700. *The Mechanism of Electrophilic Substitution of Heteroaromatic Compounds. Part I.*[1] *Acid-catalysed Hydrogen Exchange of Lutidine and Collidine.*

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The rates of tritiation in the 3,5-positions of 2,6-lutidine, 2,4,6-collidine, and bis-1,2,4,6-tetramethylpyridinium sulphate have been measured in aqueous sulphuric acid in the H_0 range $-6{\cdot}3$ to $-9{\cdot}5$ and the temperature range 182—222°. 2,6-Lutidine and 2,4,6-collidine react in the form of their conjugate acids, as shown by (*a*) comparison with the quaternary derivative, (*b*) the acidity dependence of rates, and (*c*) the absolute reaction rates.

Approximate enthalpies and entropies of activation are recorded and discussed: the substitution of $=NH^{+}-$ (*i.e.*, giving pyridinium ion) for $=CH-$ in benzene decreases the rate of hydrogen exchange at the *meta*-position by a factor of *ca.* 10^{18}. It is also deduced that substitution of $=N-$ (*i.e.*, giving pyridine) for $=CH-$ in benzene is accompanied by considerable deactivation towards electrophilic substitution.

WITH recent notable exceptions concerning imidazoles and quinoline,[2] indoles,[3] thiophens, and furans,[4] little is known about the quantitative aspects of electrophilic substitution of heteroaromatic compounds (cf. ref. 5). In sulphuric acid, nitration and sulphonation of pyridines proceed with difficulty; before the present work it was not known whether this

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[1] Presented in part at the 140th Amer. Chem. Soc. Meeting at Chicago, September 3rd, 1961; for a preliminary communication see Katritzky and Ridgewell, *Proc. Chem. Soc.*, 1962, 114.

[2] Ridd and his co-workers, *J.*, 1958, 3228; 1959, 3019; 1960, 1352, 1363.

[3] Binks and Ridd, *J.*, 1957, 2398.

[4] Deans and Eaborn, *J.*, 1959, 2299, 2303.

[5] Ridd in " Physical Methods in Heterocyclic Chemistry," ed. Katritzky, Academic Press, New York, 1963, Vol. I.

was due to presence of the free base only in very small quantity or to lack of reactivity of the conjugate acid. (Recent evidence indicates that quinoline and imidazole are nitrated as conjugate acids.[6]) The vigorous conditions required for nitration and sulphonation, and the poor yields frequently encountered, led us to the study of acid-catalysed hydrogen exchange. Little previous work has been reported: nicotinic acid [7] exchanges nearly three atoms of hydrogen in deuterated 80% sulphuric acid at 300°. Our objects were (i) to elucidate whether reaction occurred on the free base or conjugate acid,[6] * and (ii) to determine the Arrhenius parameters and relate the general pattern of reactivity in the pyridine series with the extensive data on acid-catalysed hydrogen exchange and other electrophilic substitutions for benzenoid compounds. The present paper concerns the tritiation of 2,6-lutidine and 2,4,6-collidine. One of the three methods used for our object (i) involves comparison of the rate of reaction of a base with that of the corresponding quaternary salt; bis-1,2,4,6-tetramethylpyridinium sulphate was therefore also studied.

Base, sulphuric acid, and tritiated water, in known proportions, were heated at a constant temperature for a predetermined time. The base was isolated as the picrate and this (too effective a " quencher " for direct liquid scintillation estimation; cf. ref. 10) was burnt and the water was counted by liquid scintillation.

EXPERIMENTAL

Purification of Compounds.—Commercial 2,6-lutidine was azeotropically distilled with an excess of acetic acid [11] and then redistilled; it had b. p. 143·5°/760 mm. (lit.,[11] b. p. 144°/760 mm.) and m. p. −6·0° (lit.,[11] m. p. −5·9°), and an infrared spectrum identical with that published.[12]

Commercial 2,4,6-collidine, purified by recrystallisation of the hydrochloride, followed by regeneration and distillation,[13] had b. p. 169·5—170·0°/760 mm. (lit.,[13] b. p. 170·4°/760 mm.) (Found: C, 79·1; H, 9·3; N, 11·25. Calc. for $C_8H_{11}N$: C, 79·3; H, 9·1; N, 11·6%). The picrate had m. p. 153—154° (latest lit.,[13] m. p. 155—156°) (Found: C, 48·3; H, 4·1; N, 16·3. Calc. for $C_{14}H_{14}N_4O_7$: C, 48·0; H, 4·0; N, 16·0%.)

Bis-1,2,4,6-tetramethylpyridinium sulphate was prepared from 2,4,6-collidine through the methiodide. The methiodide,[14] which is stable and non-hygroscopic only when uncontaminated with collidine, had m. p. 213—213·5° after two recrystallisations from methanol (lit.,[14] m. p. 204°). Ion-exchange of an aqueous solution on a Dowex 2 column in the sulphate form gave the extremely hygroscopic sulphate, m. p. 232° (decomp.), [lit.,[15] m. p. 230—232° (decomp.)] (Found: C, 58·35; H, 8·0; N, 7·3. Calc. for $C_{18}H_{28}N_2O_4S$: C,58·7; H, 7·6; N, 7·6%). The picrate had m. p. 131·5—132° (lit.,[16] m. p. 130—131°).

The liquid scintillator [17] used was: naphthalene 60 g., PPO (2,5-diphenyloxazole) 4 g., POPOP [*p*-di-(5-phenyloxazol-2-yl)benzene] 0·2 g. (all scintillation grade), dried absolute methanol 100 ml., purified [18] ethylene glycol 20 ml., and purified [19] 1,4-dioxan to make 1 l.

2 Ml. of tritiated water (A.E.R.E., Harwell, 1 c/10 ml.) was diluted to 1 l. For kinetic runs

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* It has been shown [8] that guanidine is nitrated as the free base. Previous evidence for pyridine has been equivocal: *e.g.*, the statement [9] that " the rather drastic experimental conditions . . . accord with reactivities predicted for a pyridine salt." However, if reaction *via* the free base were easier, then it would undoubtedly occur.

[6] Austin, Brickman, Ridd, and Smith, *Chem. and Ind.*, 1962, 1057.
[7] Trenner, Walker, Arison, and Trumbauer, *Analyt. Chem.*, 1951, **23**, 487.
[8] Kirkwood and Wright, *Canad. J. Chem.*, 1957, **35**, 527.
[9] Barnes, *J. Amer. Chem. Soc.*, 1959, **81**, 1935.
[10] Peng, *Analyt. Chem.*, 1960, **32**, 1292.
[11] Coulson and Jones, *J. Soc. Chem. Ind.*, 1946, **65**, 169.
[12] Coulson, Ditcham, Hales, and Holt, *J. Appl. Chem.*, 1952, **2**, 71.
[13] Engel, U.S.P. 2,426,442.
[14] Takahashi and Satake, *J. Pharm. Soc. Japan*, 1954, **74**, 135.
[15] R. A. Jones, Ph.D. Thesis, Cambridge, 1960.
[16] Lukes and Jizba, *Chem. listy*, 1958, **52**, 1126.
[17] Bray, *Analyt. Biochem.*, 1960, **1**, 279.
[18] Smyth and Walls, *J. Amer. Chem. Soc.*, 1931, **53**, 527, 2115.
[19] Hess and Frahm, *Ber.*, 1938, **71**, 2627.

1·01039 g. of this stock solution was diluted to 500 ml., and 0·100 ml. aliquot parts were used as standards (" Agla " micrometer syringe pipette) for the liquid scintillation counting.

General Experimental Procedure.—Sulphuric acid (of known normality), water, tritiated water, and the pyridine base were successively weighed by difference into a 50 ml. narrow-necked flask cooled in acetone–carbon dioxide. The reaction mixture (1 or 2 ml., depending on the acidity and the concentration of pyridine base) was pipetted into a Pyrex reaction tube, *ca.* 100 × 10 mm., with wall thickness *ca.* 1·5 mm.

The sealed tubes were placed in a holder (an aluminium block of 3″ diameter with six ½″ holes at the periphery, and a thermometer hole), and this was immersed in a lagged (with fibre-glass) oil-bath (Shell " Nassa 87 " oil) which was heated (750 w. helical). Stirring was by remote drive and fully adequate. Temperature control (by a contact thermometer and relay) was ±1° in the range 150—220°.

After being heated for the requisite time, tubes were removed and allowed to cool. The contents of each tube were added to water (*ca.* 8 ml.) at 0°, and run through an ice-jacketed column (*ca.* 45 × 1 cm.) of Dowex 3 ion-exchange resin (*ca.* 20 ml. of wet resin, *i.e.*, *ca.* 0·05 equiv.). The column was developed with water: the initial eluate (*ca.* 15 ml., originally examined by ultraviolet absorption) was rejected. The next fraction (*ca.* 30 ml.) was added to the theoretical amount of picric acid in water (*ca.* 8 ml.) at 100°, and the picrate was collected after cooling. The m. p. of the picrates were usually within 1° of the reported values.

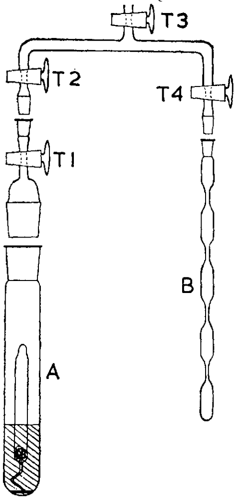

FIG. 1. Combustion apparatus.

The picrate (*ca.* 0·05 g., weighed accurately by difference), copper oxide (*ca.* 1 g., *i.e.*, at least 100% excess; of micro-analytical purity and 40—100 mesh size), and copper (*ca.* 0·5 g. of reduced copper oxide; 40—100 mesh size) were placed in a break-seal combustion tube (cf. ref. 20; it was found unnecessary to use manganese dioxide as an additional oxidant). The sealed tubes were heated at 600° for at least 8 hr. in a Wild Barfield type M252 muffle furnace.

The cold combustion tube was transferred to the distillation apparatus (Fig. 1). " Memory " effects have been reported,[21] hence the small design. To protect the hard-glass tube (A), a brass disc covered with thick aluminium foil, and a cylinder of foil 3″ deep, were used. After evacuation to 0·01 mm., taps T1 and T2 were closed and tube (A) was disconnected under a vacuum. The break-seal was broken by shaking behind a glass screen.* Tube (A) was replaced and tap T2 opened to hold it in position. The water was frozen by immersing tube (A) in acetone–carbon dioxide. After *ca.* 5 min. tap T1 was opened and the carbon dioxide pumped

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* Shattering of tube (A) by the pressure of carbon dioxide occurred with weights of picrate greater than *ca.* 75 mg.

[20] Buchanan and Corcoran, *Analyt. Chem.*, 1959, **31**, 1635.

[21] Ronzio and Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 5787; Buysche, Florini, and Peets, *Analyt. Chem.*, 1960, **32**, 1465.

off. When the vacuum (0·01 mm.) had been restored, tap T3 was closed and the acetone–carbon dioxide bath removed. A Dewar vessel containing liquid nitrogen was placed around the lowest bulb on tube (B), and the water was transferred to this by warming tube (A) first with a hair-dryer and then with a blowpipe. Tap T4 was closed and the bulb sealed, removed, and weighed.

The bulb contents were washed into a 25-ml. counting vial with liquid scintillator (*ca.* 10 ml., delivered accurately from an uncalibrated automatic pipette) and counted with a Packard " Tri-Carb " liquid scintillation spectrometer. Contrary to previous reports,[22] preparation of the vials in a dark room or in daylight gave identical results. Simultaneous counts of standard (*ca.* 10,000 counts/min.) and background (*ca.* 30 counts/min.) were recorded; efficiencies were *ca.* 10%.

Weighing the bulb fragments gave the yield (%) of water from the combustion and distillation; this was generally 98—102%. The counts were corrected to zero background, to a standard weight of picrate (50 mg.) and to 100% yield of water (if below 100%). For the reversible, pseudo-unimolecular reaction (as T^+ is greatly in excess), $Py_H \rightleftharpoons Py_T$, it may be shown that:

$$kt/2{\cdot}303 = \log_{10} [x_e/(x_e - x)] = \log_{10} [y_e/(y_e - y_t)]$$

where x, x_e are amounts of Py_T, and y_t and y_e are the counts, at time t and equilibrium, respectively. The rate constant, k, was found from the slope of the plot of $\log_{10} [y_e/(y_e - y_t)]$ against t.

The equilibrium count was found by experiment and also by calculation on the assumption that the tritium distributes itself equally among the sulphuric acid, water, and the 3- and the 5-position of the pyridine base.

Measurement of H_0.—From the ultraviolet absorption of sulphuric acid solutions of known strength containing anthraquinone (at 410 mμ) and nitrobenzene (at 365 mμ) as indicators at 18° ± 2°, calibration curves of extinction coefficient against % H_2SO_4 were established in the ranges 75–99·5% and 99·5—108% H_2SO_4, respectively.

For determination of the acidity of the run solution, a suitable quantity of indicator (determined from the calibration curve and the approximately known % H_2SO_4 was weighed on a micro-balance and dissolved in 100 ml. of " AnalaR " sulphuric acid. This solution (1 ml.) (together with the small amount of water that rough calculation indicated would bring it to approximately the H_0 of the run solution) was diluted (to 20 ml.) with the run solution, and the optical density measured, giving the % H_2SO_4 and thus the Hammett acidity function, H_0.[23]

RESULTS

Equilibrium isotope effects for tritium–hydrogen and deuterium–hydrogen exchange are known to be small.[24, 25] Theoretical work by Russian authors [25] for the vapour phase suggests that for hydrogen–deuterium exchange the equilibrium isotope effect should be temperature-dependent: the factor for the C_6H_6–H_2O system should be 1·02 at 20° but 0·88 at 180°. However, most published results for solutions indicate that the factor is near unity and not highly temperature-dependent.[25, 26] Under the conditions of the present work, exchange of 2/9, 2/11, and 2/14 of the hydrogen atoms in lutidine, collidine, and the 1,2,4,6-tetramethylpyridinium ion, respectively, occurred when the reaction was allowed to proceed to completion (see Table 1). This is strong evidence that exchange occurs in the 3- and the 5-position of the pyridine ring in these compounds (I—III). Support for this is provided by deuterium exchange of collidine and the corresponding 1-methyl cation, as studied by proton resonance spectroscopy; [15] the intensity ratio of the methyl peaks to the sum of the 3,5-hydrogen and sulphuric acid peaks was constant for both compounds.

The kinetic results showed that tritium exchange was a first-order reaction: plots of $\log_{10} [y_e/(y_e - y_t)]$ against time were reasonably linear. Detailed results for three typical runs are

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[22] Butler, *Analyt. Chem.*, 1961, **33**, 409.

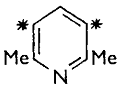
[23] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.

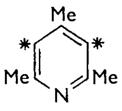
[24] Lozhkina, Shatenshtein, and Varshavsky, *Zhur. fiz. Khim.*, 1957, **31**, 1377; Shatenshtein, *Doklady Akad. Nauk S.S.S.R.*, 1951, **79**, 479.

[25] Varshavsky and Vaysberg, *Uspekhi Khim.*, 1957, **26**, 1434.

[26] Harada and Titani, *Bull. Chem. Soc. Japan*, 1936, **11**, 465.

given in Tables 2 and 3. Results for all the runs are summarised in Table 4; plots of $-\log k$ against $-H_0$ are given in Figs. 2 and 3, and the slopes of these plots are summarised in Table 5. The results of Arrhenius plots are given in Table 6.


(I)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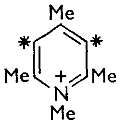
(III)

In this work the variation of H_0 with temperature has been neglected, because of lack of data. Russian work [27] is available for temperatures up to 80°; although the acidity function

TABLE 1.

Equilibrium isotope effect.

Compound	Run no.	H_0	Temp.	Time (hr.)	Counts/min.		
					exp.	theor.	100 exp./theor.
Collidine	2	−8·59	182° ± 1°	21	14,980	15,000	99·9
				45	14,640		97·8
Lutidine	9	−9·16	203 ± 1	*ca.* 350	9,470	9,910	95·7
	11	−9·66	203 ± 1	*ca.* 350	9,920	10,150	98·0
Tetramethylpyridinium	1	−7·00	182 ± 1	170	14,570	14,680	99·3
sulphate	5	−7·61	182 ± 1	56	12,640	12,960	97·7

TABLE 2.

Composition of three typical runs.

	Run no.	Wt. of compound (g.)	Wt. of 99·8% H_2SO_4 (g.)	Wt. of 102·3% H_2SO_4 (g.)	Total wt. of water (g.)	Wt. of titrated water (g.)	Measured % H_2SO_4	H_0
2,6-Lutidine	18	2·7591	71·4128	—	2·9655	0·9338	93·1	−8·64
2,4,6-Collidine	14	1·8600	—	58·2341	6·2550	1·9819	88·0	−8·03
Bis-1,2,4,6-tetramethyl-pyridinium sulphate	5	1·4232	13·3067	—	1·7270	1·0653	85·0 *	−7·61

* See footnote ‡ of Table 4.

TABLE 3.

Exchange results of three runs.

Compound	Reaction time (hr.)	Temp. (±1°)	M. p. of picrate	Yield (%) of picrate	Wt. (mg.) of picrate burnt	Yield (%) of water	Corr. count/ min.	Exchange (%)	k (hr.$^{-1}$)
2,6-Lutidine; run 18	30	204°	163·5—164°	24	49·3	115	1,126	18·6	0·0067 ±0·0004
	55	,,	,,	36	61·4	107	1,967	32·4	
	80	,,	164—164·5	35	45·0	97·7	2,435	40·3	
	96	,,	,,	49	49·2	102	2,910	48·1	
2,4,6-Collidine; run 14	2	204°	152—153·5	56	64·4	108	3,590	30·7	0·22 ±0·01
	4·17	,,	154—156	41	52·0	95	7,020	60·0	
	8	,,	154·7—156·5	71	50·1	—	9,710	82·8	
Bis-1,2,4,6-tetramethylpyridinium sulphate; run 5	7	182°	131·5—132·5	—	53·7	102	3,200	24·7	0·050 ±0·006
	12·2	,,	,,	—	63·5	91·7	5,000	38·6	
	25	,,	,,	—	64·2	98·3	9,550	73·7	
	98·7	,,	,,	—	53·9	101	12,640	97·7	

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[27] Gel'bshtein, Schcheglova, and Temkin, *Zhur. neorg. Khim.*, 1956, **1**, No. 3, 506.

appeared to become less negative as temperature increased, at least plots of H_0 against % H_2SO_4 were essentially parallel.

TABLE 4.

Measured rate constants.

Run no.	No. of points*	Temp.	Measd. H_0	k (hr.$^{-1}$)
		2,6-Lutidine		
9	2	203° ± 1°	−9·16	0·0148 ± 0·0007
10	2		−9·66	0·027 ± 0·002
12	3	182 ± 1	−8·68	0·0020 ± 0·0005
13	3		−8·59	0·00203 ± 0·00003
14	3	204 ± 1	−9·11	0·0181 ± 0·0008
15	3		−8·97	0·0094 ± 0·0003
16	4		−8·97	0·0164 ± 0·0008
17	2		−9·11	0·017 ± 0·001
18	4		−8·64	0·0067 ± 0·0004
19	4		−8·87	0·0096 ± 0·0004
20	4		−9·01	0·0131 ± 0·0005
21	3		−9·52	0·034 ± 0·006
22	3	222 ± 1	−8·58	0·0257 ± 0·0006
23	4		−8·86	0·0356 ± 0·0007
24	4		−8·96	0·041 ± 0·001
25	4		−9·36	0·071 ± 0·003
		Bis-1,2,4,6-*tetramethylpyridinium sulphate*		
3	3	182 ± 1	−7·00 ‡	0·014 ± 0·002
4	2		−7·11 ‡	0·018 ± 0·002
5	3		−7·61 ‡	0·050 ± 0·006
6	3		−7·95 ‡	0·075 ± 0·006
		2,4,6-*Collidine*		
1	2	182° ± 1°	−6·96 †	0·009 ± 0·001
4	4		−7·11	0·010 ± 0·001
6	5		−7·61	0·024 ± 0·002
7	3		−6·51	0·0050 ± 0·0005
8	3		−7·00	0·0080 ± 0·0008
9	3		−7·95	0·039 ± 0·004
10	2	204 ± 1	−6·22	0·021 ± 0·002
11	2		−7·05	0·052 ± 0·004
12	3		−7·35	0·090 ± 0·009
13	4		−7·68	0·093 ± 0·009
14	3		−8·03	0·22 ± 0·01
15	4		−6·75	0·043 ± 0·004
16	4		−7·00	0·063 ± 0·007
17	4		−7·48	0·097 ± 0·009
18	4		−8·13	0·24 ± 0·02
19	3	219 ± 2	−6·75	0·13 ± 0·01
20	4		−7·00	0·17 ± 0·01
21	4		−7·48	0·28 ± 0·03
22	4		−8·13	0·48 ± 0·03
23	4		−6·30	0·076 ± 0·003
24	4		−6·86	0·110 ± 0·007
25	4		−7·38	0·24 ± 0·01
26	4		−8·08	0·48 ± 0·03

* Not including the zero point through which all plots pass. † Estimated H_0. ‡ Bis-1,2,4,6-tetramethylpyridinium sulphate runs 3, 4, 5, and 6 were made up in the same molar quantities as 2,4,6-collidine runs 8, 4, 6, and 9, respectively, and the acidities were assumed to be the same.

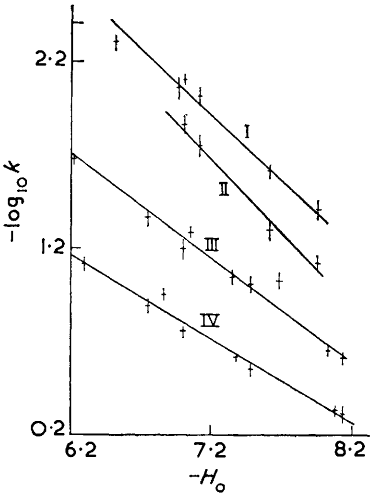


FIG. 2. Plots of $-\log_{10} k$ against $-H_0$ for 2,4,6-collidine and its 1-methyl salt. (I, III, IV) 2,4,6-Collidine at (I) 182° ± 1°, (III) 204° ± 1°, and (IV) 219° ± 2°. Bis-1,2,4,6-tetramethylpyridinium sulphate at 182° ± 1° (II).

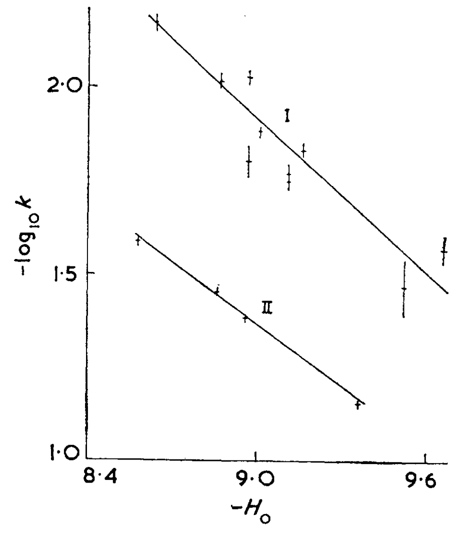


FIG. 3. Plots $-\log_{10} k$ against $-H_0$ for 2,6-lutidine at (I) 204° ± 1° and (II) 222° ± 1°.

TABLE 5.

Slopes of plots of $-\log k$ against $-H_0$.

	2,6-Lutidine		2,4,6-Collidine			Bis-1,2,4,6-tetramethyl-pyridinium sulphate
Run nos.	9, 10, 14 to 21	22 to 25	1, 4, 6 to 9	10 to 18	19 to 26	3 to 6
Temp.	204° ± 1°	222° ± 1°	182° ± 1°	204° ± 1°	219° ± 2°	182° ± 1°
Slope	$-0{\cdot}69 \pm 0{\cdot}03$	$-0{\cdot}57 \pm 0{\cdot}02$	$-0{\cdot}66 \pm 0{\cdot}04$	$-0{\cdot}56 \pm 0{\cdot}02$	$-0{\cdot}45 \pm 0{\cdot}01$	$-0{\cdot}77 \pm 0{\cdot}06$

TABLE 6.

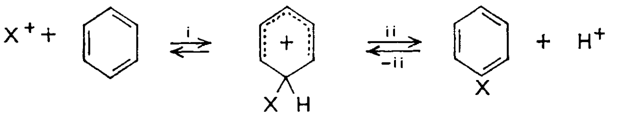
Results of Arrhenius plots for conjugate acid reactivity.

Compound	H_0	10^{-3} Slope	Intercept	ΔH ‡ (kcal. mole^{-1} at 200°)	$\log_{10} A$ *	$\log_{10} B$ †	ΔS ‡ (note §) at 200° (e.u.)
2,4,6-Collidine	$-6{\cdot}33$	$-8{\cdot}2 \pm 0{\cdot}2$	$15{\cdot}6 \pm 0{\cdot}5$	37 ± 1	$12{\cdot}1 \pm 0{\cdot}5$	$5{\cdot}8 \pm 0{\cdot}5$	-35 ± 2
	$-7{\cdot}40$	$-6{\cdot}9 \pm 0{\cdot}1$	$13{\cdot}3 \pm 0{\cdot}2$	$30{\cdot}5 \pm 0{\cdot}5$	$9{\cdot}8 \pm 0{\cdot}2$	$2{\cdot}4 \pm 0{\cdot}2$	$-50{\cdot}5 \pm 1$
	$-8{\cdot}40$	$-5{\cdot}3 \pm 0{\cdot}3$	$10{\cdot}7 \pm 0{\cdot}6$	$23{\cdot}5 \pm 1{\cdot}5$	$7{\cdot}2 \pm 0{\cdot}6$	$-1{\cdot}2 \pm 0{\cdot}6$	-67 ± 3
2,6-Lutidine	$-8{\cdot}40$	$-8{\cdot}2 \pm 0{\cdot}3$	$15{\cdot}0 \pm 0{\cdot}6$	$36{\cdot}5 \pm 1{\cdot}5$	$11{\cdot}3 \pm 0{\cdot}6$	$2{\cdot}9 \pm 0{\cdot}6$	$-48{\cdot}5 \pm 3$
	$-9{\cdot}00$	$-7{\cdot}3 \pm 0{\cdot}1$	$13{\cdot}5 \pm 0{\cdot}2$	$32{\cdot}5 \pm 0{\cdot}5$	$9{\cdot}9 \pm 0{\cdot}2$	$0{\cdot}9 \pm 0{\cdot}2$	$-57{\cdot}2 \pm 1$

* Pseudo-unimolecular frequency factor; units of A in sec.$^{-1}$. † $\log_{10} A$ corrected for acidity; $\log_{10} B = \log_{10} A + H_0$. Units are l. mole^{-1} sec.$^{-1}$. § Calc. from $\log_{10} B$ by using eqn. (6) (see below).

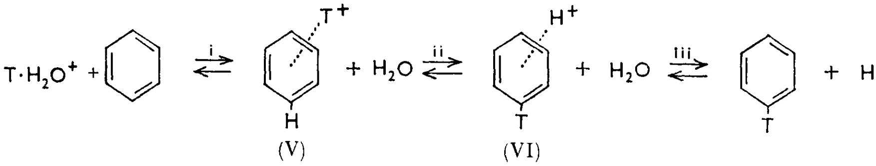
DISCUSSION

Mechanism of Substitution.—In the accepted mechanism (1) (denoted $A S_E 2$) for the electrophilic substitution of benzene, species (IV) is a true intermediate; steps i and ii are slow. This mechanism probably applies to acid-catalysed hydrogen exchange (here $X^+ = H^+$ is always solvated). However, in an alternative mechanism (2) (denoted $A1$), stages i and ii are fast and reversible. Interconversion of the π-complexes (V) and (VI) was considered to be the slow stage.



(IV)

....(1)



(V) (VI)

....(2)

The Zucker–Hammett hypothesis distinguishes (i) rate-dependence on $C_{H_3O^+}$ (or C_{HX}); general acid catalysis [proton transfer from H_3O^+ (or HX): solvent molecule bound in transition state; $A2$ or in this case $A S_E 2$ mechanism] from (ii) logarithmic rate-dependence on H_0 [specific acid catalysis (no solvent molecule involved in the transition state); $A1$ mechanism]. Gold *et al.*[28] found that logarithms of the first-order rate constants for dedeuteration of *para*-substituted phenols, benzene, toluene, anisole, etc., varied linearly with H_0.

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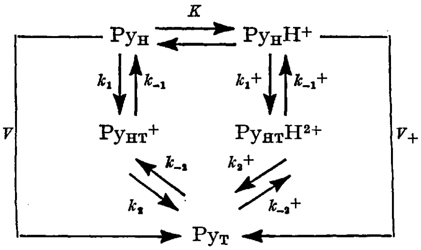
[28] Gold *et al.*, *J.*, 1955, 3609 and subsequent papers.

However, this argument has not been accepted as disproving the AS_E2 mechanism.[23,29,30] General acid catalysis applies to the protodetritiation of 1,3,5-trimethoxy-2-tritiobenzene[30] and for the protodedeuteration of azulene.[31] Bunnett,[32] in a recent detailed discussion of the Zucker–Hammett hypothesis, concludes that basic hydrocarbons must be considered separately from oxygen or nitrogen bases, and that acid-catalysed hydrogen exchange does occur by the AS_E2 mechanism (cf. also Melander's discussion[33] of the energy–reaction co-ordinate plot).

Acidity Function.—The acidity functions for *C*- and *N*-protonation of pyridine bases are required for treatment of our data. Although it is often stated (see, *e.g.*, refs. 23 and 34) that there is no reason why bases of different type should follow the Hammett acidity function H_0 (derived mainly for amine-type bases), it is usually assumed that they do, because of the lack of alternative acidity functions. The ionisation of carbinol-type bases ($ROH + H^+ \rightleftharpoons R^+ + H_2O$) follow a function J_0 (or H_R) (for review see ref. 23), and olefin-type bases a related acidity function H_R',[35] but it has been shown recently that the H_R' function is not general for protonation of hydrocarbon bases.[36] Protonation of positively charged bases may follow a H^+ function,[23] but little work is available and it cannot be considered as rigorously established[23] (see, however, Brand[37]).

In our laboratory, evidence has recently become available that uracil derivatives[38] and amides in general[39] are not Hammett bases: the proportion protonated increases more slowly than expected, *i.e.*, $\partial \log (C_{BH^+}/C_B)/\partial H_0$ is *ca.* 0·5. At present we have to assume that pyridines are Hammett bases; it is hoped to test this later.

Criteria for Reaction Occurring on Free Base or Conjugate Acid.—We have applied three criteria. (*a*) The most direct is to compare the rate of exchange of a base with that of its *N*-methyl cation under identical conditions: if the free base undergoes exchange (with the conjugate acid less reactive), then reaction of the *N*-methyl derivative should be considerably slower. If the conjugate acid of the base undergoes exchange, then the *N*-methyl derivative should show a small rate enhancement. The results shown in Fig. 2 clearly indicate reaction through the conjugate acid for 2,4,6-collidine. (*b*) The second criterion utilises the different acidity-dependence expected for the two possibilities. For an AS_E2 mechansim, we have the interaction illustrated. The overall rate constants for



reaction *via* the free base, and conjugate acid, and the measured overall rate constant are denoted below by k', k'', and k, respectively.

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[29] Melander and Myhre, *Arkiv. Kemi*, 1959, **13**, 507; Willi, *Chimia* (*Switz.*), 1961, **15**, 239; Eaborn and Taylor, *J.*, 1960, 3301.

[30] Kresge and Chiang, *J. Amer. Chem. Soc.*, 1959, **81**, 5509; *Proc. Chem. Soc.*, 1961, 81.

[31] Colpietro and Long, *Chem. and Ind.*, 1960, 1056; Long and Schulze, *J. Amer. Chem. Soc.*, 1961, **83**, 3340.

[32] Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956 and subsequent papers.

[33] Melander, *Arkiv Kemi*, 1961, **17**, 291.

[34] Long and Paul, *Chem. Rev.*, 1957, **57**, 935.

[35] Deno, Groves, and Saines, *J. Amer. Chem. Soc.*, 1959, **81**, 5790.

[36] Schubert and Quacchia, *J. Amer. Chem. Soc.*, 1962, **84**, 3778.

[37] Brand, *J.*, 1957, 367.

[38] Katritzky and Waring, *J.*, 1962, 1540.

[39] Katritzky, Waring, and Yates, *Tetrahedron*, 1963, **19**, 495.

If reaction occurs *via* the free base, applying the Brönsted equation gives [40] the rate of reaction,

$$V = \frac{k_1k_2}{k_2 + k_{-1}} \cdot \frac{(\mathrm{Py_H})(\mathrm{H^+})}{f_\ddagger}$$

$$= ch_0[\mathrm{Py_H}] \cdot \frac{\mathrm{f_{BH}f_{Py_H}}}{\mathrm{f_Bf_\ddagger}}, \text{ where } c = k_1k_2/(k_2 + k_{-1}).$$

Therefore, $$k' = V/[\mathrm{Py_H}] = ch_0 \,.\, \mathrm{f_{BH^+}f_{Py_H}/f_Bf_\ddagger}. \qquad (3)$$

However, $$k = V/[\mathrm{Py_H}]_{\mathrm{stoich}} \doteqdot V/[\mathrm{Py_HH^+}].$$

Therefore, $$k = k'K/h_0, \qquad (4)$$

if Py is a Hammett base with respect to *N*-protonation.

Therefore, $$k = cK(\mathrm{f_{BH^+}f_{Py_H}/f_Bf_\ddagger}).$$

If Py is also a Hammett base with respect to *C*-protonation, then the activity coefficient ratio will be unity and k should not vary with H_0.

If reaction occurs *via* the conjugate acid, we have similarly

$$k = V_+/[\mathrm{Py_H}]_{\mathrm{stoich}} \doteqdot V_+/[\mathrm{Py_HH^+}] \quad k'' = = \frac{k_1{}^+k_2{}^+}{k_2{}^+ + k_{-1}{}^+} \cdot h_+ \cdot \frac{\mathrm{f_{BH^{2}+}f_{Py_HH^+}}}{\mathrm{f_{B^+}f_\ddagger{}^+}} \quad . \qquad (5)$$

Hence, a plot of log k against H_0 (strictly H_+ should be used, but H_0 and H_+ are reasonably parallel plots [37]) should have unit slope if PyH$^+$ is a Hammett base with respect to *C*-protonation. Benzenoid species undergoing exchange at 25° have been found to have slopes of 0·9—1·4.[28]

The experimental slopes (Figs. 2 and 3; Table 5) are most compatible with reaction occurring on the conjugate acid, especially in view of the increasing slope with decreasing temperature. However, the force of this argument is diminished by the uncertainty as to the acidity function followed by pyridine bases during *C*- and *N*-protonation. The similarity of the slopes for lutidine and collidine do at least indicate that they react by the same mechanism.

The slopes do not provide any further evidence on the question of *A*1 *versus* $A S_E2$ mechanism: it seems proved that benzenoid compounds react by the $A S_E2$ mechanism, and we assume that this also applies to the pyridine series. We have obtained *w* values from our data by the Bunnett method,[24] and the plots * are of slope —0·55 to —0·21. Bunnett [24] found that aromatic CH exchange gave plots of slope —1·09 to +6·0 at 25°. We find that the slopes become less negative with decreasing temperature; this is hardly surprising in view of the variation of $\partial \log k/\partial \mathrm{H}_0$ with temperature.

(*c*) The third criterion involves consideration of the absolute rates of reaction. The slopes and intercepts of the Arrhenius plots of $\log_{10} k$ against $1/T$ (at a constant acidity) give, respectively, the enthalpies of activation, $\Delta H^\ddagger$, and the frequency factors, *A*. The frequency factors are related to the entropies of activation, $\Delta S^\ddagger$, according to transition-state theory, by the expression

$$A = \frac{\boldsymbol{k}T}{\boldsymbol{h}} \cdot \exp(\Delta S^\ddagger/\boldsymbol{R})$$

or $$\Delta S^\ddagger = 4{\cdot}576 \log_{10} A/T - 49{\cdot}203 \qquad (6)$$

where time is in seconds, and entropy in standard units (e.u.).

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* For detailed calculations and results see B. J. Ridgewell, Ph.D. Thesis, Cambridge, 1963.

[40] Olsson, *Arkiv Kemi*, 1961, **16**, 489.

In Table 4, experimental values of k are given; these are also directly applicable to the reaction proceeding *via* the free base because from equation (4) we have:

$$\log_{10} k' = \log_{10} k + \mathrm{p}K_\mathrm{a} - H_0.$$

Collidine has $\mathrm{p}K_\mathrm{a}$ 7·6,[41] and lutidine has $\mathrm{p}K_\mathrm{a}$ 6·5.[42]

It can thus be shown * that reaction *via* the free bases would require $\log_{10} A$ in the range 25—30. These are calculated from the pseudo-unimolecular rate constants k'. Taking into account that the reaction is bimolecular (see below) gives $\log_{10} B$ frequency factors of 16—23 which are quite unreasonable, and exclude reaction *via* the free base.

Enthalpies and Entropies of Activation.—Having excluded reaction *via* the free base, we can now discuss the Arrhenius parameters for reaction *via* the conjugate acid (Table 6). We emphasise, however, that the errors, approximations, and uncertainties in this work, in particular the unknown variation of H_0 with temperature, make the discussion tentative.

Overall, the large $\Delta H^{\ddagger}$ are expected, with those for lutidine greater than those for collidine. However, the appreciable variations of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with H_0 were initially unexpected, although this type of variation appears from the limited literature data to be general (see below). If at constant temperature the rate varied as h_0^x (where x is positive, and reflects the acidity function for *C*-protonation of pyridines), and if at constant H_0 the rate varied as $\exp(-\Delta H^{\ddagger}/\boldsymbol{R}T)$, an equation is expected of the form:

$$k = ch_0^x \exp(-\Delta H^{\ddagger}/\boldsymbol{R}T). \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The results in Table 6 show that $\Delta H^{\ddagger}$ varies linearly with H_0, and the slopes for lutidine (—6·3) and collidine (—6·4) are the same within experimental error. An attempt * to fit the results to an equation of the form (7) gives absurd values of x (—2·3 for lutidine and —2·4 for collidine). Hence, $\Delta S^{\ddagger}$ must vary with H_0. The form of this variation depends on the value of x in equation (7). In Table 6, values of $\Delta S^{\ddagger}$ are given for $x = 1$ (*i.e.*, on the assumption of Hammett base behaviour for *C*-protonation; cf. ref. 36). For $x = 0·5$ (*i.e.*, for approximately $H_{\mathrm{R}'}$ base behaviour; cf. ref. 30), values of $\Delta S^{\ddagger}$ (corresponding to those in Table 6) ranging from —49 to —86 for collidine and from —68 to —78 for lutidine are obtained.* We consider it unlikely that x lies outside the limits 0·5 and 2, and within these limits the form of the variation of $\Delta S^{\ddagger}$ with H_0 is similar.* The observed variations of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with H_0 depend directly on the variation with temperature of the slopes of plots of log k against H_0 (Table 5). Thermodynamically, this indicates that the activity-coefficient ratio in the derived rate expression (5) varies with temperature (cf. ref. 43). While the H_0 values in the 180—220° range may be considerably different from those at 20°, the relative changes over this 40° range (*i.e.*, contraction or expansion of the scale) are unlikely to be of magnitude comparable with the variation in slope (this conclusion is supported by results over the 20—80° interval [27]). Provided this holds, *t*-tests indicate that the difference in slopes of plots of log k against H_0 are highly significant at the 1% level.

Variation of Arrhenius parameters with acidity was demonstrated in 1938—1939 for the hydrolysis of sucrose and ethylal.[43] Winkler and his co-workers,[44] from their results on the hydrolysis of amides and nitriles, later concluded that a parallel variation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with acidity occurred generally, vindicating the prediction of Ogg and Rice.[45] In protodesilylation,[46] $\Delta H^{\ddagger}$ decreases with acidity and so * does $\Delta S^{\ddagger}$, although the pseudo-unimolecular frequency factor A shows no significant trend. Inspection * of published

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* See preceding footnote.

[41] Ikewawa, Sato, and Maeda, *Pharm. Bull.* (*Japan*), 1954, **2**, 205.

[42] Brown and Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.

[43] Kilpatrick and Leninger, *J. Amer. Chem. Soc.*, 1938, **60**, 2891; 1939, **61**, 2510.

[44] Winkler and his co-workers, *Canad. J. Res.*, 1942, *B*, **20**, 73, 121, 168, 221.

[45] Ogg and Rice, *J. Chem. Phys.*, 1937, **5**, 140.

[45a] Chapman, Shorter, and Utley, *J.*, 1963, 1291.

[46] Deans and Eaborn, *J.*, 1959, 2299.

results[47] for the hydrolysis of sulphites also discloses parallel variation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with H_0 (see also results for sulphation of 2,4-dinitrobenzyl alcohol,[48] and unpublished results of Adams, quoted on p. 945 of ref. 23). No variation of $\Delta H^{\ddagger}$ (or, probably, of $\Delta S^{\ddagger}$) occurs for the depolymerisation of trioxan,[49] or for the rearrangement of pinacol,[50] but this behaviour appears to be exceptional.

The large negative values of $\Delta S^{\ddagger}$ are as found for other reactions involving two similarly charged ions,[51] and are interpreted as reflecting the greater solvation of the highly charged transition-complex than of the individual ions (cf. ref. 52). (The variations of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ with H_0 are greater in our work than in the examples from the literature discussed above, probably because only the present work involves a transition state which carries a double positive charge.)

The increasingly negative values of $\Delta S^{\ddagger}$ as acidity increases require that this difference in solvation be greater in solutions of greater acidity. As the acidity increases, the hydroxonium ion and the pyridinium ion are desolvated more rapidly than the doubly-charged transition complex. A quantitative interpretation is difficult as the range of acidity used lies on both sides of sulphuric acid monohydrate, and there are several possible solvating species.

The appreciable variation of $\partial \log k/\partial H_0$ with variation of T suggests that the Zucker–Hammett and similar[32] treatments should be applied with caution.

Differential Effect of Ring-methyl Groups on the Rate.—By extrapolating the results for collidine to stronger and for lutidine to weaker acidities, a direct comparison is possible. It is found * that at H_0 $-8{\cdot}40$, $\Delta\Delta H^{\ddagger} = 13 \pm 3$ kcal. mole^{-1}, $\Delta\log_{10}B = 4 \pm 1$, and $\Delta\Delta S^{\ddagger} = 19 \pm 6$ e.u.; these quantities show no significant variation with H_0. The $\Delta\Delta H^{\ddagger}$ value is such that the collidine reacts more quickly, but the $\Delta\Delta S^{\ddagger}$ value operates in the opposite direction and partially compensates for this. A similar though smaller effect is deducible * from published protodesilylation data.[46] A possible explanation of the (at first surprising) sign and magnitude of $\Delta\Delta S^{\ddagger}$ is suggested by Chapman's work.[45a] In the transition state the hydrogen atom becoming attached retains some solvated proton character, and steric repulsion with the methyl group will be appreciable; this effect evidently outweighs the favourable effect of steric inhibition of general solvation.*

Mackor *et al.*[53] claimed that the $\Delta\Delta S^{\ddagger}$ for the effect of a methyl group on the protodedeuteration of alkylbenzenes was such as to increase the rate, and that $\Delta\Delta H^{\ddagger}$ was insignificant. Deans and Eaborn[46] have, however, shown that these conclusions are probably incorrect.

Our values of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ lead to a partial rate factor of *ca.* 100 for the 4-methyl group at 200°. Eaborn and Taylor[29] found 243 as the partial rate factor for the protodetritiation in the benzene series at 25° for *o*- or *p*-methyl groups: for protodedeuteration, Gold[28] found 83.

Comparison of equivalent runs on collidine and its 1-methyl quaternary derivative (Table 4) indicates a rate enhancement of $1{\cdot}9 \pm 0{\cdot}1$ by the *N*-methyl group.

Comparison of Pyridine and Benzene Reactivity.—Unfortunately a direct comparison is not possible, and many uncertainties are involved. By using the results of Eaborn and Taylor[29] for the protodetritiation of benzene and toluene at 25° in 75·3% sulphuric acid (H_0 $-6{\cdot}33$), it is possible to estimate * rates for *m*-xylene and mesitylene under these conditions. By a long extrapolation * (that neglects changes in H_0 with temperature)

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* See footnote on p. 3761.

[47] Bunton, de la Mare, and Tillett, *J.*, 1958, 4754; 1959, 1766.

[48] Clark and Williams, *J.*, 1956, 1304.

[49] Brice and Lindsay, *J. Amer. Chem. Soc.*, 1960, **82**, 3538.

[50] Bunton, Hadwick, Llewellyn, and Pocker, *J.*, 1958, 403.

[51] Moelwyn-Hughes, "Kinetics of Reactions in Solution," Clarendon Press, Oxford, 1947, pp. 91—94.

[52] Robinson and Stokes, "Electrolyte Solutions," Butterworths Scientific Publns., London, 1959, Chapter 3.

[53] Mackor, Smit, and van der Waals, *Trans. Faraday Soc.*, 1957, **53**, 1309.

rates for lutidine and collidine under these conditions can also be estimated. These calculations indicate that the substitution of a =NH⁺– group for a ring =CH– in benzene decreases the reactivity towards electrophilic hydrogen exchange by a factor of *ca.* 10^{-18}. (This is consistent with Ridd's estimate[5] of $>10^{12}$.) For *ortho-* or *para*-substitution this factor must, of course, be considerably smaller still.

When the relative concentrations are taken into account, our results indicate that reaction for the free base is less than *ca.* 10^{13} times that for the conjugate acid, *i.e.*, that substitution of =N– is deactivating by a factor of at least 10^6. After allowance for the uncertainties involved it still appears clear that such a substitution is considerably deactivating.

We hope to extend our investigation to higher temperatures and lower acidities where we expect to find reaction *via* the free base able to compete with that *via* the conjugate acid. This would permit an experimental estimate of the partial rate factors involved for the substitution of =N– for =CH–.

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