Scheme VII

$$Ar^\bullet + H_3PO_2 \rightarrow ArH + [H_2PO_2]^\bullet \quad (M33)$$

$$[H_2PO_2]^\bullet + ArN_2^+ \rightarrow Ar^\bullet + N_2 + [H_2PO_2]^+ \quad (M34)$$
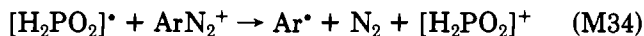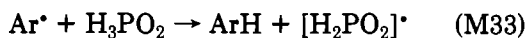
M34 was indicated to react with water to form H_3PO_3 and H^+. An electron spin resonance spectroscopic study of such systems by Beckwith[86] revealed characteristics of $[H_2PO_2]^\bullet$ radicals and their reactions with diazonium ions.

Imposter Reactions

There are a few reactions that masquerade as members of the select group that is the focus of this Account, but really are not. Sometimes you have to look twice to tell the difference. We have already encountered some alkoxide-effected dediazoniations that appear to go through carbanion intermediates. Others involve nucleophilic displacement *on* halogen, effective positive halogen capture and generating aryl anion intermediates.

Some of the positive halogen capture reactions are effected by carbanions. Rae Victor, who started Ph.D. research with me at Brown University and completed it at Santa Cruz, investigated such as case.[87] She started by looking into the debromination of 1,2,4-tribromobenzene through the action of potassium *tert*-butoxide (*t*-BuOK) in 50% *t*-BuOH/50% DMSO at 53 °C; *p*-dibromobenzene was formed in 70% yield.[88] She found evidence that the reaction involves nucleophilic displacement by dimsyl anion ($CH_3SOCH_2^-$) on the 2-bromine, the nucleofuge being 2,5-dibromophenyl anion. Two principal lines of support for this conclusion were that the halogen removed was typically ortho to another halogen (ortho halogens strongly stabilize aryl anions[89]) and that it was necessary for the cosolvent (with *t*-BuOH) to be of structure readily converted to

a carbanion by *t*-BuOK. Cosolvents that supported debromination included *N*-methylpyrrolidone and *N*,*N*-dimethylacetamide, but reaction failed when the cosolvent was HMPA or diphenyl sulfoxide.

Dehalogenations of this type, especially in 2-butanone/methanol and DMSO/methanol solvents, have been investigated extensively by Bolton and co-workers.[90] Their kinetic and other studies support the type of mechanism that Rae and I suggested.

Diethyl phosphite ions, $(EtO)_2PO^-$, react with *o*-haloiodobenzenes in the dark to generate *o*-halophenyl anions, which then capture hydrons from the ammonia solvent to form halobenzenes and, in the cases where the ortho halogen is bromine or iodine, detach halide ion to form benzyne.[91] When illuminated, the same reactants undergo $S_{RN}1$ reactions via *o*-halophenyl radical intermediates to form (*o*-halophenyl)phosphonic esters or *o*-phenylenebis(phosphonic esters).

A perceptive review of a variety of reactions of this general sort, which they call *X-phyllic* reactions, has been provided by Zefirov and Makhon'kov.[92]

Concluding Remarks

Because editors of *Accounts* don't like manuscripts to be too long, I'd better close now. Surely some work that ought to have been mentioned escaped attention in this Account, and for that I apologize. Perhaps some of my judgments will provoke challenges. If so, I hope that the challengers will perform well-designed experiments to correct my errors, and thus to advance knowledge.

(85) Cf.: Levit, A. F.; Kiprianova, L. A.; Gragerov, I. P. *Zh. Org. Khim.* **1975**, *11*, 2351; *J. Org. Chem. USSR (Engl. Transl.)* **1975**, *11*, 2395.
(86) Beckwith, A. L. J. *Aust. J. Chem.* **1972**, *25*, 1887.
(87) Bunnett, J. F.; Victor, R. R. *J. Am. Chem. Soc.* **1968**, *90*, 810.
(88) Moyer, C. E., Jr. Dissertation, Brown University, 1964; *Diss. Abstr.* **1965**, *25*, 4412.
(89) This topic was mentioned briefly in an earlier Account.[6]

(90) Bolton, R.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1977**, 278. Bolton, R.; Moore, C.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1593.
(91) Bard, R. R.; Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1979**, *44*, 4918.
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The Principle of Nonperfect Synchronization: More Than a Qualitative Concept?[1]

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In trying to understand chemical reactivity, the physical organic chemist has traditionally relied on models or concepts that are qualitative and intuitive.

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Perhaps the best-known physical organic concept is the Hammond postulate[3] along with its various extensions

(1) This Account is based, in part, on a talk I presented during a symposium honoring Professor Joseph Bunnett on the occasion of his retirement from active service at the University of California at Santa Cruz. The talk was entitled "From Bunnett's Variable Transition State Theory to the Principle of Non-Perfect Synchronization". Except for the introduction, which summarizes the basic features of the principle of nonperfect synchronization (PNS), most of the material is new. Specifically, there is very little overlap with an earlier Account that was entitled "Intrinsic Barriers of Reactions and the Principle of Nonperfect Synchronization".[2]
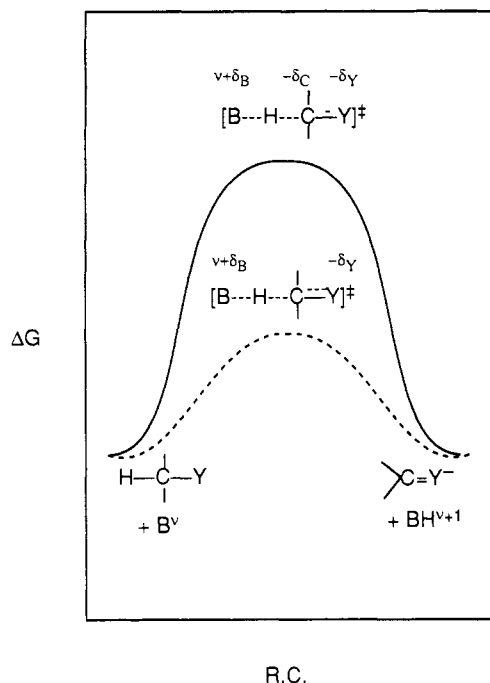
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Figure 1. Free energy vs reaction coordinate profiles for the deprotonation of a carbon acid activated by a π-acceptor substituent Y. Dashed line: hypothetical case where resonance develops synchronously with charge transfer. Solid line: actual situation where resonance development lags behind charge transfer. The smaller degree of resonance stabilization of the transition state leads to a higher barrier.

summarized by the acronym Bema Hapothle.[4] It is my contention that the principle of nonperfect synchronization (PNS) is another prime example of a physical organic concept that deals with chemical reactivity in an intuitive and qualitative way, but with a strong potential for development into a more quantitative, or at least semiquantitative, tool.

The PNS derives from the realization that the majority of elementary reactions involve more than one concurrent molecular process such as bond formation/cleavage, solvation/desolvation, delocalization/localization of charge, etc. and that often these processes have made unequal progress at the transition state. When this is the case, the reaction is said to have an "imbalanced transition state", a term originally introduced by Jencks.[4,5]

Olefin-forming E2 eliminations[6] were among the earliest reactions recognized to commonly have imbalanced transition states. The basic idea that bond changes in E2 reactions need not be completely synchronous goes back to Hanhard and Ingold.[7] Subsequently several other authors[8,9] provided evidence for

such nonsynchronous changes, which eventually culminated in what became the variable transition state theory. However, it was Bunnett[10] who put this theory on a sound footing and who systematically explored its many ramifications and implications. Although Bunnett's proposals received no major challenge, his pioneering work was obscured by a subsequent development, namely, visualization of the imbalance and variable characteristics of E2 transition states by means of More O'Ferrall[11]–Jencks[5,12] diagrams, which are now commonly used in textbooks of physical organic chemistry.[13]

Imbalanced transition states are often recognized on the basis of structure–reactivity coefficients when substituents at different positions within the transition state give conflicting reports about charge development at a reaction site. One of the best known examples is the deprotonation of arylnitroalkanes by amines or hydroxide ion (eq 1) where the Brønsted α_{CH} value (1.29) determined by varying the Z substituent is much larger than the Brønsted β_B value (0.56) obtained by varying the substituent in B^ν. The meaning of α_{CH} is
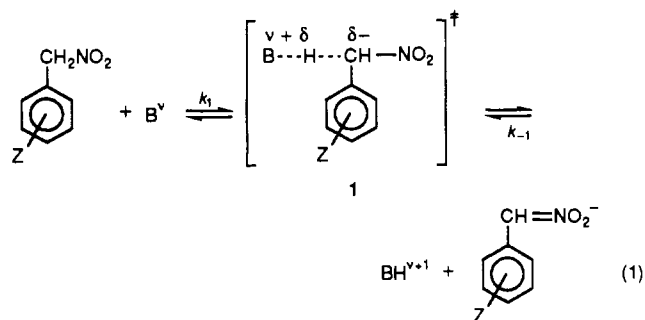
best appreciated by realizing that α_{CH} is equivalent to the ratio of the Hammett ρ-values of k_1 and the equilibrium constant K_1 ($=k_1/k_{-1}$), i.e., $\alpha_{CH} = \rho(k_1)/\rho(K_1)$. The high value of α_{CH} is then easily understood in terms of a transition state (1) in which the delocalization of the negative charge into the nitro group lags behind proton transfer, i.e., the negative charge is largely localized on the carbon, but strongly delocalized into the nitro group in the product ion. This makes the transition state more sensitive to substituent effects than the product ion, i.e., $\rho(k_1) > \rho(K_1)$.

Inasmuch as no charge delocalization is involved in the conversion of B^ν to $BH^{\nu+1}$, there is no possibility of the distortion of β_B by a lag in such a delocalization and hence β_B may be regarded as (approximately) a measure of proton or charge transfer in the transition state.[15] Without a lag in charge delocalization into the nitro

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(7) Hanhart, W.; Ingold, C. K. J. Chem. Soc. **1927**, 997.

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(13) (a) Lowry, T. H.; Richardson, K. S. Mechanism and Theory in Organic Chemistry, 3rd ed.; Harper and Row: New York, 1987. (b) Isaacs, N. S. Physical Organic Chemistry; Longman: Essex, England, 1987. (c) Ritchie, C. D. Physical Organic Chemistry, 2nd ed.; Dekker: New York, 1990.

(14) Bordwell, F. G.; Boyle, W. J., Jr. J. Am. Chem. Soc. **1972**, 94, 3907.

(15) This is the traditional view,[4,16] although this view has been challenged.[17]

(16) (a) Leffler, J. E.; Grunwald, E. Rates and Equilibria of Organic Reactions; Wiley: New York, 1963; p 156. (b) Kresge, A. J. Acc. Chem. Res. **1975**, 8, 354.

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group, α_{CH} would presumably also be a measure of the degree of proton or charge transfer in the transition state and be equal to β_B. Hence the difference $\alpha_{CH} - \beta_B$ may be regarded as a measure of the imbalance.

The lag in the charge delocalization, which implies a lag in the development of resonance stabilization of the transition state, has the effect of increasing the barrier or lowering the rate of the deprotonation reaction (k_1) compared to a (hypothetical) case where resonance develops synchronously with charge transfer. The situation is shown schematically in Figure 1 for the deprotonation of a CH acid activated by a π-acceptor group Y. For the reaction in the reverse direction, the protonation of the carbanion by BH^{r+1} (k_{-1}), there is an equivalent rate reduction. This is because most of the resonance stabilization of the carbanion has to be lost before the transition state is reached, and hence the activation barrier is higher than in the (hypothetical) synchronous situation where the amount of resonance loss corresponds only to the amount of charge transfer (Figure 1).
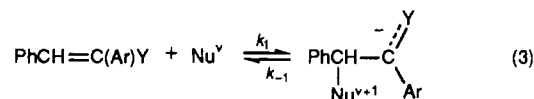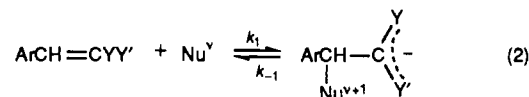
These reductions of k_1 and k_{-1} which occur without a change in the equilibrium constant ($K_1 = k_1/k_{-1}$) are equivalent to a decrease in the intrinsic rate constant (k_0) or an increase in the intrinsic barrier ($\Delta G^{\ddagger}_0$) of the reaction (for definitions, see footnote 18).

The deprotonation of nitroalkanes represents an extreme case as far as the magnitude of the transition-state imbalance and its effect on the intrinsic rate constant are concerned. In fact the imbalance is so large as to lead to α_{CH} values beyond the normal range of 0–1 ("nitroalkane anomaly");[22] e.g., for the reaction of $ArCH_2NO_2$ with morpholine, $\alpha_{CH} = 1.29$;[14] with OH^-, $\alpha_{CH} = 1.54$.[14] Correspondingly, the intrinsic rate constant for these reactions is very low (log $k_0 = -1.22$ for the reaction of $PhCH_2NO_2$ with secondary alicyclic amines in water).[23] These extreme features can be traced to the unusually strong resonance stabilization of the phenylnitronate ion, which is reenforced by hydrogen-bonding solvation in water.[2,20,24]

Qualitatively similar behavior has been observed for numerous other proton-transfer reactions, but inasmuch as the resulting carbanion is less strongly stabilized by resonance than $PhCH=NO_2^-$, the imbalance is less dramatic and k_0 is higher.[25] For example, for the deprotonation of $ArCH(CH_3)NO_2$ by R_2NH, $\alpha_{CH} = 0.94$, $\beta_B = 0.55$, and hence $\alpha_{CH} - \beta_B = 0.39$.[14] Here the methyl group hinders optimal π-overlap between the carbon and the nitro group in the nitronate ion and reduces its resonance stabilization, which leads to a smaller imbalance.[26] Another situation where resonance plays a lesser role than with $PhCH_2NO_2$ is the deprotonation of $ArCH_2CH(COMe)COOEt$ by $RCOO^-$,[27] for which $\alpha_{CH} - \beta_B = 0.76 - 0.32$. In cases where resonance stabilization of the carbanion is quite small or nonexistent, $\alpha_{CH} - \beta_B$ is correspondingly small and k_0 is high. An example is the reaction of $ArCH_2CH(CN)$ with $RCOO^-$,[27] where $\alpha_{CH} - \beta_B = 0.98 - 0.83 = 0.15$ and log $k_0 \approx 7.0$ for the reaction of $RCH(CN)_2$ with secondary alicyclic amines.[28,30]

Similar observations have been made when studying other carbanion-forming reactions, in particular, nucleophilic additions to activated olefins as shown in eqs 2 and 3. In these reactions the imbalance is measured

$$ArCH=CYY' + Nu^v \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH-\overset{\overset{Y}{\diagup}}{\underset{\underset{Nu^{v+1}}{|}}{C}}\overset{\diagdown}{\underset{Y'}{}}^{-} \qquad (2)$$

$$PhCH=C(Ar)Y + Nu^v \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhCH-\overset{\overset{Y}{\diagup}}{\underset{\underset{Nu^{v+1}}{|}}{C}}\overset{\diagdown}{\underset{Ar}{}}^{-} \qquad (3)$$

by the difference $\alpha^n_{nuc} - \beta^n_{nuc}$, with $\alpha^n_{nuc} = d \log k_1/d \log K_1$ obtained by varying the Ar substituent and $\beta^n_{nuc} = d \log k_1/d \log K_1$ obtained by varying the substituent in the nucleophile. Just as in the proton transfers, $\alpha^n_{nuc} - \beta^n_{nuc} > 0$ indicates a lag in the delocalization of the negative charge into Y or YY'. Also in analogy to the proton transfers, the size of $\alpha^n_{nuc} - \beta^n_{nuc}$ correlates with the degree of charge delocalization in the adduct and k_0 is lower for systems with better π-acceptors Y or YY'. For example, for the reaction of $PhCH=C(Ar)NO_2$ with piperidine and morpholine in 50% Me_2SO–50% water, $\alpha^n_{nuc} - \beta^n_{nuc} = 0.67 - 0.37 = 0.30$ and log $k_0 = 1.43$;[31] for the reaction of $ArCH=C(CN)_2$ with the same amines under the same conditions $\alpha^n_{nuc} - \beta^n_{nuc} = 0.56 - 0.42 = 0.14$ and log $k_0 = 5.04$.[32]

Although fewer relevant studies have been reported regarding the formation of other types of resonance-stabilized species such as carbocations,[33-37] radicals,[38,39] or olefins,[32,40,41] these reactions appear to follow patterns

(18) For a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1}, the intrinsic rate constant is usually defined as $k_0 = k_1 = k_{-1}$ when $K_1 = 1$ ($\Delta G^{\ddagger}_0 = \Delta G^{\ddagger}_1 = \Delta G^{\ddagger}_{-1}$ when $\Delta G^\circ = 0$). In proton transfers it is common practice to include statistical factors[19] so that $k_0 = k_1/q = k_{-1}/p$ when $K_1(p/q) = 0$; p is the number of equivalent protons on BH^{r+1}, q the number of equivalent basic sites on B^r. In our own work we determine k_0 by interpolation or extrapolation of Brønsted-type plots of log (k_1/q) or log (k_{-1}/p) vs log (p/q) (log $K_1 = pK_a^{BH} - pK_a^{CH}$) to log $K_1 + \log (p/q) = 0$ (variation of B^r). As explained elsewhere,[2,20] we prefer this method over the one based on the Marcus equation.[21]

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(21) (a) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891. (b) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249.

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(23) Calculated on the basis of data in ref 14.

(24) Keeffe, J. R.; Morey, J.; Palmer, C. A.; Lee, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1295.

(25) For a recent review, see ref 20.

(26) The reduced imbalance should also lead to a higher k_0. However, the actual log $k_0 = -2.62$ (ref 23) is lower. This is because the methyl group also hinders the approach of the relatively bulky amine, thereby lowering k_0 and overcompensating the increase due to the reduced resonance effect. A small contributing factor to the lowering of k_0 is the fact that $PhCH(CH_3)NO_2$ has only one acidic proton, whereas $PhCH_2NO_2$ has two.

(27) Bell, R. P.; Grainger, S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1362.

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(33) (a) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361. (b) Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455. (c) Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513.

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(38) Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 173.

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similar to those of the carbanion-forming reactions. In other words, resonance development typically lags behind bond changes at the transition state (or the loss of resonance from a reactant is ahead of bond changes), and hence strong resonance stabilization of the product (or reactant) leads to low intrinsic rate constants, and weak resonance stabilization to high intrinsic rate constants.

Why Does Delocalization Lag behind Charge Transfer?

If a balanced transition state wherein charge delocalization and resonance stabilization have progressed synchronously with bond formation would lead to a lower intrinsic barrier (Figure 1, dashed line), why is there a lag that leads to a higher barrier? Since a basic law of nature requires physical and chemical processes to follow paths of minimum free energy, a constraint must exist that makes it impossible for delocalization to be synchronous with proton transfer. A qualitative understanding of this constraint may be gained by considering the generalized representation of a proton transfer shown in eq 4. Equation 4 refers to a situation with complete charge delocalization and complete C–Y π-bond formation in the carbanion, as is probably true for Y = NO_2; the case where delocalization is only partial will be taken up below.

$$B^\nu + H-\underset{|}{\overset{|}{C}}-Y \longrightarrow \left[\begin{array}{c} \nu + \delta_B \quad -\delta_C \,-\delta_Y \\ \underset{|}{\overset{|}{B\cdots H \cdots C \doteq Y}} \end{array} \right]^{\ddagger} \longrightarrow$$

$$BH^{\nu+1} + \overset{\diagdown}{\underset{\diagup}{C}} = Y^- \quad (4)$$
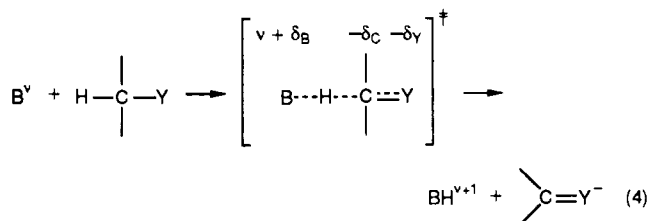
We now ask how large δ_Y, the fraction of charge that ends up on Y, could possibly be. It seems reasonable to expect that δ_Y will depend not only on δ_B, the amount of charge transferred from the base, but also on the degree of C–Y π-bond formation. In other words, if the C–Y π-bond is not fully developed, and it cannot be in the transition state, only a fraction of δ_B will end up as δ_Y. The simplest assumption is that this fraction is proportional to the C–Y π-bond order, and that in turn the C–Y π-bond order is proportional to δ_B. This means that δ_Y is proportional to $(\delta_B)^2$ and given by eq 5, with a being a proportionality constant. For the case shown

$$\delta_Y = a(\delta_B)^2 \quad (5)$$

in eq 4, $a = 1$. This can be seen when solving eq 5 for the products where $\delta_B = \delta_Y = 1$. Hence for a transition state where δ_B is, say, 0.5, we have $\delta_Y = 0.25$, implying $\delta_C = 0.25$ for the charge on the carbon.

The above model, which was first proposed by Kresge,[22] is probably an oversimplification, but it appears to capture the essence of why there is a forced lag in the charge delocalization. Some refinements to the model will be presented below.

Generalizations: The Principle of Nonperfect Synchronization

The decrease in k_0 that is caused by the delayed resonance development in so many reactions is a manifestation of a more general principle which we have

(41) Bernasconi, C. F. *Adv. Chem. Ser.* **1987**, *215*, 115.

called the principle of nonperfect synchronization (PNS).[2,20,42] The PNS states that *a product-stabilizing factor whose development at the transition state is late, i.e., lags behind the main process, always lowers* k_0, *whereas a product-stabilizing factor that develops early, i.e., ahead of the main process, enhances* k_0. *The main process is usually equated with a bond change or a charge transfer.*

Since late (early) development in the forward direction implies early (late) loss in the reverse direction, the PNS may also be formulated by the following corollary: *A reactant-stabilizing factor that is lost early (i.e., ahead of the main process) always lowers* k_0, *while a reactant-stabilizing factor that is lost late (i.e., whose loss lags behind the main process) always increases* k_0. For product- or reactant-*de*stabilizing factors, all the above statements are reversed, i.e., a product-destabilizing factor that develops late enhances k_0, etc.

Product- or reactant-stabilizing factors that typically develop late (are lost early) and hence lower k_0 include not only resonance[2,20] but also solvation,[2,20] intramolecular hydrogen bonding,[2,20] and certain electrostatic effects.[41] Factors that may develop early (are lost late) and thereby enhance k_0 are much less common; one such factor may be the soft acid–soft base interactions in reactions of polarizable nucleophiles with electrophilic olefins although the evidence for this is currently based on a very small data base.[20,43]

The PNS as defined above is very useful in a qualitative sense, e.g., in rationalizing changes in intrinsic rate constants of reactions with changes in structure. A mathematical formalism that would turn the PNS into a more quantitative tool was proposed some years ago.[2,20,42] According to this formalism, the change in log k_0 brought about by the nonsynchronous development of a product factor "f" (or the loss of a reactant factor) can be expressed by eq 6. $\delta \log k_0{}^f$ (=log $k_0{}^f$ – log $k_0{}^{ref}$)

$$\delta \log k_0{}^f = (\lambda_f - \beta)\delta \log K_1{}^f \quad (6)$$

is the change in log k_0 induced by the factor f compared to a reference reaction (with log $k_0{}^{ref}$) which is free of this factor or for which f has a different value; $\delta \log K_1{}^f$ (=log $K_1{}^f$ – log $K_1{}^{ref}$) represents the change in the equilibrium constant caused by f; β is the progress of the main reaction event such as bond changes or charge transfer (e.g., β_B in proton transfers, $\beta^n{}_{nuc}$ in nucleophilic additions), and the λ_f (=$\delta \log k_1{}^f/\delta \log K_1{}^f$)[44] is the progress in the development or loss of f at the transition state.

For the example of the formation of a resonance-stabilized carbanion (f = resonance, "R") by a proton transfer, which is the major focus of this Account, eq 6 takes on the form of eq 7. Late development of

$$\delta \log k_0{}^R = (\lambda_R - \beta_B)\delta \log K_1{}^R \quad (7)$$

resonance means $\lambda_R < \beta_B$ and thus $\lambda_R - \beta_B < 0$, while resonance stabilization of the carbanion implies $\delta \log K_1{}^R > 0$. Hence $\delta \log k_0{}^R < 0$, i.e., k_0 is decreased relative to a reference reaction in which the carbanion

(42) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219.
(43) Bernasconi, C. F.; Schuck, D. F. *J. Am. Chem. Soc.*, in press.
(44) $\delta \log k_1{}^f$ is the change in log k_1 caused by f. For a more detailed discussion of the meaning of λ_R and the derivation of eq 6, see refs 2, 20, and 42. Note that in previous treatments[2,42] the symbol α_{res} or $\alpha^C{}_{res}$ was used for λ_R. These symbols were prone to be confused with α_{CH} and hence were abandoned.

Scheme I

$$\chi = 1.0: \quad \delta_Y = (\delta_B)^2 = 0.25 \qquad \delta_C = \delta_B - (\delta_B)^2 = 0.25$$
$$\chi = 0.5: \quad \delta_Y = 0.5(\delta_B)^2 = 0.125 \qquad \delta_C = \delta_B - 0.5(\delta_B)^2 = 0.375$$
$$\chi = 0: \quad \delta_Y = 0 \qquad \delta_C = \delta_B = 0.5$$

enjoys no resonance stabilization or less resonance stabilization than the reaction under consideration.

A major problem with eq 7 is that unless $\delta \log K_1^R$ or λ_R can be evaluated or at least estimated, the equation remains basically a qualitative tool. Efforts toward estimating these two quantities have recently been presented.[20] They are summarized in the next section.

Toward a More Quantitative Treatment of Resonance Effects: Estimate of λ_R

Equation 8 is a more general representation of a proton transfer than eq 4; it differs from the latter in that the charge delocalization in the product carbanion may only be partial. With the assumptions that led

$$B^\nu + H{-}\overset{|}{\underset{|}{C}}{-}Y \longrightarrow \left[\overset{\nu+\delta_B \quad -\delta_C -\delta_Y}{B{\cdots}H{\cdots}\overset{|}{C}{=\!=}Y} \right]^{\ddagger} \longrightarrow$$

$$BH^{\nu+1} + \overset{-1+\chi \quad -\chi}{\underset{/}{\overset{\backslash}{C}{=\!=}Y}} \qquad (8)$$
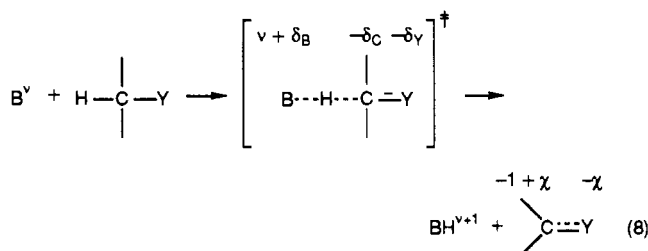
to eq 5, and setting δ_B equal to 1 for the products yields $\delta_Y = a$, i.e., a represents the charge on Y in the product carbanion and is therefore equal to χ (see eq 8). This implies that $a = \chi$ may also be equated with the C–Y π-bond order in the product ion. Scheme I shows numerical examples calculated from eqs 9 and 10 with δ_B = 0.5 for three special cases, i.e., complete delocalization of the charge in the product ion as discussed earlier (χ = 1.0), half-delocalization (χ = 0.5), and no delocalization (χ = 0).

$$\delta_Y = \chi(\delta_B)^2 \qquad (9)$$

$$\delta_C = \delta_B - \delta_Y = \delta_B - \chi(\delta_B)^2 \qquad (10)$$

As pointed out by Kresge,[22] the assumption that δ_Y is proportional to π-bond order and/or that π-bond order is proportional to δ_B may not be completely correct. For example, charge delocalization might be a stronger function of π-bond order, and the same is possible for the dependence of π-bond order on δ_B. More general expressions for δ_B and δ_C are thus given by eqs 11 and 12, respectively. As shown below, the exponent n in eqs 11 and 12 that fits best with experimental observations lies between 2 and 3.

$$\delta_Y = \chi(\delta_B)^n \qquad (11)$$

$$\delta_C = \delta_B - \chi(\delta_B)^n \qquad (12)$$

We now seek a relationship between λ_R in eq 7 and δ_Y. λ_R, we recall, is a measure of how much of the resonance stabilization of the product ion is expressed in the transition state; it is defined as $\delta \log k_1^R / \delta \log K_1^R$, which can also be written as $\delta\Delta G^{\ddagger}_R / \delta\Delta G^{\circ}_R$, with $\delta\Delta G^{\ddagger}_R$ and $\delta\Delta G^{\circ}_R$ representing the resonance stabilization of the transition state and of the product ion, respectively. If one assumes that both in the transition state and in the product ion resonance stabilization is proportional to the charge on Y (i.e., $\delta\Delta G^{\ddagger}_R \propto \delta_Y$ and

$\delta\Delta G^{\circ}_R \propto \chi$), we obtain eq 13. In combination with eq

$$\lambda_R = \delta_Y / \chi \qquad (13)$$

11 and equating δ_B with the Brønsted β_B value, λ_R is thus given by

$$\lambda_R = (\delta_B)^n = (\beta_B)^n \qquad (14)$$

and eq 7 by eq 15.

$$\delta \log k_0^R = [(\beta_B)^n - \beta_B]\delta \log K_1^R \qquad (15)$$

This is a remarkably simple relationship whose validity can be tested, for example, by solving it for $\delta \log K_1^R$ and comparing $\delta \log K_1^R$ thus obtained with an independent estimate of this quantity. This test was recently applied to seven different proton-transfer reactions and gave reasonable values for $\delta \log K_1^R$ with n between 2 and 3.[20] We illustrate the procedure with the example of the deprotonation of CH_3NO_2 by the piperidine/morpholine pair in water, for which $\log k_0$ = −0.59.[45] Using $\log k_0 \approx 9.0$ for the deprotonation of a reference carbon acid whose conjugate base is devoid of any resonance effect yields $\delta \log k_0^R \approx -0.59 - 9.0 \approx$ −9.6. With β_B = 0.59 (ref 45) and assuming n = 3, one calculates $(\beta_B)^3 - \beta_B$ = −0.39, which yields $\delta \log K_1^R \approx$ 24.6 from eq 15. Since the pK_a of nitromethane is 10.3,[45] and that of methane ≈ 56,[46] the overall acidifying effect of the nitro group amounts to ≈ 46 pK units. This means that $\delta \log K_1^R \approx$ 24.6 accounts for slightly more than half of the acidifying effect, the balance of 21.4 being due to the inductive/field effect ($\delta \log K_1^I$) of the nitro group, and hence $\delta \log K_1^R / \delta \log K_1^I \approx 1.15$. An independent estimate of $\delta \log K_1^R / \delta \log K_1^I$ may be based on the ratio of $\sigma_R^-/\sigma_I = 0.46/0.65 = 0.71$[47] or of $(\sigma_p^- - \sigma_m)/\sigma_m = 0.52/0.71 = 0.73$.[47] These ratios are somewhat smaller than the estimate derived from eq 15; this is not unexpected because the nitro group in $CH_2{=\!=}NO_2^-$ is directly attached to the reaction center, which probably enhances the resonance effect and reduces the inductive/field effect. Hence it was concluded[20] that the $\delta \log K_1^R / \delta \log K_1^I$ ratio calculated on the basis of $\delta \log K_1^R$ obtained from eq 15 with n = 3 is "reasonable".[48]

Hydrogen-Bonding Stabilization of the Transition State in Proton Transfers

Along with delayed resonance development, nonsynchronous solvation/desolvation effects can affect k_0 in a major way.[2,20,42] This includes solvation/desolvation of the base and its conjugate acid as well as of the carbon acid and the carbanion; the solvation of the carbanion is usually the most important factor, particularly when hydrogen-bonding solvation is involved, as is the case for nitronate[45] and enolate ions.[49] Just as resonance effects, solvation generally lags behind charge or proton transfer (or desolvation is ahead of these processes) at the transition state, which, according

(45) Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J. X. *J. Org. Chem.* **1988**, *53*, 3342.

(46) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 457.

(47) σ-Values taken from the following: Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975; Chapter 3.

(48) A similar calculation with n = 2 yields $\delta \log K_1^R / \delta \log K_1^I$ = 6.67,[20] an unrealistically high ratio.

(49) (a) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420. (b) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969.

to the PNS, lowers k_0. Thus the low k_0 values for the deprotonation of nitroalkanes[45] or 1,3-diketones[49] are largely a consequence of the combined PNS effects of late development of resonance and solvation. This notion is supported by the fact that k_0 for these reactions increases dramatically upon changing the solvent to Me_2SO.[24,45,49] Since this topic was extensively covered in a previous Account[2] and is also treated in detail in a recent review,[20] we shall not discuss it further. Instead we shall focus on a point which has received less attention in the past, namely, the effect of transition-state hydrogen bonding on k_0.

The hydrogen-bonding abilities of proton donor and acceptor have long been known to be an important factor in making proton transfers between *normal*[50] acids and bases very fast,[51] but the potential importance of hydrogen bonding in the deprotonation of *carbon* acids has only recently been recognized. Bednar and Jencks[52] have shown that such hydrogen bonding can lead to significant transition-state stabilization. For example, the deprotonation of HCN by $HOCH_2CH_2S^-$ in water is approximately 200-fold slower than the deprotonation by oxyanion bases of comparable basicity. This was attributed to the reduced hydrogen-bonding ability of sulfur compared to that of oxygen.

Other cases where thiolate ions are less effective proton acceptors than oxyanions of the same pK_a include the deprotonation of 4-(4-nitrophenoxy)-2-butanone (**2**)[53] and acetylacetone (acac).[54] In the former reaction, k_0 for thiolate ions is 30–50-fold lower than for oxyanions; in the latter, about 5-fold lower.

$$CH_3\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}(CH_2)_2O-\!\!\!\bigcirc\!\!\!-NO_2$$

2
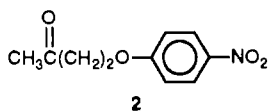
The trend toward smaller k_0^O/k_0^S ratios along the series HCN > **2** > acac suggests a decrease in the importance of hydrogen-bonding stabilization of the transition state along this series. This is consistent with the notion that hydrogen bonding should be most effective when the developing negative charge in the transition state is mainly localized on carbon, but less effective if this charge is being (partially) delocalized away from the carbon. In general the reactions that lead to the most delocalized carbanions are also the ones with the most delocalized transition states. This can be seen from eq 9 or 10: as long as $\beta_B = \delta_B$ is not vastly different from one reaction to another, δ_Y increases and δ_C decreases with increasing χ, i.e., with increasing delocalization in the carbanion.[55] Thus the trend in the k_0^O/k_0^S ratios apparently reflects the increase in the delocalization in the order $CN^- < \mathbf{2} < acac^-$.

Further support for the above inferences comes from a recent determination of k_0 for the deprotonation of phenylnitromethane by thiolate ions and aryloxide ions.[56] Since the phenylnitronate ion is significantly

more delocalized than even the acetylacetonate ion, hydrogen bonding should become essentially negligible[57] and hence the k_0^O/k_0^S ratio should be further reduced and approach unity. This expectation is fully confirmed by the experimental results. In fact, the k_0^O/k_0^S ratio of ca. 0.25 is even smaller than unity, which can be attributed to the stronger solvation of the aryloxide ions compared to thiolate ions. Since, as mentioned above, desolvation of the base is ahead of proton transfer, k_0 is reduced. The stronger solvation of aryloxide ions compared to thiolate ions[58] thus leads to a larger reduction of k_0. In the reactions of HCN, **2**, and acac, this desolvation effect is overshadowed by the stronger hydrogen-bonding stabilization of the transition state in the reactions with the oxyanions.

Polarizability Effects on Intrinsic Rate Constants

A potential effect on intrinsic rate constants which in previous discussions of the PNS has been ignored is the stabilization of the carbanionic charge due to the polarizability of an adjacent sulfur or phosphorus atom.[59,60] Reaction 16 with $X = Ph_3P^+$ or Me_2S^+ is a case in point. In both of these reactions the ylide is
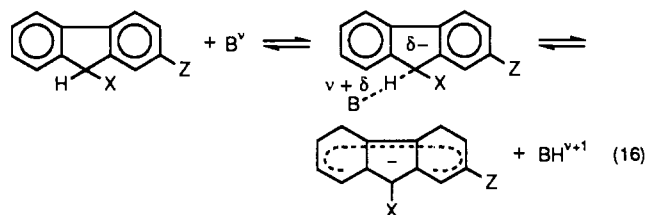
believed to derive a significant fraction of its stability from the polarizability (P) effect of the Ph_3P^+ and Me_2S^+ groups, respectively.[29,61] Applying the formalism of eq 6 to the P effect of X, we may write eq 17 for the change in log k_0.

$$\delta \log k_0^P(X) = (\lambda_P^X - \beta_B)\delta \log K_1^P(X) \qquad (17)$$

$\delta \log K_1^P(X)$ is the increase in stabilization of the product ion attributed to the P effect, and λ_P^X is defined by eq 18, with $\delta \log k_1^P(X)$ being the increase in the rate constant due to the P effect. λ_P^X may be

$$\lambda_P^X = \delta \log k_1^P(X)/\delta \log K_1^P(X) \qquad (18)$$

estimated on the basis of the model used to calculate λ_R (eq 14) and by assuming that the P effect is limited to the stabilization of the negative charge on the carbon *directly adjacent* to the substituent. This is a reasonable assumption since P effects fall off with the fourth power of distance.[62] P effects being proportional to the *square* of the charge,[62] the transition-state stabilization must be proportional to $(\delta_C)^2$ (see eq 19) and product

(50) Normal acids are OH, NH, and SH acids.[51a]

(51) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. (b) Ahrens, M.-L.; Maass, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 818.

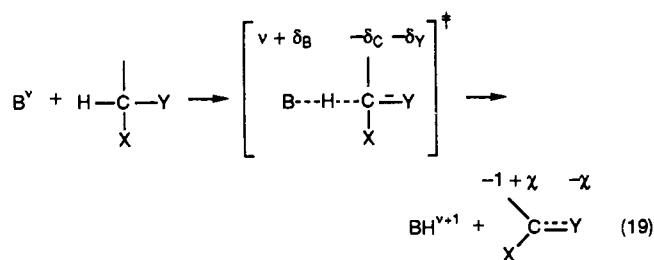(52) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 7117.

(53) Pohl, E. R.; Hupe, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8130.

(54) Ahrens, M.-L.; Eigen, M.; Kruse, W.; Maass, G. *Ber. Bunsen-Ges. Phys. Chem.* **1970**, *74*, 380.

(55) β_B for the deprotonation of **2** and acac are ca. 0.59, and that of HCN probably close to this value.

(56) Bernasconi, C. F.; Wiersema, D., to be published.

(57) β_B for the deprotonation of phenylnitromethane is 0.48 for $B^\nu = RS^-$, 0.58 for $B^\nu = ArO^-$.[56]

(58) (a) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1. (b) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 3224.

(59) (a) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. (b) Spinner, E. *J. Org. Chem.* **1975**, *40*, 3580.

(60) (a) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467. (b) Wolfe, S.; LaJohn, L. A.; Bernardi, F.; Mangini, A.; Tonachini, G. *Tetrahedron Lett.* **1983**, *24*, 3789. (c) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. (d) Epiotis, N. D.; Yates, R. L.; Bernardi, F.; Wolfe, S. *J. Am. Chem. Soc.* **1976**, *98*, 5435. (e) Streitwieser, A., Jr.; Williams, J. E. *J. Am. Chem. Soc.* **1975**, *97*, 191.

(61) Bernasconi, C. F.; Fairchild, D. *J. Am. Chem. Soc.*, in press.

(62) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.

stabilization must be proportional to $(-1 + \chi)^2$.

$$B^{\nu} + H-\underset{\underset{X}{|}}{\overset{\overset{|}{}}{C}}-Y \longrightarrow \left[\begin{array}{c} \nu + \delta_B \quad -\delta_C \quad -\delta_Y \\ B\text{---}H\text{---}\underset{\underset{X}{|}}{\overset{\overset{|}{}}{C}}\text{=:}Y \end{array} \right]^{\ddagger} \longrightarrow$$

$$BH^{\nu+1} + \underset{X}{\overset{-1+\chi \quad -\chi}{>}}C\text{=:}Y \qquad (19)$$

Hence $\lambda_P{}^X$ is given by

$$\lambda_P{}^X = \frac{(\delta_C)^2}{(-1 + \chi)^2} \qquad (20)$$

Substituting $\delta_B - \chi(\delta_B)^n$ (from eq 12) for δ_C and again equating δ_B with β_B leads to eq 21.

$$\lambda_P{}^X = \frac{[\beta_B - \chi(\beta_B)^n]^2}{[-1 + \chi]^2} \qquad (21)$$

In contrast to λ_R, which depends only on β_B (eq 14) and hence can be calculated, $\lambda_P{}^X$ is a function of β_B as well as of χ. This latter quantity is generally not known, and therefore $\lambda_P{}^X$ cannot be calculated. It is nevertheless instructive to consider some special cases which provide insights into whether $\lambda_P{}^X$ is greater or smaller than β_B and thus allow one to predict whether P effects enhance or lower k_0.

Case I: $\chi = 0$. This limiting case refers to a situation where Y has no π-acceptor properties, i.e., there is no delocalization of charge into Y. Equation 21 simplifies to $\lambda_P{}^X = (\beta_B)^2$, and eq 17 becomes

$$\delta \log k_0{}^P(X) = [(\beta_B)^2 - \beta_B]\delta \log K_1{}^P(X) \qquad (22)$$

Since $(\beta_B)^2 - \beta_B < 0$ and $\delta \log K_1{}^P(X) > 0$, we have $\delta \log k_0{}^P(X) < 0$, i.e, the P effect lowers k_0.

Case II: $\chi = 1.0$. This represents the other extreme from case I where the negative charge is completely delocalized in the product. Equations 17 and 22 are not applicable since $\delta \log K_1{}^P(X) = 0$ and $\lambda_P{}^X = \infty$, but qualitatively it is clear that since only the transition state has negative charge on carbon, only the transition state benefits from the P effect, i.e., k_0 is enhanced.

Cases III–V. On the basis of cases I and II one expects a gradual change from a k_0-lowering effect at low χ to a k_0-enhancing effect as χ increases. Calculated values of $\lambda_P{}^X - \beta_B$ as a function of β_B shown in Figure 2 for $\chi = 0.3$ (case III), $\chi = 0.5$ (case IV), and $\chi = 0.7$ (case V) confirm this expectation but also show a strong dependence on β_B and n. Figure 2 suggests that, except for Y groups that are very weak π-acceptors ($\chi \leq 0.3$), $\lambda_P{}^X - \beta_B$ is positive for any $\beta_B > 0.4$ and hence $\delta \log k_0{}^P(X) > 0$; typically, experimental β_B values for proton transfers from carbon acids are >0.5.[25] For example, for reaction 16, $\beta_B = 0.61$ with X = Ph_3P^+ and B^{ν} = primary aliphatic amines.[61] Assuming that $\chi \geq 0.5$, eq 21 yields $\lambda_P{}^X \geq 0.72$ with $n = 2$ and $\lambda_P{}^X \geq 0.99$ with $n = 3$, and thus $\lambda_P{}^X - \beta_B \geq 0.11$ and ≥ 0.38, respectively.

Two points regarding eqs 17 and 21 need to be stressed. (1) The strong dependence of $\lambda_P{}^X - \beta_B$ on χ (Figure 2) does not imply a similarly strong dependence of $\delta \log k_0{}^P(X)$ because $\delta \log K_1{}^P(X)$ also depends on χ, and in a way which largely compensates for the effect on $\lambda_P{}^X - \beta_B$. In other words, a high χ which leads to a large $\lambda_P{}^X - \beta_B$ also means a small charge on the carbon
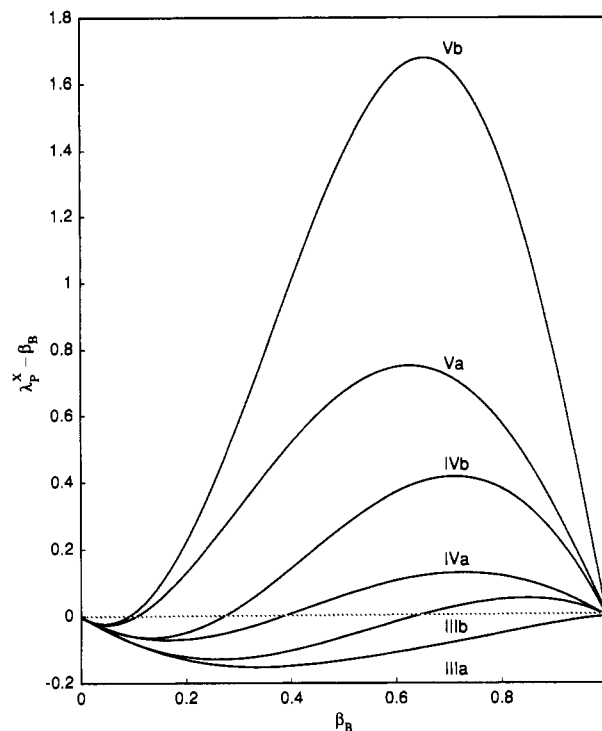

Figure 2. Dependence of $\lambda_P{}^X - \beta_B$, with $\lambda_P{}^X$ calculated from eq 21, on χ and β_B. Numbers refer to cases III, IV, and V in the text; a refers to $n = 2$, b to $n = 3$.

in the product ion, which renders $\delta \log K_1{}^P(X)$ small. An extreme manifestation of this compensation effect is seen in case II, where $\chi = 1.0$ leads to $\lambda_P{}^X - \beta_B = \infty$ and $\delta \log K_1{}^P(X) = 0$.

(2) As elaborated upon elsewhere,[61] when the polarizable group X is also a π-acceptor, eq 21 needs to be modified and becomes

$$\lambda_P{}^X = \frac{[\beta_B - (\chi_X + \chi_Y)(\beta_B)^n]^2}{(-1 + \chi_X + \chi_Y)^2} \qquad (23)$$

where χ_X and χ_Y are the respective charges on X and Y in the product ion. Equation 23 is probably more appropriate than eq 21 for reaction 16 with X = Ph_3P^+.[61] Note, however, that eqs 21 and 23 give the same result as long as $\chi_X + \chi_Y$ in eq 23 is equal to χ in eq 21.

Summary and Conclusions

The PNS provides a simple and intuitive interpretation of a variety of structure–reactivity relationships. It is based on the realization that factors which stabilize (destabilize) reactants or products frequently do not develop synchronously with bond changes along a reaction pathway. As a consequence, transition-state stabilization (destabilization) is usually not commensurate with the progress of bond changes; in most cases this leads to an increase in the intrinsic barrier or a decrease in the intrinsic rate constant. The essence of the PNS is described by eq 6. Among the stabilizing or destabilizing factors, the most thoroughly investigated one is resonance, but other factors such as intramolecular hydrogen bonding, certain electrostatic effects, soft acid–soft base interactions, and very prominently, solvation effects have also been shown to follow the rules of the PNS.[2,20]

For the most part, the PNS and eq 6 have been used as a *qualitative* tool to understand trends in reactivity

data or some unusual deviations from expected behavior. This is particularly true for resonance effects since heretofore no method was available to evaluate $\lambda_R - \beta_B$ (eq 7) apart from predicting whether it is positive or negative. As shown in this Account and further elaborated upon in a recent review,[20] eq 14 now provides a means to estimate λ_R numerically that elevates eq 7 (which becomes eq 15) to at least a semiquantitative tool in dealing with the effect of delayed resonance development in proton transfers. We have further demonstrated that the model which forms the basis of eq 14 also allows the development of eq 21, which, through eq 17, provides a qualitative assessment of how k_0 is affected by the polarizability of an adjacent sulfur or phosphorus substituent.

Although not discussed in this Account due to space limitations, the possibility of estimating λ_R also facilitates the semiquantitative treatment of nonsynchronous solvation/desolvation effects of carbanions, another important factor that affects the magnitude of intrinsic rate constants and their variation with changing solvent.[63] Since the lag in the solvation of a developing carbanion is strongly affected by the lag in the charge delocalization, the capability of estimating λ_R helps in evaluating the solvational lag. A recent application of this type of treatment has been published elsewhere.[64]

(63) For a detailed discussion, see ref 20.
(64) Gandler, J. R.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1992,** *114,* 631.

Asymmetric Reduction with Chiral Organoboranes Based on α-Pinene[†]

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Current trends in organic synthesis show that asymmetric synthesis has become a primary focus of activity for many of the leading researchers in both the academic and industrial worlds.[1] The tragedy of the thalidomide babies emphasized the importance of achieving the synthesis of optically pure drugs.[2] Optical resolution as a method to prepare optically pure compounds is often uneconomical and impractical. Frequently the most desirable method for synthesizing optically pure materials is asymmetric synthesis.[3] A decade ago we initiated a program on asymmetric synthesis via chiral organoboranes derived from terpenes.[4] The program included asymmetric reduction, asymmetric synthesis via hydroboration, asymmetric allyl- and crotylboration, asymmetric enolboration, asymmetric ring opening of epoxides, and asymmetric homologation. α-Pinene and pinene-derived chiral auxiliaries proved to be exceptionally successful for all of our programs in asymmetric synthesis. We have reviewed our success in asymmetric hydroboration in an earlier Account.[5] In this Account we are discussing our progress in the field of asymmetric reduction, especially those with chiral organoboranes based on α-pinene and its simple derivatives.

Asymmetric reduction of the ubiquitous carbonyl group occupies a position of prime importance in asymmetric synthesis.[6] The optically active alcohol products, if not the desired end product, serve as starting materials for many syntheses. Selection of an appropriate chiral reducing agent for a particular type of ketone in hand often posed major difficulty a decade ago. However, brisk research in this area has largely solved these problems, leading to various reagents that can mimic enzymes in their selectivity.

Recently we compiled the data available in the literature for all the asymmetric reducing agents reported

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[†]Based on a lecture at the Retirement Symposium for Professor Joseph F. Bunnett. This lecture, entitled "Discovery of New Continents of Chemistry Through Research", dealt with a number of approaches based on chiral organoboranes for asymmetric synthesis. Since developments in the asymmetric hydroboration area were the subject of a recent Account, it appeared desirable to emphasize an area that has not been reviewed previously. Therefore this Account deals solely with asymmetric reduction.

(1) Crosby, J. *Tetrahedron* **1991,** *47,* 4789.
(2) Thalidomide is a tragic example of one optical isomer being a safe drug, whereas the other is a potent mutagen. Teratogenic activity is ascribed exclusively to the *S* isomer. Blaschke, G.; Kraft, H. P.; Fickentscher, K.; Koehler, F. *Arzneim.-Forsch.* **1979,** *29,* 1640.
(3) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic: New York, 1983; Vols. 1–5.
(4) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1991,** *63,* 307.
(5) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988,** *21,* 287.
(6) (a) Reference 3, Vol. 2, Chapters 2–5. (b) Midland, M. M. *Chem. Rev.* **1989,** *89,* 1553.