Solution and Gas-phase Basicities of Pyridines with Bulky α-Substituents

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Steric hindrance to solvation of pyridinium cations is largest for two α-t-butyl substituents, less for one t-butyl and one phenyl, less for two α-phenyl groups, and least for one phenyl and one alkyl. The effect of α-phenyl groups is reduced by buttressing. Gas-phase proton affinities of the pyridine determined by dimer dissociation do not correlate with the solution pK_a values. Steric accelerations of pyridinium dealkylation show fair correlation with solution pK_a; reasons for discrepancies are discussed.

The low basicity of 2,6-di-t-butylpyridine (pK_a *ca.* 1.4 units less than expected on additivity principles), first thought to be due to steric requirements of the proton,[1] is now considered to be a manifestation of steric inhibition of solvation.[2] Such inhibition of solvation affects the pK_a of other hindered bases [3] to an extent which varies with the composition of the solvent in alcohol–water mixtures.[4] Increased rotational barriers may also play a part.[5] Temperature jump methods show that rates of deprotonation are effectively diffusion controlled and that a reduction in the rate of protonation accounts for the low basicity of 2,6-di-t-butylpyridine.[6] The subject has recently been reviewed.[7] In the gas phase, 2,6-di-t-butylpyridine is a *stronger* base than pyridine.[8]

Bulky α-substituents are well known to cause both steric hindrance in *N*-alkylation reactions of pyridines,[9,10] and steric acceleration in *N*-dealkylation reactions of pyridiniums.[11] The present work was undertaken to ascertain if there was any quantitative correlation of the effects of α-substituents on steric acceleration with the pK_a values.

Experimental

pK_a Values were determined spectrophotometrically [12] with a Pye-Unicam model SP 8–100, and a 10 cm path length cell. Standard 0.2M-HCl was prepared by diluting a CVS 50 ml ampoule to 500 ml with 70% v/v EtOH (70% EtOH was prepared by mixing 300 ml of H_2O with 700 ml of EtOH) to give 1M-HCl. 50 ml of this solution was further diluted to 250 ml with 70% v/v EtOH. Standard 0.2M-NaCl was prepared by dissolving NaCl (5.85 g) in 500 ml of 70% v/v EtOH. Standard 0.1M-$ClCH_2COOH$ was prepared by dissolving $ClCH_2COOH$ (4.725 g) in 500 ml of 70% v/v EtOH. Standard 0.1M-HCOOH was prepared by diluting 98—100% HCOOH (19.25 ml) to 500 ml with 70% v/v EtOH. Standard 0.1M-NaOH was prepared by diluting a CVS 50 ml ampoule to 500 ml with 70% v/v EtOH. Buffer solutions were prepared by mixing standard HCl and standard NaCl to give solutions in the range pH 1.2—2.6, standard 0.1M-$ClCH_2COOH$ with standard 0.1M-NaOH to give pH 3.2—4.6, or standard 0.1M-HCOOH with standard 0.1M-NaOH to give pH 5.0—5.8 (*cf.* ref. 13). Solutions of the pyridine bases were 8×10^{-6}M.

Separate portions (20 ml) of a stock solution (4×10^{-5}M in pyridine base) were diluted to 100 ml with (a) 1M-hydrochloric acid, (b) 0.1M-NaOH, and (c) at least six different buffer solutions to obtain the spectra of the pure cation and neutral forms of the pyridine as well as those of mixtures at known pH. All pH values were checked with a Pye 290 pH meter, calibrated before each set of measurements. The ionic strength of all buffer solutions was 0.01 except those made with HCl–NaCl which were 0.1. The temperature of the measurements was 20 °C. Results are given in Table 1.

Gas-phase Basicities.—Experiments were performed on a Varian Mat 311A reversed geometry mass spectrometer fitted with a chemical ionization source. Methane was used as reagent gas. Samples were prepared by mixing two compounds and introduced *via* the direct insertion probe. After selection of the unsymmetrical proton-bound dimers by the magnet, the ions issued from unimolecular fragmentations in the second field-free region were recorded by scanning the field of the electric sector. Typical conditions were 3 kV accelerating voltage, 1 mA emission current, 100 eV electron energy and a *ca.* 1 Torr methane pressure.

Discussion

Because of solubility difficulties in more aqueous media, the pK_a measurements of this study were carried out in 70% ethanol. pK_a Data for 2- and 4-monosubstituted and 2,3-disubstituted pyridines are given in Table 2, for measurements in aqueous and, where available, in aqueous ethanolic media. Table 2 also gives extrapolated values for the mono- and di-substituted pyridines in 70% ethanol: they were obtained taking the differences $(pK_a)_{H_2O} - (pK_a)_{70\%} = 1.56$ and $(pK_a)_{50\%} - (pK_a)_{70\%} = 0.73$ for pyridine as applicable to all the compounds. Finally Table 2 also gives the incremental values for various 2- and 4-mono- and 2,3-di-substitutions which were subsequently used.

Table 3, in addition to the measured pK_a values, gives ' additive ' pK_a values, obtained using the summed incremental values of Table 2 for the individual substituents. The Δ value reflects the difference between the measured and ' additive ' pK_a values for each individual compound: a positive Δ indicates that the measured pK_a is *higher* than the ' additive value.' The compounds are considered in the following groups.

(i) Compounds with two α-t-butyl groups [(1) and (2)] for which Δ is −1.9 to −2.1. Our result for compound (2) agrees well with the literature value for compound (1) and demonstrates the considerable hindrance to solvation of these cations.

(ii) Compounds with one α-t-butyl and one α-phenyl [(3) and (4)], for which Δ is −1.6 to −1.9. Again severe hindrance to solvation is found; the extra effect of the ring fusion in (4) over (3) is not large.

(iii) Compounds with two α-phenyl groups (5)—(8) (except those in Group iv, see below), for which Δ is −0.8 to −1.5.

Table 1. Determination of pK_a values

Compound	M.p. (°C)	Lit. ref.	Pyridine		Pyridinium		Analytical wavelength: Pyridine		Analytical wavelength: Pyridinium	pK_a	S.d.
			$\lambda_{max.}$/nm	$10^{-3}\varepsilon$	$\lambda_{max.}$/nm	$10^{-3}\varepsilon$	λ/nm	$10^{-3}\varepsilon$	$10^{-3}\varepsilon$		
(2)	50—51	*a*	277	15.1	282	26.5	300	0.38	18.8	2.65	0.16
(3)	87—88	*b*	295	10.8	289	17.5	320	2.50	23.5	2.23	0.01
(4)	97	*c*	312	12.1	339	17.6	340	0.09	17.5	2.13	0.01
(5)	139	*d*	311	8.0	307	23.8	375	0.13	23.3	1.84	0.03
(6)	128	*b*	321	13.8	353	21.5	353	0.09	21.4	1.77	0.01
(7)	156	*c*	318	17.3	352	24.0	352	1.00	10.0	2.31	0.01
(8)	166—167	*b*	335	15.4	374	20.9	374	0.00	20.9	1.73	0.02
(9)	65—66	*e*	308	2.4	287	1.36	282	5.00	17.0	5.28	0.02
(10)	71	*f*	295	8.0	298	22.0	298	8.00	23.0	3.89	0.03
(11)	144—146	*c*	301	8.0	292	16.0	325	1.00	11.3	3.89	0.08
(12)	103—104	*c*	286	10.3	308	16.6	305	5.30	16.5	4.18	0.04
(13)	151—152	*c*	313	20.5	339	21.6	339	0.25	21.6	4.38	0.01
(14)	229—230	*g*	302	19.9	329	13.0	334	1.89	13.1	1.95	0.03
(15)	246	*h*	297	9.0	325	6.63	330	1.00	6.38	2.52	0.04

[a] S. S. Thind, Ph.D. Thesis, University of East Anglia, 1980. [b] A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1895. [c] Ref. 15. [d] A. Chermprapai, Ph.D. Thesis, University of East Anglia, 1981. [e] Ref. 14. [f] M. Elisseou, Ph.D. Thesis, University of East Anglia, 1982. [g] A. R. Katritzky, B. Plau, and K. Horvath, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2554. [h] F. A. Al-Omran, M.Sc. Thesis, University of East Anglia, 1978.

Table 2. 2- and 4-mono- and 2,3-di-substituted pyridines

Substituent(s)	Measured pK_a (at 25 °C except where indicated)			Assumed pK_a in 70% EtOH	Increment
	H_2O	50% EtOH	70% EtOH		
None	5.21 [a]	4.38 [b]	3.65 [c,e]	3.65	0.00
2-Me	6.00 [d,f]	5.05 [b]		4.32	+0.67
None				4.44	+0.79
2-Bu^t	5.89 [c,e]	4.68 [b]	4.15 [c,e]	4.15	+0.50
2-Ph	4.77 [f]			3.21	−0.44
3-Me	5.64 [d,g]			4.08	+0.43
3-Ph	4.74 [d,h]			3.18	−0.47
4-Ph	5.35 [a]			3.79	+0.14
2,3-Me_2	6.64 [d,g]			5.08	1.43
2,3-$(CH_2)_4$					1.49 [i]
2,3-(*o*-C_6H_4)CH_2		4.1 [a,l]		3.37	−0.28

[a] A. Fischer, W. J. Galloway, and J. Vaughn, *J. Chem. Soc. B*, 1964, 3591. [b] Ref. 10. [c] Corrected to 25 °C from 24 °C by equation dpK_a/dT = −0.011 °C.[12] [d] Similarly corrected to 25 °C from 20 °C. [e] Ref. 4. [f] K. Kahmann, H. Sigel, and H. Erlenmeyer, *Helv. Chim. Acta*, 1964, **47**, 1754. [g] H. H. Perkampus and G. Puscher, *Ber. Bunsenges. Phys. Chem.*, 1968, **72**, 429. [h] A. R. Katritzky and P. Simmons, *J. Chem. Soc.*, 1960, 1511. [i] From pK_a (16) [j] − pK_a (17) [k]. [j] A. Albert, *J. Chem. Soc.*, 1965, 4653. [k] E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, 1964, **86**, 2671. [l] In 50% MeOH, no temperature given, J. N. Chaterjee and K. Prasad, *J. Indian Chem. Soc.*, 1955, **32**, 371.

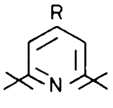
The hindrance to solvation is now rather less, and the effect of ring closure becomes noticeable: for closure to a six-membered ring [in (6) and twice in (8)] the Δ is more negative than in (5), whereas for closure to a five-membered ring [in (7)] there is a smaller negative Δ.

(iv) Compounds with one α-phenyl and one α-alkyl substituent [(10)—(13)], for which Δ is −0.3 to −0.9, again a small range. Here the values of Δ are larger when the α-alkyl group is part of a ring.

(v) Compound (9) with two α-methyl groups shows essentially zero Δ. A similar result was found previously [1] for 2,6-lutidine.

(vi) Compounds with α-phenyl groups each buttressed by a second phenyl group in the β-position [(14) and (15)], for which Δ is +0.1—+0.6. Now the buttressing turns the α-phenyl groups out of the pyridinium ring plane and causes *much* less hindrance to solvation such that a significantly positive Δ is found for (15).

Correlation of Pyridine pK_a *Values with their Nucleofugacity.*—The k_2 second-order rate constants for the reactions of the corresponding *N*-benzylpyridinium cations with piperidine in chlorobenzene solution at 100 °C afford a quantitative measure of the tendency of a pyridine to act as a leaving group. Comparison of these k_2 values with the measured pK_a gives a scatter pattern.[14] Graphical comparisons of k_2 with Δ are given in the Figure. There is a rough correlation of increasing k_2 with increasingly negative Δ, which is in agreement with the concept of steric acceleration as being important in determining k_2.[15] Two points fail badly for the correlation. The tetraphenyl compound (14) is more basic and/or reacts faster than expected: evidently the twisting of the phenyl groups is more effective in allowing the solvation of the cation than in reducing steric hindrance in *N*-benzylpyridinium. Conversely, 2-t-butyl-4,6-diphenylpyridine (3) is less basic and/or reacts slower than expected. t-Butyl groups are very effective in reducing solvation, and less so in causing steric acceleration—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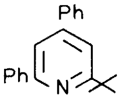
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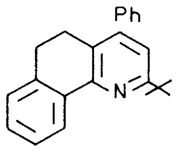
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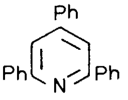
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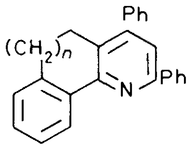
(6) n = 2
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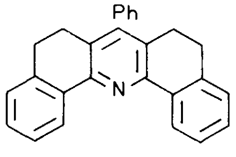
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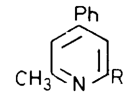
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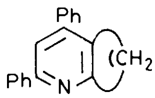
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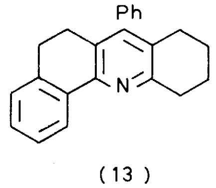
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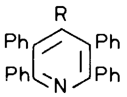
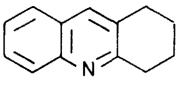

(14) R = H
(15) R = Ph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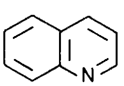
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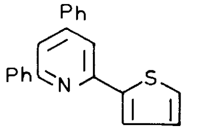
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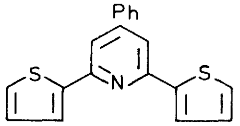
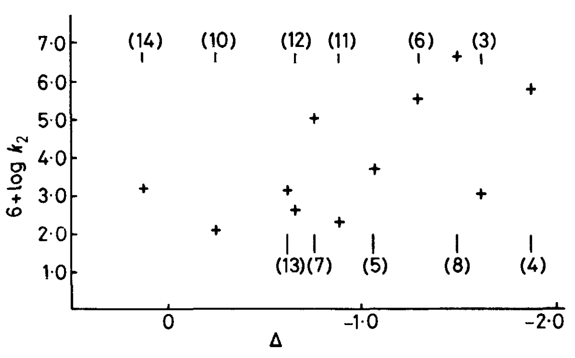

(19)

Table 3. Measured and calculated pK_a values for 2,6-disubstituted pyridines

	Substituents	Measured pK_a	Increments	Calculated pK_a	Δ	6 + log k_2 [a]
(1)	2,6-Bu^t_2	2.78	2 × 0.50	4.65	−1.87	
(2)	2,6-Bu^t_2; 4-Ph	2.65	(2 × 0.50) + 0.14	4.79	−2.14	
(3)	2-Bu^t; 4,6-Ph_2	2.23	0.50 + 0.14 − 0.44	3.85	−1.62	3.03
(4)	2-Bu^t; 4-Ph; 6,5(o-C_6H_4)C_2H_4	2.13	0.50 + 0.14 − 0.28	4.01	−1.88	5.78
(5)	2,4,6-Ph_3	1.84	(2 × −0.44) + 0.14	2.91	−1.07	3.69
(6)	2,4-Ph_2; 6,5(o-C_6H_4)C_2H_4	1.77	−0.44 + 0.14 − 0.28	3.07	−1.30	5.53
(7)	2,4-Ph_2; 6,5(o-C_6H_4)CH_2	2.31	−0.44 + 0.14 − 0.28	3.07	−0.76	5.03
(8)	2,3;5,6-di-(o-C_6H_4)C_2H_4	1.73	(2 × −0.28) + 0.14	3.23	−1.50	6.65
(9)	2,6-Me_2; 4-Ph	5.28	(2 × 0.79) + 0.14	5.37	−0.09	
(10)	2-Me; 4,6-Ph_2	3.89	0.79 − 0.44 + 0.14	4.14	−0.25	2.08
(11)	2,3-$(CH_2)_3$; 4,6-Ph_2	3.89	1.43 − 0.44 + 0.14	4.78	−0.89	2.34
(12)	2,3-$(CH_2)_4$; 4,6-Ph_2	4.18	1.49 − 0.44 + 0.14	4.84	−0.66	2.63
(13)	2,3-$(CH_2)_4$; 4-Ph; 6,5-(o-C_6H_4)C_2H_4	4.38	1.49 + 0.14 − 0.28	5.0	−0.62	3.13
(14)	2,3,5,6-Ph_4	1.95	(2 × −0.44) + (2 × −0.47)	1.83	+0.12	3.21
(15)	2,3,4,5,6-Ph_5	2.52	(2 × −0.44) + (2 × −0.47) + 0.14	1.97	+0.55	

[a] Ref. 15.



log k_2 for debenzylation of N-benzylpyridinium against Δ

perhaps there is still strain in the S_N2 transition state and the *decrease* in strain (which determines k_2) is less. The effect is seen to a lesser degree for compound (4).

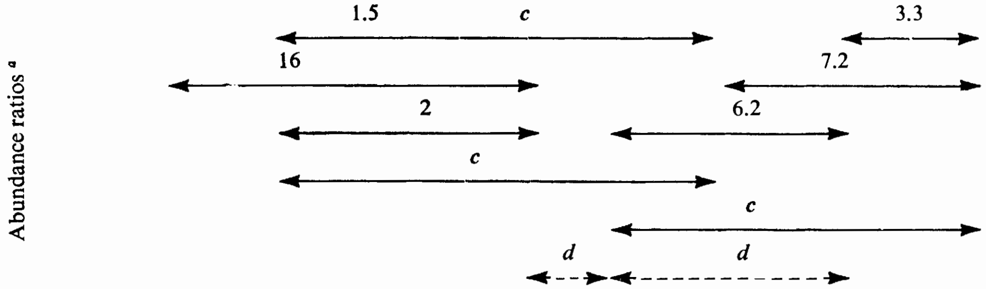
Pyridine Gas-phase Basicities.—Cooks *et al.* have recently shown that relative gas-phase proton affinities are accessible in an experiment in which two bases B_1 and B_2 are bound by a proton and the resulting dimer is dissociated.[16,17] This method employs a chemical ionization source to generate the proton-bound dimer and a reverse sector mass spectrometer to select the dimer and record the mass spectrum of its fragmentation products.

$$B_1 \cdots \overset{+}{H} \cdots B_2 \longrightarrow B_1H^+ \text{ and/or } B_2H^+$$

The relative peak heights of the fragment ions are indicative of the relative proton affinities of the parent bases.

Table 4. Relative gas-phase basicities

Compounds	(15)	>	(13)	>	(8)	>	(14)	>	(12)	>	(5)	>	(11)	>	(3)
pK_a[b]	2.52		4.38		1.73		1.95		4.18		1.84		3.89		2.23



[a] $[B_1H^+]/[B_2H^+]$ ratios uncorrected for the electron multiplier response. [b] Values from Table 1. [c] Greater than the signal to noise ratio. [d] Relative basicities of (11), (12), and (14) checked by using 2-thienylpyridines (18) and (19) as reference compounds.

We have applied this technique to various mixtures of compounds (3), (5), (8), and (11)—(15) and the sequence of relative proton affinities is shown in Table 4. Surprisingly, we found no correlation between these relative gas-phase basicities and the sequence of pK_a values determined in EtOH–H_2O mixtures. However, if we compare only the pyridines with similar substituents, a good agreement with the pK_a values is observed. For instance, we find the sequence (12) > (11) > (3) for ' alkylated ' pyridines and (15) > (14) > (5) for ' phenylated ' pyridines.

Among the factors which could restrict application of the technique, the formation of a covalently bonded dimer structure appears to be the major limitation.[17] However, our results seem to indicate that the partners in the dimer must be of very similar structure in order to get positive results.

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