327. *Catalytic Power of Pyridine and Related Brönsted Bases in the Iodination of Ketones and Nitromethane*

By J. A. Feather and V. Gold

The rates of proton transfer from ketones (acetone, isopropyl methyl ketone, diethyl ketone, pinacolone, and cyclohexanone) and from nitromethane to pyridine, nine methylpyridines, and 2-ethylpyridine, have been measured. The results are analysed in terms of the Brönsted catalysis law and indicate that steric hindrance retards the reaction of ketones with 2-substituted bases, its magnitude depending on the structure of the ketone and the nature and number of α-substituents in the base. It is suggested that proton abstraction occurs preferentially from a planar *trans*-conformation of the breaking C–H bond and the carbonyl group, with the ring of the pyridine base lying in the same plane. Compared with unhindered bases, the transfer of the proton to a hindered base has progressed less far when the transition state is reached. Possible complications in the exact separation of steric and electronic effects, arising from hyperconjugation, are pointed out.

An appendix deals with a steric effect in the gas–liquid chromatography of pyridine bases on a diglycerol column.

METHYL substituents in the pyridine nucleus increase the basic strength (as measured by the p*K* value in aqueous solution) in a regular and additive manner, with the implication that their effect is essentially electronic and not steric in origin. The irregular effect of large substituent groups in the α-positions is compatible with the superposition of steric and electronic factors.[1,2] On the other hand, even methyl substituents in α-positions reduce the catalytic power of these compounds in certain reactions in solution. A systematically studied example is the hydrolysis of acetic anhydride for which a single α-methyl substituent inhibits the catalysis.[3] In this reaction pyridine does not function as a Brönsted base but as a nucleophilic catalyst, involving association of a larger entity than the proton (*viz.*, the acetyl cation) with the heterocyclic nitrogen atom. However, the unexpectedly large effect in this reaction suggested to us that pyridine bases were particularly susceptible to steric hindrance and might therefore allow the detection of a steric effect on the velocity of a proton-transfer reaction. In fact, several isolated instances of unusual catalytic effects (generally, but not always, smaller than expected) in base-catalysed reactions have already been reported.[4–8] Not all of these relate to simple proton transfers or to unambiguously established mechanisms. With one exception [4] they involve the pyridine bases.

Since the dissociation constants of methylpyridines in aqueous solutions do not suggest that steric hindrance to ionisation is important, an unusual catalytic activity by a member of this group of compounds must be connected with an unusual effect in the transition state of the reaction investigated, and cannot be attributed to an anomalous thermodynamic base strength. It also follows that low catalytic power cannot be ascribed to steric

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[1] Brown, McDaniel, and Häfliger in " Determination of Organic Structures by Physical Methods," ed Braude and Nachod, Academic Press, New York, 1955.

[2] Gold, in " Progress in Stereochemistry," Vol. 3, ed. de la Mare and Klyne, Butterworths, London, 1962.

[3] Gold and Jefferson, *J.*, 1953, 1409; Butler and Gold, *J.*, 1961, 4362.

[4] Bell, Gelles, and Möller, *Proc. Roy. Soc.*, 1949, *A*, **198**, 308.

[5] Bell and Trotman-Dickenson, *J.*, 1949, 1288.

[6] Bell and Wilson, *Trans. Faraday Soc.*, 1950, **46**, 407.

[7] Pearson and Williams, *J. Amer. Chem. Soc.*, 1953, **75**, 3073.

[8] Zollinger, *Helv. chim. acta*, 1955, **38**, 1623; Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.*, 1956, **52**, 1100; Willi, *ibid.*, 1959, **55**, 433; Bell and Jensen, *Proc. Roy. Soc.*, 1961, *A*, **261**, 38; Mairanovskii, *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.*, 1962, 731; Gutsche, Buriks, Nowotny, and Grassner, *J. Amer. Chem. Soc.*, 1962, **84**, 3775; Covitz and Westheimer, *ibid.*, 1963, **85**, 1773.

hindrance to solvation in the transition state,[2] since the charge to be stabilised in the transition state is not as large as that of the pyridinium ion and since there is no steric hindrance to ionisation (which might be ascribed to steric hindrance to solvation) in these pyridinium ions. In any event, the electric charge would be screened from solvent effects by the ketonic component of the transition state.

The present study of the iodination of ketones and of nitromethane was accordingly undertaken with the specific object of assessing the importance of steric effects in the transfer of a proton from carbon to pyridine bases. The base-catalysed halogenation reactions of ketones were selected, since they are well known to involve a rate-limiting proton transfer,[9] and the absence of a ternary term in the rate equation [10] (*i.e.*, a contribution to the reaction velocity from a term proportional to the product of the concentrations of pyridine and pyridinium ion) suggests that the proton transfer is bimolecular. The behaviour of nitromethane is known to be analogous to that of ketones in many respects.[9]

The ketones were acetone, diethyl ketone, isopropyl methyl ketone, pinacolone (methyl t-butyl ketone), and cyclohexanone. The bases were pyridine, the three picolines, five lutidines, 2,4,6-collidine, and 2-ethylpyridine: five of these compounds do not contain an α-substituent, the other six do. Their pK values have been measured by two independent groups; [1,11] the agreement between the two sets of results is only fair but close enough to suggest that the values are sufficiently accurate for our present purpose.

EXPERIMENTAL

Pyridine bases were purified by the methods described below. Their purity was established by gas chromatography, with either hydrogen (flame-ionisation detector) or argon (tritium-ionisation detector) as carrier gas. A column packing of diglycerol (bis-2,3-dihydroxypropyl ether) on Celite (80—85 mesh) gave a good separation of the bases [12] (see Figure 2, Appendix); a packing prepared from paraffin wax (3 parts) and Celite (100—150 mesh; 7 parts) in a column operated at 145° was suitable for the detection of non-basic impurities. Nevertheless, it was impossible to detect small amounts of 3-picoline in 4-picoline and vice versa. Specific methods of removing likely impurities were employed whenever possible, especially for the bases with low catalytic activity. Solid adducts were generally decomposed by aqueous alkali and distillation (of the azeotrope with water). All bases were stored over solid sodium or potassium hydroxide and redistilled immediately before use. Pyridine (AnalaR) of stated minimum purity 99% was used without purification except in the studies of acetone and nitromethane, for which it was purified by recrystallisation of the zinc chloride complex.[13] 2-Picoline (Hopkin and Williams), fractionally distilled from barium oxide, was found by gas chromatography to contain less than 0·2% pyridine. For the experiments with acetone and nitromethane a sample purified by recrystallisation of the zinc chloride complex was employed.[13]

3-Picoline was treated twice with a mixture of acetic and phthalic anhydrides,[14] to remove 2- and 4-substituted impurities, and fractionally distilled (b. p. 142—143°). 4-Picoline (B.D.H.) was purified by crystallisation of the hydrogen oxalate salt from ethanol.[15] It then had b. p. 145·5—145·9°. 2,4-Lutidine (Light & Co.) was purified by crystallisation of the mercuric chloride complex from 0·1N-aqueous hydrochloric acid [16] (m. p. 132·5—133°; lit., 131—132°,[17] 132° for a hydrated,[18] 127° for the anhydrous complex [13,16]) (b. p. 157·5—157·9°). The impurities in the original material (2,5-lutidine and 2-ethyl-6-methylpyridine) were removed by this treatment. 2,5-Lutidine (Light & Co.) was found to be highly pure and was used directly. 2,6-Lutidine (Hopkin & Williams) of stated purity of 99% was freed from slight impurities

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[9] Bell, " Acid-Base Catalysis," Oxford Univ. Press, Oxford, 1941.
[10] Swain, DiMilo, and Cordner, *J. Amer. Chem. Soc.*, 1958, **80**, 5983.
[11] Andon, Cox, and Herington, *Trans. Faraday Soc.*, 1954, **50**, 923.
[12] Fitzgerald, *Austral. J. Appl. Sci.*, 1961, **12**, 51.
[13] Heap, Jones, and Speakman, *J. Amer. Chem. Soc.*, 1921, **43**, 1936.
[14] Riethof, Richards, Savitt, and Othmer, *Ind. Eng. Chem., Analyt.*, 1946, **18**, 458.
[15] Kolloff and Hunter, *J. Amer. Chem. Soc.*, 1941, **63**, 490.
[16] Gero and Markham, *J. Org. Chem.*, 1951, **16**, 1836.
[17] Eguchi, *Bull. Chem. Soc. Japan*, 1929, **2**, 182.
[18] Ladenburg, *Annalen*, 1888, **247**, 36.

(3- and 4-picoline) *via* the urea complex.[19] 2,4,6-Collidine (B.D.H.) was purified by a combination of two processes.[20] Collidine (89 g., 0·74 mole) was dissolved in sulphuric acid (80 g. diluted with 150 ml. water) and insoluble and non-basic material removed by separation of layers and extraction with chloroform. The solution was almost neutralised with concentrated sodium hydroxide. Sodium dichromate solution (4M) and sulphuric acid (3·5M) were then added dropwise to the stirred solution until a dark material, assumed to be an oxidation product, began to form. A precipitate of collidinium dichromate [21] was filtered off, recrystallised from water, washed with dilute sodium dichromate solution, and decomposed with sodium hydroxide. The collidine–water azeotrope was distilled from the mixture, dried (NaOH), refluxed over barium oxide, and distilled (yield 46 g.). Boron trifluoride etherate (10 ml.) was added. After a few days a precipitate was filtered off and the liquid distilled (b. p. 89—91°/86 mm.). The product was allowed to stand over water (35 ml.) in order to remove traces of boron trifluoride, separated, and dried and distilled as before (b. p. 170—171°; yield 23 g.).

2-Ethylpyridine (Light & Co.) was distilled (b. p. range $<0·3°$ at 148°).

In the purification of ketones particular attention was paid to eliminating oxidising agents (presumed to be hydroperoxides [22]) formed by certain ketones on standing in contact with air and which liberate iodine from iodide solutions. This complication was absent with acetone and not serious with diethyl ketone and pinacolone. Cyclohexanone autoxidised slowly and isopropyl methyl ketone very rapidly. These materials were distilled and stored under nitrogen. Absence of peroxides was established by tests with a mixture of potassium thiocyanate and ferrous ammonium sulphate. The purified ketones and nitromethane were stored in the dark in stoppered bottles inside desiccators.

Acetone (May & Baker) was purified *via* the sodium iodide complex,[23] pinacolone (prepared from acetone [24]), and diethyl ketone (Harrington) by crystallisations of the semicarbazone (m. p. 140·5—141·5°), and cyclohexanone (Hopkin and Williams) by crystallisations of the bisulphite compound.

Isopropyl methyl ketone (B.D.H.) was purified by crystallisations of the semicarbazone from aqueous ethanol (50% v/v). The product (m. p. 114·5—115°) was decomposed by addition of dilute sulphuric acid containing ferrous ammonium sulphate and distillation of the water–ketone azeotrope (b. p. 78°). This was kept over ferrous ammonium sulphate and distilled in a stream of nitrogen (b. p. 90—92°: the wide range is attributed to the presence of a small quantity of water).

Nitromethane (Eastman Kodak, " Spectro " grade) was dried ($CaSO_4$) for several days and then refluxed for several hours with a stream of nitrogen to remove volatile impurities. It was then distilled under nitrogen (b. p. range $<0·1°$ at 100·5°).

Stock buffer solutions were prepared from the bases by partial neutralisation with hydrochloric acid. At least two buffer solutions with the same concentration (0·1M) of pyridinium (or substituted pyridinium) ion and varying concentrations of free base were used in each reaction. Iodine stock solutions were *ca.* 10^{-4} to 10^{-3}M in 0·1M-aqueous potassium iodide. They were analysed by spectrophotometry. The presence of iodide reduces the concentration of free iodine and thereby prevents the precipitation of amine–iodine complexes in reaction solutions. It also converts iodine into the much more strongly absorbing tri-iodide ion ($\varepsilon_{max.} = 26,400$ at 3530 Å; for iodine, $\varepsilon_{max.} = 746$ at 4600 Å).[25]

Reaction mixtures were prepared by mixing appropriate amounts of the stock buffer solution, 0·1M-potassium chloride solution (to maintain a constant ionic strength of 0·1M for all reactions), and the substrate, and, finally, adding iodine stock solution to produce an initial concentration of iodine in the range 10^{-5} to 10^{-4}M. The substrate was added either neat or (for nitromethane) as a stock solution in 0·1M-potassium chloride solution, or (for pinacolone) as a stock solution in ethanol.

Reaction rates were followed by spectrophotometry in the constant-temperature (25·00° ± 0·05°) cell compartment of a Beckman DU spectrophotometer by the disappearance of the tri-iodide absorption at 3530 Å. The concentration of the substrate being *ca.* 10^4 times

[19] Biddiscombe, Coulson, Handley, and Herington, *J. Chem. Soc.*, 1954, 1957.
[20] Brown, Johnson, and Podall, *J. Amer. Chem. Soc.*, 1954, **76**, 5557.
[21] Profft and Melichar, *J. prakt. Chem.*, 1955, **2**, 87.
[22] Sharp, Patton, and Whitcomb, *J. Amer. Chem. Soc.*, 1951, **73**, 1842.
[23] Shipsey and Werner, *J.*, 1913, **103**, 1255.
[24] *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 459, 462.
[25] Awtrey and Connick, *J. Amer. Chem. Soc.*, 1951, **73**, 1842.

that of iodine in solution, graphs of optical density against time were linear. There was a slight tailing-off near the end of a run: this is the expected behaviour when the halogen concentration is so low that its reaction with the conjugate base of the ketone becomes rate-limiting. In addition, there was in some runs a slight increase in rate over a short initial part so that the entire reaction curves were very slightly S-shaped. These disturbances did not affect the accuracy of determination of the zero-order rate (of disappearance of iodine) from the linear parts of the reaction curves. For each ketone it was shown that the same zero-order rate was observed if the initial concentration of iodine was doubled, which establishes, *inter alia*, that the ketones used were free from reactive impurities. The zero-order rate coefficients (k) were calculated from the steady rate of fall in the optical density (D), the optical density of an equivalent solution without addition of ketone (D_0) and the initial concentration of iodine ($[I_2]_0$) by the equation $k = (\mathrm{d}D/\mathrm{d}t)[I_2]_0/D_0$. Two buffer concentrations were used for each buffer ratio. Duplicate runs were performed in some of the systems: these showed good reproducibility of results (within 1%).

In the case of pinacolone a slight modification of the procedure[7] was used, in that the reaction velocity was calculated from the total reaction time for a given initial concentration of iodine, the " completion " time being obtained as the intercept of the linear portion of the optical density–time graph on the time axis. It was verified for all bases (except 2-picoline) that the total reaction time was directly proportional to the initial concentration of iodine. For reasons of solubility, pinacolone was added to the buffer solution as a stock solution in ethanol, resulting in the presence of 3·7% of ethanol in the reaction mixture. This was found to result in a slow side-reaction removing iodine which became significant (10—30% of the total rate) for catalysis by 2,6-lutidine. The effect was corrected for by plotting the rate against the concentration of base for a number of runs and obtaining the velocity of the side-reaction (presumed not to be base-catalysed) as the intercept for zero concentration of base. Because of this complication the catalytic coefficient of 2,6-lutidine for pinacolone is estimated to be less accurate ($\pm 5\%$) than that for reactions for which the reaction velocity was directly proportional to the concentration of free base.

The solutions of 2,4,6-collidine buffers were sufficiently alkaline for catalysis by hydroxide ion to become significant for the reaction with acetone. At a constant buffer ratio the variation of the rate with buffer concentration was linear, the extrapolated rate at zero buffer concentration corresponding to hydroxide-ion catalysis. Because of the discrepancy between the available pK values for this base (7·45 and 7·59)[11,1] the hydroxide-ion concentration is not known with certainty, and the catalytic coefficients k_{OH^-} corresponding to the two values are 0·36 and 0·26 $\mathrm{sec.^{-1}\ l.\ mole^{-1}}$. Taking the mean value of k_{OH^-}, a small correction was applied to the rates of reactions catalysed by 2,6-lutidine; none was required for the others.

In a similar way acid-catalysis by pyridinium ion was detected in the reactions of diethyl ketone and isopropyl methyl ketone in pyridine buffers, the catalytic coefficients being *ca.* 7×10^{-7} and 6×10^{-8} $\mathrm{sec.^{-1}\ l.\ mole^{-1}}$, respectively. Acid-catalysis was not detected in other systems.

Because of the high reactivity of nitromethane, low substrate concentrations (0·01—0·02M)

TABLE 1

Summary of catalytic coefficients (values of $10^6 k_b$)

		I	II	III	IV	V	VI
	Concn. of substrate (M):	0·262	0·184	0·225	0·14	0·287	$\sim 10^{-2}$
(1)	Pyridine	5·7	2·4	1·84	0·85	11·5	640
(2)	2-Picoline	15·2	6·5	4·2	0·87	16·8	2430
(3)	3-Picoline	13·4	6·7	4·8	1·78	26	—
(4)	4-Picoline	20·4	9·2	7·1	3·65	32	2150
(5)	2,4-Lutidine	44	15·5	11·8	—	43	—
(6)	2,5-Lutidine	32	11·6	9·0	—	33	—
(7)	2,6-Lutidine	10·2	3·1	2·6	0·63	2·9	—
(8)	3,4-Lutidine	38	19·8	16·3	—	64	—
(9)	3,5-Lutidine	29	13·7	10·8	—	51	—
(10)	2,4,6-Collidine	18·5	5·2	5·4	—	4·9	—
(11)	2-Ethylpyridine	10·9	—	3·0	—	11·4	—

(I = acetone; II = diethyl ketone; III = isopropyl methyl ketone; IV = pinacolone; V = cyclohexanone; VI = nitromethane.) The Arabic numerals in the first column indentify the experimental points in the figures.

were needed and, to reduce hydroxide-catalysis, the buffer solutions were more acidic ([free base]/[conjugate acid] = 0·016—0·028). With iodine concentrations of *ca.* 6×10^{-4}M at an ionic strength of 0·1M (adjusted with potassium chloride) the graphs of optical density against time were distinctly S-shaped and, for comparison purposes, *initial* rate constants were evaluated as the mean of seven or eight experiments for each catalyst. A small correction for hydroxide-catalysis [26] was applied. These results do not have the same high precision as the measurements on ketones.

All catalytic coefficients for base-catalysis (k_b) were evaluated by combining measured zero-order rates of iodine consumption with the concentrations of substrate and free base. They are summarised in Table 1, the units throughout being sec.$^{-1}$ l. mole^{-1}.

DISCUSSION

All rate constants and catalytic coefficients evaluated in this study relate to the disappearance of iodine and not to that of the ketone or nitromethane. To obtain the latter information it would be necessary to know the number of iodine atoms introduced into each reacting molecule of the substrate. In base-catalysed halogenations of this type multiple substitution tends to occur, since a halogen substituent increases the acid strength of the molecule and hence its susceptibility to further substitution. Under such conditions the rate of halogen consumption increases until the rate of disappearance of reactant ketone is equal to the rate of formation of the final product.[27] A linear decrease of iodine concentration with time was found over most of the length of all runs, although a slight initial acceleration was sometimes noticeable. Our experiments include a fine gradation in reactivity of both ketone and catalyst, but we did not detect any systematic change in the initial curvature with structure of catalyst or substrate. For this reason we consider that the number of iodine atoms introduced per molecule of ketone does not vary with the catalyst employed. The catalytic coefficients of different bases with the same substrate are therefore comparable. Further, the reaction product may not be an iodoketone but the product of further reaction between iodoketone and base, as in the reaction between iodine and acetophenone in high concentrations of pyridine.[28,29] However, it is known that the rate of this reaction is governed by the initial proton transfer from acetophenone to pyridine.[29] This complication does not, therefore, affect the question whether the initial rate of proton transfer (which is the same as the rate of disappearance of ketone) is equal to the zero-order rate of disappearance of iodine or to one-half or one-third of that rate.

The low relative concentration of iodine and the known difficulty (presumably for steric reasons) of obtaining substitution of three iodine atoms, even under forcing conditions,[30,31] make it probable that either one or two iodine atoms are consumed per molecule of ketone. The *maximum* uncertainty in the comparison of the rates of different ketones from this cause is a factor of two or three. Because of this uncertainty we do not attempt a precise comparison of the reactivity of different ketones. The general result with open-chain ketones is the same as for the hydroxide-catalysis.[30] In comparisons of different bases for a single ketone the effects to be discussed sometimes involve much larger factors than two or three, and the regularity of the pattern of results obtained does not suggest that a variable multiplying factor should be used for different catalysts.

The occurrence of a zero-order reaction over the largest part of the reaction also indicates that for all substrates used the concentration of enol-form in aqueous solution was low compared with the concentration of iodine. Since the relative concentrations of iodine and ketone were in the ratio *ca.* 1 : 3000, the enol proportion, even for cyclohexanone, must have been significantly less than this ratio. This conclusion agrees with the report that the

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[26] Elving and Lakritz, *J. Amer. Chem. Soc.*, 1955, **77**, 3217.

[27] Bell and Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88; Bell and Yates, *J.*, 1962, 1927.

[28] King, *J. Amer. Chem. Soc.*, 1944, **66**, 894.

[29] Pearson, *J. Amer. Chem. Soc.*, 1947, **69**, 3100.

[30] Cullis and Hashmi, *J.*, 1956, 2512; 1957, 3080.

[31] Johnson and Fuson, *J. Amer. Chem. Soc.*, 1935, **57**, 919; Poggi, *Gazzetta*, 1940, **70**, 337.

ketone : enol ratio for liquid cyclohexanone[32] is 5000, provided that the solvent effect of water further increases the ratio. A solvent effect in this unexpected direction has in fact been observed.[32]

For all ketones it is considered that substitution occurs to a significant extent only in one of the methyl, methylene, or methine groupings adjacent to carbonyl. This is plausible in view of the disparity of concentrations of ketone and iodine and the expectation that the activation of C–H bonds by an iodine substituent would only weakly be transmitted across the carbonyl group.

For isopropyl methyl ketone (our only example with two non-equivalent potential reaction sites in a molecule) it is likely that reaction occurs preferentially in the methyl group. This is reasonable because the hydroxide-ion catalysed halogenation of di-isopropylketone is slower than that of acetone, and also because the reaction velocity for isopropyl methyl ketone is somewhat less than half that for acetone, with hydroxide ions[30] or pyridine as catalyst.

A comparison of the catalytic efficiency of the bases for isopropyl methyl ketone is illustrated in Figure 1 on the basis of the Brönsted catalysis law. The pattern of results is typical also of that for the other ketones, and indicates that points for bases carrying one or more alkyl substituents in α-positions fall below the line defined by the other pyridine bases. This reduction in catalytic strength to below that predicted from the dissociation constant of the base is slightly more marked for a 2-ethyl substituent than for a 2-methyl group, and considerably more evident in pyridines with two methyl substituents in 2,6-positions. If a second comparison is confined to the three bases with a single 2-methyl substituent, a separate Brönsted relation is found to hold. The slope of this line (middle line in Figure 1) is less than that for bases without 2-substituents. If the two points for 2,6-substituted pyridines are held to define yet another line, its slope is lower still (see below).

In Table 2 the results are expressed in the form

$$\Delta\log k = \log k_b - \log k_{\text{calc.}}$$

where $\log k_b$ is the experimental result for a particular catalyst and $\log k_{\text{calc.}}$ is the corresponding value calculated according to the Brönsted catalysis law, $\log k_{\text{calc.}} = \log G_0 + \beta_0 \mathrm{p}K$, where the parameters G_0 and β_0 are defined by the experimental points for pyridine

TABLE 2

Departures from Brönsted catalysis law

Catalyst	pK value of catalyst		$\Delta\log k_b$ ‡				
	A *	B †	I	II	III	IV	V
3-Picoline	5·63	5·68	+0·07	+0·13	+0·10	−0·02	+0·11
3,5-Lutidine	6·15	—	+0·03	+0·04	+0·05	—	+0·10
3,4-Lutidine	6·46	—	−0·08	−0·04	−0·01	—	+0·01
Pyridine	5·22	5·17	(0)	(0)	(0)	(0)	(0)
4-Picoline	5·98	6·02	(0)	(0)	(0)	(0)	(0)
2,5-Lutidine	6·40	6·51	−0·11	−0·22	−0·23	—	−0·24
2-Piccoline	5·96	5·97	−0·12	−0·14	−0·22	−0·60	−0·27
2,4-Lutidine	6·63	6·79	−0·14	−0·28	−0·28	—	−0·26
2-Ethylpyridine	5·89	5·92	−0·21	—	−0·30	—	−0·40
2,6-Lutidine	6·72	6·75	−0·84	−1·05	−1·01	−1·38	−1·49
2,4,6-Collidine	—	7·59	−1·12	−1·38	−1·26	—	−1·69

(I) = acetone; (II) = diethylketone; (III) = isopropyl methyl ketone; (IV) = pinacolone; (V) = cyclohexanone.

* Ref. 11. † Ref. 1. ‡ $\Delta\log k_b = \log k_b - \beta_0 \mathrm{p}K - \log G_0$; β_0 and G_0 being the parameters of the Brönsted catalysis law calculated from experimental results and pK values of pyridine and 4-picoline. Except for collidine, the pK values are those of series A.

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[32] Schwarzenbach and Wittwer, *Helv. Chim. Acta*, 1947, **30**, 656; Cf. Gero, *J. Org. Chem.*, 1954, **19**, 469, 1960.

and 4-picoline. The negative entries in the Table, corresponding to 2-substituents in the catalyst, are seen to increase with increasing encumbrance of the ketone. In particular, there is an increase along the series acetone, isopropyl methyl ketone, pinacolone, indicating an increasing importance of 2-substituents. In addition, the effect of 2,6-dimethyl-substitution is more than twice the effect of a single 2-methyl group, again suggesting a steric rather than an electronic effect of methyl groups.

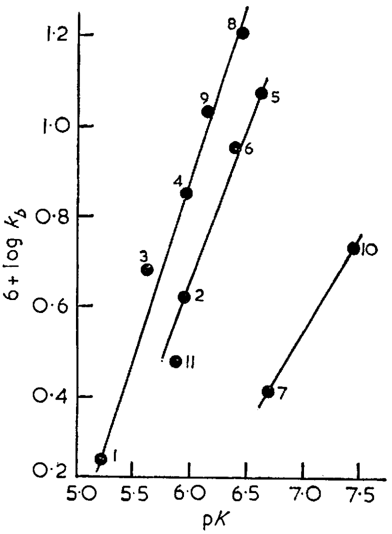
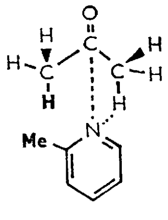


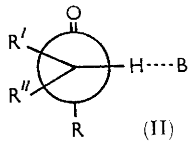
FIGURE 1. Brönsted plot for iodination of isopropyl methyl ketone (for key to identification of individual points see Table 1)

The changing effect along the series of the three methyl ketones suggests that the breaking C–H bond and the carbonyl group are in a planar *trans*-conformation in the transition state. In this arrangement it is possible for the non-reacting alkyl group of the ketone to come close to the approaching base and for the reaction velocity to be influenced by the bulk of that group, as the results indicate. In a *gauche* or *cis* transition-state only the carbonyl group could be involved in steric interaction with the base, and such interaction would be constant along the series. It also appears that the heteroaromatic ring of the base lies preferentially in the same plane as the C=O and C–H bonds just mentioned. If this factor were absent, steric hindrance by 2-substituents in the base could always be relieved by rotation of the pyridine ring relative to this plane and, for example, the steric effect of a single 2-substituent should be the same for all methyl ketones, which it is not.

The suggested requirement of coplanarity implies some kind of conjugative interaction between the carbonyl group and the heteroaromatic ring which is formally indicated by one of the dotted lines in formula (I). The groups mainly affected by steric strain are shown in bold type. The theoretical explanation of this postulated unorthodox interaction is not clear. However, we have previously pointed out that the marked effect of a single 2-methyl substituent on the stability of 1-acetylpyridinium ions [3] indicates energetically important conjugative interaction between the heteroaromatic ring and the adjacent carbonyl group in that ion.



(I)



(II)

This stereochemical model of proton transfer from a ketone offers a new interpretation of the preferred proton loss from axial positions in cyclohexanone systems.[33] Corey and Sneen explained this observation in terms of the overlap between the forming *p*-orbital and the π-orbital of the carbonyl group in the incipient enolate-ion structure of the transition state. This overlap would be largest for the conformation (II) (which would be highly strained in cyclohexanone) about the bond joining the two carbon atoms concerned. The axial α-C–H bonds in cyclohexanone are closer than the equatorial ones to this desirable conformation. However, in view of the above suggestion of a preferred *trans*-conformation of the C=O and C–H bonds in the transition state for proton loss from an open-chain ketone, the preferred loss of axial protons from a cyclohexanone could be interpreted as a consequence of the fact that axial α-C–H bonds are closer to the *trans*-conformation than equatorial ones. On the other hand, it is possible that our considerations apply only to proton-abstraction by pyridine bases (which impose an additional stereochemical limitation) and not to proton abstraction by other bases, in which case the conclusion drawn from our results on pyridine bases would be invalid for proton transfers from ketones to other bases. This problem remains to be resolved.

Table 3 lists the slopes of the straight lines exemplified by Figure 1 for all substrates studied in sufficient detail. The values of β_1 are derived from the rates for 2-picoline and 2,4-lutidine; β_2 is similarly taken from the experimental points for 2,6-lutidine and 2,4,6-collidine. Thus, for all three lines the slope is calculated from the effect of 4-methyl substitution on p*K* and rate. The absolute values of β_0, β_1, and β_2 are subject to the considerable uncertainty as to the p*K* values involved in this calculation. For the four ketones about which sufficient data are available there is a decrease $\beta_0 \gtrsim \beta_1 > \beta_2$, except that $\beta_0 \sim \beta_1$ for acetone and cyclohexanone, possibly because steric hindrance by a single 2-methyl substituent can in these cases be relieved by rotation of the base moiety through 180°.

The value of the Brönsted exponent β in a series of related reactions is a measure of the degree of proton transfer in the transition state. A value of unity implies complete transfer and represents the limiting case in which the distinction between general and specific catalysis disappears. We therefore interpret the decreasing value of β with increased steric hindrance as indicating that steric hindrance by 2-substituents to approach of the reagents causes the proton transfer to be less complete when the most energised configuration is reached.

Apart from this main pattern a further minor deviation is noticeable in 3-(or 5-)substituted pyridines. Points for 3-picoline and 3,5-lutidine lie above the top line in Figure 1, and the point for 2,5-lutidine above the middle line. Again, if a straight line is drawn through the points for 3-picoline and 3,4-lutidine, the result for 3,5-lutidine falls above the line. These positive deviations are much less marked than the negative effects of 2-substitution and, were it not for their consistent association with a 3-substituent in different bases, might be dismissed as due to errors in the experimental values of either the rate measurements or dissociation constants. (Indeed, the uncertainty in the latter quantities, as suggested by discrepancies between series A and B in Table 3, may well be as large as this effect).

TABLE 3

Values of Brönsted exonent for different reactions and types of catalyst

		Acetone	Diethyl ketone	Isopropyl methyl ketone	Pinacolone	Cyclohexanone
β_0	A *	0·73	0·77	0·77	0·75	$0{\cdot}58_5$
	B †	0·65	0·69	0·69	0·67	0·52
β_1	A	0·69	0·56	0·67	—	0·61
	B	0·56	0·46	0·55	—	0·50
β_2	B	0·31	0·27	0·38	—	0·27

* A: Values of p*K* taken from ref. 11. † B: Values of p*K* taken from ref. 1.

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[33] Corey and Sneen, *J. Amer. Chem. Soc.*, 1956, **78**, 6269.

This effect may be due to important hyperconjugative stabilisation of the pyridinium ion by methyl substituents in 2- or 4- but not in 3-positions. This stabilisation is, at least in part, responsible for the greater basic strength of the 2- and 4-picolines. In the transition state of the reaction the positive charge on nitrogen is smaller than in the pyridinium ion and thus the effect of hyperconjugation is less marked. It follows that 2- or 4-substituted pyridines may be slightly less reactive base-catalysts than their dissociation constants would suggest (*i.e.*, a single set of σ-constants is not applicable to dissociation constants and reactions). In other words, pyridine and 3-substituted pyridines represent the norm defining uncomplicated behaviour, and the reactivity of 2- and 4-methyl-substituted pyridines should be regarded as " abnormally " low, because of this electronic effect. In the present example this phenomenon does not seriously blur the steric effect, which is very much larger. This electronic explanation seems more probable than any other based on steric effects of substituents in 3-positions, particularly since abnormally high reactivity of 3-picoline relative to 2- or 4-picoline is also evident in some other reactions where steric effects of the type considered in this Paper are smaller or absent.[5,7,34] According to our interpretation, these deviations should be most marked for reactions with a low value of the Brönsted exponent β. The smaller differences between 2- and 4-methyl-substituents, as in the cases of nitroethane [34] and nitromethane (Table 1), may similarly be due to a difference in the transmission of hyperconjugation from these two positions such as could arise from secondary steric effects in the formation of the transition state. It follows that small discrepancies associated with 2-substituents in other reactions are not necessarily due to steric strain.

APPENDIX

A note on steric effects in gas–liquid chromatography

Figure 2 shows a plot of the logarithm of the retention times of the pyridine bases (on a Celite/diglycerol column at 90—95° with hydrogen as carrier). The results follow a pattern similar to that of the kinetic data and suggest that steric hindrance to hydrogen-bonding between the bases and diglycerol is important. This interpretation requires some qualification in that most column materials investigated for the separation of pyridine bases [12] produce groupings of this kind. The reason for this lies in the fact that boiling points of these compounds fall into a somewhat less spaced-out pattern of this type, and boiling points largely govern the separation performance of chemically-inert stationary phases. The importance of steric hindrance to hydrogen-bonding on the diglycerol column (and with other hydroxylic stationary

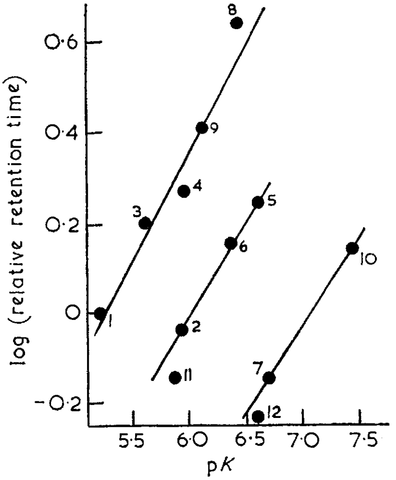

FIGURE 2. Correlation between pK values and retention times of pyridine based on diglycerol column (for key to identification of individual points see Table 1; 12 = 2-ethyl-6-methylpyridine)

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[34] Allen and Lewis, *J. Amer. Chem. Soc.*, 1964, **86**, 2022; results kindly communicated before publication by Professor E. S. Lewis.

phases) nevertheless becomes apparent from the progressively decreasing retention times of 4-picoline, 2,4-lutidine, and 2,4,6-collidine. This sequence is opposed to the trends of boiling points or p*K* values. Because of the superposition of at least two effects, *viz.*, boiling point and hydrogen-bonding, a more exact analysis of the results for different stationary phases [12] is not attempted.

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