N-substituents with Pauling electronegativity values of 0 (for the lone pair),[31] 2.1 (for hydrogen), and 3.5 (for oxygen). In Figure 2a–c the J(C,H) values available for **5**, **1**, and **6** are plotted against the electronegativity of these substituents. With use of two criteria, namely, a large range for J ($\Delta J > 1$ Hz) and a unique sign for $\partial J/\partial E$, three coupling constants are distinguished from the rest by significant trends. These are $^3J(6,\alpha)$, $^2J(3,\alpha)$ and $^3J(5,\beta)$. Similar observations were made for C,H coupling constants in monosubstituted benzenes.[32] The first two parameters are also closely related to $^4J(\alpha,\alpha')$ and $^3J(\alpha,\beta)$, the two H,H coupling constants that showed the most pronounced substituent effect[10] as well as significant protonation effects.[12] In both pairs $^3J(6,\alpha)/^4J(\alpha,\alpha')$ and $^2J(3,\alpha)/^3J(\alpha,\beta)$ the spin–spin interactions are transmitted through the same bond fragments, and the correlation shown in Figure 3 indicates that similar mechanisms are responsible. It is important to note, however, that $\partial J/\partial E$ is of opposite sign for both parameters as are their protonation effects. This observation can be rationalized within the MO formalism of spin–spin coupling,[19] where, according to Pople and Santry,[33] the Fermi contact term that is believed to dominate H,H as well as C,H coupling constants can be approximated by eq 2. Here,

$$J_{\mathrm{N,N'}}{}^{\mathrm{cont}} = (16/9)\beta^2 h\gamma_{\mathrm{N}}\gamma_{\mathrm{N'}}s_{\mathrm{N}}{}^2(0)\ s_{\mathrm{N'}}{}^2(0)\pi_{\mathrm{N,N'}} \qquad (2)$$

β, h, $\gamma_{\mathrm{N'}}$, and $s_{\mathrm{N}}(0)$ are well-known constants,[19,33] and $\pi_{\mathrm{N,N'}}$ is the mutual atom–atom polarizability at the two centers. The change in the coupling constants, ΔJ_{ij}, may thus be related to the change of the atom–atom polarizabilities, $\Delta\pi_{ij}$. From the CNDO/2 calculations for pyridine and pyridinium ion we indeed find a negative sign for $\Delta\pi_{ij}$ in the case of the above-mentioned C,H interactions and a positive sign in the case of the H,H interactions.

As for $^3J(5,\beta)$, the corresponding H,H coupling constant $^4J(\beta,\beta')$ is less sensitive to substituent effects and no significant correlation seems to exist. Similarly, the sign change for $\partial J/\partial E$ found for the remaining J(C,H) values, most notably for $^1J(1,\alpha)$ and $^1J(2,\beta)$, precludes any straightforward interpretation based on a single dominating mechanism.

Experimental Section

Samples of hydrochlorides **2–4** were prepared from the corresponding pyridines as described.[34] The measurements were made with ca. 1 molar solutions in $CHCl_3$ by using 10-mm o.d. sample cells. Since we were not interested in measuring C,H coupling constants of the N^+–H proton in **1**, no provisions were made to exclude traces of water present due to the hygroscopic nature of pyridine hydrochloride. The absence of any observable splittings due to these interactions in the specta of **2–4** thus indicates rapid exchange of the N^+–H proton under these conditions.

FT-NMR spectra were recorded at 22.63 MHz with a Bruker HX-90 spectrometer equipped with a 16K Nicolet 1080 computer and ^{1}H lock channel. The solvent signal served as internal lock, and ^{2}H decoupling was applied at 13.81 MHz by using a Schomandl M-100 MS frequency synthesizer and a Bruker BSV-3B broadband decoupler. The spectral width was 1 kHz, and 16K data points were collected. The digital resolution in the frequency domain was 0.12 Hz.

The assignment of the ^{13}C resonances and C,H coupling constants of **2–4** was based on the chemical shifts for **1**,[1] and $\delta(3)$ and $\delta(5)$ as well as $\delta(2)$ and $\delta(6)$ in **2** and **3** respectively were distinguished through the isotope effect due to ^{2}H substitution.[11]

Acknowledgment. We are grateful for the financial support received from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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(31) H. A. Bent, *Chem. Rev.*, **61**, 275 (1961).

(32) L. Ernst, V. Wray, V. A. Chertkov, and N. M. Sergeyev, *J. Magn. Reson.*, **25**, 123 (1977).

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(34) B. Chenon and C. Sandorfy, *Can. J. Chem.*, **36**, 1181 (1958).

Superiority of Very Weakly Basic Amines as Catalysts for Alpha-Proton Abstraction via Iminium Ion Formation

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Contribution from the Department of Chemistry, Dartmouth College,
Hanover, New Hampshire 03755. Received February 13, 1980

Abstract: Catalysis of the conversions of beta-ketol **6** and beta-acetoxy ketone **7** to enone **3** via amine–carbonyl condensation has been studied by using eight nontertiary amines having a pK_a range from 10.61 to 1.22, including the very weakly basic 3,3,4,4-tetrafluoropyrrolidine (pK_a = 4.05) and 1,1,1,3,3,3-hexafluoroisopropylamine (pK_a = 1.22). Kinetic terms reflecting rate-determining alpha-proton abstraction via iminium ion formation were identified. Primary kinetic isotope effects were observed when appropriately deuterated **6** and **7** were used. Intermediate eniminium and enimmonium ions **17** were detected. Unlike general-base catalysis, catalysis via iminium ion formation becomes more effective as the base strength of the catalyst decreases. With 1 M hexafluoroisopropylamine as catalyst, formation of **3** from **7** occurs >10^4 times via the iminium ion pathway for every time it occurs via direct general-base-catalyzed alpha-proton abstraction.

In previous studies[1-4] of amine catalysis of the conversions of beta[5]-ketol **1** and beta-acetoxy ketone **2** to enone **3** we were able to identify and study rate-limiting alpha-proton abstraction occurring via iminium ion formation through transition states **4** and **5**. The value of the rate constant k_{AB} characterizing formation of **3** from **1** or **2** via **4** was essentially independent of catalyst base strength over the pK_a range 10.61 (n-butylamine) to 5.34 (cyanomethylamine),[3] and the value of the rate constant k_{A} characterizing formation of **3** via **5** increased as the catalyst became less basic.[1,3] The implications of these findings with respect to enzymic processes involving iminium ion formation were discussed.[3,4] In particular, it was shown that maximum catalytic effectiveness is obtained when pH = p$K_a{}^{\mathrm{N}}$ = p$K_a{}^{\mathrm{B}}$, i.e., when the pH, the base strength of the amine which forms the iminium ion, and the base strength of the proton-accepting base are the same.[3] It was estimated[1,3] that when this condition is met at physiological pH, the iminium ion pathway has an inherent rate advantage of ca.

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(1) Hupe, D. J.; Kendall, M. C. R.; Spencer, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 1254.

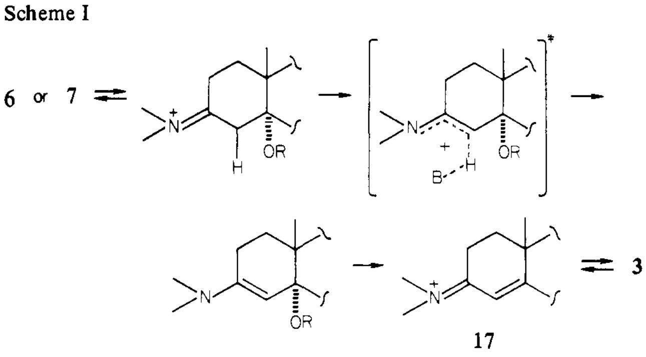
(2) Hupe, D. J.; Kendall, M. C. R.; Sinner, G. T.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 2260.

(3) Hupe, D. J.; Kendall, M. C. R.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 2271.

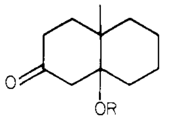
(4) Review: Spencer, T. A. "Bioorganic Chemistry"; Academic Press: New York, 1977; Vol. I, p 313.

(5) To avoid confusion, we use the words alpha and beta to denote the positions of carbons relative to the carbonyl or derived functional group and the symbols α and β to denote substituents respectively underneath and above the decalin ring system.

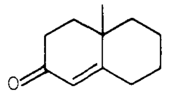
Scheme I



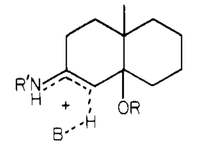
10^5 over direct proton abstraction from the parent carbonyl compound.



1, R = H
2, R = Ac



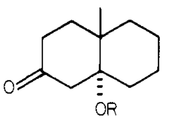
3



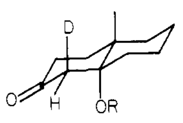
4, B = R'NH$_2$, R = H or Ac
5, B = H$_2$O, R = H or Ac

We wished to extend these studies of alpha-proton abstraction to even more weakly basic catalysts because, if the trends observed for k_{AB} and k_A in the reactions of **1** and **2** persist, amines less basic than cyanomethylamine should be the best monofunctional nucleophilic catalysts yet observed.

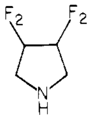
It was also decided that further studies of this type should be made by using the trans-fused analogues of **1** and **2**, **6** and **7**. The decision to switch to these synthetically less accessible substrates was based on the belief that **6** and **7** would effectively serve the same purposes as **1** and **2**, while in addition permitting study of the stereochemistry of alpha-proton abstraction, owing to their conformationally unambiguous *trans*-decalin structures. We have, in fact, recently reported[6] that there is stereoelectronic control of alpha-proton abstraction from **6** and **7** and derived iminium ions, on the basis of comparison of the reactions of **6** and **7** with their alpha axial mondodeuterated analogues **8** and **9**.



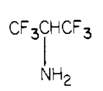
6, R = H
7, R = Ac



8, R = H
9, R = Ac



10



11

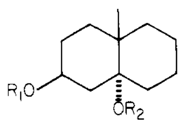
This paper describes the kinetic study of the elimination reactions of **6** and **7** to form **3** as catalyzed by eight nontertiary amines, ranging in base strength from *n*-butylamine through cyanomethylamine to the very weakly basic 3,3,4,4-tetrafluoropyrrolidine (TFP, **10**) and 1,1,1,3,3,3-hexafluoroisopropylamine (HFI, **11**). All the data obtained suggest that we were indeed able to monitor alpha-proton abstraction via iminium ion formation, as depicted in Scheme I, across the entire catalyst pK_a range.

Results and Discussion

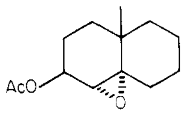
Ketol **6** was prepared essentially by the method of Henbest and McEntee.[7] Acetoxy ketone **7** was prepared from diol **12**[7] by the same sequence used to prepare **2**,[1,8] involving bis-acetylation to form **13**, selective hydrolysis to **14**, and Jones oxidation.[9] The overall yield of **7** from **12** was 76%.

In our earlier studies of the conversions of **1** and **2** to **3** via iminium ion formation we established that alpha-proton abstraction was the rate-determining step by observation of large, invariant primary kinetic isotope effects when appropriately deuterated **1** and **2** were used as substrates. In the present study the axial alpha monodeuterated **8** and **9** served the same purpose, while also being an essential part of our determination of stereoelectronic control of alpha-proton abstraction.[6] Syntheses of **8** and **9** were accomplished by the same pathway used for **6** and **7** except that **12** with a C-1 β-D was prepared by reduction of epoxyacetate **15**,[7] using LiAlD$_4$ instead of LiAlH$_4$. Mass spectra of **8** and **9** confirmed that these species were monodeuterated (>98%), and the assigned stereochemistry was confirmed by ^{1}H NMR. Compound **7** (in CDCl$_3$) showed the C-1 α-proton as a doublet at δ 3.29[10] (J = 15 Hz) and the C-1 β-proton as a doublet at δ 2.41 (J = 15 Hz). In the spectrum of **9** the higher field doublet had disappeared and the C-1 α-proton appeared as a singlet at δ 3.26.[11]

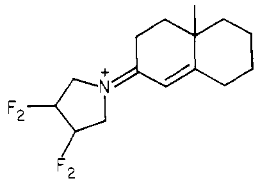
The preparation of TFP (**10**) has been described,[12,13] and HFI (**11**) was prepared by the method of Middleton and Krespan.[14] The pK_a of **10** was determined by the half-neutralization method at 25 °C with μ = 0.4 (the conditions used in the kinetic studies) to be 4.05. In the case of the extremely weakly basic **11**, the pK_a determined by this method, after correction for the significant hydrogen ion concentration at the low pH involved,[15] was 1.22.



12, R$_1$ = R$_2$ = H
13, R$_1$ = R$_2$ = Ac
14, R$_1$ = H, R$_2$ = Ac



15



16

The conversions of **6** and **7** to **3**, like those of **1** and **2**, are essentially quantitative and can be conveniently monitored by ultraviolet spectroscopy. In almost all cases the reaction could be followed simply by monitoring the increase in absorbance at 247 nm, the $\lambda_{max}^{H_2O}$ of **3**. When TFP was used as catalyst, however, it was necessary also to monitor the development of the longer wavelength absorption of enimmonium ion **16**, $\lambda_{max}^{H_2O}$ 286 nm (ϵ = 27 000),[13] as discussed below.

As in the case of **1**[2,3] and **2**,[1] numerous kinetic runs using different catalyst concentrations at different pHs were made to determine the rate law for the formation of **3** from **6** and **7**. With **7**, as with **2**,[1] the formation of **3** can be described by eq 1, in which [H$_3$O$^+$] is a_H as measured by pH meter, [OH$^-$] is K_w/a_H, AM

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(6) Ferran, H. E., Jr.; Roberts, R. D.; Jacob, J. N.; Spencer, T. A. *J. Chem. Soc., Chem. Commun.* **1978**, 49.

(7) Henbest, H. B.; McEntee, J. *J. Chem. Soc.* **1961**, 4478.

(8) Isolation of **7** from direct acetylation of **6** with isopropenyl acetate was achieved in one trial but could not be repeated.

(9) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.

(10) Equatorial protons generally appear 0.1–0.7 ppm downfield from axial protons: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 3rd ed.; Wiley: New York, **1974**; p 169. The "doublet" at 3.29 for the C-1 α-proton actually shows a small (~1 Hz) further splitting, presumably due to long-range "W" coupling with the C-3 α-proton.

(11) The C-1 β-D should shift the resonance of the C-1 α-H to a slightly higher field, as observed: Batiz-Hernandez, H.; Bernheim, R. A. *Prog. Nucl. Magn. Spectrosc.* **1967**, *3*, 63.

(12) TFP was originally prepared by: Chaudhry, M. T.; Powers, G. A.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc.* **1964**, 874. Owing to an erroneous listing of TFP under C$_4$H$_5$F$_4$NO$_2$ in the *Seventh Collective Formula Index* of *Chemical Abstracts*, we were unaware of this paper when we also reported preparation of TFP.[13] We thank Dr. Tatlow for informing us of his work, and we apologize to him and his collaborators.

(13) Roberts, R. D.; Spencer, T. A. *Tetrahedron Lett.* **1978**, 2557.

(14) Middleton, W. J.; Krespan, C. G. *J. Org. Chem.* **1965**, *30*, 1398.

(15) Bell, R. P. "Acids and Bases", Methuen and Co., Ltd., London, 1969, p 19.

Table I. Rate Constants for the Reactions of 6 and 7 To Form 3 in H_2O at 25 °C[a]

		substrate 6[b]			substrate 7		
catalyst	pK_a[c]	$10^4k'_B$, $10^4k'_{OH}$, 10^4k_H M^{-1} s^{-1}	10^4k_{AB} M^{-2} s^{-1}	10^4k_A M^{-1} s^{-1}	10^4k_B, 10^4k_{OH}, 10^4k_H M^{-1} s^{-1}	10^4k_{AB} M^{-2} s^{-1}	10^4k_A M^{-1} s^{-1}
hydroxide ion	15.7	190			15,000		
hydronium ion		0.32			0.38		
n-butylamine	10.61	4.6	5.7				
allylamine	9.85[d]	1.1	5.5		160		
ethoxyethylamine	9.44	0.84	4.0				
ethyl glycinate	7.73	~0.1	29	~0.01	9.6	63	~0.1
trifluoroethylamine	5.70	0.017	8.2	0.041	0.29	33	0.24
cyanomethylamine	5.34	0.02	13	0.077	0.30	47	0.32
TFP	4.05[d]	~0.01	42	2.5	0.05	98	9.5
HFI	1.22[e]		17	1.5		100	7.5

[a] All reactions were adjusted to $\mu = 0.4$ by the addition of KCl; a few reactions had $\mu > 0.4$ because they contained high catalyst concentrations or too much KCl. [b] As mentioned in the text and discussed in detail in ref 2, the rate constants k'_B and k'_{OH} for base-catalyzed conversion of 6 to 3 do not represent simple rate-determining proton abstraction, as do the corresponding rate constants for conversion of 7 to 3. [c] See ref 3 for sources of pK_a values, unless otherwise indicated. [d] Determined by the half-neutralization method at 25 °C with $\mu = 0.4$. [e] Determined as described in the text.

is unprotonated amine catalyst, AMH^+ is protonated amine catalyst, k_B is the rate constant for general-base-catalyzed proton abstraction by free amine, and k_{AB} and k_A are rate constants characterizing alpha deprotonation via iminium ion formation through the transition state shown in Scheme I with B = free amine and water, respectively. As noted earlier, in the case of TFP, the product included enimmonium ion **16**, and d[**3**]/d*t* in eq 1 had to be replaced by d([**3**] + [**16**])/d*t*.

$$d[3]/dt = [k_H[H_3O^+] + k_{OH}[OH^-]] + k_B[AM] + k_{AB}[AM][AMH^+] + k_A[AMH^+][7] \quad (1)$$

The formation of **3** from a beta-ketol such as **1** or **6** is more complicated, as discussed in one of our earlier papers,[2] because the reaction catalyzed by hydroxide ion or general bases ($k_{OH}[OH^-]$ or $k_B[AM]$ terms) occurs under most conditions by a reversible E1cB mechanism, in which an intermediate enolate anion is reprotonated more rapidly than it loses hydroxide ion to form **3**. The $k_{OH}[OH^-]$ and $k_B[AM]$ terms thus must be replaced by a more complex function in order to be precise. However, ignoring this complexity introduces only a negligible error in the values of the nucleophilic catalysis terms $k_{AB}[AM][AMH^+]$ and $k_A[AMH^+]$.[3] For the present purposes of studying catalysis via iminium ion formation, therefore, we will, as before,[3] use eq 1 with $k'_B[AM]$ in place of $k_B[AM]$ as a satisfactory approximation of the kinetic behavior of **6**, recognizing that the rate is not, strictly speaking, linearly dependent on $k'_B[AM]$ throughout the formation of **3**.

Intermediate eniminium ions (**17**, Scheme I) could be detected under appropriate conditions (high catalyst concentrations) with all seven primary amines used, in the same manner as previously described.[16] In the case of TFP (**10**), a readily detectable equilibrium amount of enimmonium ion **16** was present even at low catalyst concentrations.[13] This is a consequence of the fact that TFP has a K_{eq} for formation of **16**[13] that is an order of magnitude greater than the K_{eq}'s for the formation of eniminium ions from **3** and primary amines.[17] Our study of the equilibrium **3** + **10** $\rightleftarrows$ **16** + H_2O has been described elsewhere.[13]

Table I lists the results obtained with the eight amines studied, plus hydroxide ion and hydronium ion. The rate constants k_B for the reactions of five of the amines as general bases with **7** show the expected[1] Brønsted dependence on base strength with $\beta = 0.62$. The rate constants k'_B for **6** are, as explained earlier, more complicated functions owing to the incursion of reversible E1cB behavior when the poorer leaving group, hydroxide, is present. Values of k_B or k'_{AB} for HFI (**11**) were not obtained because free HFI has such low solubility in water that measurement of these very small rate constants was for all practical purposes impossible.

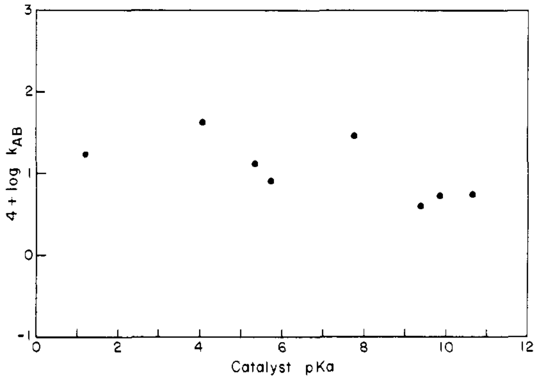

Figure 1. Values of log k_{AB} (M^{-2} s^{-1}) for the eight amine catalysts listed in Table I for the conversion of **6** to **3** as a function of catalyst pK_a. The least-squares slope of a line through the eight points is −0.07.

In the case of **7**, values of k_{AB} could be obtained only for the more weakly basic amine catalysts, owing to the dominance of the k_B term with stronger bases. With beta-ketol **6**, however, the values of the $k'_B[AM]$ terms are significantly smaller and it is possible to measure k_{AB} for all eight amines. As discussed below, the $k_{AB}[AM][AMH^+]$ term reflects rate-determining proton abstraction throughout the catalyst pK_a range. The value of k_A becomes too small with either substrate to measure with amine catalysts having $pK_a > 8$.[1,3]

The values of k_A and k_{AB} obtained are consistent with what was expected on the basis of our earlier study of **1**[3] and **2**.[1] As the catalyst becomes less basic, the values of k_A increase. The values of k_{AB}, on the other hand, are relatively independent of catalyst pK_a. Figure 1 shows k_{AB} for **6** as a function of catalyst pK_a, and there is remarkably little variation over the entire range of catalysts ($\Delta pK = 9$). If anything, there is a slight trend toward more effective catalysis as pK_a decreases.

All available evidence, such as the detection of intermediate eniminium ions (**17**), indicated that the k_{AB} and k_A terms corresponded to catalysis via iminium ion formation as shown in Scheme I. It was important, however, to confirm that alpha-proton abstraction from intermediate iminium ions was indeed the rate-determining step, by comparing the reactivity of **6** and **7** with that of their monodeuterated analogues **8** and **9**. As noted earlier, we had previously shown that it is the C-1 β-proton, the one which has been replaced by deuterium in **8** and **9**, which is selectively removed in formation of **3**.[6]

With low-pK_a amines it is possible to run the conversions of **6** or **7** to **3** under conditions such that the $k_{AB}[AM][AMH^+]$ term contributes nearly all of the observed rate (k_{obsd}). One can thus determine a kinetic isotope effect unambiguously associated specifically with the $k_{AB}[AM][AMH^+]$ term. This was done with trifluoroethylamine, cyanomethylamine, and TFP for that term,

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(16) Ferran, H. E., Jr.; Drake, D. A.; Spencer, T. A. *J. Org. Chem.* **1975**, *40*, 2017.

(17) Cunningham, W. C.; Gula, M. J.; Spencer, T. A., unpublished results.

Table II. Observed Kinetic Isotope Effects for the Reactions of 6 vs. 8 and 7 vs. 9 To Form 3 under Various Catalytic Conditions in H_2O at 25 °C[a]

	β-hydroxy ketones 6 and 8		β-acetoxy ketones 7 and 9	
catalyst	dominant[b] kinetic term	KIE_{obsd}[c]	dominant[b] kinetic term	KIE_{obsd}[c]
hydroxide ion	k_{OH}	5.5[d]	k_{OH}	6.2
allylamine	$k_{AB} + k'_B$[e]	5.7[d]		
ethoxyethylamine	$k_{AB} + k'_B$[e]	5.7[d]		
trifluoroethylamine	k_{AB}	5.3	k_{AB}	7.4
cyanomethylamine	k_{AB}	5.0	k_{AB}	8.8
TFP	k_{AB}	3.5	k_{AB}	6.0
	k_A[f]	5.2	k_A[f]	5.4
HFI	$k_{AB} + k_A$[g]	4.7	$k_{AB} + k_A$[g]	5.6

[a] Ionic strength adjusted to $\mu = 0.4$ with KCl. [b] An entry here means that the experiments were performed under conditions in which that catalytic term (e.g., $k_{AB}[AM][AMH^+]$) accounted for >90% of the formation of 3, as calculated from the appropriate rate constants in Table I. The reactions in which the dominant kinetic term includes k_{AB} were run at pH = pK_a with 0.4 M total buffer concentration, unless otherwise specified. [c] $KIE_{obsd} \equiv (k_{ax}^H + k_{eq}^H)/(k_{ax}^D + k_{eq}^H)$ as discussed in the text. [d] Estimated from initial rates, owing to isotopic exchange; the $k'_B[AM]$ term reflects formation of 3 by a reversible E1cB mechanism as discussed in the text. [e] The $k_{AB}[AM][AMH^+]$ term contributed about 50% and the $k_B'[AM]$ term about 50% to k_{obsd} in these reactions. [f] From reactions run at pH ~2.2 with 0.2 M total buffer concentration. [g] From reactions run at pH ~1.2 with 0.1–0.2 M total buffer concentration.

and the values of KIE_{obsd} are listed in Table II.

It will be noted that the values of KIE_{obsd} for **6** vs. **8** are consistently smaller than the values of KIE_{obsd} for **7** vs. **9**. However, this is at least in part a consequence of the fact that the magnitude of stereoelectronic control, which we have called the stereoelectronic factor (SEF $\equiv k_{ax}^H/k_{eq}^H$),[6] is less for alpha-proton abstraction from **6** than it is from **7**.[6] As previously discussed,[6] this difference in SEF arises from a greater relative value of k_{eq}^H for **6** than for **7**. Since the kinetic isotope effects observed in this study correspond to $KIE_{obsd} \equiv (k_{ax}^H + k_{eq}^H)/(k_{ax}^D + k_{eq}^H)$, the values of KIE_{obsd} will be affected by this difference in k_{eq}^H. A more appropriate quantity for comparison in the present context is $k_{ax}^H/k_{ax}^D \equiv KIE_{max}$. Simple manipulation of the definitions for SEF and KIE_{obsd} allows one to obtain for KIE_{max} the following expression: $KIE_{max} = SEF \cdot KIE_{obsd}/(SEF - KIE_{obsd} + 1)$. As an example of the differences between KIE_{obsd} and KIE_{max} consider the k_{AB} terms for trifluoroethylamine. The value of KIE_{obsd} for **6** vs. **8** of 5.3 converts, by using the previously determined value of SEF = 18,[6] to KIE_{max} = 7.0, and the value of KIE_{obsd} for **7** vs. **9** of 7.4 converts, by using SEF = 110,[6] to KIE_{max} = 7.9.

When TFP was used as catalyst, it was also possible to run the elimination reactions under conditions where the $k_A[AMH^+]$ term dominated catalysis so as to contribute greater than 90% of k_{obsd}. Again, for both **6** vs. **8** and **7** vs. **9**, substantial values of KIE_{obsd} were obtained.

In the case of HFI (**11**), the limited solubility of the free amine makes it infeasible to conduct the reaction under conditions such that $k_{AB}[AM][AMH^+]$ is dominant, and the contribution of $k_H[H_3O^+]$ at pHs much below the pK_a of **11** makes it infeasible to conduct the reactions under conditions where $k_A[AMH^+]$ is dominant. However, KIE's were observed for both **6** vs. **8** and **7** vs. **9** under conditions where the k_{AB} and k_A terms were of approximately equal magnitude and together constituted >90% of the observed rate.

The situation is complicated with more strongly basic amines by the inevitably greater contribution from general-base catalysis. Since, as discussed above, the $k'_B[AM]$ terms for **6** are smaller than the $k_B[AM]$ terms for **7**, it is possible to determine values of KIE_{obsd} under conditions such that the $k_{AB}[AM][AMH^+]$ term contributes about 50% of k_{obsd} with catalysts as basic as ethoxyethylamine and allyamine. This must be done, however, by comparing initial rates, because the general-base-catalyzed process ($k'_B[AM]$) causes isotopic exchange as the reaction progresses (reversible E1cB mechanism).

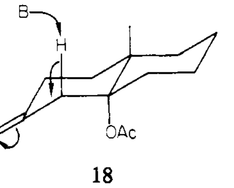
The values of KIE_{obsd} obtained in this manner for ethoxyethylamine and allylamine are too large to be attributed to the $k'_B[AM]$ term alone. Even complete removal of the 50% contribution of that term to k_{obsd} would leave a value of k_{obsd} far larger than that found for **8**, so there has to be a significant isotope effect in the $k_{AB'}[AM][AMH^+]$ term as well. Rate-determining proton abstraction via iminium ion formation is thus confirmed over the entire catalyst pK_a range with the exception of *n*-butylamine. Also shown in Table II are the values of KIE_{obsd} for alpha-proton abstraction by hydroxide ion. In the case of **6** vs. **8**, the value of KIE_{obsd} again was necessarily estimated from initial rates, as it was with the more basic amines.

On the basis of the data in Table II we feel confident that we have been able to study alpha-proton abstraction via iminium ion formation over a catalyst pK_a range from 10.61 to 1.22. Since the effectiveness of any amine in such a process is given by the sum of the $k_{AB}[AM][AMH^+]$ and $k_A[AMH^+]$ terms, it is clear that more weakly basic amines are actually superior as nucleophilic catalysts.

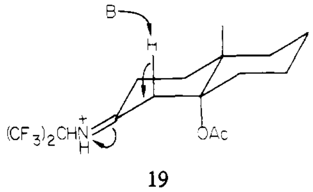
It is worth noting that there is an enormous difference between the effectiveness of very weak bases such as HFI as nucleophilic catalysts and their effectiveness as general-base catalysts. The Brønsted β of 0.62 for k_B for the conversion of **7** to **3** leads to an estimated value of $k_B = 1.2 \times 10^{-7}$ M^{-1} s^{-1} for HFI. If one uses this value of k_B and considers a 1 M HFI solution at pH = pK_a, it can be calculated that for each time formation of **3** occurs via **18** (B = HFI or H_2O) it will occur more than 10^4 times via **19** (B = HFI or H_2O).

It has also been of interest[1,18-20] to try to evaluate the relative ease with which a given general base can abstract an alpha-proton from an iminium ion as compared to the parent carbonyl compound. In other words, one would like to compare k_B for reaction of the carbonyl compound, as shown in **18**, with $k_B^{im^+}$ for the reaction of the iminium ion, as shown in **19** with HFI as the nucleophilic catalyst. In order to do this, it is necessary to estimate the concentration of intermediate iminium ion, because $k_B^{im^+} = k_{obsd}/[{>}C{=}NHR^+][B]$. This estimate depends on measuring or assuming values for the equilibrium constant for imine formation ($K_{eq} = [{>}C{=}NR]/[{>}C{=}O][RNH_2]$) and the ratio of dissociation constants for the iminium ion (K_a^{im}) and the ammonium ion (K_a^{am}). The relative concentrations of iminium ion and carbonyl compound can then be obtained from $[{>}C{=}NHR^+]/[{>}C{=}O] = K_{eq}[RNH_3^+]K_a^{am}/K_a^{im}$.

Previous evaluations of this type[18,19] have assumed that K_{eq} for imine formation is 0.1 M^{-1} and that $K_a^{im} = 10^3 K_a^{am}$. We have used these assumptions to come to the previously mentioned conclusion[1,3] that the iminium ion pathway has an inherent rate advantage of ca. 10^5 at physiological pH. With HFI, the same analysis indicates that $k_B^{im^+}$ for the reaction of a given general base with the iminium ion formed from **7** plus HFI·HCl, as in **19**, is at least 10^8 times greater than k_B for **18**.



18



19

Experimental Section

Melting points were determined in a Thomas-Hoover apparatus in unsealed capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137, 257, or 599 spectrophotometer.

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Proton nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solution, unless otherwise indicated, on a Perkin-Elmer R-24 instrument or on a JEOL FX-60Q multinuclear Fourier transform spectrometer. Chemical shifts are reported in parts per million downfield from Me_4Si. Mass spectra were determined at the MIT Mass Spectrometry Facility, sponsored by USPHS Division of Research Resources Grant PR00317. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

Amines. Commercially available amines were purified either by two recrystallizations of their hydrochloride salts from 1:1 methanol–1-propanol or by distillation twice from barium oxide directly before use.

3,3,4,4-Tetrafluoropyrrolidine (TFP, 10) was prepared by a modfication of the method of Tatlow.[12] Borane in THF[21] was used instead of $LiAlH_4$ to reduce 3,3,4,4-tetrafluorosuccinimide.[22] To a solution of 8.99 g (48.5 mmol) of the succinimide in 20 mL of dry tetrahydrofuran at 0 °C under nitrogen was added 125 mL of a 2.5 N solution of borane in tetrahydrofuran dropwise with stirring. The reaction mixture was stirred overnight at room temperature, cooled to 0 °C, and treated dropwise with 58 mL of absolute ethanol. After bubbling ceased, dry HCl gas was bubbled through the cooled mixture. The resulting precipitate of TFP hydrochloride was collected, washed with ether, dried in vacuo, and sublimed at 140 °C (760 torr) to afford 5.92 g (68%) of pure TFP hydrochloride: IR (KBr) 2370, 1430, 1370, 1240, 1170, 1075, 1020, 990, 920, and 745 cm^{-1}; NMR (Me_2SO-d_6) ^1H δ 4.07 (m, 4) and 9.25 (s, 2); ^{19}F δ 41.74 upfield from TFA (m); $pK_a(25\ °C, \mu = 0.4) = 4.05$ (half-neutralization).

1,1,1,3,3,3-Hexafluoroisopropylamine (HFI, 11) was prepared from the hexafluoroimine[23] essentially according to the procedure of Middleton and Krespan,[14] except that **11** was precipitated as its hydrochloride salt from a dried ether extract and purified by sublimation at 60 °C (7–8 torr) in ca. 70% yield, rather than being purified by distillation.[14] The pK_a of **11** was determined by titration with base of 0.4 and 1.5 M solutions of the hydrochloride of **11** and correction of the observed half-neutralization points according to ref 15. Both determinations gave $pK_a = 1.22 \pm 0.05$.

Synthesis of Substrates 6, 7, 8, and 9. 2β,9α-Dihydroxy-10β-methyldecalin (**12**), mp 157–160 °C (lit.[7] mp 161.5–162.5 °C), was prepared essentially by the procedure of Henbest and McEntee,[7] except that *m*-chloroperbenzoic acid was used instead of perbenzoic acid to epoxidize the mixture of 2β- and 2α-acetoxy-10β-methyl-$\Delta^{1,9}$-octalin.[7] The yield of desired diol from 10-methyl-$\Delta^{1,9}$-octal-2-one, prepared by the method of Ross and Levine,[24] was 44%.

9α-Hydroxy-10β-methyldecal-2-one (6) was prepared by Jones oxidation[9] (3 min, 0 °C) of **12** in 86% yield after recrystallization: mp 157–158 °C (lit.[7] mp 162–163 °C); IR (KBr) 3440 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 3) and 2.62 (d, 1, $J = 15$ Hz); mass spectrum *m/e* 182 (M^+) (calculated for $C_{11}H_{18}O_2$, 182).

9α-Acetoxy-10β-methyldecal-2-one (7) was prepared from **12** by the sequence used previously to prepare **2**.[2] A solution of 0.800 g (4.35 mmol) of **12**, 8 mL of freshly distilled isopropenyl acetate, and several small crystals of *p*-toluenesulfonic acid was refluxed under nitrogen for 17 h. The solution was diluted with 50 mL of ether, extracted with $NaHCO_3$ solution, dried over $CaSO_4$, and evaporated in vacuo to afford 1.22 g (104%) of crude oily 2β,9α-diacetoxy-10β-methyldecalin (**13**): IR (neat) 1740 cm^{-1}.

A solution of 1.1 g of this material in 40 mL of methanol was mixed with 8.0 mL of 50% aqueous KOH solution and stirred for 5 min at room temperature. The mixture was cooled, neutralized with concentrated HCl, extracted with 4 × 20 mL of ether, washed with 25 mL of $NaHCO_3$ solution, dried over $CaSO_4$, and evaporated to afford a clear oil which solidified to afford 0.81 g (91% from **12**) of 9α-acetoxy-10β-methyldecalin-2β-ol (**14**) which was used without purification for conversion to **7**. Recrystallization from ether–hexane afforded pure **14**: mp 90–91 °C; IR (KBr) 3310 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (s, 3) and 2.03 (s, 3). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.05; H, 9.87.

To a solution of 1.50 g (6.63 mmol) of **14** thus prepared in 60 mL of spectrograde acetone at 0 °C was added 4.0 mL of cold Jones reagent.[9] The mixture was stirred for 3 min and poured into 200 mL of ice water. The resulting solution was extracted with methylene chloride, and the combined organic layers were washed with 30 mL of cold 1 M HCl and twice with 30 mL of saturated $NaHCO_3$ solution, dried over $CaSO_4$, and evaporated to afford 1.37 g (92%) of crude **7**. Recrystallization from 30 mL of hexane gave 1.234 g (83%) of **7**: mp 88–89 °C; IR (KBr) 1735–1715 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (s, 3), 1.97 (s, 3), 2.41 (d, 1, $J = 15$ Hz), and 3.29 (dd, 1, $J = 15$ and 1 Hz); mass spectrum *m/e* 224 (M^+) (calculated for $C_{13}H_{20}O_3$, 224). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.68; H, 8.98.

1β-Deuterio-9α-hydroxy-10β-methyldecal-2-one (8) was prepared in the same manner as **6** from [1β-*d*]**12** prepared by $LiAlD_4$ reduction of epoxy acetate **15**:[7] IR (KBr) 3440 and 1690 cm^{-1}; NMR δ 1.21 (s, 3); mass spectrum *m/e* 183 (M^+) (calculated for $C_{11}D_1H_{17}O_2$, 183), <2% at 182.

1β-Deuterio-9α-acetoxy-10β-methyldecal-2-one (9) was prepared in the same manner as **7** from [1β-*d*]**12**: IR (KBr) 1735–1715 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3), 1.98 (s, 3), and 3.26 (bs, 1); mass spectrum, *m/e* 225 (M^+) (calculated for $C_{13}D_1H_{19}O_2$, 225), <2% at 224.

Kinetics. Ultraviolet absorption data were obtained by using either a Unicam SP 800B spectrophotometer equipped with an automatic cell changer timed by a Cary 1116100 program timer or a Varian Cary 219 spectrophotometer equipped with an automatic cell changer. Temperature in the cuvettes was maintained at 25.0 ± 0.1 °C by circulation of water through the cuvette housing from a Tamson or a Forma-Temp Model 2095 thermostated bath. Measurements of pH were made by using either a Radiometer Model 26 pH meter equipped with a GK 2302 C combination electrode or a Corning Model 130 pH meter equipped with a Fisher glass-body E-5A electrode or a Markson PolyMark combination semimicro electrode.

Reactions were monitored by following the increase in absorption at 247 nm, the $\lambda_{max}^{H_2O}$ of **3**, of ca. 10^{-3} M solutions of substrate **6**, **7**, **8**, or **9** in the presence of concentrations of amine catalysts usually ranging from 0.05 up to 0.4 M. With all catalysts other than TFP (**10**), catalyst concentrations could be kept low enough when desired to avoid accumulation of intermediate eniminium ions (**17**). With **10**, increase at 286 nm caused by enimonium ion **16** was also monitored, as explained above. Ionic strength was maintained at $\mu = 0.4$ with added potassium chloride as necessary. Good pseudo-first-order kinetics were obtained in all cases, involving typically 10–20 runs with each catalyst. Reproducibility of any value of k_{obsd} for a specific set of reaction conditions was ca. ±15%. The kinetic runs were conducted and the resulting data were analyzed as previously described.[1]

It was often possible to run the reactions under conditions such that one kinetic term, e.g., $k_{AM}[AM][AMH^+]$, dominated catalysis to an extent that the desired rate constant could be obtained essentially directly after subtracting hydroxide ion or hydronium ion catalysis. When this was not possible, the rate constants involved were determined by iterative fitting of data to an expression such as $k_{obsd} - k_{OH}[OH^-] = k_{obsd}' = k_{AB}[AM][AMH^+] + k_B[AM]$ for a reaction with a high-pK_a amine in which both the k_{AB} and k_B terms are important, after initial estimation of k_B from the intercept of the least-squares line defined by $k_{obsd}'/[AM] = k_{AB}[AMH^+] + k_B$ from a reaction where $k_B[AM]$ constituted most of k_{obsd}.

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