Formation and Stability of Carbocations and Carbanions in Water and Intrinsic Barriers to Their Reactions

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ABSTRACT

Lifetimes in water as short as 10^{-11} s have been determined for carbocations and carbanions by referencing the rate of their reaction with solvent species to that for the appropriate "clock" reaction, and equilibrium constants have been determined as the ratio of rate constants for their formation and breakdown. Rate—equilibrium correlations for these organic ions are often poor and sometimes even defy the simple generalization that *reactivity increases with decreasing stability.* This seemingly confusing body of data can be understood through consideration of the both the Marcus intrinsic barrier and the thermodynamic driving force to reaction of these organic ions.

Introduction

The generation of most localized and many delocalized carbanions and carbocations in water is problematic, because the chemical barrier to their Brønsted base or Lewis acid reactions with solvent is often smaller than that for a bond vibration.[1] An important challenge to laboratory chemists and living systems is the development of methodology for cleavage and synthesis of carbon—carbon bonds through carbanion or carbocation intermediates. The formation of these species is often facilitated by delocalization of charge away from carbon and onto distant electronegative atoms. However, these ions are referred to as carbocations and carbanions even when the bulk of the charge lies distant from the reacting carbon, because the preponderance of their chemical reactions occur at carbon. Such resonance-stabilized carbocations and carbanions are ubiquitous intermediates of metabolic and synthetic organic reactions, and the study of their

chemical reactivity is of interest to both organic chemists and biochemists.

**Carbocation**   **Carbanion**
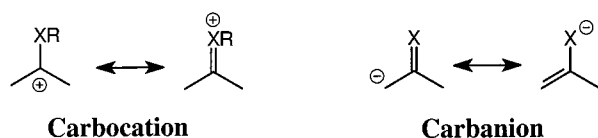
Only a few laboratories are investigating the reactions of carbocations and carbanions in aqueous solution. The restricted interest in these important reactions has provided motivation for the following work described in this Account. (1) Development of experimental methods to obtain reliable estimates of lifetimes, down to the picosecond regime, of carbocations and carbanions in water, which are intermediates of chemical and biochemical reactions. (2) Characterization of the dynamics of carbocation—anion ion pair intermediates of solvolysis reactions. (3) Determination of equilibrium constants for formation of carbocations and carbanions. (4) Rationalization of the changes in these rate and equilibrium constants that occur with variations in substrate structure.

Reaction "Clocks"

Many sophisticated studies of reactive intermediates have focused on determination of absolute rate constants by directly monitoring the disappearance of the intermediate generated by laser flash photolysis.[2] We have used simpler, but effective, indirect methods which reference the unknown rate constant for reaction of the intermediate with solvent water to that for a second reaction which serves as a "clock". The rate constants for these "clock" reactions are known with good precision, because they are limited by the rate constant for a physical transport step which is largely independent of the structure of the intermediate.

Scheme 1
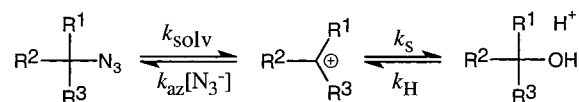
Clocks for Carbocations. There are sharp decreases in the rate constant ratio k_{az}/k_s (M^{-1}) for partitioning of 1-arylethyl and 1-aryl-2,2,2-trifluoroethyl carbocations between nucleophilic addition of azide ion, k_{az} (M^{-1} s^{-1}, Scheme 1), and solvent, k_s (s^{-1}), when the carbocation is destabilized by the addition of electron-withdrawing aromatic ring substituents.[3,4] This is because k_{az} is the invariant rate constant for a diffusion-limited reaction, but k_s is limited by the chemical barrier to solvent addition and increases with decreasing carbocation stability. Values of k_s for reaction of a variety of carbocations with aqueous solvents have been obtained from k_{az}/k_s (M^{-1}) determined by product analysis (eq 1), using $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} (Scheme 1).[3,4] In cases where a comparison is possible, provided $k_{az}/k_s \leq \sim 10^4$ M^{-1}, the values of k_s from this azide

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ion clock are in excellent agreement ($\pm20\%$) with those determined directly by generation of the same carbocation by laser flash photolysis.[2a,5]

$$k_{az}/k_s = \frac{[RN_3]}{[ROH][N_3^-]} \qquad (1)$$

$$k_{az} = 5 \times 10^9 \ M^{-1} \ s^{-1} \qquad (2)$$

$$pK_R = -\log K_R = \log(k_H/k_s) \qquad (3)$$

Absolute rate constants for carbocation–nucleophile addition have been used to calculate equilibrium constants for carbocation formation. (1) Values of k_s (s^{-1}) have been combined with rate constants k_H ($M^{-1} \ s^{-1}$) for acid-catalyzed cleavage of the corresponding alcohols to give values of pK_R for α-substituted benzyl, benzhydryl, and 9-fluorenyl carbocations (eq 3, Scheme 1).[6] (2) Rate constants k_{solv} (s^{-1}) for the stepwise solvolysis of *gem*-diazides, α-alkoxy azides, and α-substituted benzylic azides through carbocation intermediates have been determined and combined with $k_{az} = 5 \times 10^9 \ M^{-1} \ s^{-1}$ for the diffusion-controlled capture of these carbocations by azide ion to give equilibrium constants $K_{az} = k_{solv}/k_{az}$ (M) for formation of the carbocation from the neutral azide ion adduct (Scheme 1).[7]

**Clocks for Ion Pairs.** The estimated value of $k_{-d} = 1.6 \times 10^{10} \ s^{-1}$ for diffusional separation of carbocation–anion ion pairs to give the free ions in 50:50 (v/v) water/trifluoroethanol[8] serves as a useful clock for other reactions of ion pairs. We have used this clock to determine a number of rate constants that describe the dynamics of these short-lived intermediates.

(1) Reaction of 1-(4-thiomethylphenyl)ethyl thionobenzoate (**1**, X = S, Y = O, Z = MeS, Ar = C$_6$H$_5$) in 50:50 (v/v) water/trifluoroethanol gives 84% of the rearranged thiolbenzoate ester **2** and 14% of the solvent adducts **3** (Scheme 2).[9] It was shown that $k_c > k_{-r}$ and $k_{-d} \gg k_s'$, so that the product ratio [**2**]/[**3**] = 84/16 corresponds to $k_r/k_{-d} = 6$ for partitioning of the ion pair intermediate between reorganization that exchanges the positions of O and S at the leaving group anion and diffusional separation to give the free ions.[9] This was combined with

$k_{-d} = 1.6 \times 10^{10} \ s^{-1}$ to give $k_r = 10^{11} \ s^{-1}$ as the absolute rate constant for *reorganization* of the ion pair intermediate within an aqueous solvation shell (Scheme 2).[9]

(2) The rate constant ratios for partitioning of the ion pair intermediate generated by cleavage of 4-MeC$_6$H$_4$-^{13}CH(Me)^{18}OC(^{16}O)C$_6$F$_5$ (**1**, X = ^{16}O, Y = ^{18}O, Z = Me, Ar = C$_6$F$_5$) between diffusional separation (k_{-d}) and direct nucleophilic addition of solvent (k_s') to give **3**, and internal return with ^{18}O scrambling (k_c) to give the isomerization product **2**, have been determined and combined with the known values of k_{-d} and k_s' to give $k_c = 7 \times 10^9 \ s^{-1}$ ($k_c < k_r$, Scheme 2) for unimolecular collapse of the ion pair intermediate (Scheme 2).[10] This relatively large value of k_c shows that $k_{Nu} = 5 \times 10^8 \ M^{-1} \ s^{-1}$ for bimolecular nucleophilic addition of carboxylate anions to the free carbocation 4-MeC$_6$H$_4$CH(Me)$^+$ is limited by the partial desolvation of the carboxylate anion that is required for formation of an intimate ion pair.[8]

Clocks for Carbanions. There are several cases for which proton transfer to a carbanion is limited by the physical transport of the reacting acid into a "reactive" position with a known rate constant. These physical processes serve as clocks and have been used to determine the lifetimes of simple carbanions and to obtain reliable carbon acid pK_a's for their formation in water.
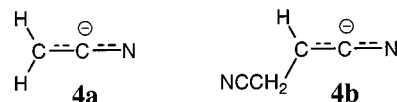
The limiting rate constant (k_{HOH})$_{lim}$ (s^{-1}) for protonation of carbanions by solvent water is that for rotation of a molecule of water into a position where proton transfer to the carbanion can occur. It is given by the rate constant for the dielectric relaxation (reorganization) of solvent water, (k_{HOH})$_{lim} = k_{reorg} \approx 10^{11} \ s^{-1}$.[11] Therefore, solvent reorganization serves as a clock for the reactions of carbanions which are formed in water but which exist in this solvent only for the time required for solvent reorganization. The primary deuterium isotope effect on the hydroxide-ion-catalyzed exchange of hydrons from water into acetonitrile and succinonitrile that proceeds through the α-cyano carbanions **4a** and **4b**, respectively, is not much larger than unity.[11] This provides good evidence that the isotope-dependent *chemical* barrier to protonation of these carbanions by solvent water (k_{HOL}) is smaller than the isotope-independent barrier to solvent reorganization (k_{reorg}), so that solvent reorganization is rate-limiting for k_{HOL} (Scheme 3).[11] A carbon acid pK_a of 28.9 for acetonitrile in water was calculated from the experimental rate constants k_{HO} ($M^{-1} \ s^{-1}$) for deprotonation of the carbon acid by hydroxide ion and $k_{HOH} = (k_{HOH})_{lim} = 10^{11} \ s^{-1}$ for carbanion protonation (eq 4 derived for Scheme 3).[11]

Scheme 2
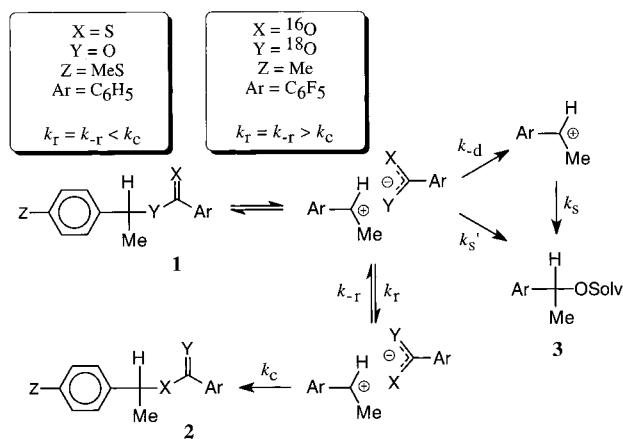
**Scheme 3**
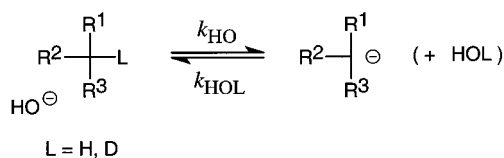
$$pK_a = pK_w + \log\left(\frac{k_{HOH}}{k_{HO}}\right) \qquad (4)$$

Figure 1 shows the linear correlations of log k_{HOH} (s^{-1}) for protonation and log k_{HO} (M^{-1} s^{-1}) for deprotonation, with slopes of +0.60 and −0.40, respectively, with the pK_a's of *neutral* α-carbonyl carbon acids in water (Scheme 3).[12−14] The values of k_{HOH} increase with decreasing carbanion stability to $k_{HOH} \approx 10^9$ s^{-1} for protonation of the enolate of acetamide (**5**),[14] but must level off at $k_{HOH} = (k_{HOH})_{lim} \approx 10^{11}$ s^{-1} when proton transfer is limited by solvent reorganization. A short extrapolation of the linear
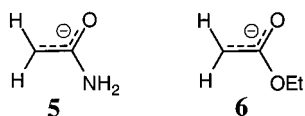
correlation for log k_{HOH} shows that this leveling will occur for an enolate that is formed by deprotonation of a carbon acid of p$K_a \approx 30$. We have determined $k_{DO} = 8.4 \times 10^{-9}$ M^{-1} s^{-1} for deuterioxide-ion-catalyzed exchange for deuterium from D$_2$O of the α-protons of acetate ion.[14] If isotope exchange proceeds through the enolate dianion, then we estimate $k_{HO} = 3.5 \times 10^{-9}$ M^{-1} s^{-1} for deprotonation of acetate ion by hydroxide ion (Scheme 3).[14] However, this value of k_{HO} cannot lie on the line obtained by linear extrapolation of the correlation for log k_{HO} (Figure 1, ○), because this would require p$K_a = 38.0$ for acetate ion and $k_{HOH} = 3 \times 10^{15}$ s^{-1} (Figure 1, □) for protonation of the enolate dianion by solvent water! The *extrapolated* lifetime of the putative enolate dianion intermediate is even shorter than the time for a bond vibration ($\approx 10^{-13}$ s).[1] Therefore, if the enolate dianion forms as an intermediate of the deuterium exchange reaction of acetate ion, then $k_{HOH} = (k_{HOH})_{lim} = 10^{11}$ s^{-1} for its protonation by solvent water, which gives p$K_a = 33.5$ for acetate ion (eq 4).[14]

The Brønsted coefficient $\beta = 1.09$ was determined for exchange for deuterium from D$_2$O of the α-protons of
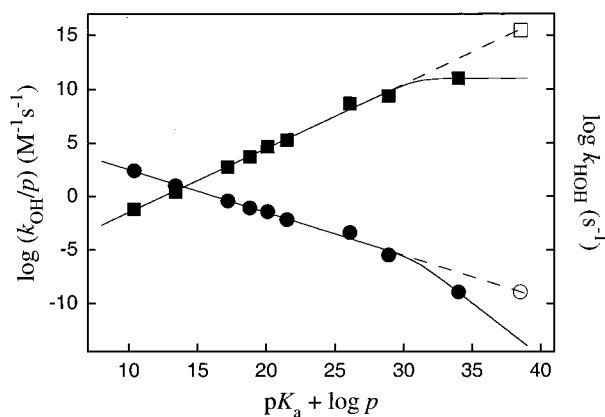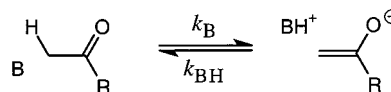
FIGURE 1. Rate−equilibrium correlations for deprotonation of neutral α-carbonyl carbon acids by hydroxide ion, k_{HO} (●, M^{-1} s^{-1}), and the reverse protonation of the enolates by solvent water, k_{HOH} (■, s^{-1}), with the pK_a of the carbon acid. (○, □) Extrapolated data for proton-transfer reactions of acetate ion and its enolate dianion (see text).

Scheme 4

ethyl acetate catalyzed by 3-substituted quinuclidines, which proceeds through the ester enolate **6**.[13] This shows that there is complete proton transfer from the carbon acid to the amine base in the transition state for deuterium exchange, and it requires that the rate-determining step for formation of the free enolate **6** (k_B, Scheme 4) be the diffusional separation of a reversibly formed enolate−ammonium ion complex. Therefore, the reverse protonation of **6** by ammonium cations is limited by the essentially diffusion-controlled encounter of these ions, with $k_{BH} \approx 5 \times 10^9$ M^{-1} s^{-1}.[13] The enolate of acetamide, **5**, is even less stable than **6** and also undergoes diffusion-limited protonation by buffer acids.[14] The second-order rate constants k_B for deprotonation of ethyl acetate and acetamide by quinuclidine (p$K_{BH} = 11.5$) were combined with $k_{BH} = k_d \approx 5 \times 10^9$ M^{-1} s^{-1} for diffusion-limited protonation of the enolate (eq 5 derived for Scheme 4) to give pK_a's of 25.6 and 28.4, respectively, for these carbon acids in water.[13,14]

$$pK_a = pK_{BH} + \log\left(\frac{k_{BH}}{k_B}\right) \qquad (5)$$

The limiting rate constant for protonation of Brønsted bases by hydronium ion is $k_H \approx 10^{10}$ M^{-1} s^{-1},[15] which is close to $k_H = 7 \times 10^9$ M^{-1} s^{-1}, reported for protonation of the enolate of acetone.[16] There is evidence that, in water, the zwitterionic enolate of betaine methyl ester is only slightly more stable than the enolate of acetone, so that $k_H = 5 \times 10^9$ M^{-1} s^{-1} was estimated for its protonation by hydronium ion (Scheme 5).[12] This was combined with the experimental rate constant $k_w = 5 \times 10^{-9}$ s^{-1} for deprotonation of betaine methyl ester by solvent water to give a carbon acid pK_a of 18.0 for betaine methyl ester (p$K_a = \log\{k_H/k_w\}$, Scheme 5).[12]

Scheme 5
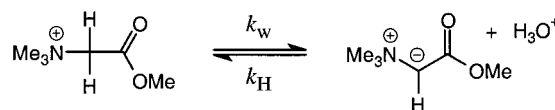
Reliable estimates of the carbon acid pK_a's in water for ethyl thiolacetate (p$K_a = 21.0$),[17] *N*-protonated glycine methyl ester ($^+$H$_3$NCH$_2$CO$_2$Me, p$K_a = 21.0$),[12,18] glycine zwitterion ($^+$H$_3$NCH$_2$CO$_2^-$, p$K_a = 28.9$),[12] and betaine ($^+$Me$_3$NCH$_2$CO$_2^-$, p$K_a = 27.3$)[12] were obtained by comparison of experimentally determined rate constants for deprotonation of these carbon acids with those for deprotonation of structurally related carbon acids of known pK_a. In general, reliable pK_a's of simple *neutral* α-carbonyl carbon acids may be obtained from k_{HO} (M^{-1} s^{-1}) for deprotonation of the carbon acid by interpolation of the excellent linear correlation between log k_{HO} and pK_a shown in Figure 1.[13,14]
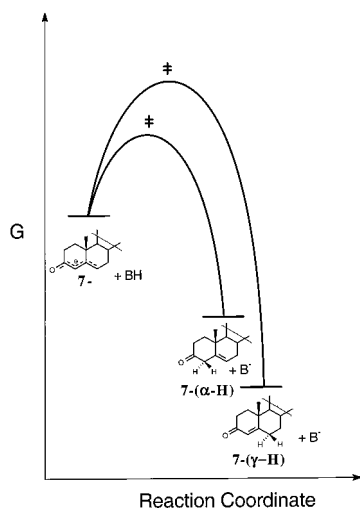
FIGURE 2. Free energy reaction coordinate profiles for protonation of the steroid enolate 7^- emphasizing the difference in the products formed under conditions of kinetic and thermodynamic control.

Kinetic and Thermodynamic Substituent Effects

The products of competing reactions of organic ions formed under conditions of *kinetic* control are sometimes different from those formed under conditions of *thermodynamic* control. Figure 2 illustrates this for protonation of the delocalized steroid enolate ion 7^-, which gives mainly 7-(α-H) under conditions of kinetic control and mainly 7-(γ-H) under conditions of thermodynamic control.[19] This difference in the products of reactions under kinetic and thermodynamic control shows that protonation of 7^- at C-α is intrinsically easier than its protonation at C-γ and, therefore, occurs with a smaller Marcus intrinsic barrier for thermoneutral proton transfer (Λ, Scheme 6).[20] The reaction is under *kinetic* control, because the effect of the smaller intrinsic barrier Λ for protonation of 7^- at C-α overwhelms the greater thermodynamic driving force $\Delta G°$ for its protonation at C-γ. This notion that a substituent effect on Λ may be different from, and dominate over, the substituent effect on the thermodynamic driving force was suggested over 30 years ago by R. A. Marcus in his explanation for the unusually large Brønsted coefficient β for deprotonation of aryl substituted nitroalkanes by carboxylate anions.[21] It is a recurring theme from our own work, and that of others, that is deserving of wider recognition within the community of organic chemists.

Scheme 6
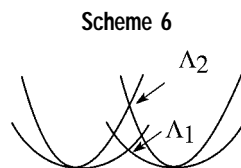
Origin of and Changes in Intrinsic Barriers

Consider the hypothetical addition of a nucleophile to the methyl carbocation, a reaction which is strongly favored thermodynamically and has essentially no activation barrier (Figure 3A). The stabilization of CH_3^+ by resonance
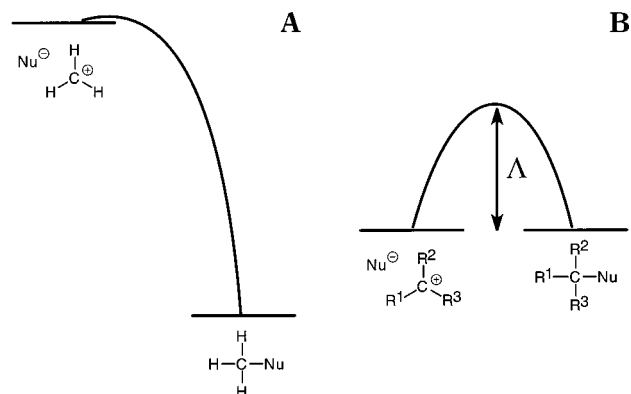

FIGURE 3. Free energy reaction coordinate profiles for addition of nucleophiles to carbocations. (A) Essentially barrierless addition of nucleophiles to the methyl carbocation. (B) Thermoneutral addition of nucleophiles to a resonance-stabilized carbocation with an intrinsic barrier Λ.

electron-donating substituents will result in a change to a thermoneutral reaction when the stabilization resulting from formation of the new bond to the nucleophile is exactly balanced by the destabilization resulting from the loss of resonance electron donation to the cationic center (Figure 3B). An intrinsic barrier Λ for this thermoneutral nucleophile addition to a resonance-stabilized carbocation will be observed when the energetic cost of the loss of the stabilizing resonance interactions at the transition state exceeds the compensating transition state stabilization resulting from partial carbon–nucleophile bond formation,[22] so that there is an *imbalance* in the changes in these opposing interactions.

The work of C. F. Bernasconi has provided many examples of correlations between the increase in the intrinsic barrier to protonation of carbanions with increasing stabilization of the carbanion by resonance delocalization of negative charge and the requirement for a relatively large or "early" loss of these stabilizing resonance interactions in the transition state.[23] This rapid falloff in resonance stabilization with formation of a partial covalent bond to sp^2-hybridized carbon is proposed to result from (1) a decrease in the stabilizing resonance interaction with increasing bond formation, which is expected to be roughly proportional to the fractional formation of the new covalent bond, and (2) an *additional* falloff in the *remaining* resonance interaction, which is due to the change from sp^2 hybridization of the planar central carbon, for which there is optimal delocalization of charge, toward sp^3 hybridization at the transition state.[3,24,25]

The defining property of most carbocations and carbanions with significant lifetimes in water is the large stabilization of these ions by delocalization of charge away from the central carbon and onto distant atoms. However, a number of other interactions are known to affect the thermodynamic driving force associated with formation of chemical bonds to carbocations and carbanions, including geminal interactions between electron-withdrawing substituents at sp^3-hybridized carbon,[26] steric interactions,[27] and differential solvation of reactants and

products.[23] Any such interaction which stabilizes product relative to reactant will result in an increase in the intrinsic barrier Λ when the fractional expression of the interaction at the transition state is small and a decrease in Λ when its expression is large, relative to bond making/breaking at the reacting central carbon.[23]

Resonance Effects

Much of the difficulty experienced in interpreting structure–reactivity effects on the reaction of resonance-stabilized carbocations[28] and carbanions arises from the failure to appreciate fully the complexity of resonance effects on these reactions. The results of our work suggest two generalizations about these resonance substituent effects. (1) The stabilization of carbocations or carbanions by resonance delocalization of positive or negative charge is not constant but, rather, is attenuated by polar substituents attached to the charged center. For example, the addition of polar electron-withdrawing α-substituents to the 4-methoxybenzyl carbocation (Scheme 7A) enhances resonance electron donation from the aromatic ring. This increases the separation between the interacting positive charge and dipole(s) and therefore reduces their destabilizing interaction. By contrast, the addition of polar electron-withdrawing substituents to the α-carbon of an enolate reduces the resonance delocalization of negative charge onto the carbonyl group. This results in an increase in the localization of negative charge at the α-carbon, thereby increasing its stabilizing interaction with the polar substituent (Scheme 7B). (2) The fractional loss of resonance stabilization from electron-donating α-substituents in the transition state for the reactions of carbocations may not always be constant but may vary with the nature of the electron-donating substituent. These two generalizations are useful in explaining several of the following results.

Scheme 7

R = CF$_3$, CHF$_2$, CH$_2$F, CO$_2$Me, CONMe$_2$

R = NH$_3^+$, NMe$_3^+$
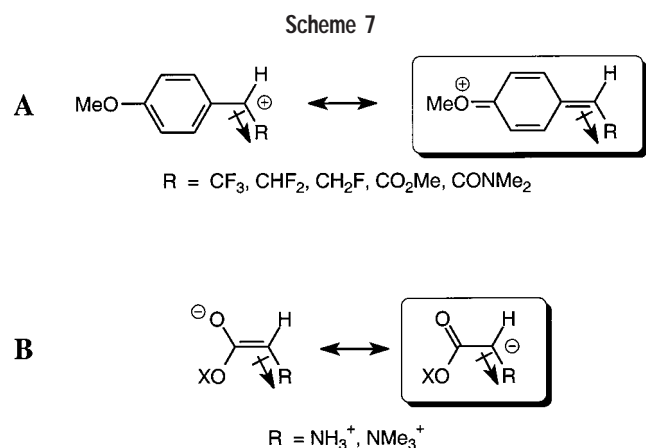
Carbocations. The rate constants k_s for addition of a largely aqueous solvent to α-substituted 4-methoxybenzyl carbocations remain nearly constant as the thermodynamic driving force for nucleophile addition is varied by 23 kcal/mol (!) by the addition of polar electron-withdrawing α-substituents (Scheme 7A).[4,7,29–31] We have proposed that these nearly invariant rate constants result

from attenuation of destabilizing polar interactions at the cationic center by the *enhancement* of resonance delocalization of the positive charge onto the 4-methoxyphenyl ring (Scheme 7A).[32] This results in an increase in the intrinsic barrier Λ for nucleophile addition and a decrease in k_s which opposes the increase in k_s that is due to the polar substituent effect on the thermodynamic driving force.[4,7,28]

An α-OR carbocation is generally less stable thermodynamically than the corresponding α-SR carbocation, but it is both formed more rapidly in solvolysis reactions and reacts more rapidly with nucleophilic solvent.[33] This shows that there is a smaller intrinsic barrier to the formation and reaction of α-OR compared with α-SR stabilized carbocations. We have proposed that this is the result of greater stabilization of the partially sp^3-hybridized cationic center in the transition state for solvent addition by electron donation from an α-OR substituent (**8**, X = O) than from an α-SR substituent (**8**, X = S)[33] and have provided solid theoretical justification for this proposal.[28]

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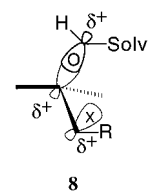
A comparison of the effect of α-oxygen, α-azido, and α-(4-methoxyphenyl) substituents on the equilibrium constant $K_{az} = k_{solv}/k_{az}$ for formation of carbocations from the neutral azide ion adduct (Scheme 1) and on k_s for nucleophilic addition of solvent water shows that the α-oxygen substituent provides the largest *thermodynamic* stabilization of a simple primary carbocation, but that it also results in the smallest *kinetic* barrier associated with loss of the stabilizing resonance interactions in the transition state for nucleophile addition (Table 1).[34] In other words, nucleophilic addition to α-oxygen carbocations is *easier* and proceeds over a smaller intrinsic barrier than addition to α-azido and α-(4-methoxyphenyl) carbocations. The order of reactivity of these carbocations (Table 1) shows that resonance electron donation to a *partly filled* π-orbital at the cationic center in the transition state for nucleophile addition (see **8**) is maximal for direct electron donation from an α-ethoxy group and decreases as the number of atoms through which the effect is expressed is increased on moving to the α-azido and α-(4-methoxyphenyl) groups.[34]

The geminal interaction between first-row electronegative atoms at sp^3-hybridized carbon (**9**) is stabilizing by up to 17 kcal/mol.[35] We have shown that substrates with a strong stabilizing geminal interaction at the central reacting carbon, such as methoxymethyl fluoride (MeOCH$_2$F), are strongly stabilized toward solvolysis in comparison with substrates such as 4-methoxybenzyl fluoride.[26] A large fractional development of stabilizing geminal interactions in the transition state for addition of oxygen nucleophiles to α-oxygen stabilized carbocations might contribute to the smaller intrinsic barrier

Table 1. Effects of Strongly Electron-Donating α-Substituents on the Thermodynamic Stability of Primary Alkyl Carbocations and on the Rate Constant for Nucleophilic Addition of Solvent Water (Scheme 1)[a]

Resonance Stabilized Carbocation	$\Delta G°_{az}$ (kcal/mol)[b]	k_s (s-1)[c]
EtO–C⁺ H Et ↔ EtO=C⁺ H Et	18.0	2 x 10^10
MeO–⟨⟩–C⁺ H Me ↔ MeO=⟨⟩=C H Me	20.8	1 x 10^8
N=N=N–C⁺ H Et ↔ N≡N–N=C H Et	22.3	3 x 10^9

[a] In water at 25 °C. [b] $\Delta G°_{az} = -RT \ln K_{az}$ (Scheme 1). Values of $K_{az} = k_{solv}/k_{az}$ were taken from ref 34. [c] Rate constant for nucleophilic addition of solvent water taken from ref 34.

for nucleophile addition to α-OR stabilized carbocations compared with α-SR and α-(4-methoxyphenyl) stabilized carbocations.[33,34] However, the expression of these geminal interactions at the transition state for nucleophilic addition to carbocations has not been evaluated.

R¹
|
X–C–Y   X, Y = F, O, N
|
R²

9
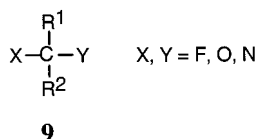
Carbanions. The addition of cationic α-NH₃⁺ or α-NMe₃⁺ substituents to the enolate of ethyl acetate results in a decrease in the intrinsic barrier Λ for protonation of the carbanion by solvent water (Scheme 7B).[12] We have proposed that there is a relationship between this decrease in Λ and the tendency of these charged α-substituents to lead to an increase in the *localization* of the negative charge at the α-amino carbon, which enhances the stabilizing polar interaction between unlike charges at the zwitterionic enolate (Scheme 7B).[12]

Figure 1 (●) shows the good linear correlation (slope = −0.40) up to pK_a ≈ 30 between log k_{HO} for (mostly) thermodynamically unfavorable deprotonation by hydroxide ion and the pK_a of neutral α-carbonyl carbon acids (Scheme 3).[13,14] This extended linear relationship is surprising, because proton-transfer reactions are expected to show a change to a more productlike transition state with decreasing thermodynamic driving force (increasing carbon acid pK_a), which should result in downward curvature and an absolute slope of >|−0.5| for unfavorable proton transfer. This curvature is predicted by different forms of the Marcus equation, but the data in Figure 1 do not show satisfactory fits to these models.[13] Much of the change in the thermodynamic driving force for proton transfer that

occurs with increasing pK_a of these α-carbonyl carbon acids is due to a decrease in the resonance stabilization of the enolate product, which is also expected to lead to a decrease in the Marcus intrinsic barrier for proton transfer.[23] We have therefore proposed that the change to a steeper, more negative, slope of the correlation in Figure 1 with increasing thermodynamic barrier to carbon deprotonation that is predicted by the Marcus equation is masked by opposing increases in k_{HO} resulting from concomitant decreases in Λ.[13]
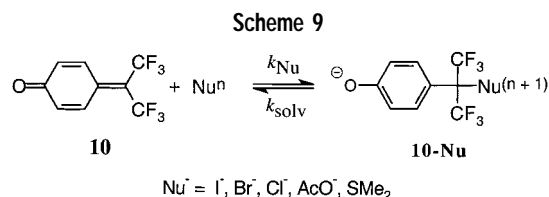
The intrinsic barrier for protonation of α-cyano carbanions is substantially smaller than that for protonation of enolates and other resonance-stabilized carbanions,[36] but there has been little consideration of the broader implication of this small barrier. We have found it useful to compare C-protonation of the cyanomethyl carbanion (Scheme 8) with O-protonation of acetate ion.[15] The small intrinsic barrier to O-protonation of acetate ion reflects the *small* stabilization associated with delocalization of charge between the two oxygens.[37] There is a similar small intrinsic barrier associated with C-protonation of α-cyano carbanions (k_{HOH}, Scheme 8),[11] where the charge is distributed approximately equally between carbon (~60%) and the α-cyano group (~40%)[38] and the stabilization associated with charge delocalization is presumably *small*.

Scheme 8

H₂C=C=N⁻ ↔ ⁻CH₂–C≡N →(k_{HOH}) H–CH₂–C≡N
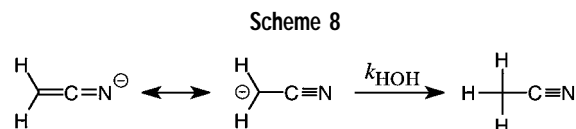
## Absolute and Relative Magnitudes of Intrinsic Barriers to Organic Reactions

We have determined absolute and relative intrinsic barriers for several organic reactions and have offered sensible interpretations of these data. These determinations are limited; our interpretations are complex and undergoing constant evaluation. Input from the organic community would be valued.

Nucleophile Addition to a Quinone Methide. The reactivity of the quinone methide **10** toward nucleophiles is similar to that of other strongly resonance-stabilized carbocations.[22,39] There is no simple relationship between the rate and equilibrium constants $K_{eq} = k_{Nu}/k_{solv}$ (M⁻¹) for addition of halide and acetate ions to **10** (Scheme 9), because there are differences of up to 7 kcal/mol in the Marcus intrinsic barrier Λ for addition of different nucleophiles: Nu⁻, Λ (kcal/mol) I⁻, 12.4; Br⁻, 13.9; Cl⁻, 15.4; AcO⁻, 19.8.[22] Similar differences in Λ are observed for addition of halide ions to the trityl carbocation.[22]

Scheme 9

O=⟨⟩=C(CF₃)(CF₃) + Nuⁿ ⇌(k_{Nu}/k_{solv}) ⁻O–⟨⟩–C(CF₃)(CF₃)–Nu^(n+1)

10   **10-Nu**

Nu⁻ = I⁻, Br⁻, Cl⁻, AcO⁻, SMe₂

The α-deuterium isotope effect for concerted bimolecular nucleophilic substitution at N-(methoxymethyl)-

N,N-dimethylanilinium ions decreases with increasing "hardness" of the nucleophile: Nu^-, k_H/k_D I^-, 1.18; Br^-, 1.16; Cl^-, 1.13; AcO^-, 1.07.[40] Therefore, the hybridization of the central carbon in the transition state for nucleophilic substitution by iodide ion is close to that for the methoxymethyl carbocation ($MeOCH_2^+$), and there is a shift to a transition state with greater bonding between the nucleophile and the central carbon on moving along the series I^-, Br^-, Cl^-, AcO^-. These results suggest that the transition state for nucleophile addition to **10** and the trityl carbocation is reached "earlier" (more cationic), and with a lower intrinsic barrier, for "soft" strongly polarizable nucleophiles such as iodide ion compared with "hard" weakly polarizable nucleophiles such as acetate ion, because the former nucleophiles provide greater orbital overlap at longer bond distances.[22] If different degrees of bond formation are observed at the transition state for thermoneutral addition of different nucleophiles to **10**, then the intersecting curves that constitute the reaction coordinate profile for nucleophile addition must in some cases exhibit pronounced asymmetry (Scheme 10).

Scheme 10
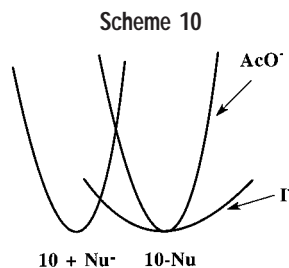
We have examined the addition of thiols and sulfides to **10**.[27] The polarizable methyl group at dimethyl sulfide provides significant stabilization of the charge at the cationic sulfur of the nucleophile addition product, but it creates an even larger destabilizing steric/electrostatic interaction with the α-CF_3 groups. The reaction proceeds through a transition state at which there is an *imbalance* between the large expression of the stabilizing interactions of the polarizable methyl group and the smaller expression of destabilizing steric/electrostatic interactions.[27] These data suggest that bonding interactions between **10** and Me_2S in the transition state for nucleophile addition are expressed at a large distance, which minimizes steric/electrostatic interactions between the nucleophile and the α-CF_3 groups, so that these destabilizing interactions develop *after* the transition state has been traversed on the reaction coordinate.

Reactions of Oxocarbenium Ions. The intrinsic barrier for nucleophilic addition of methanol to the oxocarbenium ion **11H$^+$** to give **12H$^+$**, $\Lambda_{MeOH} = 6.5$ kcal/mol, is about 50% smaller than that for deprotonation of **11H$^+$** at carbon by solvent water to give **11**, $\Lambda_p = 13.8$ kcal/mol (Scheme 11).[41] The difference in these intrinsic barriers may be related to the requirement for more extensive electronic reorganization on proceeding to the transition state for deprotonation of **11H$^+$** compared with the transition state for direct nucleophile addition to the carbocation.[41]

Scheme 11

Scheme 12
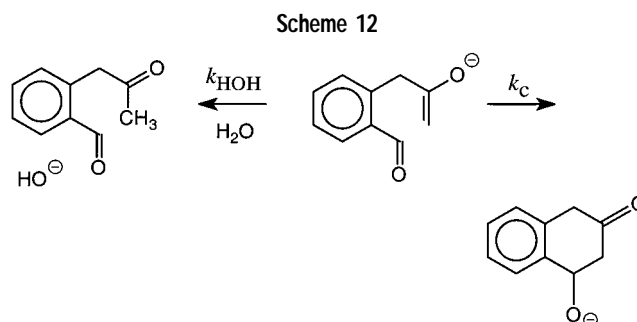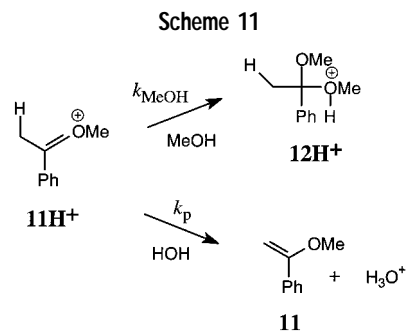
Aldol Addition Reactions. The requirement for rehybridization and electronic reorganization at the benzaldehyde carbonyl group upon formation of the tetrahedral adduct with hydroxide ion results in an 8 kcal/mol larger Marcus intrinsic barrier Λ compared with that for direct proton transfer between hydroxide ion and water.[42] Similarly then, the intrinsic barrier for addition of an enolate ion to the benzaldehyde carbonyl group (k_c, Scheme 12) might also be expected to be larger than that for protonation of the enolate by solvent water (k_{HOH}, Scheme 12). In fact, we have shown that these processes have very similar Marcus intrinsic barriers of $\Lambda = 14.1$ kcal/mol for k_c and $\Lambda = 14.7$ kcal/mol for k_{HOH}.[42] This suggests that there may be compensating stabilization of the transition state for aldol addition by favorable interactions between the HOMO of the "soft" enolate nucleophile and the LUMO of the "soft" carbonyl group electrophile.[42]

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