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^{13}C,^{1}H Spin-Spin Coupling. 7. Pyridinium Ion

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Abstract: ^{13}C,^{1}H coupling constants for pyridinium ion have been obtained from the ^{13}C NMR spectra of the three isomeric pyridinium-d_4 ions by using the ^{13}C{^{2}H} double-resonance method. The most pronounced protonation effects are observed for the one-bond C,H coupling constants and for $^{2}J(3,\alpha)$ and $^{3}J(6,\beta)$. CNDO/2 as well as FP-INDO calculations fail to reproduce the large protonation effect for $^{1}J(2,\alpha)$. The experimental results are compared with the corresponding J(C,F) data, and the electronegativity effect for J(C,H) data is investigated in the series pyridine, pyridinium ion, and pyridine *N*-oxide. Correlations between J(C,H) and J(H,H) in these compounds are found.

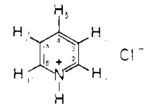
Introduction

Protonation effects for ^{13}C chemical shifts and one-bond ^{13}C,^{1}H coupling constants in nitrogen heterocycles are well-known,[1,2] and the usefulness of these parameters for the detection of protonation sites has been demonstrated.[3] More recently, C,H coupling constants over more than one bond, now available through FT-NMR, have been recognized as sensitive parameters that allow structure determinations for mono- and diprotonated species.[4-6] These data are thus expected to support and extend earlier attempts to investigate such structures on the basis of H,H coupling constants.[7]

Since the protonation effects for the C,H coupling constants of the parent compound pyridine were not known, we decided to determine these parameters by an analysis of pyridine hydrochloride (**1**) by using the ^{13}C{^{2}H} double-resonance technique[8] in order to have a firm basis for further studies in this area. In addition, protonated pyridine served as an important model for the interpretation of trends observed for H,H coupling constants in substituted benzenes,[9,10] and it was hoped to gain similar useful information for C,H coupling constants.

Results

The three pyridinium-d_4 ions, **2**–**4**, were prepared from the α-,



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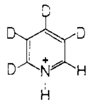

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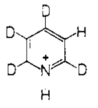

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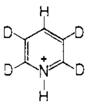

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β-, and γ-*H*-pyridine-d_4 (cf. Experimental Section) and their ^{13}C{^{2}H} double-resonance spectra measured as previously described.[8,11] The results are shown in Figure 1. The line-broadening observed for the α-carbon resonances is attributed to unresolved ^{13}C,^{14}N spin-spin coupling. Analogous effects have been recognized in the ^{1}H NMR spectrum of **1** and explained on the basis of ^{1}H,^{14}N coupling.[12] In our case, ^{13}C{^{1}H,^{14}N} triple resonance experiments performed with **1** led to a considerable sharpening of the α-carbon resonances (half-width change from 13.3 to 1.7 Hz). Corresponding changes for the β- and γ-carbon resonance were much smaller (3.3–1.7 Hz and 6.6–2.3 Hz, respectively). In fact, the line width in the undecoupled spectrum was in the order $\Delta_\alpha > \Delta_\gamma > \Delta_\beta$, in accord with findings for the magnitude of ^{13}C,^{15}N coupling constants in [^{15}N]pyridine hydrochloride:[13] $^{1}J(^{13}C_\alpha,^{15}N) > {}^{3}J(^{13}C_\gamma,^{15}N) > {}^{2}J(^{13}C_\beta,^{15}N)$. ^{13}C{^{2}H,^{14}N} triple resonance experiments for **2**–**4** indicated by these results were, however, unsuccessful, most probably due to the fact that the sum of the frequencies used to excite ^{2}H and ^{14}N at the available magnetic field of 2.11 T is close to the ^{13}C resonance frequency [$\nu(^{14}N) = 6.50$, $\nu(^{2}H) = 13.91$, and $\nu(^{13}C) = 22.63$ MHz]. The coupling constants for C-2,6 are therefore less well determined, and a number of long-range interactions could not be resolved. For $^{3}J(3,\gamma)$ and $^{3}J(4,\beta)$ upper limits were estimated from the observed line width. Splittings due to coupling to the N^{+}–H proton were not observed (cf. Experimental Section). Since from our results the signs of the C,H coupling constants are not available, they have been assumed to be positive as in the free base.[14] The only two negative interactions $^{4}J(5,\alpha)$ and $^{4}J(6,\beta)$ found for pyridine were not resolved in the ion.

Table I. ^{13}C,^{1}H Coupling Constants for Pyridine Hydrochloride (Hz)[a]

	C-2	C-3	C-4	C-5	C-6
H_α	190.7	5.1 ± 1.0	6.10	*b*	6.4
H_β	3.3 ± 1.0	173.95	≤0.7[c]	7.20	*b*
H_γ	6.9	≤1.0[c]	169.43	≤1.0[c]	6.9

[a] Experimental error due to digital resolution ±0.12 Hz were not stated otherwise. [b] Not resolved. [c] Estimated from line width at half-height.

Table II. Protonation Effects for the ^{13}C,^{1}H Coupling Constants in Pyridine (Hz)[a]

	C-2	C-3	C-4	C-5	C-6
H_α	+13.3	−3.4	−0.25		−4.7
	+7.5	*−39.8*	*−3.9*		*−42.3*
H_β	+0.2	+11.36		+0.61	
	+6.7	*+7.0*		*+9.3*	
H_γ	+0.1		+8.30		+0.1
	+1.5		*+5.2*		*+1.5*

[a] Percental change in italics.

The results of our measurements are given in Table I and Table II presents the protonation effects for the J(C,H) values on the basis of the data for pyridine.[8a,14]

Discussion

Protonation Effects. The protonation effects of largest magnitude are observed for the one-bond C,H coupling constants. They are in the order $\Delta^{1}J(2,\alpha) > \Delta^{1}J(3,\beta) > \Delta^{1}J(4,\gamma)$, and they

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Table III. Calculated Fermi Contact Contributions to J(C,H) in Pyridine (**5**) and Pyridinium Ion (**1**) and Protonation Effects ΔJ^a

		SOS-CNDO/2			FP-INDO			
	J(C,H)	**5**	**1**	ΔJ	**5**	**1**	ΔJ	ΔJ_{exptl}
^1J	2,α	62.13	62.84	*+0.70*	154.70	159.50	*+4.80*	*+13.3*
	3,β	58.92	64.95	*+6.03*	144.54	164.25	*+19.71*	*+11.36*
	4,γ	57.87	61.25	*+3.38*	141.52	151.73	*+10.21*	*+8.30*
^2J	2,β	1.07	2.24	+1.17	−4.12	2.62	+6.74	+0.2
	3,α	1.28	0.78	*−0.50*	0.91	−1.77	*−2.66*	*−3.4*
	3,γ	0.37	0.82	+0.45	−5.70	−2.53	−3.17	
	4,β	0.37	0.39	+0.02	−5.62	−4.34	−1.28	
^3J	2,γ	2.19	2.53	+0.34	8.77	9.68	+0.91	+0.1
	5,β	2.13	2.35	*+0.22*	8.33	7.88	*−0.55*	*+0.61*
	4,α	2.24	2.07	−0.17	8.76	7.33	−1.43	−0.25
	6,α	3.05	1.82	*−1.23*	13.74	5.56	*−8.18*	*−4.7*
^4J	6,β	0.10	0.06	−0.04	−2.72	−1.77	−0.95	
	5,α	0.02	0.11	+0.09	−2.47	−1.36	−1.11	

[a] The experimentally most pronounced data are given in italics.

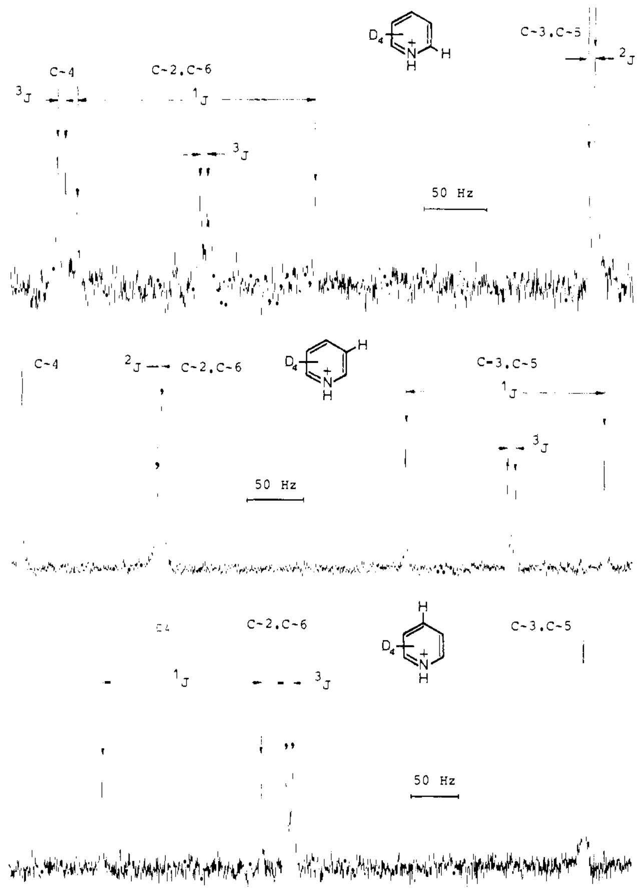

Figure 1. ^{13}C{^{2}H} double-resonance spectra of pyridinium ions **2**–**4**.

seem sufficiently different to be of diagnostic value for the assignment of ^{13}C resonances as well as for the detection of protonation sites. The large one-bond coupling $^1J(2,\alpha)$ in pyridine (Δ^1J = 19.8 Hz if compared to ^1J(C,H) in benzene) has been attributed to the influence of the nitrogen lone pair.[2] Since delocalization of the lone pair is blocked in the ion, one would expect to find a decrease of this coupling upon protonation. However, the opposite is observed experimentally, apparently as a consequence of the inductive effect associated with the positively charged nitrogen. The positive change for $^1J(^{13}\text{C},^1\text{H})$ in the α position is thus in fact much larger than that in the β and γ positions.

As for the other coupling constants, significant changes are found only for $^2J(3,\alpha)$, $^3J(6,\alpha)$, and $^3J(5,\beta)$. The unusually large geminal coupling $^2J(3,\alpha)$ in pyridine is reduced, an observation that has already been rationalized[4] on the basis of the Pople–Bothner-By theory for geminal H,H coupling constants,[15] where lone-pair delocalization into σ orbitals leads to large positive ^2J(H,H) values. The usefulness of this theory for the interpretation of ^2J(C,H) was pointed out also by others.[16–18] In the present case it explains the experimental findings nicely.

Similarly, a considerable reduction in magnitude is observed for the vicinal interaction $^3J(6,\alpha)$ by lone-pair protonation in accord with theoretical considerations.[17] Here again the coupling becomes more benzene-like in the ion. The same is true for ^4J(H,H) in the HC–N–CH fragment which increases from −0.15 to 0.99 Hz.[12] In fact, considering the percental change (cf. Table II), $^2J(3,\alpha)$ and $^3J(6,\alpha)$ are the C,H coupling constants that are most strongly affected by protonation. It follows that the nitrogen lone pair contributes significantly to these interactions in the free base. It is furthermore interesting to note that—with the exception of $^1J(2,\alpha)$—all coupling constants involving H_α show negative protonation effects, whereas the changes determined for the interactions of H_β and H_γ are exclusively positive. This again points to the importance of lone-pair contributions to the coupling constants of H_α in the free base and to a removal of these contributions by protonation as well as to the existence of a large positive protonation effect of different origin in the case of $^1J(2,\alpha)$.

Finally, the small change found for $^3J(5,\beta)$ brings this coupling also closer to the benzene value (7.63 Hz[11]). Within our experimental error all other constants are hardly affected. Apparently neither lone-pair effects in the free base nor the substituent effect of N^+ in the ion are of great importance in these cases. Accordingly, $^2J(3,\alpha)$, $^3J(6,\alpha)$, and the one-bond coupling constants are the parameters most sensitive for the detection of protonation sites in polyaza compounds.

Calculations. Using the Pople–Santry approximation for the Fermi contact contributions to spin–spin coupling[19] and CNDO/2 calculations to derive the atom–atom polarizabilities, we have already shown that the experimental trends observed for J(C,H) data in nitrogen heterocycles and their ions are reproduced.[5] For the present case, the results of such a treatment, based on standard geometry[20] (R_{CC} = 0.140, R_{CN} = 0.134, R_{CH} = 0.108 nm) and $R_{\text{N}^+\text{H}}$ = 0.1034 nm for the ion[21] are given in Table III. As usual, the absolute magnitudes of the calculated J(C,H) values are too low, but the most significant protonation effects ($\Delta^1J(3,\beta)$, $\Delta^1J(4,\gamma)$, $\Delta^2J(3,\alpha)$, $\Delta^3J(6,\alpha)$, and $\Delta^3J(5,\beta)$, italics in Table III) are correctly predicted. A notable exception is the result for $^1J(2,\alpha)$ where only a modest increase is found.

The results of similar calculations by the more advanced FP-INDO method[22] are also given in Table III. Again standard

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Table IV. Calculated ^1J(C,H) Data (Hz) of Pyridinium Ion and Pyridine as Corrected for Charge Density Effects (cf. text)

	f_C	f_H	f_Cf_H	$^1J_{corr}$	$^1J_{exptl}$
			Pyridine		
C-2	1.047	0.975	1.021	157.92	177.37
C-3	0.988	0.998	0.986	142.52	162.69
C-4	1.019	0.990	1.009	141.79	161.13
			Pyridinium Ion		
C-2	1.047	1.029	1.077	179.85	190.7
C-3	1.001	1.049	1.050	172.53	173.95
C-4	1.013	1.036	1.050	159.30	169.43

geometry and R_{N^+H} = 0.1034 nm for the ion was used. The absolute values calculated are closer to the experimental data, but agreement between theory and experiment is still modest. As in other cases,[19] especially the ^2J(C,H) values are at variance with the observations. The signs of the important protonation effects (italics in Table III) are correctly predicted, but again the calculated increase of $^1J(2,\alpha)$ is smaller than that for the other two ^1J(C,H) values. This indicates that an additional mechanism, not accounted for by the theoretical model, contributes to this coupling in the ion. Since it is known that the effective nuclear charge at the two nuclei ^{13}C and ^{1}H plays an important part in the dependence of ^1J(C,H) on substituent effects,[23,24] we have considered this influence by calculating a correction factor f_Cf_H for $^1J(2,\alpha)$ in **1** and pyridine by using eq 1 proposed by Pople et al.[25] With

$$f_Cf_H = (1.00 - 0.30q_H)^3([3.25 - 0.35q_C]/3.25)^3 \quad (1)$$

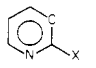
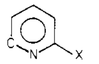
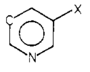
the net electron densities q_H and q_C on hydrogen and carbon, respectively, from the CNDO/2 calculations, we derive the data presented in Table IV. The results for $^1J(2,\alpha)$ are certainly improved. However, if the corrections are applied to the other ^1J(C,H) values as well, which seems to be a logical and necessary step, the calculated trend for the ΔJ(C,H) values is again at variance with the experimental observation of an attenuated protonation effect in the order $\Delta J(2,\alpha) > \Delta J(3,\beta) > \Delta J(4,\gamma)$. The reasons for the failure of the FP-INDO method to predict $\Delta J(2,\alpha)$ correctly are, therefore, not clear and the possibility that geometrical changes not accounted for by our approach are responsible is presently under investigation.

Comparison with ^{13}C,^{19}F Coupling Constants. In a similar study on the three isomeric fluoropyridines and their ions Lichter and Wasylishen[26] reported protonation effects for the C,F coupling constants that are of interest with respect to our results.

In the case of one-bond couplings the magnitude of the changes found in the α and γ positions parallel those observed for the ^1J(C,H) values. They are, however, of opposite sign, since C,F coupling constants over one bond are known to be negative.[27] At the β position ^1J(C,F) is hardly affected by protonation, contrary to the findings for ^1J(C,H). This indicates that, at least in part, different mechanisms operate in both cases and that conjugative interactions and the partial double-bond character of the C,F bond make an important contribution to the ^1J(C,F) values at C-2 and C-4.

For the other spin–spin interactions we find a parallel behavior of J(C,F) and J(C,H) in the case of the reduction observed for $^2J(3,\alpha)$ and $^3J(6,\alpha)$ and the increase measured for $^3J(5,\beta)$. This supports the suggestion[26] that these C,F coupling constants are also affected by the nitrogen lone pair in the free base. In fact, protonation brings these couplings closer to the values of the corresponding interactions in fluorobenzene, as it brings the particular C,H coupling constants closer to the values found for benzene (Table V).

Table V. Comparison of Selected C,F Coupling Constants in Fluoropyridine, Fluoropyridinium Ion, and Fluorobenzene and the Corresponding C,H Coupling Constants in Pyridine, Pyridinium Ion, and Benzene (all data in Hz)

		free base	ion	benzene
	X = F	37.6	24.4	21.0
	X = H	8.47	5.1	1.1
	X = F	14.6	1.5	7.7
	X = H	11.0	6.4	7.6
	X = F	4.2	7.0	7.7
	X = H	6.59	7.20	7.6

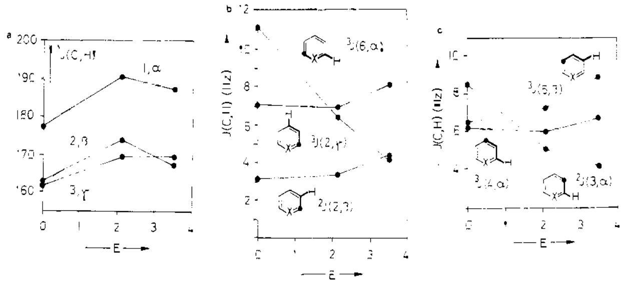


Figure 2. (a) Correlation between one-bond C,H coupling constants in pyridine, pyridinium ion, and pyridine *N*-oxide and the Pauling electronegativity of the substituent at the nitrogen (cf. text). (b) and (c) Correlation between J(C,H) data and Pauling electronegativity (X = N, N$^+$–H, N$^+$–O$^-$).

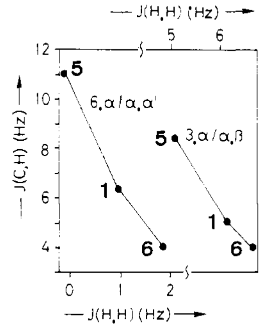


Figure 3. Correlation between J(C,H) and J(H, H) data in pyridine (**5**), pyridinium ion (**1**), and pyridine N-oxide (**6**).

The remaining J(C,H) values only show minor changes upon protonation, whereas the J(C,F) data appear to be more sensitive in general.

***J*(C,H) Data and Substituent Electronegativity.** The electronegativity effect of substituents on H,H coupling constants in monosubstituted benzenes has been studied in detail,[28,29] and Castellano and Kostelnik were the first to point out that similar mechanisms operate for H,H coupling constants in a series of N-substituted pyridines.[10] Since data for pyridine *N*-oxide have recently become available,[30] a similar approach for the analysis of J(C,H) values is now possible with our results for **1**, the missing link between pyridine (**5**) and pyridine *N*-oxide (**6**). As the smaller long-range couplings for **1** were not determined, the discussion is still somewhat incomplete, but the major effects should clearly be recognized.

Following Castellano and Kostelnik,[10] we consider pyridine, pyridinium ion, and pyridine *N*-oxide as systems containing

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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]

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

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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 = pK_a^N = pK_a^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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