2^-	4.18		76	87	55
$C_6H_5^-$	4.27		100	111	77
O_2^-	4.31		31[d]	49[g]	7
CH_2CN^-	4.59		81	93	51
H^-	4.68		104	104	22
NH_2^-	4.72		85	107	52
HSe^-	5.12	9.0	67	79	24
$CH_3COCH_2^-$	5.14		86	98	43
n-$C_3H_7S^-$	5.24	10	72	87	27
$C_6H_5S^-$	5.26	9.9	69	83	23
HO_2^-	5.33	7.8	69	88	32
NO_2^-	5.39	5.4	61	78	13
$C_6H_5O^-$	5.42	5.8	64	87	14
HS^-	5.58	8.5	74	91	24
CH_3O^-	5.60	6.3	83	104	29
I^-	5.69	7.4	56	71	0
N_3^-	5.82	5.8		92	
SCN^-	6.16	6.6	70[e]	96[h]	3
HC_2^-	6.18		121	130	54
OH^-	6.22		92	119	24
Br^-	6.35	5.8	70	88	-1
$CH_3CO_2^-$	6.54	4.3	83	106	7
$C_6H_5CO_2^-$		4.5			6[j]
NO_3^-	6.78	1.5	80	102	-1
Cl^-	6.81	4.4	84	103	2
CN^-	7.02	6.7	122	124	36
F^-	7.88	2.7	109	136	2

[a] One-electron oxidation potential in water at 25 °C, V. Reference 9, except for benzoate ion. [b] log (k/k_s) in methanol, 25 °C. Reference 10, except n-$C_3H_7S^-$, ref 35. [c] Gas-phase dissociation energy, 25 °C, kcal/mol. Data from reference 48, except as indicated. Some values calculated from D_{HX} and heats of formation of CH_3X and HX, ref 21. [d] Seagle, I. R.; Gutman, D. *J. Am. Chem. Soc.* **1985**, *107*, 5342. [e] For S-bonded isomer. [f] Reference 48, except as indicated. [g] McDonald, R. N.; Chowdhury, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 4123. [h] For N-bonded isomer. From dissociation free energy in solution, corrected to gas phase. Reference 9. [i] For reaction 10, kcal/mol, 25 °C. [j] From $\Delta H°_f$ of $C_6H_5CO_2^-(g)$ (-71 kcal). *Gas Phase Ion Chemistry*; Bowers, M., Ed.; Academic Press: New York, 1979; p 101.

Oxidation Potentials. The one-electron oxidation potential, I', refers to the processes 5 and 6. The symbol

$$X^-(aq) = X(aq) + e^-(g) \qquad I', \text{eV} \qquad (5)$$

$$B(aq) = B^+(aq) + e^-(g) \qquad I', \text{eV} \qquad (6)$$

I' is used to show that it is the aqueous-phase ionization potential. It is defined as the standard Gibbs free energy change at 25 °C, of reactions 5 and 6.[9] The free energy of the electron at rest in the gas phase is set at zero.

To obtain a value for I', we need the gas-phase ionization potential, I, for X^- or B, and the free energies of hydration for X^- and X, or B and B^+. The free energies of hydration of the ions requires that a value be adopted for the absolute potential of the hydrogen electrode. There is now widespread agreement on a figure near 4.50 V.[14]

$$H^+(aq) + e^-(g) = \tfrac{1}{2}H_2(g) \qquad E°_H = 4.50 \text{ V} \qquad (7)$$

Tables I and II list the previously calculated values of I' for anions and neutral molecules, respectively.[9] Data for benzoate ion and for thiophenol have also been added. The standard state is an ideal 1 M solution. Comparison with experimental values, when possible, shows that I' for anions is good to ±0.1 V, and for neutrals, about ±0.2 V. The conventional (thermodynamic) value of the oxidation potential in volts is given by $E°' = 4.50 - I'$.

Table II. Some Properties of Selected Molecules, B

B	I'[a]	n[a]	$D_{CH_3B^+}$[d]	D_{HB^+}[e]	$-\Delta G°$[i]
$C_6H_5NH_2$	4.60	5.7	63	74	17
$C_6H_5N(CH_3)_2$	4.91	5.6		74	
N_2H_4	5.15	6.6	82	93	19
$(CH_3)_3N$	5.21	6.7[c]	79	91	26
$(C_6H_5)_3P$	5.57	7.0		86	
C_6H_5SH	5.80[b]	5.7	67	76	~0[g]
pyrolidine	5.91	7.2	91	105	23
$(CH_3)_2Se$	6.01	6.3		87	
$(CH_3)_2S$	6.11	5.5	84	88	11
NH_3	6.11	5.5	111	126	18
piperidine	6.25	7.3	98	113	23
C_2H_5SH	6.27		89	92	
$(CH_3)_3P$	6.34	8.7[c]	110	111	34
$(CH_3)_3As$	6.34	6.9[c]	94	99	17
imidazole	6.53	5.0	96	113	14
$(CH_3O)_3P$	6.75	5.2		113	
α-picoline	6.79	4.7		119	
pyridine	6.82	5.2		120	
CH_3CO_2H	7.10		99	115	-7
CH_3OH	7.25	0.0	107	121	-1
$(CH_3)_2SO$	7.46	0.0		126	
H_2O	7.94		132	145	-5
$(CH_3)_2O$	7.00		91	106	(-3)

[a] See footnotes for Table I. [b] This work. [c] Rate data for triethyl derivative. [d] Calculated from data in ref 16, 21–23. [e] From proton affinities and ionization potentials, ref 21, 23. [f] For reaction 11, kcal/mol, 25 °C. [g] Product is $C_6H_5SHCH_3^+$.

A related potential of interest is the reduction potential of CH_3I. This may be calculated in the gas phase by standard free energies of formation,[15,16] and then corrected to aqueous solution. The free energy of hydration of the methyl radical is taken to be +4.0 kcal/mol. This is the same as for CH_4 or C_2H_6. The standard state for the gas phase is the ideal gas at 1 atm pressure.

$$CH_3I(g) + e^-(g) = CH_3(g) + I^-(g) \qquad \Delta G° = -23.9 \text{ kcal/mol} \qquad (8)$$

$$CH_3I(aq) + e^-(g) = CH_3(aq) + I^-(aq) \qquad \Delta G° = -81.9 \text{ kcal/mol} \qquad (9)$$

The value of $\Delta G°$ corresponds to a solution-phase electron affinity, A', for CH_3I of 3.55 eV. On the hydrogen scale, the reduction potential would be 3.55 - 4.50 = -0.95 V. This is in excellent agreement with a recent calculation by Eberson.[17] Compared to Tables I and II, only the benzyl anion, if it could exist in water, would spontaneously transfer an electron to CH_3I.

Standard Free Energy Changes. We next calculate $\Delta G°$ for the reactions 10 and 11. For the anions F^-, Cl^-, Br^-, CN^-, OH^-, and NO_3^-, there is enough data on free energies of formation and free energies of solution to calcualte $\Delta G°$ directly.[18] To extend the list, it is necessary to make one assumption.

$$X^-(aq) + CH_3I(aq) = CH_3X(aq) + I^-(aq) \qquad (10)$$

$$B(aq) + CH_3I(aq) = CH_3B^+(aq) + I^-(aq) \qquad (11)$$

Reactions 5 and 9 may be added to reaction 12 to give (10). The bond dissociation energy, D_{CH_3X}, of CH_3X in the gas phase is known for all X in Table I, except N_3. This

$$CH_3(aq) + X(aq) = CH_3X(aq) \qquad (12)$$

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(12) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.

(13) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141.

(14) See ref 9 for detailed references to this important problem. Any future changes from 4.50 V will probably be very small.

(15) ΔH_f for CH_3 is 34.6 kcal/mol. Castelhano, A. L.; Griller, D. *J. Am. Chem. Soc.* **1982**, *104*, 3655.

(16) Remaining data from Wagman, D. D.; et al. *J. Phys. Chem. Ref. Data* **1982**, *11*, Suppl. No. 2.

(17) Eberson, L. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 533.

(18) Abraham, M. H.; McLennan, D. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 873.

gives $\Delta H°$ for reaction 13. To obtain the free energy

$$CH_3(g) + X(g) = CH_3X(g) \qquad -D_{CH_3X} = \Delta H° \quad (13)$$

change for (13), we need to estimate $T\Delta S°$. For the known cases we find that $T\Delta S° = -10$ kcal/mol, within ±0.4 kcal. This corresponds to $-\Delta S° = 33.5$ eu, which is almost exactly equal to the translational entropy of the methyl radical, 33.8 eu.[19]

With the free energy change for (13) known, we can find that for (12) readily, and hence $\Delta G°$ for (10). The final equation is

$$\Delta G° = (I' - 3.55)23.06 - D_{CH_3X} + 6 \text{ kcal/mol} \quad (14)$$

Note that any errors in the free energies of hydration of X and CH_3 will cancel in the final result.[20]

Table I shows the results calculated from eq 14. The more accurate results from free energies of formation were used as a check. The differences averaged ±1 kcal/mol, with a maximum deviation of 2 kcal for OH^-. Values of D_{CH_3X} are also shown (gas-phase values). Since the bond dissociation energies for the HX bond are also known, they have been included for comparison.

Calculations of $\Delta G°$ for reaction 11 are more difficult. For the molecules CH_3COOH, H_2O, CH_3OH, and NH_3 there are free energies of formation available[16] to calculate the free energy change for reactions such as

$$H_2O(g) + CH_3I(g) = CH_3OH(g) + HI(g) \quad (15)$$

The free energy of solution of HI is −12.8 kcal/mol, the products being the ions.[16] Knowing the pK_a of $CH_3OH_2^+$ in aqueous solution (−3.9) enables the computation of $\Delta G°$ for (11) to be completed.

For a number of other molecules, an equation similar to (14) can be used. First the heat of formation of CH_3B^+ in the gas phase must be found. An example is given where B is $C_6H_5NH_2$. The numbers are heats of formation at 25 °C.[16,21] That for $C_6H_5NH_2CH_3^+$ is found from $\Delta H°$ for reaction 16, which is simply the negative of the proton

$$\underset{20.8 \text{ kcal}}{C_6H_5NHCH_3(g)} + \underset{367.2}{H^+(g)} = \underset{169}{C_6H_5NH_2CH_3^+(g)} \quad (16)$$

$$\underset{169 \text{ kcal}}{C_6H_5NH_2CH_3^+(g)} = \underset{198}{C_6H_5NH_2^+(g)} + \underset{34.4}{CH_3(g)} \quad (17)$$

affinity of methylaniline.[22] That for $C_6H_5NH_2^+$ is $\Delta H°_f$ for aniline, plus the ionization potential of aniline.[23] $\Delta H°$ for reaction 17 is then $D_{CH_3B^+}$, equal to 63.4 kcal/mol.

The equation for $\Delta G°$ becomes

$$\Delta G° = (I' - 3.55)23.06 - D_{CH_3B^+} + 6 - (\Delta G°_{B^+} - \Delta G°_{BCH_3^+}) \quad (18)$$

$\Delta G°_{B^+}$ and $\Delta G°_{CH_3B^+}$ are the free energies of hydration of the radical cation, $C_6H_5NH_2^+$, and the methylammonium ion, $C_6H_5NH_2CH_3^+$, respectively. These can no longer be considered to cancel, as for X and CH_3X. However $\Delta G°_{B^+}$ has already been evaluated in calculating I', and $\Delta G°_{BCH_3^+}$ is readily found from the proton affinity and the aqueous pK_a.[9] For $C_6H_5NH_2CH_3^+$ it is −59 kcal/mol. While $\Delta G°_{B^+}$ is not known very accurately, any error cancels exactly in using eq 18. This eliminates the error in I' as well.

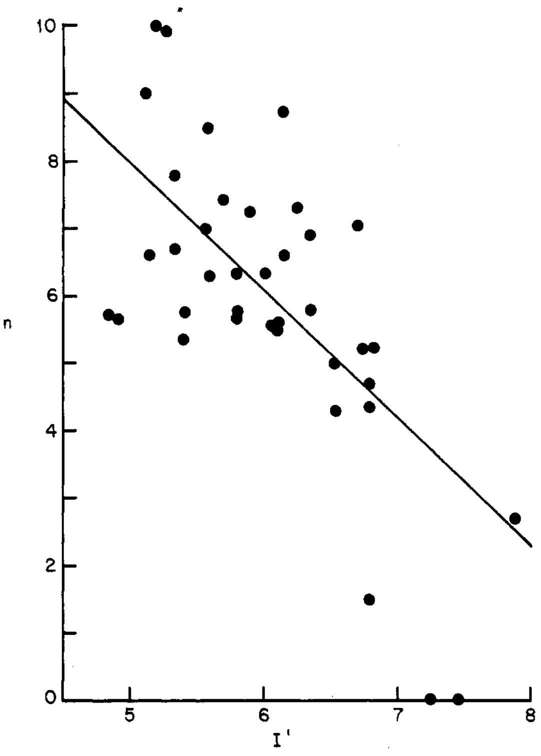

Figure 1. Plot of one-electron oxidation potentials in water, I', eV, against nucleophilic reactivity parameter, n, for neutral and anionic bases.

This procedures can only be used where the donor atom is bound to a hydrogen atom. Another method was used for $(CH_3)_3N$, $(CH_3)_3P$, $(CH_3)_3As$, $(CH_3)_2O$, and $(CH_3)_2S$. Using the procedure illustrated in (16) and (17), the following were found:

$$CH_3NH_3^+(g) = CH_3(g) + NH_3^+(g) \qquad D = 111 \text{ kcal}$$

$$(CH_3)_2NH_2^+(g) = CH_3(g) + CH_3NH_2^+(g) \qquad D = 95$$

$$(CH_3)_3NH^+(g) = CH_3(g) + (CH_3)_2NH^+(g) \qquad D = 85$$

Extrapolating from these results, a value of $D_{CH_3B^+} = 79$ kcal/mol is estimated for the reaction

$$(CH_3)_4N^+(g) = CH_3(g) + (CH_3)_3N^+(g) \quad (19)$$

The same calculations for the series $CH_3PH_3^+$, $(CH_3)_2PH_2^+$, and $(CH_3)_3PH^+$ gave values of D equal to 112, 110, and 112 kcal/mol. That for $(CH_3)_4P^+$ was estimated to be 110 kcal. Similar calculations were made for $(CH_3)_4{}^+As$, $(CH_3)_3O^+$, and $(CH_3)_3S^+$.

The free energy of hydration of $(CH_3)_4N^+$ has been estimated to be −47 kcal/mol by a lattice energy calculation.[24] This completes the series NH_4^+ (−77), $CH_3NH_3^+$ (−68), $(CH_3)_2NH_2^+$ (−61), and $(CH_3)_3NH^+$ (−54) in a reasonable way. Since values are also available for the other onium ions,[9] reasonable estimates can be made for $\Delta G°_{CH_3B^+}$ of $(CH_3)_4P^+$ (−45), $(CH_3)_4As^+$ (−44), $(CH_3)_3O^+$ (−61), and $(CH_3)_3S^+$ (−51).

The results for $\Delta G°$ calculated from eq 18 are listed in Table I. The more accurate data for the four molecules mentioned above were used as a check. The agreement was about as good as for the anions, and the maximum difference was still only 2 kcal/mol, for CH_3OH. The free energy of hydration of $(CH_3)_3O^+$ and $D_{CH_3B^+}$ are the most uncertain numbers used. The values of D_{HB^+} are also listed in Table II. These are readily calculated from the proton affinities and ionization potentials of B.

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[19] This result is similar to that for H(g) + X(g) = HX(g), where $-\Delta S° \simeq 25$ eu, the translational entropy of the hydrogen atom.

[20] The free energy of hydration of X has already been set equal to that of CH_3X in calculating I'. Also that for CH_3 equal to 4 kcal/mol has already been used in eq 9.

[21] Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *Chem. Thermodynamics of Organic Compounds*; Wiley: New York, 1969.

[22] Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695. Heats of formation of the protonated species are listed, as well as the proton affinties.

[23] Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. No. 1.

[24] Boyd, R. H. *J. Chem. Phys.* **1969**, *51*, 1470.

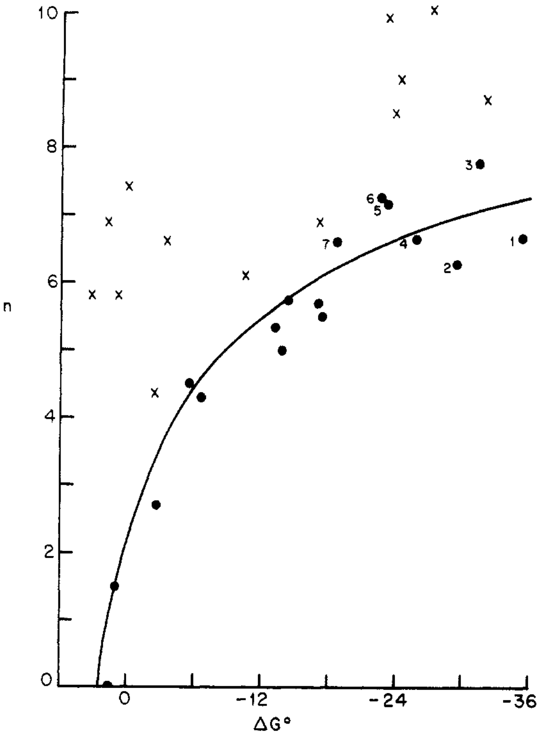

Figure 2. Plot of n against $\Delta G°$, kcal/mol, in water, 25 °C, for reaction of methyl iodide with nucleophiles. Circles are for second-row donors (F, O, N, C), and crosses for heavier donors. No. 1 = CN^-, 2 = CH_3O^-, 3 = HO_2^-, 4 = $(C_2H_5)_3N$, 5 = piperidine, 6 = pyrolidine, 7 = N_2H_4.

Discussion

In Figure 1, the values for I' are plotted against the kinetic parameters n for all nucleophiles in Tables I and II where n is known. The scatter is far greater than the probably errors in I'. A least-squares line is drawn through the points. The slope, when both n and I' are converted to the same energy units, is only −0.11. The correlation coefficient is only −0.66. No distinction is found between neutral and anionic nucleophiles, nor between donors of the second row and donors from the third and higher rows.

While there is certainly some correlation between nucleophilic reactivity and the one-electron oxidation potentials, the dependence is surprisingly small and the scatter surprisingly large. This is particularly true since methyl iodide is a substrate in which partial transfer of the nucleophile electrons is believed to play a significant role.

There are some anions in Table I, such as CH_3^-, NH_2^-, and PH_2^-, which have low values of I' and are believed to be powerful nucleophiles, though they cannot exist in a protic solvent. However they are also strong proton bases, and their nucleophilicity may reside in that property. This suggests that a modified oxibase scale might be better used to predict n values.[25]

The use of eq 20 implies a linear relation between free energy changes for protonation and methylation. But we

$$n = \alpha I' + \beta H \qquad (20)$$

have calculated $\Delta G°$ for reactions 10 and 11 directly, so that we need not rely on pK_a as a measure of reactivity. Figure 2 shows a plot of n ($\Delta G^\ddagger$) against $\Delta G°$ for all cases where the data is available. Second-row donors are shown with circles and higher row donors with crosses. The former all lie close to the smooth curve that has been drawn, the latter are all above it.

The curve acts as a reference line, but it also shows that the slope, α, in eq 1 has a value near one for $\Delta G°$ near zero, and approaches zero as $\Delta G°$ becomes a large negative number. Such behavior is an expected consequence of the Bell–Evans–Polanyi–Leffler–Hammond principle.[8,26] It corresponds to a late transition state for the more difficult reactions and a progressively earlier transition state for more exergonic reactions. However, the curve appears to level off at an n value near 8, which corresponds to a second-order rate constant of about 1 $M^{-1}\ s^{-1}$ at 25 °C, far from the diffusion controlled limit.

Recent developments, both of an experimental nature[27] and of a theoretical nature,[28] help explain this behavior. The energy barrier to reaction consists of a part that exists in the gas phase and in solution, and a solvation part found only in solution. The gas-phase barrier exists because five groups attached to carbon in the transition state are at a higher energy than four. The solvation barrier results because the nucleophile must be partly desolvated before it can react, and the transition state (TS) must be solvated. For the reaction of Cl^- with CH_3Cl, the two parts are of comparable magnitude in water, which being about 14 kcal/mol.[28] Desolvation of Cl^- requires more energy than is returned in solvating the TS.

For neutral nucleophiles the situation is somewhat different. The gas-phase energy barrier is very large, so that reactions such as (11) simply do not occur. For example, when B is NH_3 we have

$$NH_3(g) + CH_3I(g) = CH_3NH_3^+(g) + I^-(g) \qquad \Delta G°(g) = 108 \text{ kcal} \quad (21)$$

Obviously only strong solvation of the polar TS allows reaction 21 to go with a measurable rate in solution.[29] Desolvation of the reactants introduces a much smaller energy loss.

The estimation of the gas-phase energy barrier is difficult for anions, even when the rate constants are available.[27] However, we can be reasonably sure that it gets smaller as $\Delta G°(g)$ becomes a more negative number. For CH_3O^-, HO_2^-, and CN^-, $\Delta G°(g)$ is −57, −62, and −48 kcal, respectively. It is likely in these cases that the gas-phase barrier has become negligible, and only the solvation barrier remains. This would account for the leveling off of the rate constants shown in Figure 2.

The limiting rate constant corresponds to a value of $\Delta G^\ddagger$ of about 20 kcal/mol, which is reasonable. The scatter of the n values for these three anions would then be due to variations in the solvation energy barrier. The difference between CH_3O^- and HO_2^- is 4 kcal/mol, favoring the latter. It appears that the α-effect in this case is indeed due to solvation effects, as DePuy has recently demonstrated.[30]

For neutral nucleophiles, the gas-phase barrier can become smaller, but can never become negligible. Therefore no leveling off will occur. The n values for such nucleophiles, in fact, continue to rise as $\Delta G°$ becomes more negative in Figure 2. It is noteworthy that N_2H_4, another α-effect nucleophile, does not show any enhanced re-

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[25] Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *74*, 1540. Davis, R. E. *Ibid.* **1965**, *87*, 3010.

[26] For references, see: Wolfe, S.; Mitchell, D. J.; Schlegel, H. B. *J. Am. Chem. Soc.* **1981**, *108*, 7692, 7694.

[27] (a) Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 5993; (b) **1983**, *105*, 2672.

[28] Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 154.

[29] The solvation free energy of the transition state must be at least 86 kcal/mol. The overall solvation free energy of the reaction is −128 kcal/mol.

[30] DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481.

activity. In this case the α-effect is simply due to a stronger methyl cation affinity than its pK_a value would suggest.

We turn next to the crosses in Figure 2 which refer to donor atoms other than the second row. It is seen that all crosses are well above the reference curve, indicating greater reactivity than predicted by the $\Delta G°$ values. The maximum deviation, about 7.5 kcal, is shown by I^-. These reactive nucleophiles are of the kind commonly called soft, whereas all the second-row donors in Figure 2, including CN^-, are hard nucleophiles.[31] The deviations shown by the crosses are examples of the rule "softness is more important in rates than in equilibria".[32]

Since there is some confusion about the role of solvent effects on hard–soft (HSAB) behavior, a brief discussion is in order. The absolute hardness, η, is operationally defined by[33]

$$\eta = (I - A)/2 = 1/\sigma \tag{22}$$

where I is the gas-phase ionization potential and A is the electron affinity. The softness, σ, is the inverse of the hardness. Equation 22 applies to any atom, molecule, radical, or ion. In molecular orbital theory, $(I - A)$ is equal to the energy gap between the HOMO and the LUMO.[9,34] This ensures that a correspondence exists between polarizability, an older criterion of softness,[32] and the newer definition of (22).

Solvents do not change the absolute hardness,[9] but they certainly can change the chemical consequences. For example, we have the following:

$$CH_3I(g) + F^-(g) = CH_3F(g) + I^-(g) \qquad \Delta G°(g) = -47 \text{ kcal} \tag{23}$$

The methyl cation, like all Lewis acids, binds F^- more strongly than I^- in the gas phase.[32] But in water, $\Delta G°$ becomes −1.7 kcal (Table II) as a result of the much larger free energy of hydration of F^- (−106 kcal) than of I^- (−61 kcal).

In principle, this dramatic lowering of the reactivity of F^- compared to I^- has been completely accounted for in Figure 2, by the value of $\Delta G°$. But it is still possible that the enhanced reactivity of I^-, and other soft nucleophiles, is due to solvation effects. A LFER can only be expected if all energy changes occur synchronously. If desolvation leads bond breaking and bond making, then Figure 2 could be explained.[36] Hard bases are usually more strongly hydrated than soft bases.

Another explanation is based on HSAB concepts. The TS is assumed to be stabilized for soft bases, mainly by π-back bonding for neutral bases and by mutual polarization for anions.[34,35,37] Alternatively, we can say that hard bases are destabilized by filled orbital interactions.

Such additional stabilization should appear in the gas-phase energy barrier. This is difficult to demonstrate because of the large effect of exothermicity, and because the stabilization is usually small. For example, in the gas-phase reactions of CH_3Cl with CH_3O^- and CH_3S^-, the barrier height is 2.6 kcal higher for the soft CH_3S^-.[27b] The reaction with CH_3O^- is 13 kcal more exothermic, which could reduce its barrier by 5–6 kcal, relative to CH_3S^-. The expected TS stabilization is only about 3 kcal (see below), which is not inconsistent.

Table III. Ionization Potentials and Electron Affinities for Some Neutral Molecules

	I^a	A^c		I^a	A^c
$(CH_3)_3N$	7.9	−4.8	$(CH_3)_4C$	10.4	−6.1
$(CH_3)_3P$	8.6^b	−3.1	$(CH_3)_4Si$	9.9	−3.9
$(CH_3)_3As$	8.6^b	−2.7	CH_3F	12.5	-6.2^e
H_2O	12.6	-6.4^d	CH_3Cl	11.2	−3.7
H_2S	10.6	−2.1	CH_3I	9.5	$+0.2^f$
$(CH_3)_2O$	10.0	−6.0	HCl	12.7	−3.3
$(CH_3)_2S$	8.7	−3.3	HI	10.4	0.0^g

[a] In eV. Reference 23, except as indicated. [b] Cradock, S.; Ebsworth, E. A. V.; Savage, W. J.; Whiteford, R. A. *J. Chem. Soc. Faraday Trans. 2* **1972**, *68*, 934. [c] Vertical electron affinities in eV. Tossell, J. A.; Moore, J. H.; Giordan, J. C. *Inorg. Chem.* **1985**, *24*, 1100; *J. Am. Chem. Soc.* **1985**, *107*, 5600. [d] Melton, C. E. *J. Chem. Phys.* **1972**, *57*, 4218. [e] Reference 55. [f] Reference 23. [g] Spence, N.; Chupka, W. A.; Stevens, C. M. *J. Chem. Phys.* **1982**, *76*, 2759.

There is an experimental test for the reality of the stabilization effect in solution. The theory predicts that the effect is greatest if both the electrophile and nucleophile are soft.[32,34,37] Table III shows the ionization potentials and electron affinities of a number of molecules of interest. The values of $(I - A)/2$, or η, can be calculated and it can be seen that the hardness of second-row bases resides mainly in their large, negative electron affinities. Also it is seen that CH_3I is the softest and CH_3F the hardest of the methyl halides.

The prediction is that the relative rate constants for reaction with CH_3I and with CH_3F will become larger as the softness of the nucleophile increases. The data for reaction in H_2O shows just such an effect.[11]

	log k, $M^{-1}\ s^{-1}$	
base	CH_3F	CH_3I
H_2O	−10.8	−8.9
OH^-	−6.1	−4.3
Cl^-	−8.6	−5.5
I^-	−7.7	−3.5

To understand these results better, imagine a plot of n vs. $\Delta G°$ for the reaction

$$CH_3F(aq) + X^-(aq) = CH_3X(aq) + F^-(aq) \tag{24}$$

For hard bases the curves would be very similar for CH_3F and for CH_3I. But for soft bases, the deviations above the line would be sharply reduced for CH_3F.

The phenomenon of extra stabilization of the TS when both entering and leaving groups are soft has been called the symbiotic effect.[38] At one time it was thought that the interaction was between the two large groups, a kind of London force stabilization.[39] However it is more accurate to describe it as a nucleophile–electrophile interaction. The same behavior has been found for alkyl sulfates, nitrates, and sulfonates,[11,38–40] all of which contain hard leaving groups.

An important requirement is that symbiosis should be relatively independent of the solvent. In particular, it should occur in dipolar, aprotic solvents, where the fluoride ion, and other hard bases, is not so strongly stabilized. This requirement has been tested in the solvent acetonitrile, where symbiosis has been found to be somewhat greater than in methanol,[41] and in dimethylformamide, where it is somewhat less.[42] Solvation seems to play only a minor role in the symbiotic effect.

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(31) Cyanide ion is probably the hardest of the carbon donor nucleophiles as a result of sp hybridization.

(32) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.

(33) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512.

(34) Pearson, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8440.

(35) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1961**, *84*, 16.

(36) See: Jencks, W. P.; Haber, M. P.; Herschlag, D.; Nazaretion, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 479.

(37) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223.

(38) Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899.

(39) Bunnett, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 5969.

(40) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541.

(41) Engemyr, L. B.; Songstad, J. *Acta Chem. Scand.* **1972**, *26*, 4179.

(42) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

The easiest way to identify symbiosis is to examine a ratio such as k_{CH_3I}/k_{CH_3F}, which will be large for soft nucleophiles and small for hard ones. A convenient probe is an ambident nucleophile which usually has a hard site and a soft site.[43] An example is Me_2SO, which reacts at oxygen with methyl benzene sulfonate and at sulfur with methyl iodide.[44] These changes in selectivity have been found in all solvents, including dipolar, aprotic ones.[45]

The values of $\Delta G°$ in Table I and II may be used in one other way. By changing the sign, and adding 5 kcal, they become the standard free energy changes for the hydrolysis reactions:

$$\begin{aligned} CH_3X(aq) + H_2O(l) &= CH_3OH_2^+(aq) + X^-(aq) \\ CH_3B^+(aq) + H_2O(l) &= CH_3OH_2^+(aq) + B(aq) \end{aligned} \qquad (25)$$

Thus $-\Delta G°$ can be used as a measure of the thermodynamic leaving group ability. The order is $H_2O > CH_3OH$ $Br^- \sim NO_3^- > I^- > F^- > Cl^- > SCN^- > CH_3COO^- > (CH_3)_2S > NO_2^- > C_6H_5O^- > (CH_3)_3As > NH_3 > C_6H_5S^- > n\text{-}C_3H_7S^- > CH_3O^- > CH_3P > CN^- \gg NH_2^- \sim CH_2CN^- \gg H^- > CH_3^- \sim C_6H_5^-$.

This order is in good agreement with the kinetic leaving group ability, the nucleofugality, when these are measurable.[46] For the poorest leaving groups, there is no rate data available. Some minor inversions occur. For example, nitrate ion is more difficult to displace than Cl^-.[47] The overall range in the thermodynamic values covers 56 powers of ten.

Summary and Some Comparisons

Figures 1 and 2 show that nucleophilic reactivity is much less dependent on either the oxidation potential or the overall free energy change than might have been expected. Figure 1 offers little support for the two-state model of S_N2 reactions.[49] In this model the energy barrier to reaction is a fraction, f, of the energy gap between the ground state and the state with one electron transferred from the nucleophile to the alkyl halide.

The energy gap is a linear function of I' for anionic nucleophiles. The factor f is estimated as between 0.25 and 0.50.[49] Variations in f, and in the crossing avoidance factor, B, might account for the scatter in Figure 1. But the mean slope should be about −0.3, instead of the −0.11 found experimentally. While the electron-transfer state is probably the most important, the perturbation theory of chemical reactions shows that a number of excited states must contribute.[50] Examples of other important states would be those corresponding to mutual polarization of the reactants, and to π-back bonding.

Figure 2 supports some of the ideas expressed recently by Bordwell. He has argued forcefully against a simple interpretation of α as a measure of the degree to which the TS resembles the reactants or the products.[51] In some cases, he suggests, α may measure the strength of bonding in the ion–dipole complexes formed prior to any significant bond making or bond breaking. This seems very reasonable for carbanionic nucleophiles, which should have large negative values of $\Delta G°$. These correspond to the cases in Figure 2 such as CN^- and CH_3O^-, where the barrier should be due to desolvation, accompanied by ion–dipole complexation.

The Marcus theory, originally designed for electron-transfer reactions, has also been applied to methyl-transfer reactions.[52] If the theory was always valid, it would be possible to calculate unknown rate constants from several known ones. However, there is a serious problem. Lewis and his co-workers[53] have applied the Marcus equation to the reactions

$$CH_3\,X + Y \rightarrow CH_3Y + X \qquad k_X \qquad (26)$$

$$CH_3\,Z + Y \rightarrow CH_3Y + Z \qquad k_Z \qquad (27)$$

The result is

$$\ln (k_X/k_Z) = 1/2\ (\ln k_{XX} + \ln k_{ZZ}) + \ln K_{XZ} \quad (28)$$

where k_{XX} and k_{ZZ} are the rate constants for the identity reaction, and K_{XZ} is the equilibrium constant for the reaction of CH_3X with Z.

The prediction is that the ratio of rate constants, k_X/k_z, is a constant that is independent of Y. But we have just shown that k_{CH_3I}/k_{CH_3F} can vary by a factor of 200. In other cases[54] the ratio can change by as much as 10^6. The reason for these conspicuous failures of the Marcus theory is easy to see.[53] The theory, while otherwise admirable, makes no allowance for the symbiotic effect, or any factors present in the TS that are not present in the ground states or the identity reaction.

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(43) For a discussion of local softness, see: Parr, R. G.; Yang, W. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6273.

(44) Smith, S. G.; Winstein, S. *Tetrahedron* **1958**, *3*, 317. Note that methyl tosylate is hard at the methyl site and soft at the aromatic ring.

(45) Meek and Fowler [Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422] have a typical example.

(46) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 315. Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198. Thorstenson, T.; Songstad, J. *Acta Chem. Scand., Ser. A* **1978**, *A32*, 139.

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(48) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley-Interscience: New York, 1976; p 309.

(49) Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3692; *Prog. Phys. Org. Chem.* **1985**, *15*, 197.

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(51) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737; **1986**, *108*, 7300.

(52) Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227.

(53) Lewis, E. S., McLaughlin, M. L.; Douglas, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 6668. While eq 28 comes from the linear terms in the Marcus equation, inclusion of the quadratic terms makes no significant difference for any of the common leaving groups.

(54) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541.

(55) Giordan, J. C.; Moore, J. H.; Tossell, J. A. *Acc. Chem. Res.* **1986**, *19*, 281.