compounds has already proved a challenging field for both experiment and theory; the additional dimension of the crystal lends further challenges in both respects.

This work would have been impossible without the collabo-

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Intrinsic Barriers of Reactions and the Principle of Nonperfect Synchronization

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Introduction

When discussing chemical reactivity, one needs to distinguish between the thermodynamic driving force of the reaction ($\Delta G°$) and a purely kinetic factor known as the intrinsic barrier ($\Delta G_0^{\ddagger}$). For a reaction with forward and reverse rate constants k_1 and k_{-1}, the intrinsic barrier is generally defined as $\Delta G_0^{\ddagger} = \Delta G_1^{\ddagger} = \Delta G_{-1}^{\ddagger}$ (the intrinsic rate constant as $k_0 = k_1 = k_{-1}$) for $\Delta G° = 0$ ($K_1 = 1$). The theoretical as well as practical significance of $\Delta G_0^{\ddagger}$ or k_0 is that, at least in principle, they are representative of a whole reaction *series* and independent of the thermodynamics of a particular member within that series. Hence, understanding the factors that affect intrinsic barriers is to understand a great deal about chemical reactivity. This Account deals with some of these factors in carbanion-forming reactions, but the principles to be discussed are quite general. *A recurrent theme will be that high intrinsic barriers are typically associated with a lack of synchronization between concurrent reaction events such as bond formation/cleavage, solvation/desolvation, development (loss) of resonance, etc.*

The concept of the "intrinsic barrier" was introduced by Marcus[1,2] when he developed his theory of electron-transfer reactions. Marcus theory was later also applied to proton,[3] hydride,[4] and methyl transfers,[2,5] as well as some other processes.[6] Equations 1 and 2 express the two main facets of Marcus theory. Equation 1 describes how a reaction barrier ($\Delta G^{\ddagger}$) depends on the *intrinsic* barrier ($\Delta G_0^{\ddagger}$), the exothermicity (endothermicity) ($\Delta G°$) of the reaction, and the energy of bringing the reactants (w_R) and products (w_P) together; for reactions with high intrinsic barriers these latter "work terms" are usually neglected, though.

$$\Delta G^{\ddagger} = w_R + \Delta G_0^{\ddagger}\left\{1 + \frac{\Delta G° - w_R + w_P}{4\Delta G_0^{\ddagger}}\right\}^2 \quad (1)$$

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$$\Delta G_0^{\ddagger}(A/B) = \frac{1}{2}\{\Delta G_0^{\ddagger}(A/A) + \Delta G_0^{\ddagger}(B/B)\} \quad (2)$$

Equation 2 relates the intrinsic barrier of a reaction (e.g., $AH + B^- \rightleftharpoons A^- + HB$) to the intrinsic barrier of the corresponding exchange reactions ($AH + A^- \rightleftharpoons A^- + HA$ and $BH + B^- \rightleftharpoons B^- + HB$). For electron-transfer reactions Marcus theory also relates $\Delta G_0^{\ddagger}$ to molecular size, charge, and solvent polarity,[1] but no such relationships have been proposed for the other reactions treated by the Marcus formalism. In other words, even though eq 2 is quite successful in correlating or predicting intrinsic barriers in terms of other intrinsic barriers, it does not provide a molecular understanding of what determines the height of intrinsic barriers.

Our aim has been to seek such understanding without necessarily adhering to the Marcus formalism. Our starting point is the growing realization by many workers that most elementary reactions in chemistry are not adequately described by the traditional free energy vs. reaction coordinate profile. Usually more than one concurrent process such as bond formation/cleavage, solvation/desolvation, delocalization/localization of charge, etc., is involved, and typically these processes have made unequal progress at the transition state ("imbalanced" transition state).[7-13] "Reaction progress" at the transition state then becomes an ambiguous concept that depends on which process is chosen as the reaction coordinate.

Energy surfaces based on two progress variables (More O'Ferrall[7]–Jencks[8] diagrams) deal qualitatively with this problem.[7-15] Such a diagram is shown in

(1) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155.
(2) Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227.
(3) (a) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891. (b) Cohen, A. O.; Marcus, R. A. *Ibid.* **1968**, *72*, 4249.
(4) Kreevoy, M. M.; Han Lee, I.-S. *J. Am. Chem. Soc.* **1984**, *106*, 2550.
(5) (a) Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87. (b) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3792.
(6) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701.
(7) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274.
(8) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.
(9) Harris, J. C.; Kurz, J. L. *J. Am. Chem. Soc.* **1970**, *92*, 349.
(10) (a) Harris, J. M.; Shafer, S. G.; Moffatt, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 3295. (b) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11.
(11) Kreevoy, M. M.; Lee, I. S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550.
(12) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3292.
(13) Murdoch, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2660.
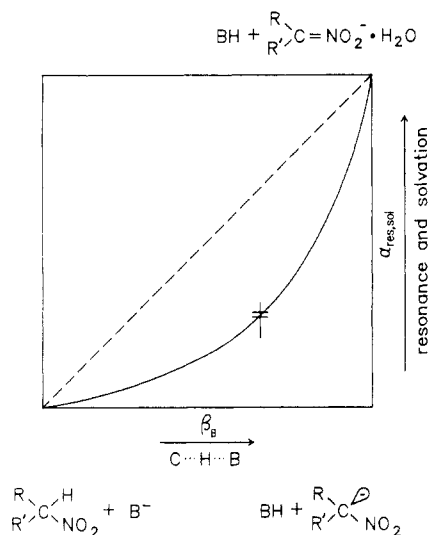(14) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937.

Figure 1. More O'Ferrall–Jencks diagram for the deprotonation of phenylnitromethane.

Figure 2. Schematic Brønsted plots for reaction 3 with solid lines referring to the change in k_1 with changing K_1 that is induced by varying pK_a^{BH}. Also shown is the effect on k_1 of increasing K_1 by introducing a Y substituent that is a stronger π-acceptor. (A) Resonance development is synchronous with proton transfer, $\alpha_{res}^C = \beta_B$. Effect of change in Y can be described by the same Brønsted plot as effect of change in pK_a^{BH}. (B) Resonance development lags behind proton transfer, $\alpha_{res}^C < \beta_B$. This leads to a new Brønsted plot (dashed line) and a decrease in the intrinsic rate constant ($\delta \log k_0^{res}(C^-) < 0$).

Figure 1 for the deprotonation of phenylnitroalkanes,[16] one of the best known examples. The lower left corner represents the reactants, the upper right corner represents the products, while the lower right corner is a hypothetical[17] intermediate whose negative charge is localized on the sp³-hybridized carbon. Here the progress variables are the degree of proton transfer[18] (horizontal axis) and the degree of charge delocalization into the nitro group with concurrent solvation (vertical axis). Synchronous development of the two progress variables would correspond to the diagonal reaction coordinate. The curved reaction coordinate which represents the true situation (see below) implies that charge delocalization and solvation lag behind proton transfer; i.e., the transition state is imbalanced.[19]

It appears that reactions with strongly imbalanced transition states also have large intrinsic barriers. This observation led us to formulate a rule, called the principle of nonperfect synchronization (PNS),[21] which reads as follows: A product stabilizing factor that develops late along the reaction coordinate or a reactant stabilizing factor that is lost early always lowers k_0. Conversely, a product destabilizing factor that develops late or a reactant destabilizing factor that is lost early increases k_0. "Early" and "late" are defined in relation to the "main process" which is equated with bond formation or cleavage or the transfer of a charge from one reactant to another; in the nitroalkane deprotonation it would be the degree of proton transfer.[18] Product or reactant stabilizing (destabilizing) factors include resonance, hydrogen bonding, solvation, and some types of steric and electrostatic effects.

In previous formulations of the PNS[21] the following corollary was included: a product stabilizing factor that develops *early* or a reactant stabilizing factor that is lost *late* enhances k_0. Even though consistent with the
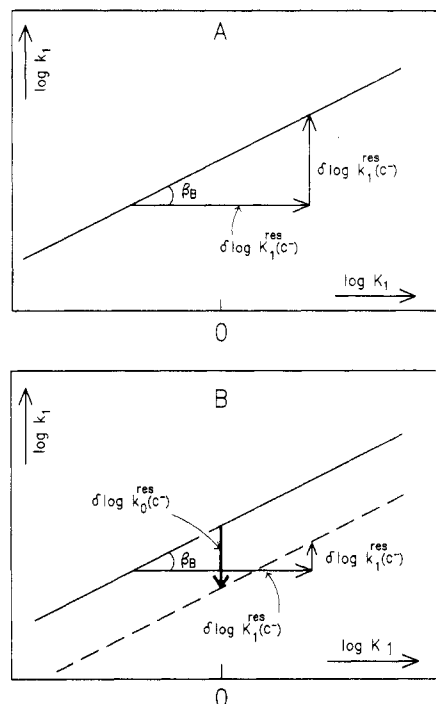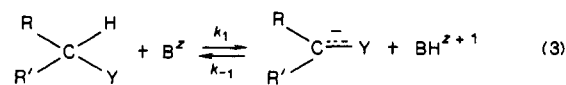
mathematical formalism developed below, for the factors considered here the situation described in the corollary are *physically* impossible. This is because asynchrony implies disequilibrium and hence always *de*stabilizes the transition state.

The PNS can be cast into a simple mathematical form after choosing the appropriate progress variables. In general, a Brønsted type coefficient, based on the variation of a reactant whose transformation does not involve resonance or unusual solvation effects, can serve as the progress variable of the main process.[22] For example, in the deprotonation of a carbon acid by an amine or by a *weakly basic* oxyanion, the Brønsted

$$\begin{array}{c} R \\ \diagdown \\ R' \end{array}\!\!C\!\!\begin{array}{c} H \\ \diagup \\ Y \end{array} + B^z \;\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}\; \begin{array}{c} R \\ \diagdown \\ R' \end{array}\!\!C\!\!\overset{-}{=}\!\!Y + BH^{z+1} \qquad (3)$$

coefficient obtained by varying the pK_a of the amine or oxyanion (β_B)[23] is usually assumed to meet this criterion adequately. On the other hand, α_{CH},[23] obtained by varying the pK_a of the carbon acid, would be a poor choice because α_{CH} is distorted by the lag in the resonance development in the carbanion.[16,21,24] Another poor choice is β_B obtained by varying the pK_a of *strongly basic* oxyanions, because here the strong solvation of the oxyanion severely affects β_B.[15,24]

(15) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.
(16) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907; **1975**, *97*, 3447.
(17) Bordwell[16] has suggested that it may be a real intermediate.
(18) Degree of charge transfer is often used interchangeably with degree of proton transfer.
(19) For a different approach to deal with this situation, see ref 20.
(20) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 187, 1129.
(21) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219.

(22) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.
(23) We use the symbol β_B to distinguish it from β_C obtained in the reverse direction by varying the pK of the carbanion and α_{CH} to distinguish it from α_{BH} obtained in the reverse direction by varying the pK_a of the oxyacid or ammonium ion.
(24) For a recent review, see: Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.

Table I.
Intrinsic Rate Constants, log k_0, for Carbanion Forming Reactions in 50% Me$_2$SO–50% Water at 20 °C

$<^X_Y$	CH$_2$XY + R$_2$NH (eq 8)	ArCH=CXY + R$_2$NH (eq 9)	ArCH=CXY + OH⁻ (eq 9)	ArCH(O⁻)CHXY (eq 10)	ArCH(NR$_2$)CHXY (eq 11)
$<^{CN}_{CN}$	≈7.0[a]	4.94[g]	≈−0.20[l]	≈4.96[l]	≈0 (rel)[g,l,n]
$<^{COO\,CH_3}_{COO\,CH_3}$	≈3.9[b]	4.10[m]			
$<^{CN}_{C_6H_4-4-NO_2}$	3.95[c]	3.35[h]			≈−2.7 (rel)[l,n]
(CO/CO benzene ring)	3.13[d]		≈−2.05[l]	≈3.18[l]	
$<^{CN}_{C_6H_3-2,4-(NO_2)_2}$	2.90[c]	2.65[h]			
$<^{COCH_3}_{COCH_3}$	2.75[e]	0.30[i]			
$<^H_{NO_2}$	0.73[f]	2.55[i]	≈−4.03[l]	≈1.05[l]	
$<^{C_6H_5}_{NO_2}$	−0.25[f]	1.42[k]			

[a] In water: Hibbert, F. *Compr. Chem. Kinet.* 1977, *8*, 97. [b] Bernasconi, C. F.; Oliphant, N., unpublished results. [c] Reference 41. [d] Reference 44b. [e] Reference 44a. [f] Reference 50a. [g] Bernasconi, C. F.; Cox, J. P.; Fornarini, S. *J. Am. Chem. Soc.* 1980, *102*, 2810. [h] Reference 42. [i] Reference 53. [j] Reference 42a. [k] Reference 35. [l] Bernasconi, C. F.; Laibelman, A.; Zitomer, J. L. *J. Am. Chem. Soc.* 1985, *107*, 6563. [m] Bernasconi, C. F.; Panda, M. *J. Org. Chem.* 1987, *52*, 3042. [n] Relative values.

The choice of the *second* progress variable, and the derivation of the mathematical form of the PNS, are best illustrated with our example of eq 3. Figure 2 shows schematic Brønsted plots (solid lines) in which the variation in k_1 and K_1 is brought about by changing pK_a^{BH}. As is apparent from the figure, log k_0 can be obtained from any k_1–K_1 pair via eq 4.[26] Assume now

$$\log k_0 = \log k_1 - \beta_B \log K_1 \qquad (4)$$

that Y is made a stronger π-acceptor, e.g., by changing from CN to NO$_2$. This increases the acidity of the carbon acid and enhances K_1 for a given pK_a^{BH} (horizontal arrows labeled δ log K_1^{res}(C⁻) in Figure 2A,B). k_1 should also increase. The extent of this increase, δ log k_1^{res}(C⁻), depends on how far resonance has developed in the transition state. One may define the progress variable, $\alpha_{res}^{C^-}$, for resonance development by eq 5.

$$\delta \log k_1^{res}(C^-) = \alpha_{res}^{C^-} \, \delta \log K_1^{res}(C^-) \qquad (5)$$

Figure 2A shows a (hypothetical) situation in which resonance development has made equal progress as proton transfer, implying $\alpha_{res}^{C^-} = \beta_B$. In this ("synchronous") case a change in K_1 induced by a change in Y has the same effect on k_1 as one induced by a change in BH and can thus be described by the same Brønsted plot; i.e., the change in Y does not affect k_0.

Figure 2B shows a case where resonance development lags behind proton transfer, i.e., $\alpha_{res}^{C^-} < \beta_B$, as is believed to be generally the case.[16,24] Here δ log k_1^{res}(C⁻) is small and k_1 for the carbon acid with the stronger π-acceptor (NO$_2$) falls below the Brønsted plot of the cyano compound. This implies that for the nitro compound

changes in K_1 induced by changes in pK_a^{BH} should generate a new Brønsted plot (dashed line). This is tantamount to a lower k_0 for the nitro compound. The decrease in log k_0 is given (provided that β_B is independent of Y)[28] by

$$\delta \log k_0^{res}(C^-) = (\alpha_{res}^{C^-} - \beta_B)\delta \log K_1^{res}(C^-) \qquad (6)$$

Equation 6 can be generalized to

$$\delta \log k_0^f = (\alpha_f - \beta_M)\delta \log K_1^f \qquad (7)$$

for any factor "f" that affects the free energy of a reactant or product in any reaction. δ log k_0^f and δ log K_1^f are the changes induced by "f", compared to a reference reaction where "f" either is absent or has a different value. If "f" is in a product, α_f measures the progress in the development of "f" in the transition state; if "f" is in a reactant, α_f measures how much of "f" has been lost in the transition state. β_M is the progress variable of the main reaction. Note that the limiting case $\alpha_f = 1$ will usually mean that the factor is developed (lost) in a preequilibrium[29] while $\alpha_f = 0$ implies the factor develops (is lost) in a postequilibrium. Note also that when several factors "f" are involved, each contributes a term, given by eq 7, to the overall δ log k_0.
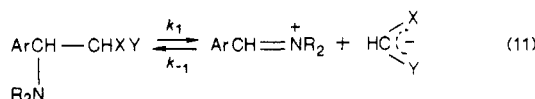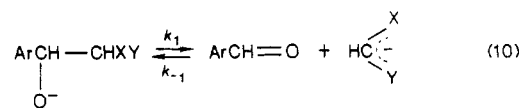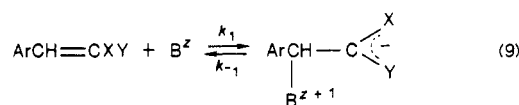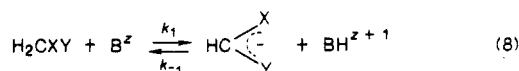
The PNS and eq 7 are very general and should be applicable to many different types of reactions. In this Account I shall apply them mainly to carbanion forming processes. In the closing paragraphs the possible relevance of the PNS to enzyme reactions will be touched upon.

Resonances Stabilization of Carbanions

Table I summarizes representative log k_0 values for the following types of reactions.

(25) (a) Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* 1977, *99*, 7653. (b) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *Ibid.* 1982, *104*, 7045.

(26) Since such Brønsted plots are usually straight lines, we prefer this method over the one which is based on the Marcus equation[1] and which implies curvature in the plot.

(27) If statistical factors are included, we have log k_0 = log (k_1/q) − β_B(log K_1 + log (p/q)).

(28) For cases where this assumption is not valid see ref 23.

(29) This limiting case has been discussed by Jencks,[25b] where f is solvation of an oxyanion.

$$H_2CXY + B^z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HC\overset{X}{\underset{Y}{\diagdown}} + BH^{z+1} \qquad (8)$$

$$ArCH=CXY + B^z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH-C\overset{X}{\underset{Y}{\diagdown}} \atop B^{z+1} \qquad (9)$$

$$ArCH-CHXY \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH=O + HC\overset{X}{\underset{Y}{\diagdown}} \atop O^- \qquad (10)$$

$$ArCH-CHXY \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH=\overset{+}{N}R_2 + HC\overset{X}{\underset{Y}{\diagdown}} \atop R_2N \qquad (11)$$

The largest data base obtained under uniform reaction conditions is for eq 8 and 9 where B is piperidine and morpholine. k_0 for eq 9 was obtained via eq 4, and k_0 for eq 8 via the statistically corrected[27] version of eq 4. For eq 9 with B = OH$^-$ and eq 10, k_0 was estimated by arbitrarily assuming that the experimentally inaccessible β_M is 0.5. These latter log k_0 values are therefore less certain. There also exists a crude estimate for the *relative* intrinsic rates constants, log $(k_0^{(CN)C_6H_4-4-NO_2}/k_0^{(CN)_2}) \approx -2.6$ for eq 11 with R_2N referring to piperidine and morpholine.[30]

The most notable feature of the data is that they show a general trend of decreasing k_0 with increasing resonance stabilization of the carbanion in all four reaction types. (The "abnormally" low k_0 for amine addition to benzylideneacetylacetone will be discussed below.) This trend is easily understood in terms of the equation

$$\delta \log k_0^{res}(C^-) = (\alpha_{res}^{C^-} - \beta_M)\delta \log K_1^{res}(C^-) \qquad (12)$$

with $\alpha_{res}^{C^-} < \beta_M$ where $\beta_M = \beta_B$ (eq 6) for the proton transfers, $\beta_M = \beta_{nuc}^n$[31] for the nucleophilic addition reactions, and $\beta_M = \beta_N^n$[32] for eq 10 and 11; XY = $(CN)_2$ may be regarded as the reference. A few comments about eq 12 are in order, though.

(1) It should be understood that delocalization of the negative charge into XY is intimately related to how well this charge is solvated. This point is evident from the fact that upon transfer from water to Me_2SO the pK_a of nitromethane increases by 7.0 units, that of acetylacetone by 4.4 units, while that of malononitrile remains virtually unchanged,[33] showing that hydrogen bonding solvation plays a key role. Hence, the term "resonance" should be understood to include a solvational component, particularly in hydroxylic solvents.

(2) What is the evidence that resonance development lags behind the main process? In proton transfers this lag is indicated by Brønsted α_{CH} values[23] which are larger than β_B.[23] Relevant α_{CH} and β_B values are summarized in Table II. The exalted α_{CH} values reflect a disproportionately large negative charge on the central carbon atom in the transition state, while in the product ion the charge is largely delocalized into XY. As is apparent from the data, the difference $\alpha_{CH} - \beta_B$ increases as resonance stabilization of the carbanion in-

Table II. Representative α_{CH} and β_B Values for Proton Transfers

C–H acid	base	α_{CH}[a]	β_B[b]	$\alpha_{CH} - \beta_B$
$ArCH_2CH(CN)_2$[c,e]	$RCOO^-$	0.98	≈1.0	≈0
$ArCH_2CH(COMe)COOEt$[c,e]	$RCOO^-$	0.76	0.44	0.32
$ArCH_2C_6H_3-2,4-(NO_2)_2$[d,f]	R_2NH	0.87	0.45	0.42
$ArCH_2NO_2$[c,g]	R_2NH	1.29	0.55	0.74

[a] α_{CH} = d log k_1/d log K_1 (change in pK_a^{CH}). [b] β_B = d log k_1/d log K_1 (change in pK_a^{BH}). [c] In water at 20 °C. [d] In 50% $Me_2SO-50\%$ water at 25 °C. [e] Bell, R. P.; Grainger, S. *J. Chem. Soc., Perkin Trans. 2* 1976, 1367. [f] Terrier, F.; Lelièvre, J.; Chatrousse, A.-P.; Farrell, P. G. *J. Chem. Soc., Perkin Trans. 2* 1985, 1479. [g] Reference 16.

Table III. Representative α_{nuc}^n and β_{nuc}^n Values for Nucleophilic Addition to Olefins

olefin	nucleophile	α_{nuc}^n[a]	β_{nuc}^n[b]	$\alpha_{nuc}^n - \beta_{nuc}^n$
$ArCH=C(CN)_2$[c,e]	R_2NH	0.43	0.30	0.13
$ArCH=C(COO)_2C(CH_3)_2$[d,f]	R_2NH	0.25	0.15	0.10
$ArCH=CHNO_2$[c,g]	R_2NH	0.51	0.25	0.26
$PhCH=C(Ar)NO_2$[d,h]	R_2NH	0.67	0.37	0.30

[a] α_{nuc}^n = d log k_1/d log K_1 (change in Ar). [b] β_{nuc}^n = d log k_1/d log K_1 (change in pK_a^{NucH}). [c] In water at 25 °C. [d] In 50% $Me_2SO-50\%$ water at 20 °C. [e] Bernasconi, C. F.; Killion, R. B., unpublished results. [f] Bernasconi, C. F.; Panda, M. *J. Org. Chem.* 1987, *52*, 3042. [g] Reference 36. [h] Reference 35.

creases. This mainly reflects the increasing difference between the charge distribution in the transition state and in the product ion, although the magnitude of β_B also plays a role.[34] Thus, the vanishing $\alpha_{CH} - \beta_B$ for the malononitriles is probably to a large extent caused by the large value of β_B.[34]

In the nucleophilic addition reactions the lag in resonance development manifests itself in a similar way, i.e., in $\alpha_{nuc}^n > \beta_{nuc}^n$,[31] with α_n^n = d log k_1/d log K_1 obtained by varying Ar in ArCH=CXY or in PhCH=CYAr. Representative α_{nuc}^n and β_{nuc}^n are in Table III. It should be noted that for reactions with amine nucleophiles the observed α_{nuc}^n values are distorted by the positive charge that develops on the amine, and $\alpha_{nuc}^n - \beta_{nuc}^n$ calculated from *experimental* α_{nuc}^n values overestimate the imbalance.[35,36] The α_{nuc}^n values reported in Table III have been corrected for this effect,[35,36] while those reported in ref 24 have not.

For eq 10 or 11 only few data indicating an imbalance are available as yet. That resonance development lags behind C=O π-bond formation when XY = $(COO)_2C(CH_3)_2$ (eq 10) was deduced by comparing kinetic isotope effects with substituent effects.[37]

(3) Can eq 12 account for all the results in Table I, at least in principle? The simplest assumption is that, for a given reaction type and constant conditions, $\alpha_{res}^{C^-} - \beta_M$ is constant, so that $\delta \log k_0^{res}(C^-)$ is linear with $\delta \log K_1^{res}(C^-)$. Plots of log k_0 (eq 9) vs. log k_0 (eq 8) give linear correlations[38] which supports this hypothesis but does not prove it. These correlations have slopes of 0.45 (B = R_2NH) and 0.57 (B = OH$^-$), indicating that the sensitivity of k_0 to XY is lower in the nucleophilic additions than for the proton transfers. $\delta \log K_1^{res}(C^-)$

(30) Bernasconi, C. F.; Murray, C. J. *J. Am. Chem. Soc.* 1984, *106*, 3257.

(31) β_{nuc}^n is a normalized β_{nuc} value ($\beta_{nuc}^n = \beta_{nuc}/\beta_{eq}$).

(32) β_N^n is the normalized β_N value for the "push" by a lone pair on O$^-$ or R_2N.

(33) (a) Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* 1980, *45*, 3299. (b) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* 1967, *89*, 2752.

(34) β_B values close to 0 or 1 lead to small $\alpha_{CH} - \beta_B$ while β_B values in the midrange tend to maximize $\alpha_{CH} - \beta_B$.[35]

(35) Bernasconi, C. F.; Renfrow, R. A. *J. Org. Chem.* 1987, *52*, 3035.

(36) Bernasconi, C. F.; Renfrow, R. A.; Tia, P. R. *J. Am. Chem. Soc.* 1986, *108*, 4541.

(37) Bernasconi, C. F.; Leonarduzzi, G. D. *J. Am. Chem. Soc.* 1982, *104*, 5143.

(38) Bernasconi, C. F. *Adv. Chem. Ser.* 1987, *No. 215*, 116.

should vary little from one type of reaction to another; this result implies that $|\alpha_{res}^{C^-} - \beta_M|$ is smaller for eq 9 than for eq 8. This conclusion is corroborated by $\alpha_{nuc}^n - \beta_{nuc}^n$ being smaller than the corresponding $\alpha_{CH} - \beta_B$ values (Tables II and III), suggesting a smaller lag in resonance development in the nucleophilic additions. This smaller lag may be attributed to the sp^2 hybridization of the α-carbon (carbon bearing XY) which facilitates the shift of the charge into XY even in the transition state. It is therefore possible that the observed lag in resonance development in the olefin additions is mainly a consequence of the late solvation of the charge on XY.

The differences in hybridization cannot be the whole story, though, because they do not explain why the sensitivity of k_0 to XY in eq 10 and 11 is also reduced,[38] even though here the α-carbon in the reactant is sp^3-hybridized. The uncertainty in the data for eq 10 and 11 and their paucity do not allow us to decide whether this sensitivity is as low as for the nucleophilic addition (data columns 3 vs. 4 in Table I) or somewhat higher (data columns 5 vs. 1 and 2). There is little doubt, though, that the sensitivity to XY is highest for the proton transfers, indicating an additional factor is present in these latter reactions. This factor could be hydrogen bonding between the carbanionic carbon and BH in the transition state. Since hydrogen bonding should be more effective when the negative charge is more localized on carbon,[39] transition-state stabilization would have a larger effect on k_0 when XY are weak π-acceptors, thereby enhancing the sensitivity of k_0 to XY in the observed direction.

Effects of Remote Substituents

In reactions where resonance development is late, k_0 depends strongly not only on the substituents directly responsible for the resonance effect (X and Y in eq 8–11) but also on remote substituents (Z). As shown elsewhere,[21] for remote substituents that exert a *polar* effect only, the change in $\log k_0$ relative to Z = H for a proton transfer (eq 8 with Z–C$_6$H$_4$CHXY) is given by

$$\delta \log k_0^{pol}(Z) = (\alpha_{CH} - \beta_B)\delta \log K_1^{pol}(Z) \quad (13)$$

For a nucleophilic addition (eq 9 with Z—C$_6$H$_4$CH= CXY) it would be

$$\delta \log k_0^{pol}(Z) = (\alpha_{nuc}^n - \beta_{nuc}^n)\delta \log K_1^{pol}(Z) \quad (14)$$

In contrast to eq 12, all quantities on the right side of eq 13 and 14 are measurable, and $\delta \log k_0^{pol}(Z)$ can be calculated quantitatively. Since $\alpha_{CH} > \beta_B$ and $\alpha_{nuc}^n > \beta_{nuc}^n$ (Tables II and III), eq 13 and 14 state that k_0 increases for an electron withdrawing substituent and decreases for an electron donating one. These changes in k_0 can again be understood in the context of the PNS: an electron withdrawing substituent is a product stabilizing factor that is relatively more important in the transition state than in the product ("early development of the factor") and hence k_0 must increase. Note, though, that this is not due to any special characteristics of Z; rather, it is a consequence of the lag in the resonance development, a phenomenon caused by XY, not by Z.

π-acceptors that stabilize reactants or products by resonance may influence k_0 through a PNS effect of their own. For example, the rate constants for depro-

tonation of *p*-cyano- and *p*-(nitrophenyl)nitromethane by benzoate ion in Me$_2$SO deviate negatively from the Brønsted line defined by Z = H, *p*-CH$_3$, *m*-NO$_2$, and 3,5-(NO$_2$)$_2$.[40a] This effect is the result of delayed charge delocalization into the *p*-CN and *p*-NO$_2$ groups. Similarly, the introduction of a 2-NO$_2$ group into (4-nitrophenyl)acetonitrile lowers k_0 for deprotonation,[41] and the introduction of a 2-NO$_2$ group into α-cyano-4-nitrostilbene lowers k_0 for nucleophilic addition.[42] These effects can either be viewed in the context of adding a remote π-acceptor substituent or of changing the entire Y group from 4-NO$_2$-C$_6$H$_4$ to 2,4-(NO$_2$)$_2$-C$_6$H$_3$[21] (Table I).

Solvation

In principle, the solvation of each reactant, product, as well as transition state contributes to k_0. For the semiquantitative understanding we are aiming for, though, it is sufficient to consider ions only. Since with carbanions resonance and solvation are so intimately related, we have treated them as a single factor; i.e., "res" in eq 12 is understood to include solvation. Strictly speaking, such a treatment presumes the two factors can be described by the same progress variables ($\alpha_{sol}^{C^-} = \alpha_{res}^{C^-}$). There is reason to believe, though, that solvation of the charge lags somewhat behind its delocalization into XY.[21] However, eq 12 can still be used if $\alpha_{res}^{C^-}$ is assumed to be a "weighted average" of the progress of resonance and solvation.[21]

Turning to B$^-$ and BH$^+$ (eq 8 and 9), the strong solvation of highly basic oxyanions in hydroxylic solvents often leads to a substantial reduction in k_0. This typically manifests itself as negative deviations from Brønsted plots.[15,25,43-45] The effect arises from desolvation being ahead of bond formation in the transition state.[15,25] This can be expressed by

$$\delta \log k_0^{des}(B^-) = (\alpha_{des}^{B^-} - \beta_M)\delta \log K_1^{des}(B^-) \quad (15)$$

with $\delta \log K_1^{des}(B^-)$ being the reduction in K_1 brought about by the solvation of B$^-$. Since reduction in K_1 implies $\delta \log K_1^{des}(B^-) < 0$ and early desolvation means $\alpha_{des}^{B^-} - \beta_M > 0$, we obtain $\delta \log k_0^{des}(B^-) < 0$. For strongly solvated ions ($\delta \log K_1^{des}(B^-) \ll 0$) this is an important effect.

The usually observed reactivity order of RR'R''N > RR'NH > RNH$_2$ in proton transfers and nucleophilic reactions of amines[41,44,46,47] has generally been understood to be a consequence of the increasingly stronger solvation in the order RR'R''NH$^+$ < RR'NH$_2^+$ < RNH$_3^+$, coupled with the assumption that solvation of the incipient positive charge lags behind bond formation.[21,46,47] This, of course, is again a PNS effect.

Change of Solvent

In general, the change from a hydroxylic to a dipolar aprotic solvent enhances k_0 significantly, although there

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Table IV.
Intrinsic Rate Constants, log k_0, for the Ionization of Carbon Acids in Water and Me$_2$SO–Water Mixtures at 20 °C

CH acid	solvent[a]	log k_0 (B=RCOO$^-$)	log k_0 (RNH$_2$)	log k_0 (pip/mor)[g]
CH$_3$NO$_2$[b]	H$_2$O			−0.59
	50% Me$_2$SO			0.73
	90% Me$_2$SO			3.06
PhCH$_2$NO$_2$[b]	H$_2$O	−1.55		−1.22
	50% Me$_2$SO			−0.25
	90% Me$_2$SO	≈2.39		1.75
AcAc[c]	H$_2$O	≈3.14	1.90	2.60
	50% Me$_2$SO	≈3.80	2.06	2.75
	90% Me$_2$SO	≈5.27	2.91	3.64
ID[d]	10% Me$_2$SO	2.64	2.27	2.97
	50% Me$_2$SO	3.18	2.44	3.13
	90% Me$_2$SO	4.53	2.97	3.85
9-CN–Fl[e,f]	10% Me$_2$SO		3.60	≈4.30
	50% Me$_2$SO		3.81	≈4.56
	90% Me$_2$SO		3.61	≈4.41

[a] Percent Me$_2$SO is by volume. [b] Reference 50a. [c] Acetylacetone, ref 44a. [d] 1,3-Indandione, ref 44b. [e] Bernasconi, C. F.; Terrier, F. *Can. J. Chem.* **1986**, *64*, 1273. [f] Fl = fluorene. [g] Pip = piperidine and mor = morpholine.

are exceptions. Table IV summarizes relevant data on proton transfers. It bears recalling that we are dealing with *intrinsic* rate constants (k_0) rather than actual rate constants (k_1); i.e., the effects reported in the table do not just represent the well-known rate enhancements of reactions with bases or nucleophiles in dipolar aprotic solvent.[48] (The solvent effect on the *actual* rate constants k_1 is usually larger than that on k_0, because the reactions are thermodynamically more favorable in the dipolar aprotic solvents.)

The results in Table IV can, for the most part, be understood in terms of late solvation of product ions and/or early desolvation of reactant ions. For a reaction with an anionic base we express the change in k_0 upon transfer from water (W) to a Me$_2$SO–water mixture (D) by

$$\delta \log {}^{W}k_0{}^{D}(CH/B^-) = \delta_{B^-} + \delta_{C^-} + \delta_{SR} \qquad (16)$$

while for a reaction with an amine base we have

$$\delta \log {}^{W}k_0{}^{D}(CH/N) = \delta_{NH^+} + \delta_{C^-} + \delta_{SR} \qquad (17)$$

δ_{B^-} is the contribution from early desolvation of B$^-$, δ_{C^-} and δ_{NH^+} are the contributions from late solvation of carbanion and protonated amine, respectively, while δ_{SR} is a contribution that cannot be accounted for by the other terms and may contain a solvent reorientation effect (see below).

δ_{B^-} can be obtained as the difference between $\delta \log k_0{}^{des}(B^-)$ in the two solvents; i.e., from eq 15 we have, using $\beta_M = \beta_B$

$$\delta_{B^-} = \delta \log k_0{}^{des}(B^-)_D - \delta \log k_0{}^{des}(B^-)_W = (\alpha_{des}^{B^-} - \beta_B)_D \delta \log K_1{}^{des}(B^-)_D - (\alpha_{des}^{B^-} - \beta_B)_W \delta \log K_1{}^{des}(B^-)_W \qquad (18)$$

In a first approximation we assume that $(\alpha_{des}^{B^-} - \beta_B)_D = (\alpha_{des}^{B^-} - \beta_B)_W$ so that eq 18 simplifies to

$$\delta_{B^-} \approx (\alpha_{des}^{B^-} - \beta_B)[\delta \log K_1{}^{des}(B^-)_D - \delta \log K_1{}^{des}(B^-)_W] \qquad (19)$$

Equation 19 may be further simplified if we approxi-

(48) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
(49) For a discussion of these effects see ref 44b.

Table V.
Solvent Activity Coefficients for the Transfer of Ions from Water (W) to Me$_2$SO–Water Mixtures (D) and from 10% Me$_2$SO (10) to Other Me$_2$SO–Water Mixtures (D) at 20 °C

ion	% Me$_2$SO	log ${}^{W}\gamma^D$	log ${}^{10}\gamma^D$
AcO^{-} [a]	10	1.12	0
	50	3.08	1.96
	90	≈6.50	≈5.38
CH$_3$CH$_2$CH$_2$NH$_3$$^{+}$ [a]	10	−0.40	0
	50	−1.81	−1.41
	90	≈−2.8	≈−2.4
CH$_2$=NO$_2$$^{-}$ [b]	50	2.87	
	90	6.70	
PhCH=NO$_2$$^{-}$ [b]	50	1.99	
	90	4.09	
AcAc^{-} [b,c]	50	2.07	
	90	4.50	
9-CN–Fl^{-} [b]	50	−1.37	
	90	−4.02	

[a] Wells, C. F. In *Thermodynamic Behavior of Electrolytes in Mixed Solvents*; Furter, W. F.; Ed.; American Chemical Society: Washington, DC, 1979; Adv. Chem. Ser. No. 177. [b] Bernasconi, C. F.; Bunnell, R. D., unpublished results. [c] AcAc = acetylacetone. [d] Fl = fluorene.

mate the term in the square brackets by log $K_{des}(B^-)_D$ − log $K_{des}(B^-)_W$, with $K_{des}(B^-)$ being the equilibrium constant for desolvation of B$^-$. log $K_{des}(B^-)_D$ − log $K_{des}(B^-)_W$ is equal to the log of the solvent activity coefficient[48] for the transfer of B$^-$ from "W" to "D" (log ${}^{W}\gamma_{B^-}^{D}$), so that

$$\delta_{B^-} \approx (\alpha_{des}^{B^-} - \beta_B) \log {}^{W}\gamma_{B^-}^{D} \qquad (20)$$

In a similar way one can express δ_{C^-} and δ_{NH^+} as

$$\delta_{C^-} \approx (\alpha_{sol}^{C^-} - \beta_B)(-\log {}^{W}\gamma_{C^-}^{D}) \qquad (21)$$

$$\delta_{NH^+} \approx (\alpha_{sol}^{NH^+} - \beta_B)(-\log {}^{W}\gamma_{NH^+}^{D}) \qquad (22)$$

with ${}^{W}\gamma_{C^-}^{D}$ and ${}^{W}\gamma_{NH^+}^{D}$ being the solvent activity coefficients of C$^-$ and NH$^+$, respectively, and $\alpha_{sol}^{C^-}$ and $\alpha_{sol}^{NH^+}$ the progress in the solvation of C$^-$ and NH$^+$, respectively, at the transition state. Note the minus signs for log ${}^{W}\gamma_{C^-}^{D}$ and log ${}^{W}\gamma_{NH^+}^{D}$, owing to C$^-$ and NH$^+$ being products, while B$^-$ is a reactant.

Representative log ${}^{W}\gamma^D$ values are summarized in Table V. Assuming that the degree by which desolvation of B$^-$ is ahead of bond formation is about the same as the degree by which solvation of C$^-$ and NH$^+$ lags behind the bond change, i.e., $|\alpha_{des}^{B^-} - \beta_M| \approx |\alpha_{sol}^{C^-} - \beta_M| \approx |\alpha_{sol}^{NH^+} - \beta_M|$ for a given XY, the values in Table V imply

$$\delta_{B^-} \gg 0; \quad \delta_{NH^+} < 0$$

$$\delta_{C^-} \gg 0 \text{ for XY = R(NO}_2); \quad \delta_{C^-} > 0 \text{ for XY =}$$
$$(COR)_2; \quad \delta_{C^-} < 0 \text{ for XY = CN (fluorenyl)}$$

On the basis of these relationships one can rationalize the solvent effects as follows.

(1) For a given XY, the increase in k_0 in the Me$_2$SO richer solvents is always greater when the base is a carboxylate ion than when it is an amine. For example, for PhCH$_2$NO$_2$, $\delta \log {}^{W}k_0{}^{90}(CH/B^-) \approx 3.94$ and $\delta \log {}^{W}k_0{}^{90}(CH/N) = 2.97$; or for 1,3-indandione, $\delta \log {}^{W}k_0{}^{90}(CH/B^-) = 1.89$ and $\delta \log {}^{W}k_0{}^{90}(CH/N) = 1.04$. These results reflect the fact that $\delta_{B^-} \gg 0$ but $\delta_{NH^+} < 0$.

(2) For a given base, the magnitude of the solvent effect as a function of XY follows the relative magnitude of δ_{C^-}. For example, in the piperidine/morpholine reactions $\delta \log {}^{50}k_0{}^{90}(CH/N)$ is 2.33 (PhCH$_2$NO$_2$), 2.00

(CH_3NO_2), 0.89 (AcAc), 0.72 (ID), and ≈ -0.15 (9-CN-Fl).

The results for 9-cyanofluorene, even though consistent with the above qualitative patterns, suggest the δ_{SR} term (eq 17) is operative: The δ_{C^-} and δ_{NH^+} terms call for a decrease in k_0 in the Me_2SO-rich solvents, while k_0 is in fact virtually solvent independent. Recent evidence[50] suggests that δ_{SR} may represent a solvent reorientation effect[51] or "dynamic" solvent effect.[52]

Intramolecular Hydrogen Bonding

In the reaction of amines with olefins intramolecular hydrogen bonding between the NH proton and X or Y may occur in the zwitterionic adduct and is indeed strong for the adducts of benzylideneacetylacetone.[53] The intramolecular hydrogen bond adds stability to the adduct and hence a late development would decrease, an early development increase, k_0 according to

$$\delta \log k_0^{Hb} = (\alpha_{Hb} - \beta_{nuc}^n)\delta \log K_1^{Hb} \qquad (23)$$

Since effective hydrogen bonding requires nearly full development of both the acidity of the NH proton and the basicity of the acceptor oxygen, one expects little stabilization in the transition state, i.e., $\alpha_{Hb} < \beta_{nuc}^n$, and hence $\delta \log k_0^{Hb} < 0$. The low k_0 value for amine addition to benzylideneacetylacetone[38,53] mentioned earlier (Table I) has, in part, been attributed to this effect.

Generalizations and Conclusions

As the various examples discussed in this Account show, much of the structure–reactivity behavior of carbanion forming reactions can be satisfactorily understood by the PNS. We expect this to be true for other reaction types as well, as long as they are dominated by factors that stabilize reactant or product states (in contrast to transition states).

A major strength of the PNS that distinguishes it from other "principles" such as the reactivity–selectivity principle[54] or the Hammond–Leffler postulate[55] is that it is very general and mathematically provable (within the constraints of the definitions of the progress variables β_M and α_f), and thus it can have no exceptions. On the other hand, since α_f cannot be measured, this generality may also be considered its major weakness, because any trend in k_0 could be "explained" by arbitrarily choosing the appropriate sign and magnitude of $\alpha_f - \beta_M$ in eq 7.

What makes the PNS and eq 7 useful is that one can infer from *independent* experiment, and/or from theoretical considerations, whether α_f should be greater than or less than β_M. For example, late development of resonance/solvation in carbanions is indicated by the imbalances in the Brønsted coefficients. At the same time there is also considerable *theoretical* support for

the idea that resonance should develop late.[20,22,56-58] Hence, the accumulation of examples which fit into the framework developed in this Account strongly suggests the existence of the following rule: *whenever resonance is involved as reactant or product stabilizing factor in a reaction, this factor will develop late or be lost early, and this will depress k_0.*

Another safe generalization is that solvation always lags behind (desolvation is ahead of) bond changes and thus also invariably lowers k_0. This phenomenon may be an entropy effect.[21,59] Once a charge is being solvated, the restriction of the solvent molecules, and with it the entropy, should remain relatively independent of the *amount* of charge. On the other hand, the *enthalpy* of solvation should be approximately proportional to the charge. Hence, the gain in free energy from solvation of a *partial* charge is disproportionately small compared to that from solvation of a full charge, since most of the entropy has to be paid while only a fraction of the enthalpy is released. Hence, either the solvent molecules fail to arrange themselves around the developing charge in the transition state ("physical lag" in the solvation) or, if they do, the benefit in free energy is minimal ("energy lag"). For the reasons stated earlier as well as for entropy reasons,[21] it is likely that intramolecular hydrogen bonding, too, always develops late, even though there are at present only few examples that corroborate this rule.[60]

The above generalizations are useful in several ways. Most importantly, they bring systematic order into our understanding of how chemical reactions occur. They also help in the identification of PNS effects when it is not a priori obvious whether such an effect should be present, and they facilitate the separation of PNS effects from other factors. An example in the first category is the finding that in the deprotonation of arylnitromethanes the p-CN and p-NO$_2$ derivatives show abnormally slow rates only in Me_2SO[40] but not in water.[16] This indicates that the solvent-assisted resonance effect[62] is larger in Me_2SO than in water, a rather surprising conclusion in view of the well-known stabilization of nitronate ions by hydrogen bonding, but in agreement with gas-phase/solution-phase comparisons.[62]

Obvious situations in the second category (non-PNS effects) are electrostatic[43,63] and steric effects in proton transfers that operate only in the transition state.[64] A more interesting example relates to the possible existence of solvent reorientation effects as discussed in the section on changing the solvent. The demonstration that PNS effects are not sufficient to account for the solvent dependence of k_0 in the deprotonation of 9-cyanofluorene by amines is perhaps one of the best

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(58) Williams, I. H.; Spangler, D.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* 1985, *107*, 7717.

(59) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* 1984, *106*, 1373.

(60) The finding of Hibbert and co-workers[61] that intramolecular hydrogen bonds are almost always broken before the proton can be removed by a base is consistent with our rule.

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(63) (a) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* 1973, *95*, 803. (b) Thibblin, A. *Ibid.* 1984, *106*, 183.

(64) Note that in nucleophilic additions electrostatic and steric effects are PNS effects.[45,61]

indications yet that *dynamic* solvent effects significantly affect intrinsic rates.

Does the PNS have relevance to enzyme-catalyzed reactions? We think so. One generally recognized factor responsible for the efficiency of enzymes is that certain functional groups of the enzyme are optimally positioned with respect to the reaction center. If, for example, the purpose of such a group is to solvate a developing charge in a reaction product, the optimal positioning may lead to solvation that is essentially synchronous with charge development. This would translate into a circumvention of the typical k_0-lowering PNS effect of late solvation in solution reactions.

Another important mechanism used by enzymes is to desolvate reactants by virtue of binding them into a cavity from which the solvent is excluded.[65,66] Part of the resulting acceleration may simply be a consequence of an increase in the equilibrium constant of the reaction, as recently discussed by Gilbert.[65] However, a considerable fraction of the acceleration may again be an effect on k_0 which results from the avoidance of the k_0-lowering PNS of early desolvation.

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