**62**

more highly substituted alkenes argue against involvement of the carbene $CH_2$: in the photocyclopropanation reaction.[34] On the other hand, the presence of the usual carbocationic intermediate could be shown by the formation of bromoiodomethane when diiodomethane was irradiated in the presence of lithium bromide (Scheme IV).[28] This same intermediate meets all of the requirements for serving as the methylene transfer agent (cf. **62**): it would be highly electrophilic, not give C–H insertion products, and not have large steric demands. Thus the initial steps in the photobehavior of geminal dihalides apparently involve selective homolytic cleavage of one of the carbon–halogen bonds followed by electron transfer within the initially formed caged radical pair, in complete analogy with their monohalide analogues. The resulting $\alpha$-halo cation has highly interesting behavior.[25]

**Summary**

The photobehavior of simple alkyl bromides and iodides in solution is intriguingly more complex than originally appreciated—involving radical, carbocationic, and carbene intermediates. For most iodides ionic behavior predominates and affords a convenient method for the generation of carbocationic intermediates that are not readily available by conventional ground-state procedures—including bridgehead, small-ring cyclic vinyl, $\alpha$-unsubstituted vinyl, and 7-norbornyl cations.[35] Bromides exhibit substantially more radical behavior, but in at least some cases cationic behavior can be made to predominate by the use of a solvent of high viscosity.

The available data are most consistent with a mechanism involving initial light-induced homolytic cleavage of the carbon–halogen bond followed by electron transfer within the resulting caged radical pair to afford an ion pair (Scheme I). The resulting cationic intermediates display all of the behavior typical of carbocations—undergoing nucleophilic trapping, rearrangement, and deprotonation. Systems capable of readily undergoing elimination afford unsaturated products predominantly over nucleophilic substitution products, as is typical of carbocationic intermediates formed by high-energy processes. In many primary and secondary iodide systems the unsaturated products are also formed via a competing carbene route that appears to involve transfer of an $\alpha$ hydrogen atom or proton (Scheme III, path B or C) in competition with $\beta$-proton transfer.

Irradiation of diiodomethane in the presence of alkenes results in the formation of cyclopropane adducts and is a synthetically useful alternative to the traditional Simmons–Smith procedure, especially for sterically hindered alkenes. This reaction apparently does not involve a carbene pathway but rather methylene transfer by the $\alpha$-iodo cation formed by initial homolytic cleavage of one carbon–iodine bond followed by electron transfer (Scheme IV). Similar behavior would probably be exhibited by other geminal dihalides not bearing a $\beta$-hydrogen substituent. However, those that do bear such a substituent undergo deprotonation to afford a vinyl halide in competition with methylene transfer.

Many important questions remain—including why electron transfer occurs so readily in these systems and whether it could be extended to other systems. These are the subject of our continuing investigation.

(34) For a review of the reactions of methylene, see ref 20.
(35) By contrast, attempts to generate 1-alkynyl cations by irradiation of the corresponding 1-alkynyl iodides have afforded only radical products. See McNeely, S. A., Ph.D. Dissertation, University of North Carolina at Chapel Hill, Chapel Hill, NC, 1976. Inoue, Y.; Fukunaga, T.; Hakushi, T. *J. Org. Chem.* **1983,** *48,* 1732–1737.

# Proton-Transfer Reactions between Carbon and Oxygen

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*Received June 10, 1982 (Revised Manuscript Received November 15, 1983)*

Proton transfer from one atom to another is a fundamental reaction in chemistry. Brønsted, in his pioneering studies, used the proton-transfer process to

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classify an acid as a species having a tendency to lose a proton and a base as a species having a tendency to add a proton.[1] Bell's classic book "The Proton in Chemistry", was originally based on the Baker Lectures presented at Cornell University in 1958; however, in 1972 he prepared a second edition since:[2] "The subject as a whole has expanded greatly since 1959, especially in two fields, namely, the direct study of fast proton-

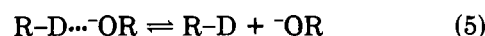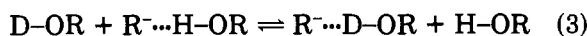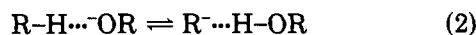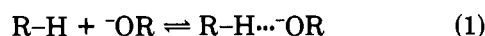(1) Brønsted, J. N. *Recl. Trav. Chim. Pays-Bas* **1923,** *42,* 718–728.
(2) Bell, R. P. "The Proton in Chemistry"; Cornell University Press: Ithaca, NY, 1973.

**Scheme I**
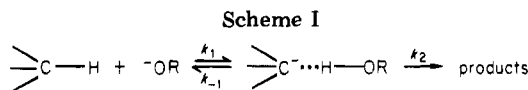


transfer reactions (notably by the relaxation methods pioneered by Eigen), and the experimental and theoretical study of hydrogen isotope effects". Since many reactions are initiated by the transfer of a proton from carbon to a base, the study of carbon acids is of particular importance to organic chemistry and biochemistry, and it would be convenient to have a list of $pK_a$ values available for such compounds.

Bordwell and co-workers have undertaken a comprehensive study of carbon acids, and their list of $pK_a$ values measured in dimethyl sulfoxide ($Me_2SO$) now exceeds 17 pages of computer printout. In an early paper of a series,[3] they discuss their choice of $Me_2SO$ and analyze problems associated with attempting to assign $pK_a$ values from measurements made in solvents of low dielectric constant. The measurement of $pK_a$ values for many carbon acids is not possible by an equilibrium method, and the determination of "kinetic acidities", which are normally measured by using base-catalyzed rates of proton exchange with solvent, has attempted to fill this void.[4] Over the last 20 years, Streitwieser and co-workers have studied both equilibrium and kinetic acidities using cyclohexylamine and methanol as solvents,[5] and their most recent studies use tetrahydrofuran.[6]

The relationship between $pK_a$ and rates of proton exchange is frequently a very complicated one; equating observed rate constants to a proton-transfer step is not always reliable. A working model for the mechanism of the exchange reaction can be represented by the following five step process:[7]

$$R-H + {}^-OR \rightleftharpoons R-H{\cdots}{}^-OR \qquad (1)$$

$$R-H{\cdots}{}^-OR \rightleftharpoons R^-{\cdots}H-OR \qquad (2)$$

$$D-OR + R^-{\cdots}H-OR \rightleftharpoons R^-{\cdots}D-OR + H-OR \qquad (3)$$

$$R^-{\cdots}D-OR \rightleftharpoons R-D{\cdots}{}^-OR \qquad (4)$$

$$R-D{\cdots}{}^-OR \rightleftharpoons R-D + {}^-OR \qquad (5)$$

Steps 1 and 5 represent the formation and destruction of encounter complexes that are necessary to align the donor and acceptor sites of the acid and base. After the proper alignment and necessary desolvation of the base has been achieved, the hydron-transfer[8] reactions of steps 2 and 4 can occur. The exchange of the protium conjugate acid and a deuterium acid occurs in step 3. Since the focus of our investigations has been the study of steps 2–4, we limit this Account to those steps.

## Internal Return

Reactions 1–3 can be abbreviated into a more general form, Scheme I. For simplicity, the formation of encounter complexes and desolvation are incorporated into the first step, and the rate constant $k_1$ therefore represents the sum total of all processes leading up to the transition state for the proton-transfer reaction. The second step in Scheme I can represent any forward reaction. This includes the expulsion of a leaving group, an exchange reaction with solvent molecules, or the formation of another intermediate. Scheme I also represents the general form for an internal-return mechanism[4a] where the proton transferred from carbon to oxygen, $k_1$, can be transferred back to the original carbon, $k_{-1}$, in competition with a forward step, $k_2$. Observed rate constants for reactions proceeding via Scheme I are a combination of the individual rate constants

$$k_{obsd} = (k_1 k_2)/(k_{-1} + k_2) \qquad (6)$$

Equation 6 can be simplified at the two extremes. If $k_2$ is at least 100 times greater than $k_{-1}$, the denominator, $k_{-1} + k_2$, will be only 1% larger than the value of $k_2$ and eq 6 would be experimentally indistinguishable from

$$k_{obsd} = k_1 \qquad (7)$$

At the other extreme, when $k_{-1}$ is 100 times greater than $k_2$, eq 6 can be approximated by

$$k_{obsd} = (k_1/k_{-1})k_2 \qquad (8)$$

Under the latter conditions, the observed rate constant cannot be related to the proton-transfer process unless the relationship between $k_{-1}$ and $k_2$ is known from other experimental data. For instance, if $k_{-1} = k_2 \times 10^2$, then $k_{obsd} = k_1 \times 10^{-2}$ and if $k_{-1} = k_2 \times 10^5$, then $k_{obsd} = k_1 \times 10^{-5}$. Therefore two different reactions could have identical values for $k_1$, but since one system features more internal return than the other, the observed rate constants would differ dramatically.

The measurement of primary kinetic isotope effects (PKIE) has been used to detect internal return, which is a no-reaction process. A maximum PKIE could result when $k_2 \geq 100k_{-1}$, and near-unity values are associated with $k_{-1} \geq 100k_2$. Measurements of PKIE between these two extremes would be obtained when $k_{-1}$ and $k_2$ are within a factor of 50. Smaller values of $k^H/k^D$ are normally attributed to proton transfer occurring in a rate-limiting step that has an asymmetric transition state,[9] and correlations of the magnitude of the PKIE and the amount of proton transfer in the transition state have been made.[10] To differentiate between the two possible explanations for moderate values of $k^H/k^D$, Streitwieser et al.[11] have proposed that the use of all three isotopes of hydrogen can in principle allow the calculation of the amount of internal return for each labeled compound and have defined an internal-return parameter $a^iH = k_{-1}{}^iH/k_2$. Their approach is based on a deviation of experimental results from the Swain–

(3) Matthews, M. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.

(4) (a) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965. (b) Jones, J. R. "The Ionization of Carbon Acids"; Academic Press: New York, 1973. (c) Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. "CH-Acids"; Pergamon Press: Oxford, England, 1978.

(5) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1980.

(6) Streitwieser, A., Jr.; Bors, D. A.; Kaufman, M. J., submitted to *Tetrahedron Lett.*

(7) Albery (Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 242–247) discusses this multistep approach to proton transfer and gives leading references.

(8) We will use the term hydron and symbol $^iH$ to refer to the three isotopic species.

(9) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265–273.

(10) (a) More O'Ferrall (More O'Ferrall, R. A. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; pp 216–227) gives a detailed discussion with references. (b) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 286–288.

(11) (a) Streitwieser, A., Jr.; Hollyhead, W. B.; Sonnichsen, G.; Pudjaatmaka, A. H.; Chang, C. J.; Kruger, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 5096–5102. (b) Boerth, D. W.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 6443–6447.

**Scheme II**



**Scheme III**
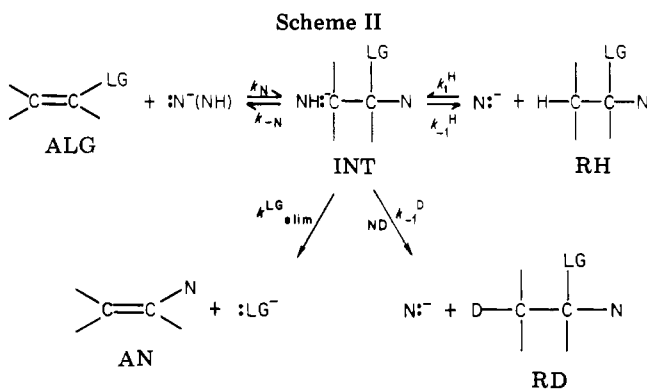


Schaad equation,[12] $k^H/k^D = (k^D/k^T)^y$, where $y$ can be 2.26 to 2.344 depending on the assumptions made in the derivation. The Streitwieser treatment is for single-temperature measurements and makes no attempt to predict the Arrhenius behavior of PKIE when the reaction pathway features internal return. We have carried out calculations to model the temperature dependence of observed $k^H/k^D$ values when neither the first or second step in Scheme I is clearly rate limiting.[13]

## Partitioning of Carbanions Generated in Protic Solvents

Over the years our research efforts have gradually shifted from studies of nucleophilic reactions of alkenes[14] to proton exchange and elimination reactions,[15] and finally to an in-depth analysis of primary kinetic isotope effects applied to proton transfer associated with dehydrohalogenation reactions.[13,16,17] The unifying theme of all our work has been the study of reactions that generate carbanion intermediates and an investigation of the fate of these intermediates in protic solvents.

A carbanion intermediate, INT, can be generated either by the reaction of a nucleophile with an alkene, ALG, or by the base-catalyzed abstraction of a proton from a saturated carbon, RH (Scheme II). The intermediate can partition to form a new alkene, AN, to form the exchange saturated compound, RD, or to regenerate starting compounds.

If the starting point of such investigations is an alkene, then the process can be described as a competition between a vinyl displacement reaction and addition across a carbon–carbon double bond. On the other hand, if one starts with the saturated compound, then the reactions studied are elimination vs. exchange. However, both reactions generate the same intermediate, which can partition by ejection of a leaving group, LG, and a hydron transfer from a solvent molecule,

$N^iH$. Problems arise when reversible reactions, such as internal return, $k_{-1}^H$, are competitive with the forward process, $k_{elim}^{LG}$ and $k_{-1}^D$. The study of elimination reactions is further complicated by the possibility that a concerted mechanism, E2, is the low-energy pathway rather than the two-step process, E1cB.

## Reactions of Alkenes with Alkoxide in Alcohol

Since alkenes with a *gem*-difluoromethylene group, $=CF_2$, undergo facile reaction with alcoholic alkoxide ions, the study of such systems seemed ideal for our purposes. Miller et al.[18] reported that reaction of methanolic methoxide with $CF_2=CCl_2$ yielded a saturated ether, $CH_3OCF_2CHCl_2$, as the sole product. When one of the chlorines is replaced with a phenyl group, $C_6H_5CCl=CF_2$ (I), the product distribution consists of both vinyl ethers and a saturated ether.[14b] Although quantitative numbers are not available regarding the leaving ability of alkoxide vs. the halides, the experimental evidence suggests that even fluoride is a better leaving group than an aliphatic alkoxide.[19] The prod-

$$CCl_2=CF_2 \xrightarrow[MeOH]{MeONa} CHCl_2CF_2OMe$$

$$C_6H_5CCl=CF_2 \xrightarrow[MeOH]{MeONa}$$

$$\underset{49\%}{C_6H_5CHClCF_2OMe} + \underset{51\%}{C_6H_5CCl=CFOMe}$$

uct distribution for the reaction of I becomes important since the ejection of fluoride from the intermediate is competitive with the proton-transfer reaction from methanol to neutralize the carbanion. The ability of fluoride to leave from different environments has been investigated by using a series of compounds, $C_6H_5CR_f=CF_2$, where $R_f = CF_3$ (II), $CF_2CF_3$ (III), or $CF_2H$ (IV), and chloride can also be included when $R_f = CF_2Cl$ (V).[14b] Since alkoxide attack always occurs at the $=CF_2$ position, the site of reaction remains constant, and halide ions leaving from the various $R_f$ substituents can be compared with both the proton-transfer reaction and the ejection of fluoride ion from $CF_2OR$. Scheme III illustrates the reaction of 2-phenylperfluoropropene (II) with ethanolic sodium ethoxide at $-78$ °C. Product ratios remain constant during the course of a kinetic run, suggesting that both VIII and

(12) Swain, C. G.; Stivers, E. C.; Reuwer, J. F., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* **1958**, *80*, 5885–5893.
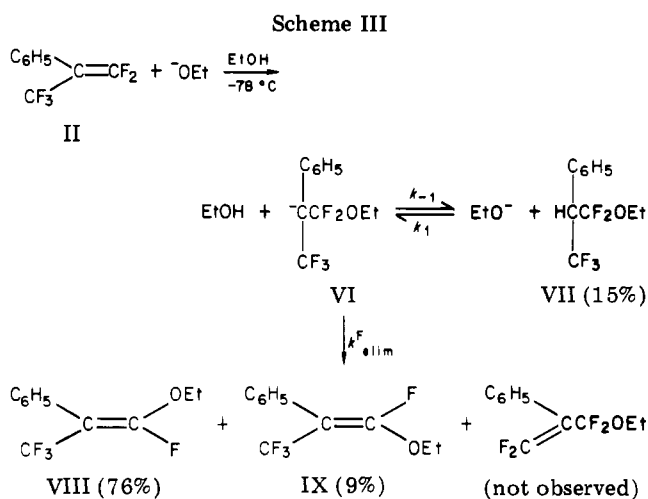
(13) Koch, H. F.; Dahlberg, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 6102–6107.

(14) (a) Koch, H. F.; Kielbania, A. J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 729–730. (b) Koch, H. F.; Koch, J. G.; Donovan, D. B.; Toczko, A. G.; Kielbania, A. J., Jr. *Ibid.* **1981**, *103*, 5417–5423.

(15) (a) Koch, H. F.; Dahlberg, D. B.; Toczko, A. G.; Solsky, R. L. *J. Am. Chem. Soc.* **1973**, *95*, 2029–2030. (b) Koch, H. F.; Dahlberg, D. B.; Lodder, G.; Root, K. S.; Touchette, N. A.; Solsky, R. L.; Zuck, R. M.; Wagner, L. J.; Koch, N. H.; Kuzemko, M. A. *Ibid.* **1983**, *105*, 2394–2398.

(16) Koch, H. F.; Dahlberg, D. B.; McEntee, M. F.; Klecha, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 1060–1061.
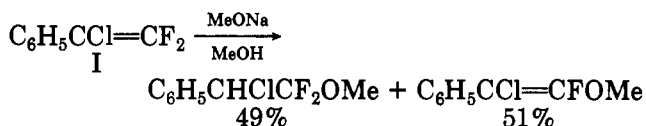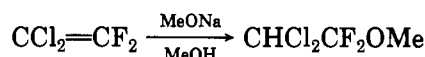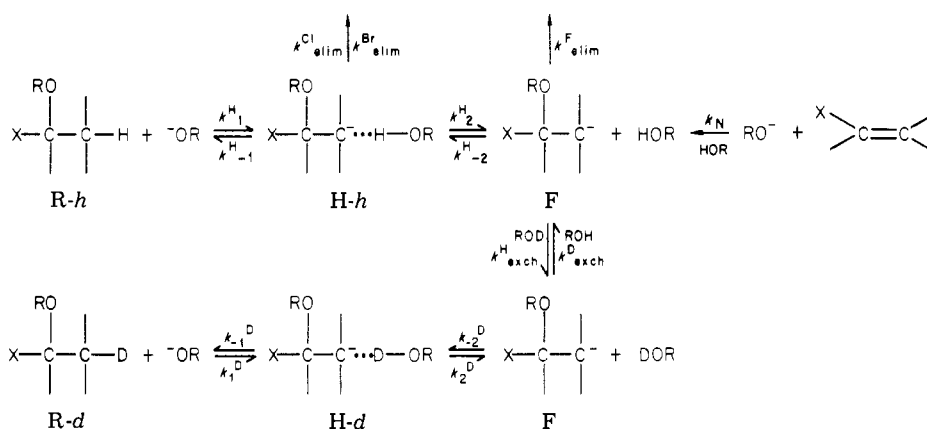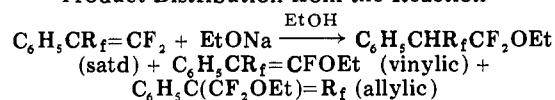
(17) (a) Koch, H. F.; Koch, J. G.; Tumas, W.; McLennan, D. J.; Dobson, B.; Lodder, G. *J. Am. Chem. Soc.* **1980**, *102*, 7955–7966. (b) Koch, H. F.; McLennan, D. J.; Koch, J. G.; Tumas, W.; Dobson, B.; Koch, N. H. *Ibid.* **1983**, *105*, 1930–1937.

(18) Miller, W. T., Jr.; Fager, E. W.; Griswold, P. H. *J. Am. Chem. Soc.* **1948**, *70*, 431–432.

(19) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198–203.

Scheme IV



### Table I
### Product Distribution from the Reaction[a]

$$C_6H_5CR_f=CF_2 + EtONa \xrightarrow{EtOH} C_6H_5CHR_fCF_2OEt$$
(satd) + $C_6H_5CR_f=CFOEt$ (vinylic) +
$C_6H_5C(CF_2OEt)=R_f$ (allylic)

| $R_f$ | temp, °C | % satd | % vinylic | % allylic |
|---|---|---|---|---|
| $CF_2Cl$ (V) | −78 | 0 | 0 | 100 |
| $CF_3$ (II) | −78 | 15 (34)[b] | 85 (66)[b] | 0 (0)[b] |
| $CF_3$ (II) | 20 | 21 (44)[b] | 79 (56)[b] | 0 (0)[b] |
| $CF_2CF_3$ (III) | −78 | 4 | 74 | 22 |
| $CF_2H$ (IV) | −50 | c | c | (≥98)[b] |
| Cl (I) | 0 | 40 (49)[b] | 60 (51)[b] | |

[a] Data from ref 14b.   [b] Values in parentheses are for reactions with MeONa in MeOH.   [c] Although we have not identified the small amount of other products from the reactions of IV, we have assumed that they are $C_6H_5C(CF_2H)=CFOR$. The retention times in GC analysis and the fact that product ratios are the same in EtOH and MeOH appear to be consistent with this assumption.

IX are formed directly from the intermediate VI rather than by a subsequent dehydrofluorination of VII. Kinetic studies on ethoxide-promoted dehydrofluorination of VII to form VIII and IX confirmed this conclusion since reaction of II occurs 6 orders of magnitude faster than does the elimination reaction. Table I summarizes product distributions for reactions of II–V.

### β-Halide Ejection vs. Proton-Transfer Reaction

The observed product distributions listed in Table I suggest that several reactions can occur at a faster rate than the protonation of a carbanion intermediate generated in alcohol. Since vinyl ethers are the major products from ethoxide reaction with II (85%) and III (74%), fluoride is ejected faster from $CF_2OEt$ by factors of 5.7 (II) and 19 (III) than the protonation of the respective carbanion intermediates. Ejection of fluoride from $CF_2CF_3$ is also faster than the protonation reaction, and it is only the loss of fluoride from trifluoromethyl that cannot compete with the proton-transfer process. At the other extreme, products from a proton-transfer reaction to neutralize the carbanions generated by reaction of IV or V were not observed. Using the data in Table I, we estimate a 3–4 kcal/mol free energy difference between the loss of fluoride from $CF_2H$ and the protonation of $[C_6H_5C(CF_2H)CF_2OEt]^-$.[20] Since chloride has a better leaving ability than fluoride,

the energetics of ejecting a β-chloride from a carbanion should be even more favorable. For this reason we concluded that *the lack of exchange of the hydrogen involved in a base-promoted elimination reaction is a poor experimental criterion to exclude an E1cB mechanism.*

The exchange of benzylic hydron and dehydrofluorination of $C_6H_5C^iH(CF_3)_2$ has been studied by using alcoholic sodium alkoxide.[15b] Exchange occurs 4–5 times faster than does elimination in ethanol and 7–8 times faster in methanol. The PKIE ($k^H/k^D$ at 25 °C) associated with these reactions are as follows: ethanol, 1.21 (exch) and 1.08 (elim); methanol, 1.10 (exch) and 1.05 (elim). The PKIE suggest there is extensive internal return, $k_{-1} \gg k_{exch} > k_{elim}^F$:
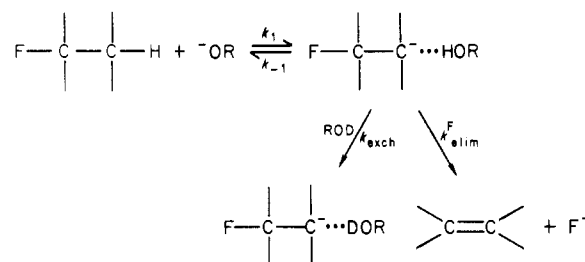


A $k^H/k^D$ (1.5 at 25 °C)[21] calculated for the ethoxide-promoted dehydrofluorination of $C_6H_5C^iH(CF_3)$-$CF_2OMe$ also suggests that $k_{-1} > k_{elim}^F$, while the product distribution for the reaction of II is consistent with $k_{elim}^F > k_{-1}$ (Scheme III). Results of other experiments lead to the conclusion that products are formed by the partitioning of the same intermediate generated by reaction of ethoxide with either the alkene or the saturated ether.[14b] This suggests that a modified version of Scheme II can best explain the experimental results (Scheme IV).

Scheme IV features two types of carbanion intermediates along the reaction pathway. One, H, is stabilized by a hydrogen bond, while the other, F, is free of contact stabilization. When reaction is initiated by an alkoxide-promoted proton abstraction from R-h, internal return, $k_{-1}$, is the low free energy process for reactions of H. Therefore the formation of F, $k_2$, would become the rate-limiting step, and near-unity isotope effects would be predicted. Approaching the same interme-

(20) (a) Koch, H. F.; Tumas, W.; Knoll, R. *J. Am. Chem. Soc.* 1981, *103*, 5423–5429.  (b) This point is discussed on p 5425.

(21) The $k^H$ was measured in EtOH and $k^D$ in EtOD. Correction was made for a kinetic solvent isotope effect, $k^{OD}/k^{OH}$ = 2.5, to give a $k^H/k^D$ of 1.5. Since the value for KSIE can vary, the error limits placed on the PKIE are ±0.3.

Table II
Primary Kinetic Isotope Effects (PKIE) for Reaction of $(XC_6H_4CHCF_2OMe)^-$ with Methanol

| | PKIE | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| X | −70 °C | −50 °C | −25 °C | 0 °C | 25 °C | 50 °C | $\Delta E_a^{D-H}$, kcal mol$^{-1}$ | $A^H/A^D$ |
| $m$-CF$_3$[a] | | | | 1.28 (1.22) | 1.34 (1.25) | 1.40 (1.28) | −0.31 ± 0.01 (−0.17 ± 0.01) | 2.2 (1.7) |
| $m$-NO$_2$ | | 1.20 | 1.24 | 1.29 | 1.35 | 1.39 | −0.22 ± 0.02 | 2.0 |
| $p$-CN | 1.33 | 1.36 | 1.53 | 1.69 | 2.04 | 2.11 | −0.56 ± 0.05 | 5.1 |
| $p$-NO$_2$ | 11.3 | 9.62 | 8.14 | 7.12 | 6.44 | | +0.72 ± 0.01 | 1.9 |

[a] Results in parentheses were obtained by mass spectrometry on $m$-CF$_3$C$_6$H$_4$CH—HCF$_2$OMe obtained when reaction was carried out in 50:50 mixture of MeOH:MeOD.

diates from an alkene would have reaction of alkene with alkoxide, $k_N$, to form F as the rate-limiting step. The partitioning of F favors fluoride ejection, $k_{elim}^F$, over the formation of H-$h$, $k_{-2}^H$, which is the rate-limiting step in the formation of R-$h$ from F. Since there is little O–H bond breaking in the transition state from F to H, a low PKIE would be anticipated for the neutralization reaction, and this has been observed.[14b] When II reacted with sodium ethoxide at 20 °C in a 1:1 mixture of EtOH:EtOD, the isolated C$_6$H$_5$C$^i$H(CF$_3$)CF$_2$OEt contained 35% D, which calculates to $k^H/k^D$ = 1.86.

If proton transfer between carbon and oxygen occurs with a highly asymmetric transition state,[23] there would be no reason to suggest extensive internal return, Scheme III would be adequate, and there would be no need to suggest Scheme IV as a working model for these reactions. The approach taken by Streitwieser et al.[11] to confirm an internal-return mechanism would make use of all three isotopes of hydrogen; however, Albery and Knowles[24] warned that very accurately measured isotope effects would be required to make use of deviations from a rather insensitive Swain–Schaad relationship to calculate amounts of internal return. Since C$_6$H$_5$C$^i$H(CF$_3$)CF$_2$OMe has an exchange reaction competing with dehydrofluorination, the measurement of $k_{elim}^T$ accurately would be difficult,[21] and for this reason we did not pursue such experimental evidence. Another experimental observation sheds some light on this question. When II reacts with sodium ethoxide at −78 °C in a 1:1 mixture of EtOH:EtOD, the isolated C$_6$H$_5$C$^i$H(CF$_3$)CF$_2$OEt contained 40% D, and this calculates to a $k^H/k^D$ = 1.50. Note that the PKIE increases with increasing temperature (1.50 at −78 °C vs. 1.86 at 20 °C), and although the values are small, this has been observed for other alkenes.[25] This experimental result is inconsistent with an argument that the PKIE for dehydrofluorination of C$_6$H$_5$CH(CF$_3$)CF$_2$OMe is due to an asymmetric transition state.

## Proton Transfer from Oxygen to Carbon

Much work has been reported on proton-transfer reactions from a neutral carbon to oxide ions; however, there is little quantitative data dealing with the reverse process, transfer of proton from neutral hydroxyl to a carbanion in protic solvents. One such investigation[26]

has been the measurement of PKIE for the protonation of a variety of benzylic anions generated in situ by reaction of methanolic sodium methoxide with ring-substituted benzyltrimethylsilanes:

$$MeO^- + Me_3SiCH_2C_6H_4X \rightarrow$$
$$MeOSiMe_3 + {}^-CH_2C_6H_4X \quad (9)$$

$$XC_6H_4CH_2^- + MeO^iH \rightarrow XC_6H_4CH_2{}^iH + MeO^- \quad (10)$$

Isotope effects can be calculated from the known initial ratio of MeOH:MeOD and the observed H:D in XC$_6$H$_4$CH$_2{}^i$H. Values of $k^H/k^D$ = 1.2–1.3 at 25 °C were calculated for a number of substituents, with $p$-CN slightly larger (2.0) and $p$-NO$_2$ increasing to $k^H/k^D$ = 10. Values of 10 were also observed for $o$-NO$_2$ and when the anion formed is fluorenyl or 9-methylfluorenyl. Low values of 1.3 were reported for (C$_6$H$_5$)$_2$CH$^-$ and (C$_6$-H$_5$)$_3$C$^-$. We had observed a $k^H/k^D$ value of 1.22 at −78 °C for the reaction of methanolic sodium methoxide and II. These results suggested a complimentary study on the reactions of MeONa/MeOH with ring-substituted $\beta,\beta$-difluorostyrenes.[25]

There is an advantage to generating carbanions in situ by the reaction of methoxide with either alkyltrimethylsilanes or $\beta,\beta$-difluorostyrenes. Reactions occur at lower temperatures, and the problem of internal return is eliminated. Solvent molecules are excellent trapping agents for carbanions, and only an intramolecular trap, such as $\beta$-halide, appears to be more efficient. The use of difluorostyrenes has an added advantage over the silanes in that the intermediates can partition between the ejection of a $\beta$-fluoride and the protonation of the carbanion. In our current study, we
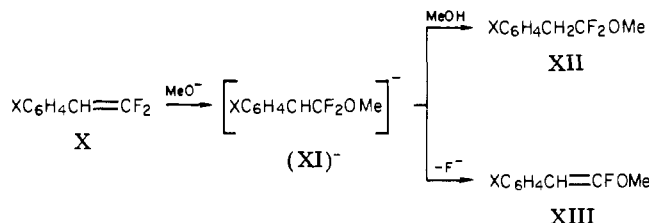
did not use mixtures of MeOH and MeOD. Instead, product ratios were analyzed for reactions carried out in pure MeOD and compared to those for reactions in MeOH. The PKIE can be calculated by assuming that the rate of fluoride ion ejection from the intermediate is approximately the same in MeOH and MeOD:[27,28]

$$\frac{k^H}{k^D} = \frac{(\% \ XII / \% \ XIII)^{MeOH}}{(\% \ XII / \% \ XIII)^{MeOD}}$$
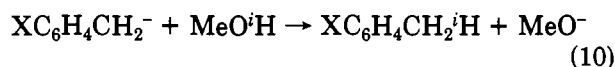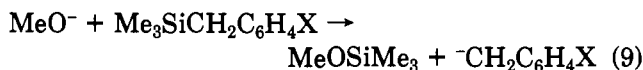
(22) This is discussed in ref 14b, p 5419.

(23) Saunders (Saunders, W. H. *Chem. Scr.* 1975, 8, 27-36) reports results of model calculations of isotope effects associated with elimination reactions. A value of $k^H/k^D$ = 1.5 would require a C–H bond breaking of >95% in the transition state of a rate-limiting step.

(24) Albery, W. J.; Knowles, J. R. *J. Am. Chem. Soc.* 1977, 99, 637-638.

(25) (a) Koch, H. F.; Koch, J. G.; Koch, N. H.; Koch, A. S. *J. Am. Chem. Soc.* 1983, 105, 2388-2393. (b) Koch, H. F.; Koch, A. S. *J. Am. Chem. Soc.*, in press.

(26) (a) Eaborn et al. (Eaborn, C.; Walton, D. R. M.; Seconi, G. *J. Chem. Soc., Perkin Trans. 2* 1976, 1857-1861) refer to this type of PKIE as a product isotope effect (PIE). (b) Macciantelli, D.; Seconi, G.; Eaborn, C. *J. Chem. Soc., Perkin Trans. 2* 1978, 834-838.

(27) This assumption has validity since a fractionation factor for fluoride ion of 1.00 has been reported for H$_2$O and D$_2$O.[28]

Table III
Rates of Protodetritiation and PKIE Values for Exchange Reactions in Methanolic Sodium Methoxide and
Ethanolic Sodium Ethoxide

| compd | base | $10^4 k$, M$^{-1}$ s$^{-1}$, 45 °C | $k^H/k^D$ (temp, °C) | $k^D/k^T$ (temp, °C) |
|---|---|---|---|---|
| XIV[a] | MeONa | 3560. | 1.2 (−15) | |
| PFB[b] | MeONa | 1840. | | 1.00 (25) |
| 9-PhFl[c] | MeONa | 328. | 6.40 (25) | 2.50 (25) |
| XV[d] | MeONa | 280. | 1.10 (25) | 1.01 (25) |
| | EtONa | 2710. | 1.21 (25) | 1.18 (25) |
| Fl[c] | MeONa | 3.95 | | 2.25 (25) |
| | | | | 2.11 (45) |
| | | | | 1.84 (100) |
| 9-MeFl[c] | MeONa | 2.20 | 5.17 (45) | 2.30 (45) |
| XVI[d] | EtONa | 1.60 | 1.07 (75) | 1.07 (75) |
| TPM[e] | MeONa | $6.41 \times 10^{-6}$ | 1.32 (97.7) | 1.34 (97.7) |

[a] 1,4-Dihydroperfluorobicyclo[2.2.1]heptane, ref 31.   [b] Pentafluorobenzene, ref 30.   [c] Fl = fluorene, 9-PhFl = 9-phenylfluorene, and 9-MeFl = 9-methylfluorene, ref 32.   [d] XV = $C_6H_5C^tH(CF_3)_2$, and XVI = $C_6H_5C^tHClCF_3$, ref 156.   [e] TPM = triphenylmethane, ref 11a.

Results are found in Table II.[25b]

The measurement of negative $\Delta E_a^{D-H}$ and large $A^H/A^D$ values confirms our belief that the neutralization reactions do not occur via a rate-limiting proton transfer that has a highly asymmetric transition state, and that these results are compatible with Scheme IV. Our current working model is that *the benzylic anions have their charge largely localized on a sp³ carbon that is capable of forming a relatively strong hydrogen bond to an alcohol. The presence of para nitro causes a delocalization of charge to the oxygens and results in an anion that is more stable than the hydrogen-bonded species.*

## Proton Transfer to Localized and Delocalized Carbanions

When a proton is transferred from oxygen to neutralize a carbanion, does it matter if the negative charge is localized on one carbon or if it is delocalized throughout a $\pi$ system? Kresge[29] has reviewed the fact that delocalization of charge slows the rate of proton transfer to carbon. What would be the consequence when the intermediates proposed for Scheme IV are delocalized? The hydrogen-bonded carbanion H must be a localized species since the proton-transfer reactions, $k_1$ and $k_{-1}$, require a tetrahedral carbon. Therefore delocalization can only affect the free carbanion F. When charge is delocalized on para nitro (or throughout a fluorenyl system), the free anion, F, has greater stability than does the corresponding hydrogen-bonded intermediate, H. The rate-limiting step becomes the proton-transfer reaction, $k_{-1}$, rather than the formation of H from F, $k_{-2}$. This suggests that $k_2 > k_{-1}$, and therefore *highly delocalized carbanions can have a return step that slows the observed rate of protonation in a similar way that internal return, $k_{-1} > k_2$, can slow the observed rate of proton abstraction by alkoxide.*

Is it reasonable that a delocalized benzylic anion is less stable than its localized hydrogen-bonded analogue? That question suggests another. Why do some proton-exchange reactions occur with near-unity PKIE? Observation of near-unity isotope effects for exchange reactions normally occur when the negative charge is largely localized on one carbon. Kresge[29] has discussed the behavior of phenylacetylene and chloroform where

the charge must remain largely on a specific carbon. These two substrates, various polyfluorobenzenes,[30] and 1,4-dihydroperfluorobicyclo[2.2.1]heptane (XIV)[31] result in PKIE values between 1.0 and 1.4 when undergoing exchange with solvent in the presence of an oxygen base. These compounds have the acidic carbon in all three hybrid states (sp, sp², sp³), but none are capable of $\pi$ delocalization of the negative charge. We have observed similar PKIE values from alkoxide-promoted dehydrofluorination and exchange of benzylic hydrogen in alcohol for $C_6H_5C^tH(CF_3)_2$ (XV) and $C_6H_5C^tHClCF_3$ (XVI)[15b] (Table III).

A benzylic anion is generally thought to be delocalized; however, the near-unity PKIE values suggest that the charge is largely localized on the benzylic position of the carbanions generated from XV and XVI. These intermediates are therefore capable of forming strong hydrogen-bonded carbanions, and this results in extensive internal return. For comparison, Table III also lists data for methoxide-catalyzed exchange of the 9-position of fluorene (Fl), 9-methylfluorene (9-MeFl) and 9-phenylfluorene (9-PhFl),[11a,32] which have PKIE values that are normal in magnitude. The corresponding fluorenyl anions are highly delocalized. With the charge distributed throughout the $\pi$ system, the unique alcohol molecule formed by a proton-transfer reaction is more likely to exchange with solvent than it is to transfer the proton back to the carbanion. In other words, the delocalization energy of the fluorenyl anions is greater than the energy obtained from the formation of a hydrogen bond to the localized carbanion.

The anions $[C_6H_5C(CF_3)_2]^-$ and $[C_6H_5CClCF_3]^-$ have groups capable of stabilizing a localized carbanion, as can be seen from the fact that XIV undergoes exchange faster than does XV. Diphenylmethane (DPM) and triphenylmethane (TPM) also exhibit extensive amounts of internal return during methoxide-catalyzed exchange with methanol.[11a] What happens when those substituents are removed? A PKIE of $k^D/k^T = 1.0$ at 178 °C was measured for the methanolic methoxide-catalyzed exchange of the benzylic hydrogens of toluene.[33] Therefore benzyl anion appears to behave in a

(28) Albery, W. J. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; p 283.
(29) Kresge, A. J. *Acc. Chem. Res.* 1975, 9, 354–360.

(30) Streitwieser, A., Jr.; Hudson, J. A.; Mares, F. *J. Am. Chem. Soc.* 1968, 90, 648–651.
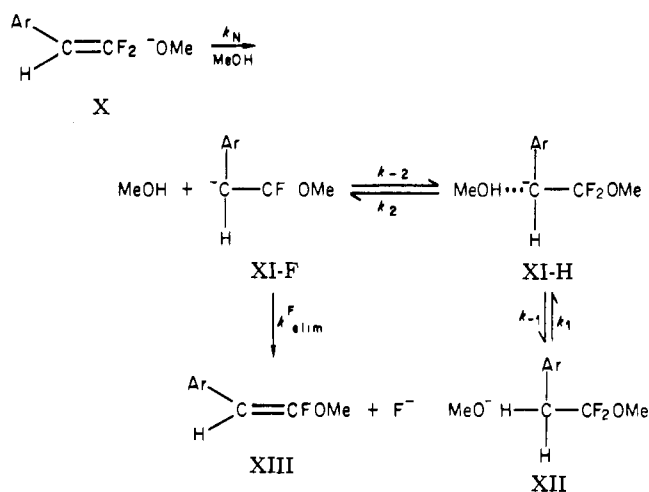(31) Streitwieser, A., Jr.; Holtz, D.; Zeigler, G. R.; Stoffer, J. O.; Brokaw, M. L.; Guibe, F. *J. Am. Chem. Soc.* 1976, 98, 5229–5234.
(32) Streitwieser, A., Jr.; Hollyhead, W. B.; Pudjaatmaka, A. H.; Owens, P. H.; Kruger, T. L.; Rubenstein, P. A.; MacQuarrie, R. A.; Brokaw, M. L.; Chu, W. K. C.; Neimeyer, H. M. *J. Am. Chem. Soc.* 1971, 93, 5088–5096.

Scheme V



manner similar to the other benzylic anions even though it is substantially less reactive. This phenomenon could occur with other oxide bases in hydroxylic solvents; however, when the exchange of toluene is catalyzed by lithium cyclohexylamide in cyclohexylamine, a normal isotope effect, $k^D/k^T = 3.0$ at 50 °C, was observed.[34]

The anomalous Arrhenius behavior of the PKIE reported in Table II can be rationalized by the stepwise mechanism proposed for reaction of MeONa/MeOH and the $\beta,\beta$-difluorostyrenes (X) (Scheme V). Although the rate-determining step is the reaction of methoxide and X, product distributions are controlled by subsequent reactions. Since XII and XIII are stable under the reaction conditions, relative amounts of each are formed according to the values of $k_{elim}{}^F$ and

$$k_{add} = (k_{-2}k_{-1})/(k_2 + k_{-1}) \qquad (11)$$

Equation 11 is similar to that for internal return, and the Arrhenius behavior of PKIE has been modeled for eq 6. Temperature-independent PKIE and values of $A^H/A^D$ that are greater than unity, less than unity, or equal to unity are possible.[13]

The PKIE associated with $k_2$ and $k_{-2}$ is small, and this results in an overall decrease in rate for the protium compound relative to the deuterium compound for an internal-return mechanism, $k_{-1}{}^H > k_{-1}{}^D$. For the neutralization reaction, $k_{-1}{}^H$ is still greater than $k_{-1}{}^D$, and this relationship will slow the rate of deuteration relative to the rate of protonation. We have estimated that $k_{-1} \sim 10^4 k_2$ for the exchange of $C_6H_5CHClCF_3$.[35] Since the PKIE associated with $k_2$ and $k_{-2}$ is small, this would account for the low isotope effect observed for the neutralization of $m$-$NO_2$-XI. A model for these low PKIE values could come from the work of Gold and Grist[36] on possible origins for the kinetic solvent isotope effect of methanol on the reactions of methoxide ion. They conclude that these effects are due to a multiple solvated methoxide ion which has a deuterium fractionation factor of 0.74. If the deuterium fractionation factor for $>C^-\cdots^iHOMe$ is similar to that for methoxide, then the PKIE values of 1.2–1.5 observed for the neu-

(33) Keevil, T. A.; Doctoral Dissertation, University of California, Berkeley, 1972.
(34) Streitwieser, A., Jr.; Langworthy, W. C.; Van Sickle, D. E. *J. Am. Chem. Soc.* **1962**, *84*, 251–254.
(35) This is discussed in ref 15b, pp 2396–2397.
(36) Gold, V.; Grist, S. *J. Chem. Soc. B* **1971**, 2282–2285.

tralization reactions could be explained.

The observed $k^H/k^D$ (6.44 at 25 °C) and $A^H/A^D$ (1.9) associated with the formation of $p$-$NO_2$-XII is consistent with the proton-transfer step for $p$-$NO_2$-XI-H being slower than the return to the more stable $p$-$NO_2$-XI-F, $k_2 > k_{-1}$. The $p$-cyano group is capable of stabilizing $p$-CN-XI-F realtive to $p$-CN-XI-H. This could represent an intermediate case where $k_2$ and $k_{-1}$ are closer in value and could result in low PKIE values that give unusually high $A^H/A^D$.

## Carbon Acids

The interest in relative $pK_a$ values of carbon acids can be attributed to a desire to predict relative reactivities for reactions that are catalyzed or promoted by a base. In some instances, the rate of proton transfer from carbon to the base would be of greater value than an equilibrium measurement. Ritchie[37] has stated that, "those carbon acids whose conjugates bases have localized charge are predicted to have proton transfer rates considerably greater than acids of the same thermodynamic strength whose conjugate bases have delocalized charges. That is, saturated hydrocarbons, alkenes, alkynes and cycloalkanes whose conjugate bases are localized are expected to show 'kinetic acidities' greater than their thermodynamic acidities". An excellent example to illustrate this point is the comparison of the rates of protodetritiation of 9-phenylfluorene (9-PhFl) and pentafluorobenzene (PFB) in methanolic sodium methoxide (Table III). Streitwieser et al.[38] report relative $pK_a$ values, measured in cyclohexylamine (CHA), of 18.5 for 9-PhFl vs. 25.8 for PFB,[39] but the observed rate constant for protodetritiation at 45 °C for PFB is 6 times greater than the measured rate constant for 9-PhFl.[40] A similar case is the comparison of 9-PhFl and 1,4-dihydroperfluorobicyclo[2.2.1]heptane (XIV). The reported $pK_a$(CHA)[31] for XIV is 22.3 and the measured exchange rate in methanolic methoxide is 11 times faster than that of 9-PhFl (Table III).

If the methoxide-catalyzed exchange reactions follow a reaction pathway similar to Scheme IV, this apparent discrepancy can be readily explained. The rate-limiting step for the exchange reaction of PFB is the formation of an intermediate similar to F, which is at a higher energy than the initially formed carbanion, H. On the other hand, the rate-limiting step for the exchange of 9-PhFl is the proton-transfer step, $k_1$, since the delocalized anion, F, is at a lower energy state. Values of $pK_a$ cited for measurements in CHA and most of the values obtained in $Me_2SO$ result from the use of an indicator method that utilizes other carbon acids within 2 $pK_a$ units of the desired carbon acid. Therefore the indicator method compares energy levels of "free" carbanions, F, and not hydrogen-bonded carbanions similar to H.

(37) Ritchie, C. D. *J. Am. Chem. Soc.* **1969**, *91*, 6479–6753.
(38) Streitwieser, Jr., A.; Scannon, P. J.; Neimeyer, N. M. *J. Am. Chem. Soc.* **1972**, *94*, 7936–7937.
(39) The $pK_a$ for PFB cannot be measured in $Me_2SO$ but should be greater than the 25.8 determined in CHA. An analogy can be the $\Delta pK_a$ of ca. 5 units between phenylacetylene (23) and 9-PhFl (18.5) in CHA compared to ca. 11 $pK_a$ units in $Me_2SO$.[3]
(40) The values in Table III are $k_{obsd}$ values. The difference between $k_1$ values should be at least 600 since hydron exchange for PFB has an observed $k^D/k^T = 1.00$ at 25 °C, which suggests extensive internal return, while 9-PhFl has a measured $k^D/k^T = 2.5$ at 25 °C. The larger PKIE suggest that there is an insignificant amount of internal return associated with the reaction of 9-PhF-9-t and methanolic sodium methoxide.

Bordwell and Boyle[41] suggested that a localized carbanion is the initial intermediate resulting from a base-catalyzed proton removal from nitroalkanes. Therefore, electron delocalization to form a more stable intermediate would lag behind proton transfer. The PKIE results for the methoxide-catalyzed exchange reactions of 9-PhFl, 9-MeFl, and fluorene[11a] are consistent with an internal-return mechanism.[42] These results also suggest that electron delocalization lags behind proton transfer and that Scheme IV can best describe a possible mechanism.

## Concluding Remarks

A major goal for the study of chemical reaction mechanisms is to understand not only the detailed pathway of a reaction but also the timing of various steps along that pathway. Proton-transfer reactions are of fundamental importance to many organic and biochemical reactions, yet many details regarding that process are still unknown. The role of solvent reorganization associated with proton-transfer reactions is a complex subject and is currently under investigation by others.[43] Careful studies of product distributions and PKIE can give meaningful insight regarding solvent reorganization during the course of nucleophilic reactions of alkenes[25] and we continue studies in the area.

The consequences of a hydrogen-bonded carbanion, H, as the initial intermediate generated by a proton transfer from carbon to oxygen has important mechanistic implications. When a leaving group can depart from H, the experimental results for that elimination reaction will be similar to those ascribed to an E2 mechanism. The hydrogen bond can preserve the stereochemistry of the carbanion, and elimination occurs with complete streospecificity.[44] Since $k_2$ is rate limiting for the exchange reaction, the leaving group departs faster than exchange can occur with solvent molecules. Therefore elimination is not accompanied

by exchange even though reaction proceeds via a carbanion intermediate.[15] The measurement of sizable isotope effects coupled with observed leaving group element effects can be associated with either an E1cB or E2 mechanism.[13,17b]

Since polar C–F bonds are capable of stabilizing localized carbanions, there are definite advantages to using highly fluorinated compounds in studies of carbanions. The reactivity of fluorinated alkenes toward nucleophiles allows for the generation of carbanions in protic solvents. Therefore we have generated carbanions that do not require $\pi$ delocalization for stability and can compare their behavior to that of highly delocalized anions.[25] There is the added advantage to generating carbanions in situ by the reaction of alkoxide with either alkyltrimethylsilanes or fluoroalkenes that reactions occur at lower temperatures than those required for a base-promoted proton abstraction, and the problem of internal return is eliminated. One should not study the chemistry of carbocations using only fluorocarbons, and for similar reasons, one should not predict the behavior of localized carbanions from model compounds that generate delocalized carbanions.

Some idea discussed in the Account are not new but are often overlooked. The ideas proposed by Richie,[37] Bordwell,[41] Kresge,[29] and Streitwieser[31] have greatly influence our thoughts. More recent studies by Jencks and co-workers[45] and Bernasconi et al.[46] are also relevant.

(41) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 3447–3452.
(42) Discussed in ref 13, pp 6105–6106.
(43) Bernasconi is active in this area and has recently published an excellent summary (Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335–2348) with pertinent references.
(44) Root, K. S.; Touchette, N. A.; Koch, J. G.; Koch, H. F. Abstracts of Papers, Euchem Conference on Mechanisms of Elimination Reactions, Assisi, Italy, Sept 12–16, 1977.

(45) Alunni, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2052–2060. Keeffe, J. R.; Jencks, W. P. *Ibid.* **1981**, *103*, 2457–2459. Gandler, J. R.; Jencks, W. P. *Ibid.* **1982**, *104*, 1937–1951.
(46) Bernasconi, C. F.; Carre, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 1698–2707. Bernasconi, C. F.; Kanavarioti, A. *J. Org. Chem.* **1979**, *44*, 4829–4832.
(47) We gratefully acknowledge a NATO grant that has made these discussions possible.

# The Mechanisms of Reactions of β-Lactam Antibiotics

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*Received March 9, 1983 (Revised Manuscript Received October 28, 1983)*

It is now more than half a century since Fleming observed the antibacterial action of penicillin and 40 years since the work of Florey and Chain led to the

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widespread use of penicillin and its congeners in medicine. Today there is a large family of antibiotics whose single common structural feature is the possession of a β-lactam ring. As a class they consist of penicillin 1, the cephalosporins 2, and the "nonclassical" β-lactam antibiotics such as clavulanic acid 3, thienamycin 4, nocardicin A 5, and the monobactams 6. All the novel β-lactam antibiotics identified over the last 10 years are