769. *The Influence of Steric Factors on the Properties of 4-Aminopyridine Derivatives.*

By J. M. Essery and K. Schofield.

The ultraviolet absorption spectra for the free bases and the monocations, the basic strengths at three temperatures, and (for the primary amines) the frequencies and intensities of the N–H stretching bands are reported for a series of 3-mono- and 3,5-di-substituted 4-dimethylamino-, 4-methylamino-, and 4-amino-pyridines. In all cases the ring-nitrogen was the basic centre.

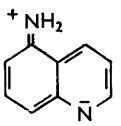
Changes in the intensities of the ultraviolet absorption bands of the 3-monosubstituted tertiary and 3,5-disubstituted secondary amines are attributed to steric inhibition of resonance. No evidence for such inhibition in the 4-aminopyridines or the 3-monosubstituted 4-methylaminopyridines is provided by the ultraviolet absorption data. The infrared measurements suggest the absence of steric inhibition of resonance in the primary amines.

The ionisation results are discussed in terms of steric inhibition of resonance, and of steric hindrance to solvation, and the base-weakening effect caused by 3,5-disubstitution in the 4-aminopyridines is attributed to the latter effect.

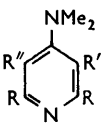
The presence of an amino-group in a nitrogen heteroaromatic system influences profoundly the properties of that system. The mutual mesomeric interactions of a nuclear nitrogen atom and the nitrogen atom of an amino-group properly sited with respect to each other, have important consequences for both. The basic strength of the nuclear nitrogen atom, which is almost always the basic centre,[1,2,3] is markedly augmented, and the infrared characteristics of the amino-group are modified.[3,4,5]

Apparent exceptions to this statement are compounds such as 4-aminoacridine, 5-aminoquinoline, and 8-aminoisoquinoline.[3,4,6] Thus, in these compounds the amino-group has very little augmenting influence on the basic stength of the nuclear nitrogen atom, and, in the other direction, the nuclear nitrogen atom has but little effect on the N–H stretching force constant of the amino-group.

Three explanations seem to be possible for these anomalous properties of *peri*-amines. First, it might be argued in terms of resonance theory that the structures contributing to the resonance hybrid which imply interaction between the two nitrogen atoms are *ortho*-quinonoid forms [*e.g.*, (I) in the case of 5-aminoquinoline], and for that reason unimportant. Secondly, the facts might be attributed to steric inhibition of resonance caused by non-bonding interaction between the amino-group and the *peri*-situated C–H group. Thirdly, steric hindrance to solvation might be the cause of the anomalies. The first possibility cannot be accepted until the second and third, which are amenable to experiment, have been tested.



(I)



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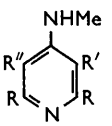

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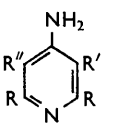


(IV)

Models indicate that in primary amines steric inhibition of resonance will be slight, if it exists at all, and the question of the existence of the effect is much in dispute. Dipole-moment studies on amines of the benzene series are interpreted as indicating a slight degree

[1] Craig and Short, *J.*, 1945, 419.
[2] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[3] Osborn, Schofield, and Short, *J.*, 1956, 4191; Schofield, *J.*, 1958, 1312.
[4] Short, *J.*, 1952, 4584.
[5] Mason, *J.*, 1958, 3619; 1959, 1281.
[6] Elliott and Mason, *J.*, 1959, 2352.

of steric inhibition of resonance.[7] Elliott and Mason,[8] from measurements of frequencies and intensities of N–H stretching vibrations in *meso*- and *peri*-amines of polynuclear aromatic systems, also argued for the existence of the effect. On the other hand, Wepster,[9] on the basis of ultraviolet and refractivity studies, has argued against the presence of appreciable resonance inhibition in primary aromatic amines. Kreuger and Thompson,[10] in infrared studies of *ortho*-substituted anilines, noted that both internal hydrogen bonding and steric hindrance might be involved, and that the simultaneous operation of several factors is complicated.

Steric hindrance to solvation accounts for the influence of *ortho*-substituents upon the basic strengths of primary and tertiary anilines.[9] These examples differ from the heterocyclic amines being discussed here, for in the anilines it is the basic centre itself which is being subjected to changing steric environments, whereas with the amino-azines the basic centre is remote from steric disturbance. Neverthless, resonance in the heterocyclic cations must distribute the positive charge between both nitrogen atoms, and solvation changes at either might be important. However, it is difficult to see that the infrared data relating to the heterocyclic amines can be explained in terms of solvation.

These considerations led us to a more general investigation of the influence of steric factors upon the properties of amino-azines. In this paper we report experiments on the three series of compounds (II; R = R′ = H, R″ = H, Br, Me, Et, or Pr^i; R = H, R′ = R″ = Me), (III; R = R′ = H, R″ = H, Br, Me, Et, or Pr^i; R = H, R′ = R″ = Me; R = R′ = R″ = Me), and (IV; R = R′ = H, R″ = H, Br, Me, Et, or Pr^i; R = H, R′ = R″ = Me; R = R′ = R″ = Me). The preparation of these compounds has been described.[11] We have examined the ultraviolet absorption spectra of these bases and their monocations, the infrared characteristics of the amino-group in the free bases, and the ionisation constants of the bases.

Discussion

Ultraviolet data are collected in Table 1, and illustrated in Figs. 1—4. Before these are discussed in the special context of the three classes of amine, some brief general remarks are appropriate. Included in Table 1 with the data for 4-dimethylaminopyridines are those for the parent 4-unsubstituted compounds. These agree fairly satisfactorily with earlier results for the alkylpyridines,[12] showing that the wavelength of maximum absorption is hardly affected by protonation, whilst intensity of absorption is grèatly increased. Cationisation of 4-aminopyridine produces a bathochromic shift of the absorption maximum, instead of leaving it stationary as reported by Steck and Ewing.[13] This is a general feature for all of the amines (II), (III), and (IV). In every case the ring-nitrogen atom is the basic centre.

The absorption bands due to $\pi \rightarrow \pi^*$ transitions in monocyclic amino-azines have been discussed by Mason [14] in terms of a benzyl anion model. The main high-intensity band in 4-aminopyridine is assigned to a transition of energy

$$E = 1{\cdot}26\beta + 0{\cdot}413\Delta\alpha_x - 0{\cdot}172\Delta\alpha_N.$$

$\Delta\alpha_x$ and $\Delta\alpha_N$ are the increments in the Coulomb integrals of the exocyclic substituent, in this case the amino-group, and of the nuclear nitrogen atom. Since $\Delta\alpha_{NH^+} > \Delta\alpha_N$ the bathochromic shift produced by cationisation of the base is understandable. As the

[7] Birtles and Hampson, *J.*, 1937, 10; Ingham and Hampson, *J.*, 1939, 981; Smith, *J.*, 1953, 109; Smith in " Steric Effects in Conjugated Systems," ed. by Gray, Butterworths, London, 1958.
[8] Elliott and Mason, *J.*, 1959, 1275.
[9] Wepster, *Rec. Trav. chim.*, 1957, **76**, 357.
[10] Kreuger and Thompson, *Proc. Roy. Soc.*, 1957, *A*, **243**, 143.
[11] Essery and Schofield, *J.*, 1960, 4953.
[12] Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26; Andon, Cox, and Herington, *Trans. Faraday Soc.*, 1954, **50**, 918.
[13] Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.
[14] Mason, *J.*, 1960, 219.

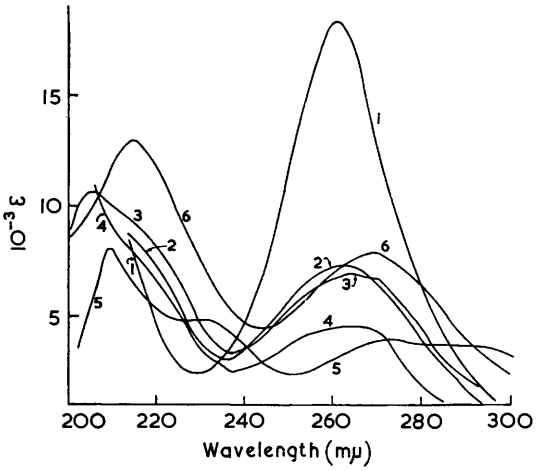


FIG. 1. *Ultraviolet absorption spectra of 4-dimethylaminopyridines (neutral molecules).* (1) *4-Dimethylaminopyridine.* (2) *4-Dimethylamino-3-methylpyridine.* (3) *4-Dimethylamino-3-ethylpyridine.* (4) *4-Dimethylamino-3-isopropylpyridine.* (5) *4-Dimethylamino-3,5-dimethylpyridine.* (6) *3-Bromo-4-dimethylaminopyridine.*

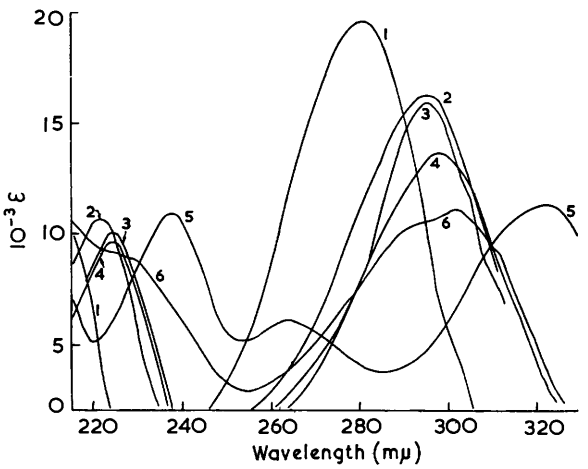


FIG. 2. *Ultraviolet absorption spectra of 4-dimethylaminopyridine (cations). Numbering as in* FIG. 1.

FIG. 3. *Ultraviolet absorption spectra of 4-methylaminopyridines (neutral molecules).* (1) *4-Methylaminopyridine.* (2) *3,5-Dimethyl-4-methylaminopyridine.* (3) *2,3,5,6-Tetramethyl-4-methylaminopyridine.*

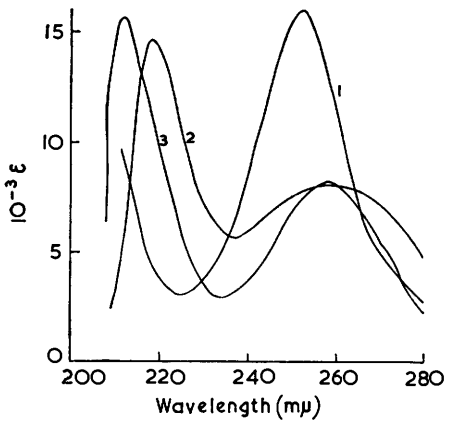
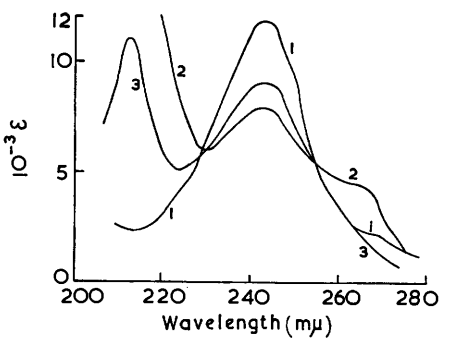


FIG. 4. *Ultraviolet absorption spectra of 4-aminopyridines (neutral molecules).* (1) *4-Aminopyridine.* (2) *4-Amino-2,3,5,6-tetramethylpyridine.* (3) *4-Amino-3,5-dimethylpyridine.*



exocyclic substituent is changed from amino, through methylamino, to dimethylamino the value of $\Delta\alpha_x$ decreases, and the wavelength of maximum absorption would be expected to increase in this sequence. This is observed (Table 1). Twisting of the exocyclic amino-group will decrease the probability of the above transition, so that steric inhibition of resonance in these amines should produce a decrease in intensity of the absorption band due to the $\pi \rightarrow \pi^*$ transition.

1. *The Tertiary Amines.*—The $\pi \rightarrow \pi^*$ transition in the 4-dimethylaminopyridines gives rise to a high-intensity band at about 260 mμ. Introduction of 3-substituents causes a

TABLE 1. *Ultraviolet absorption data for pyridines, 4-amino-, 4-methylamino- and 4-dimethylamino-pyridines in aqueous solution.*

4-Substituent: H (*i.e.*, none)

	Base		Cation	
Substituent	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
3-H	257	2920	256	5630
3-Me	262	3360	262	5650
3-Et	262	3060	262	5350
3-Pr^i	262	1980	263·5	3860
3,5-Me_2	267	3600	267	5680
3-Br	268	2630	279	9500

4-Substituent: NH_2

	Base			Cation	
Substituent	$\lambda_{max.}$ (mμ)	ε	*f*	$\lambda_{max.}$ (mμ)	ε
3-H	243	11,800	0·250	262	18,900
3-Br	267	9160	0·211	270·5	11,100
3-Me	242	9880	0·228	265	16,000
3-Et	244	9560	0·201	265	17,200
3-Pr^i	244	10,200	0·234	267	16,300
3,5-Me_2	242	9100	0·198	267	15,100
2,3,5,6-Me_4	243	7820	0·176	265	14,300

4-Substituent: NHMe

	Base			Cation	
Substituent	$\lambda_{max.}$ (mμ)	ε	*f*	$\lambda_{max.}$ (mμ)	ε
3-H	253	16,000	0·321	271·5	17,200
3-Br	254	13,000	0·286	279	15,800
3-Me	253	14,900	0·319	274	18,000
3-Et	255	14,600	0·290	274	17,700
3-Pr^i	255	15,500	0·270	275	17,100
3,5-Me_2	258	8220	0·174	284	15,500
2,3,5,6-Me_4	257	8050	0·218	280·5	15,000

4-Substituent: 4-NMe_2

	Base				Cation		
Substituent	$\lambda_{max.}$ (mμ)	ε	*f*	θ	$\lambda_{max.}$ (mμ)	ε	θ
3-H	261	18,300	0·343	(0)	280·5	19,600	(0)
3-Me	263	7240	0·163	46°	295	16,200	34°
3-Et	264·5	6960	0·158	47	296	15,900	36
3-Pr^i	265	4570	0·102	57	298	13,600	46
3,5-Me_2	272 *	3920	0·064	64	322	11,400	54
3-Br	269·5	7880	—	—	301·5	11,000	—

Values of ε are in cm.^{2} mole^{-1}, and of *f* are in cm. mole^{-1}.

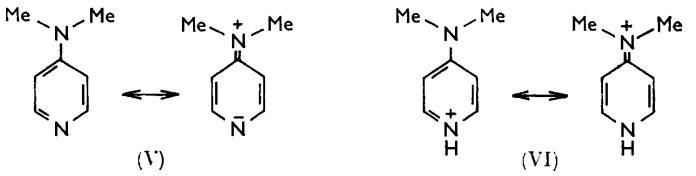
* Data for the shorter-wavelength peak: see text and Fig. 1.

marked and progressive decrease in the intensity of this band, recalling similar changes in the dimethylaniline series.[9,15,16] With decreasing intensity, the long-wavelength band loses symmetry until with 4-dimethylamino-3,5-dimethylpyridine resolution into two

[15] Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838.
[16] Klevens and Platt, *J. Amer. Chem. Soc.*, 1949, **71**, 1714.

overlapping bands occurs. With the point of overlap of these two bands (ν = 35,400 cm.$^{-1}$) as the upper limit, and the appropriate minimum as the lower limit, the oscillator strengths f have been calculated and are given in Table 1. From the oscillator strengths the apparent " effective angles of twist," θ, of the dimethylamino-group out of the plane of the pyridine ring were calculated from the relation [16] $\cos^2\theta = f/f_0$. These angles have only illustrative significance, for they make no allowance for the effect upon the intensity of the band of the hindering substituents. The data point to a sequence of increasing steric effectiveness, H < 3-Me < 3-Et < 3-Pr^i < 3,5-Me$_2$, in agreement with that reported by Wepster [9] for *ortho*-substituted dimethylanilines. The effect of a 3-methyl group is shown by the $\varepsilon_{max.}$ values to be greater than that of a 3-bromo-substituent. The oscillator strength of the high-intensity band of 3-bromo-4-dimethylaminopyridine is not included in Table 1 since the above-mentioned upper limit was not appropriate in this case. If, however, the upper wavelength limit for all the curves is set at ν = 33,000 cm.$^{-1}$ the oscillator strength for the bromo-compound (0·191) lies between that of 4-dimethylamino-3-methylpyridine (0·179) and 4-dimethylaminopyridine (0·367). This result is to be expected from the van der Waals radii of the bromine atom and the methyl group,[17] and is in line with the results of Klevens and Platt [16] for dimethylanilines.

Whilst the introduction of 3-substituents into the amines (II) causes very little change in $\lambda_{max.}$, in the derived cations $\lambda_{max.}$ increases with increasing bulk of the 3-substituent. This shift and the attendant fall in intensity are illustrated in Fig. 2. The decrease in intensity is not as marked for the cations as for the free bases, as is shown by the " angle of twist " (values of θ for the cations were calculated from the relation [18,19] $\cos^2\theta = \varepsilon/\varepsilon_0$, for, because of the wavelength shifts, comparable limits for the absorption bands were not available). Whilst delocalisation of electrons is undoubtedly important in the base (II), as indicated in structure (V), it is even more important in the cation (VI), and in the cation the localising effect of a sterically hindering group at $C_{(3)}$ will be more strongly resisted.



Further demonstration of the operation of steric inhibition of resonance is found in the ionisation constants of the bases (II). In Table 2 are recorded the thermodynamic values of pK_a at 20° for these amines and their parent 3-substituted pyridines, and the corresponding values of ΔG, ΔH, and $T\Delta S$. The source of these pK_a values is explained in the Experimental section.

Comments on the results for the 3-substituted pyridines are appropriate, before the 4-dimethylaminopyridines are discussed. The introduction of an alkyl group or bromine atom into the pyridine ring causes respectively an increase and a decrease in ΔG, as would be expected from the opposite inductive effects of these substituents. The ΔH values roughly parallel those for ΔG, showing that internal electronic effects are mainly responsible for the changes in basic strength (Mortimer and Laidler [21] call them polar effects). No trend is observable in the entropy factors, which do not differ significantly amongst themselves. The relative importance of ΔH and $T\Delta S$ in affecting the value of ΔG may be seen by comparing each substituted compound with pyridine itself. Clearly the substituents

[17] Pauling, " The Nature of the Chemical Bond," 3rd edn., Cornell University Press, New York, 1960.
[18] Braude, *Experientia*, 1955, **11**, 457.
[19] Wepster, *Rec. Trav. chim.*, 1957, **76**, 335.
[20] Wepster, " Progress in Stereochemistry," Vol. II, p. 99, ed. by Klyne and de la Mare, Butterworths, London, 1958.
[21] Mortimer and Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1731.

TABLE 2. *The ionisation of pyridines, 4-dimethylamino-, 4-amino-, and 4-methylamino-pyridines in aqueous solution at 20°.*

Substituent	pK_a	ΔG	ΔH	$-T\Delta S$	ΔpK_a
		4-*Substituent*: H (*i.e.*, none)			
3-H	5·27	7·07 ± 0·24	4·37 ± 0·17	2·70 ± 0·17	—
3-Me	5·79	7·76 ± 0·47	4·64 ± 0·33	3·12 ± 0·32	0·52
3-Et	5·80	7·77 ± 0·38	5·30 ± 0·27	2·47 ± 0·27	0·53
3-Pr^i	5·88	7·89 ± 0·05	5·57 ± 0·03	2·32 ± 0·03	0·61
3,5-Me_2	6·23	8·35 ± 0·81	5·29 ± 0·57	3·06 ± 0·57	0·96
3-Br	2·91	3·91 ± 0·16	1·85 ± 0·11	2·06 ± 0·11	−2·36
2,3,5,6-Me_4	7·88	10·57 ± 0·48	8·08 ± 0·40	2·49 ± 0·40	2·61
		4-*Substituent*: NH_2			
3-H	9·29	12·45 ± 0·11	10·88 ± 0·08	1·57 ± 0·08	4·02
3-Me	9·43	12·64 ± 0·57	11·66 ± 0·40	0·98 ± 0·57	3·64
3-Et	9·51	12·75 ± 0·49	10·89 ± 0·34	1·86 ± 0·35	3·71
3-Pr^i	9·54	12·79 ± 0·02	11·28 ± 0·01	1·51 ± 0·01	3·66
3,5-Me_2	9·54	12·79 ± 0·23	10·48 ± 0·16	2·31 ± 0·16	3·21
2,3,5,6-Me_4	10·58	14·19 ± 0·34	10·35 ± 0·24	3·84 ± 0·24	2·70
3-Br	7·04	9·44 ± 0·23	7·69 ± 0·16	1·75 ± 0·16	4·13
		4-*Substituent*: NHMe			
3-H	9·66	12·96 ± 0·43	11·02 ± 0·30	1·94 ± 0·30	4·39
3-Me	9·83	13·18 ± 0·33	10·87 ± 0·23	2·31 ± 0·23	4·04
3-Et	9·90	13·27 ± 0·19	11·54 ± 0·14	1·73 ± 0·14	4·10
3-Pr^i	9·96	13·36 ± 0·58	11·93 ± 0·41	1·43 ± 0·41	4·08
3,5-Me_2	9·43	12·65 ± 0·91	12·06 ± 0·64	0·59 ± 0·64	3·20
2,3,5,6-Me_4	10·06	13·49 ± 0·19	9·95 ± 0·14	3·54 ± 0·14	2·18
3-Br	7·47	10·02 ± 0·49	9·01 ± 0·35	1·01 ± 0·35	4·56
		4-*Substituent*: NMe_2			
3-H	9·71	13·01 ± 0·43	10·75 ± 0·31	2·26 ± 0·31	4·44
3-Me	8·68	11·64 ± 0·27	9·02 ± 0·19	2·62 ± 0·19	2·89
3-Et	8·66	11·62 ± 0·53	9·15 ± 0·38	2·47 ± 0·38	2·86
3-Pr^i	8·27	11·09 ± 0·38	8·76 ± 0·27	2·33 ± 0·27	2·39
3,5-Me_2	8·15	10·93 ± 1·00	9·83 ± 0·71	1·10 ± 0·71	1·92
3-Br	6·52	8·75 ± 0·14	6·36 ± 0·13	2·39 ± 0·14	3·61

ΔG, ΔH, and $T\Delta S$ are in kcal. mole^{-1}; they are recorded with their standard errors.

produce their effects mainly by changing ΔH. This is to be expected if internal electronic factors play the dominant rôle and if solvation changes are unimportant. The same conclusion was reached by Mortimer and Laidler.[21]

The effects of methyl groups upon ΔG, as seen in the cases of 3-methyl- and 3,5-dimethyl-pyridine, are nearly additive. Additivity was observed by Brown and Mihm [22] in pK_a values for pyridine, α-picoline, and 2,6-lutidine. They considered this result to indicate an absence of significant steric effects relating either to the addition of a proton or to solvation of the 2,6-lutidinium ion. The data of Mortimer and Laidler [21] for 2,6-lutidine show, however, that the near-additivity in ΔG is not preserved in ΔH. They concluded that the 2,6-lutidinium ion had a high entropy because of steric hindrance to solvation round the $^+$N–H bond. This effect is not revealed in ΔG (*i.e.*, in pK_a), because it produces compensating changes in ΔH and $T\Delta S$.

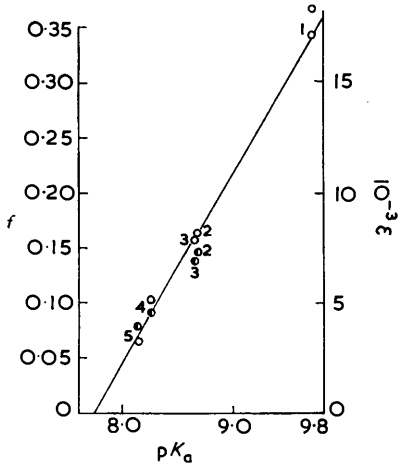
From these considerations it might have been expected that a similar situation would have been found with 2,3,5,6-tetramethylpyridine. However, the results (Table 2) show that the high value of ΔG for this compound is principally due to the increase in ΔH caused by the introduction of four methyl groups. The entropy factor seems to be normal. It is possible that in this case the expected high entropy of the cation is balanced by high entropy in the neutral molecule, caused by its high " paraffinic " character due to the conglomeration of methyl groups.

Turning to the 4-dimethylaminopyridines we see (Table 2) that the 3-substituents, Br, Me, Et, Pr^i, and 3,5-Me_2, render the dimethylamino-group progressively less effective as a

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

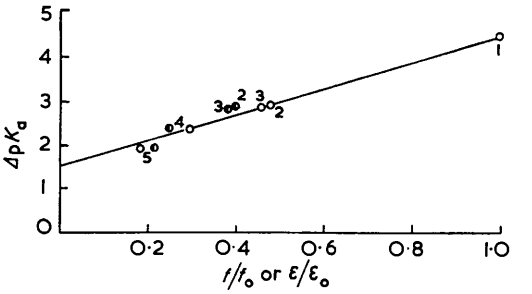
base-strengthening factor, and in that order. This is the same order as that already mentioned in discussing the ultraviolet absorption data. The progressive fall in ΔpK_a (*i.e.*, in the change in ΔG) is paralleled by a fall in the change in ΔH, as between each succeeding member of the series and 4-dimethylaminopyridine itself; and this fact, coupled with the demonstration that $T\Delta S$ does not change significantly throughout the series, fully justifies the attribution of the effect to steric inhibition of resonance. Although the $T\Delta S$ value for 4-dimethylamino-3,5-dimethylpyridine appears to be appreciably more positive than the values for the other 3-alkyl compounds, and consequently causes the change in $T\Delta S$ to appear to play a more important part in this instance in determining the change in ΔG, it is not in fact significantly different statistically * from the other $T\Delta S$ values so far as can be ascertained from our results.

FIG. 5. *Relation between absorption intensity and basic strength for 4-dimethylaminopyridines.*



○ - - - - f. ◐ - - - - $\varepsilon_{max.}$. *Numbering as in* FIG. 1.

FIG. 6. *Relation between* ΔpK_a *and* " $\cos^2\theta$ " *for 4-dimethylaminopyridines.*



○ - - - - f/f_0. ◐ - - - - $\varepsilon/\varepsilon_0$. *Numbering as in* FIG. 1.

Overall, then, our data reveal no appreciable difference in solvation effects in the series of tertiary amines, and changes in basic strength are determined by the internal steric inhibition of resonance. This is reasonable, for in these tertiary amines the main problem of solvation must relate to the nuclear nitrogen atom, and this is remote from the hindering substituents.

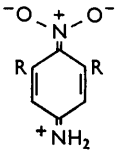
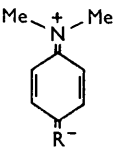
Linear relations emerge from the data for 4-dimethylaminopyridines between f and pK_a, and between f and ΔpK_a, and between f/f_0 and ΔpK_a (two of these relations are illustrated in Fig. 5 and 6). In the illustrated cases the corresponding values of $\varepsilon_{max.}$ and $\varepsilon_{max.}/\varepsilon_{0,\,max.}$ have also been plotted, but the oscillator strength gives better correlations. Wepster [19] observed a linear relation between $\varepsilon_{max.}$ and ΔpK_a for hindered derivatives of *p*-nitroaniline. In this system ΔpK_a is determined almost exclusively by the *para*-interaction energy in the nitroamine (see VII), and it was concluded that $\varepsilon_{max.}$ was proportional to the corresponding resonance energy. With the *p*-nitroanilines the physical significance of the linear relation is fairly clear, for the *para*-interaction gives rise to strong absorption

* The mean value of $T\Delta S$ for the five members of the series, excluding 4-dimethylamino-3,5-dimethylpyridine, is $2{\cdot}41 \pm 0{\cdot}12$ units. The difference between this and the value for the 3,5-dimethyl compound ($1{\cdot}10 \pm 0{\cdot}71$) is $1{\cdot}31 \pm 0{\cdot}72$ units, which is not statistically significant at the 5% level, when a *t*-distribution with four degrees of freedom is used.[23]

[23] Topping, " Errors of Observation and Their Treatment," The Institute of Physics, London, 1955.

at about 380 mμ, in which region absorption by the alkylbenzenes and alkylanilines is negligible. This is not the situation with the tertiary pyridine amines.

More interesting are the results of applying the Hammett equation to the data of Table 2. Use of the equation ($\Delta pK_a = \rho\sigma$) in the pyridine series leads to the relation

(VII)   (VIII)

shown in Fig. 7. Since resonance effects are one of the main causes of failure of the Hammett equation,[24] substituents used in constructing Fig. 7 were so chosen that resonance effects should be minimal. The sources of the basic strengths are given in footnotes to Fig. 7. The σ values are as given by Jaffé,[25] and the basic strengths are

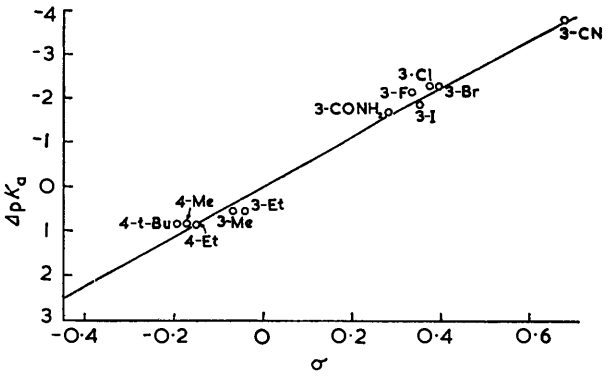


FIG. 7. *Hammett plot of* ΔpK_a *against* σ *for monosubstituted pyridines.*

taken from this paper, from Brown and Mihm,[22] from Jaffé and Doak,[26] and from Brown and McDaniel.[26a] The slope of the regression line, ($\rho = 5{\cdot}735$), the standard deviation from the line ($s = 0{\cdot}181$), and the correlation coefficient ($r = 0{\cdot}995$) are in good agreement with those obtained by Jaffé and Doak [26] using rather more extensive data. Jaffé [25] discussed the dependence of σ for electron-releasing groups such as *p*-dimethylamino on the nature of the reactive centre. The different σ values obtained for this group appear to depend on the relative importance of resonance structures (VIII), and Jaffé gives values ranging from $\sigma = -0{\cdot}425$ ($R = NH_2$, $SiHR_2$, Br) to $\sigma = -0{\cdot}972$ (R = CHO). The more negative σ, the more important must be the contribution of structures such as (VIII). For the unhindered 4-dimethylamino-group the present work yields the value $\sigma = -0{\cdot}761$, illustrating the great importance of resonance of the kind represented by (V) or (VI), in the aminopyridine series. The more important the *para*-interaction the more strongly should twisting of the amino-group be resisted. Wepster [27] has observed that the " mean angle of twist," from spectroscopic measurements, is smaller in *p*-aminonitrobenzenes than in similarly substituted nitrobenzenes, and attributed this to *para*-interaction between the functional groups. The angles of twist for the 4-dimethylaminopyridines would be expected to be smaller than those for the corresponding dimethylanilines. They are in fact slightly smaller than those recorded by Wepster.[9]

[24] Taft, in " Steric Effects in Organic Chemistry," ed. by Newman, Wiley and Sons, Inc., New York, 1956.
[25] Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[26] Jaffé and Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.
[26a] Brown and McDaniel, *J. Amer. Chem. Soc.*, 1955, **77**, 3752.
[27] Wepster in " Progress in Stereochemistry," Vol. II, ed. by Klyne and de la Mare, Butterworths, London, 1958.

Taft [28] defined the fractional steric inhibition of resonance by the expression $(\sigma_R^\circ - \sigma_R)/\sigma_R^\circ$, where σ_R and σ_R° represent the resonance contributions to the σ constants in the hindered and the unhindered compound respectively. The observed σ value is made up of the resonance contribution σ_R and the inductive contribution σ_I, and when resonance is completely inhibited $\sigma = \sigma_I$. From the Hammett plot (Fig. 7) and the pK_a data in Table 2, the substituent constants for the dimethylamino-group were obtained by using the line of slope r^2/ρ to calculate the new constants.[25] The σ values in Table 3, which have been corrected for the effect of the hindering alkyl group, represent the substituent constants for the 4-dimethylamino-group as it is subjected to an increasing degree of resonance inhibition. As is already clear, even in 4-dimethylamino-3,5-dimethylpyridine resonance is far from completely inhibited; for if it were, σ would be equal to σ_I, and that, for a dimethylamino-group, should be positive.

Taft [28] assumed that the value $\sigma_I = +0{\cdot}10$, found for the amino-group from nuclear magnetic resonance studies,[29] was applicable to the dimethylamino-group. By accepting this as a reasonable value, the fractional steric inhibition of resonance for the 4-dimethylamino-group in the pyridine derivatives has been calculated (Table 3). Its value for

TABLE 3. *Fractional steric inhibition of resonance in 4-dimethylaminopyridines.*

Substituent	σ	$(\sigma_R^\circ - \sigma_R)/\sigma_R^\circ$
3-H	−0·761	0·0
3-Br	−0·611	0·17
3-Me	−0·517	0·28
3-Et	−0·540	0·26
3-Pr^i	−0·406	0·41
3,5-Me$_2$	−0·355	0·47

4-dimethylamino-3,5-dimethylpyridine (0·47) is much smaller than that (0·75) calculated by Taft [28] for ethyl 4-dimethylamino-3,5-dimethylbenzoate. This and the σ value (−0·761), compared with −0·642 for the *p*-dimethylamino-group interacting with an ethoxycarbonyl group, stress the very great importance of *para*-interaction in the 4-dimethylaminopyridines.

If the value $\sigma_I = +0{\cdot}10$ is adopted for the completely resonance-inhibited dimethylamino-group it follows from Fig. 7 that such a substituent at $C_{(4)}$ in pyridine would weaken the base by 0·63 unit of pK_a. Accordingly, if in 4-dimethylaminopyridine the inductive effect of the substituent were not operating, ΔpK_a for this compound would become $4{\cdot}44 + 0{\cdot}63 = 5{\cdot}07$ units. The quantity $\boldsymbol{R}T\Delta pK_a = 6{\cdot}8$ kcal./mole then provides a rough measure of the increase in resonance energy brought about in cationising 4-dimethylaminopyridine, and due mainly to resonance of the type represented in (V) and (VI).

Comparisons of the protonation of 4-dimethylaminopyridine with other reactions are possible by using Taft's expression $\Delta pK_a = \rho\sigma + \psi$. In applying this equation, Taft [24] assumed that in ethyl 4-dimethylamino-3,5-dimethylbenzoate steric inhibition of resonance was complete, and so obtained from saponification rate data a crude inductive substituent

TABLE 4. *Taft's quantity ψ.*

Reaction	ψ (log units)
1. Saponification of ethyl *p*-dimethylaminobenzoate in 87·03% aqueous ethanol at 30°	−1·78
2. Saponification of ethyl 4-dimethylamino-3-methylbenzoate	−0·85
3. Basicity of 4-dimethylaminopyridines at 20°	−5·01

constant for the dimethylamino-group of −0·11. We have adopted instead the value $\sigma_I = +0{\cdot}10$ and have calculated ψ for the 4-dimethylaminopyridines and recalculated it for two of the reactions quoted by Taft.[24] The values are given in Table 4. The value of ψ for reaction (3) again demonstrates the large interaction between exocyclic and ring

[28] Taft, *J. Chem. Phys.*, 1957, **27**, 1427.
[29] Taft, *J. Amer. Chem. Soc.*, 1957, **79**, 1045.

nitrogen atom in 4-dimethylaminopyridine. A similar conclusion can be reached for the amino- and methylamino-pyridines.

2. *The Secondary Amines.*—The high-intensity absorption band in the spectra of the 4-methylaminopyridines occurs at 253—258 mμ (Table 1 and Fig. 3). The data given include the oscillator strengths measured between the absorption minimum and $\nu = 34{,}000$ cm.$^{-1}$. The changes in $\varepsilon_{max.}$ and f for the 3-monosubstituted compounds are small, and show no significant trend, thus recalling the *N*-methylanilines.[9] Resonance inhibition appears to be absent, for the conformational reasons discussed by Wepster.[9] With the 3,5-disubstituted compounds, however, the sharp decrease in absorption intensity (Fig. 3) clearly indicates resonance inhibition. Whilst $\varepsilon_{max.}$ shows the effect to be greater in 4-methylamino-2,3,5,6-tetramethyl- than in 3,5-dimethyl-4-methylamino-pyridine, the values of f would lead to the opposite conclusion. The latter result must be attributed to the intrinsic effect upon f of the hindering groups themselves. As in the case of the tertiary bases, the results suggest that the degree of resonance inhibition in the cations is smaller than in the free bases.

The ionisation data (Table 2) for the 4-methylaminopyridines show that introduction of a 3-alkyl substituent causes a decrease in ΔpK_a, in comparison with the non-substituted case, whilst the electron-attracting bromine atom causes an increase in ΔpK_a. This effect is also observed for the 4-aminopyridines. That pK_a increases as the 3-substituent varies, in the order H < Me < Et < Pr^i, whilst ΔpK_a shows no trend, indicates the absence of resonance inhibition. The sudden fall in ΔpK_a when the series reaches 3,5-dimethyl-4-methylaminopyridine suggests the onset of resonance suppression. However, ΔpK_a for 2,3,5,6-tetramethyl-4-methylaminopyridine is smaller than would be expected if the base-weakening is caused only by additional damping of the resonance over that in the 3,5-dimethyl compound, due to the " *ortho*-xylene " or " buttressing " effect.[30]

The thermodynamic data show that in the 3-monosubstituted compounds the increase in ΔG (*i.e.*, in pK_a) above that of the corresponding pyridine derivative is due mainly to increase in ΔH. With the tetramethyl compound, however, the entropy factor contributes almost as strongly as the enthalpy factor to the increase in ΔG. This is readily understood from a consideration of the solvation shell around the molecule of 2,3,5,6-tetramethyl-4-methylaminopyridine. In these secondary amines orientation of the solvent molecules can occur around $N_{(1)}$ and round the exocyclic group, which has a hydrogen atom available for hydrogen bonding. In 4-methylaminopyridine, then, there will be a well-orientated sheath of solvent molecules, and the entropy of the system will be relatively low. Four methyl groups substituted into the nucleus must disrupt the solvent shell at both ends of the molecule. Since the orientation effect will be stronger in the cation than in the free base, the disruption will be of greater importance, so that the entropy of the cation should be greater than that of 4-methylaminopyridinium. Thus, $T\Delta S$ should be more negative for the tetramethyl compound. The value observed ($-3{\cdot}54 \pm 0{\cdot}14$ units; Table 2) is significantly different from the mean value ($-1{\cdot}68 \pm 0{\cdot}13$ units) for the four 3-monoalkyl compounds and the 3-bromo-compound (see footnote to p. 3945). The very low value for ΔpK_a for 2,3,5,6-tetramethyl-4-methylaminopyridine can therefore be attributed partly to steric inhibition of resonance, and partly to steric hindrance to solvation. A similar effect might have been expected, only to a smaller extent, with 3,5-dimethyl-4-methylaminopyridine. This is, however, not revealed by the results in Table 2.

The data point, then, to the absence of significant resonance inhibition in the 3-monosubstituted 4-methylaminopyridines. Resonance inhibition is present in the 3,5-dimethyl compound, possibly accompanied by a solvation effect, and with the 2,3,5,6-tetramethyl compound both steric inhibition of resonance and steric hindrance to solvation are active.

3. *The Primary Amines.*—Here the long-wavelength maximum occurs at about 243 mμ (Table 1 and Fig. 4). The oscillator strengths for this peak were measured between the

[30] van Helden, Verkade, and Wepster, *Rec. Trav. chim.*, 1954, **73**, 39.

limits of the absorption minimum and $\nu = 35{,}000$ cm.$^{-1}$. With the 3-monosubstituted compounds there is a slight and irregular decrease of the absorption intensity, compared with that for 4-aminopyridine, in both the free bases and the cations. A larger decrease is observed with the 3,5-dimethyl compound, and the intensity loss in the tetramethyl compound is considerable. These observations might be taken to indicate the presence of a small degree of resonance inhibition in the 3-substituted compounds, which is enhanced in the last two members of the series. However, this is unlikely (see below), and a further point is to be considered. In general, the absorption maxima of polar molecules in solution vary in position and intensity with the character of the solvent.[31] The spectra of some of the amines of the present series (those which were sufficiently soluble) were determined in cyclohexane solution (Table 5). The spectra show both hypsochromic and hypochromic

TABLE 5. *Ultraviolet spectra in cyclohexane solution.*

	$\lambda_{max.}$ (mμ)	ε		$\lambda_{max.}$ (mμ)	ε
4-Aminopyridine	233	9620	4-Methylaminopyridine	242	10,500
4-Amino-3-methylpyridine.....	231	7840	3-Methyl-4-methylaminopyridine	241	9660
4-Amino-4-isopropylpyridine...	232	9500			

effects compared with those determined in aqueous solution (Table 1). Qualitatively the effect upon the intensity of the aqueous spectrum of 4-aminopyridine of placing a methyl group at $C_{(3)}$ is very like that produced by replacing the water by cyclohexane. This is true, but not so marked, in the case of 4-methylaminopyridine also. The ordering of a polar solvent around a polar solute such as 4-aminopyridine will be much greater than the ordering of a non-polar solvent. Any hindrance to the solvation of the solute in an aqueous solution might, then, be expected to cause a change qualitatively similar to the effect caused by change to a less polar solvent. The variation in the absorption intensity of the 4-aminopyridines caused by substitution might therefore be due to differences in the effectiveness of the solvation of these compounds. Wepster [32] observed small variations in absorption intensity similar to those for the 4-aminopyridines in a series of *o*-alkylanilines. He concluded that resonance inhibition was practically absent in these anilines, and claimed to strengthen the conclusion by treatment of the data by Platt's method of spectroscopic moments.[33] Whilst it is doubtful if the use of the method is justified when one of the substituents is an amino-group, and whilst the method cannot readily be applied to the aminopyridines, it is clear that the ultraviolet absorption data show no features which must of necessity be referred to the operation of steric inhibition of resonance.

If substitution adjacent to a primary amino-group can cause steric inhibition of resonance the effect must be at best a small one. If it occurs, infrared data seem most likely to reveal it, and accordingly we examined the frequencies and intensities of the N–H stretching vibrations of the aminopyridines. The frequencies of maximum absorption for the antisymmetric and symmetric stretching vibrations, the stretching force constant, k, and the H–N–H bond angle, θ, are recorded in Table 6. These were calculated from Linnett's equation.[34]

The most striking feature of the results is the constancy of the values for the stretching force constants determined in carbon tetrachloride solution, and the fact that in chloroform solution none of the substituted amines has a stretching force constant smaller than that of 4-aminopyridine itself. In general, the N–H stretching force constant increases with the " *s* " character of the N–H bond.[5] The high stretching force constant found for the aminopyridines is thus to be expected in view of the great importance in this series of delocalisation of the lone-pair of electrons from the amino-group over the pyridine ring.

[31] Gillam and Stern, " An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Arnold Ltd., London, 1954.
[32] Wepster, *Rec. Trav. chim.*, 1958, **77**, 491.
[33] Platt, *J. Chem. Phys.*, 1951, **19**, 263.
[34] Linnett, *Trans. Faraday Soc.*, 1945, **41**, 223.

TABLE 6. *Frequencies of absorption and stretching force constants of the* N–H *stretching vibrations in 4-aminopyridines and anilines.*

Subst.	Solvent	ν_a (cm.$^{-1}$)	ν_s (cm.$^{-1}$)	$10^{-5}k$ (dyne cm.$^{-1}$)	θ	Solvent	ν_a (cm.$^{-1}$)	ν_s (cm.$^{-1}$)	$10^{-5}k$ (dyne cm.$^{-1}$)	θ
				4-Aminopyridines						
3-H	CCl_4	3500	3412	6·62	112·3°	$CHCl_3$	3515	3425	6·67	112·3°
3-Br	,,	3504	3408	6·62	114·4	,,	3522	3422	6·68	115·4
3-Me	,,	3501	3411	6·62	112·8	,,	3518	3429	6·68	112·5
3-Et	,,	3499	3413	6·62	111·8	,,	3520	3430	6·69	112·3
3-Pr^i	,,	3499	3412	6·62	112·1	,,	3520	3428	6·69	113·8
3,5-Me_2	,,	3502	3413	6·62	112·7	,,	3527	3434	6·71	113·3
2,3,5,6-Me_4	,,	3498	3414	6·62	111·2	—	—	—	—	—
				Anilines						
o-H	CCl_4	3478	3396	6·55	110·8°					
o-Me	,,	3481	3394	6·55	112·2					
o-Pr^i	,,	3476	3396	6·54	110·2					
o-Bu^t	,,	3490	3402	6·58	112·4					
oo'-Me_2	,,	3482	3403	6·57	109·5					

In line with this, the Hammett constant for the 4-amino-group, deduced from the ionisation data, is $\sigma = -0{\cdot}686$. If resonance inhibition occurred, the consequent localisation of the lone-pair upon the exocyclic nitrogen atom would confer greater "p" character upon the N–H bonds and cause a decrease in the stretching force constant. The data point to the absence of such inhibition in both the pyridines and the anilines. The values of θ show the hybridisation of the amino-group to lie between sp^2 and sp^3; the changes caused by substitution are too small to be given any certain significance.

In Table 7 are recorded the intensities of the symmetric and antisymmetric N–H stretching bands, determined from the maximum extinction coefficients and the band half-widths (see Experimental section). The errors inherent in the method of determining the intensities render their absolute values unreliable, but in the series the relative values are probably significant. Whilst the intensity of the antisymmetric stretching band depends on the polar nature of the N–H bonds, the changes in hybridisation accompanying symmetric stretching render the intensity of the symmetric stretching band dependent also on the atomic dipole of the nitrogen lone-pair electrons. In aromatic amines the π-moment is tied to the symmetric vibration and contributes to its transition moment, the contribution increasing with the degree of conjugation between the amino-group and the aromatic nucleus. This contribution to the intensity of the symmetric stretching band makes it more intense than would otherwise have been expected, and the unbalance between antisymmetric and symmetric intensities should increase with increasing conjugation in the aromatic series.[5,35] It is seen from Table 7 that both antisymmetric and symmetric stretching intensities for the pyridine derivatives are greater than those for the anilines, and also that whilst the ratio of antisymmetric to symmetric intensities for the anilines is never less than 1·2, for the 3-alkyl-4-aminopyridines in carbon tetrachloride it has fallen slightly below this. For the heterocyclic compounds in chloroform solution the ratio falls further (to an average of about 0·85). This effect is most likely to be due to hydrogen bonding of the solvent to the pyridine nuclear nitrogen atom, effectively producing a structure more closely resembling a pyridine cation, and thus increasing the conjugation between the nucleus and the amino-group.

For the 4-aminopyridines the increasing bulk of a 3-substituent appears to cause no significant change in the frequency of either the antisymmetric or the symmetric N–H stretching bands, and the same seems to be true for the anilines. The intensities of the antisymmetric stretching bands reveal no regular tendencies, but in all cases the increasingly

[35] Orville-Thomas, Parsons, and Ogden, *J.*, 1958, 1047.

bulky alkyl substituent causes an unbroken fall in the intensities of the symmetric stretching bands. The effect of steric inhibition of resonance on the intensity of the antisymmetric stretching band would be expected to be small, not greatly influencing the N–H bond dipole gradient. On the other hand, resonance inhibition would cause a decrease in the intensity of the symmetric stretching band because of the segregation of the nitrogen lone-pair

TABLE 7. *Intensities of absorption of the* N–H *stretching vibrations in 4-aminopyridines and anilines.*

Subst.	Solvent	ε (cm.² mole⁻¹)	$\Delta\nu_{\frac{1}{2}}$ (cm.⁻¹)	I (cm. mole⁻¹)	ε (cm.² mole⁻¹)	$\Delta\nu_{\frac{1}{2}}$ (cm.⁻¹)	I (cm. mole⁻¹)
			4-Aminopyridines				
3-H	CCl_4	75·8	48	5712	85·0	43	5741
3-Br	,,	47·9	53	3987	46·5	45	3288
3-Me	,,	74·4	44	5140	81·1	38	4840
3-Et	,,	68·6	43	4635	75·1	36	4247
3-Pr^i	,,	72·3	42	4770	72·8	36	4117
3,5-Me_2	,,	66·5	43	4496	71·4	36	4037
2,3,5,6-Me_4	,,	57·1	37	3321	57·1	35	3140
3-H	$CHCl_3$	83·4	58	7597	113·1	46	8172
3-Br	,,	117·9	52	9629	126·6	41	8157
3-Me	,,	75·8	52	6189	116·5	44	8052
3-Et	,,	83·8	53	6978	110·5	45	7814
3-Pr^i	,,	80·1	50	6294	108·0	44	7466
3,5-Me_2	,,	73·2	48	5520	88·2	45	6236
			Anilines				
o-H	CCl_4	46·5	56	4091	49·7	42	3281
o-Me	,,	47·7	49	3668	47·9	38	2860
o-Pr^i	,,	50·2	52	4102	47·4	38	2830
o-Bu^t	,,	53·0	45	3744	39·6	35	2178
oo'-Me_2	,,	48·1	48	3628	41·2	37	2395

electrons from the π-electrons of the ring. However, the observed decrease in the intensity of the symmetric stretching band cannot safely be attributed to this effect, for, as mentioned above, it is not accompanied by a decrease in the stretching force constant. Furthermore, the situation is complicated by the changing inductive effects of the alkyl substituents. Kreuger and Thompson [10] showed that in the *para*-substituted anilines both the antisymmetric and the symmetric N–H stretching band intensities were directly related to the Hammett constants of the *para*-substituents; the more negative the constant, the smaller were the intensities. With adjacent alkyl groups the inductive effect would therefore be producing changes in the same direction as any steric inhibition of resonance which was present. In the present case the two effects cannot be disentangled, and the observed intensity changes provide no unambiguous evidence for the presence of steric inhibition of resonance.

The ionisation data for the primary amines are given in Table 2. In the monosubstituted compounds the changes in ΔpK_a with substitution are very similar to those observed with the 4-methylaminopyridines; they give no indication of steric inhibition of resonance. Bigger changes in pK_a are found in the 3,5-dimethyl and 2,3,5,6-tetramethyl compounds, but these changes are not so marked as in the corresponding cases in the 4-methylaminopyridine series. If steric inhibition of resonance is the responsible factor in the primary amines it must be less marked than in the secondary compounds, and the following considerations show that its presence is probably not indicated at all. In the sequence of series, pyridines, 4-dimethylaminopyridines, 4-methylaminopyridines, 4-aminopyridines, the average values of $T\Delta S$ (excluding the 3,5-dimethyl and 2,3,5,6-tetramethyl compounds) are $-2{\cdot}41 \pm 0{\cdot}52$, $-2{\cdot}41 \pm 0{\cdot}12$, $-1{\cdot}68 \pm 0{\cdot}13$, and $-1{\cdot}53 \pm 0{\cdot}14$ kcal. mole^{-1}. This is the sequence to be expected from a consideration of the increasing

possibilities of hydrogen bonding in the series.[36] The same situation is seen in the rather greater values of the changes in $(-T\Delta S)$ in the secondary and primary amine series than in the tertiary amine and parent pyridine series. It is noteworthy, therefore, that only in the 4-aminopyridine series do the $T\Delta S$ values of both the 3,5-dimethyl and the 2,3,5,6-tetramethyl compound prove to be significantly more negative than the values for the other members of the series. It is suggested that in the dimethyl compound solvent ordering by hydrogen bonding round the amino-group, and in the tetramethyl compound solvent ordering by hydrogen bonding at both ends of the molecule, is being interfered with by the alkyl substituents. The effect is more important for the cations than for the free bases, and consequently $T\Delta S$ for the processes $BH^+ \rightleftharpoons B + H^+$ (in which expression the solvating molecules are omitted) becomes more negative.

In sum, the available data give no clear indication for the existence of steric inhibition of resonance in the 4-aminopyridines. In view of Wepster's results in the aniline series it is probable that such an effect could only become detectable in primary aromatic amines when the additional resonance energy conferred on the system by conjugation with the amino-group represented a small contribution to the total resonance energy. This could be the case with the polynuclear compounds examined by Elliott and Mason,[8] and also with the heterocyclic amines mentioned at the beginning of this paper, as is suggested by the infrared data. The ionisation data so far available [6] are not adequate to permit an assessment of the significance of entropy factors, which our present results clearly indicate to as a possible source of some of the anomalies found in the properties of these compounds.

Experimental

Each compound (see Table 8) was purified immediately before use. The liquids were distilled in an atmosphere of nitrogen, middle fractions of successive distillations being taken until a constant b. p. was obtained. The solid compounds were recrystallised to constant m. p. Solvents for this purpose, and analytical data, have already been given.[11] 4-Amino-3-ethyl- and 4-amino-3-isopropyl-pyridine are normally hydrated: [11] for the present purpose these compounds were dehydrated by repeated sublimation at 0·1—0·2 mm. The m. p.s recorded below are for the dehydrated substances. *o*-t-Butylaniline was purified by recrystallisation of its hydrochloride to constant m. p. 208—209°, and distillation of the regenerated base under nitrogen.

Table 8.

Pyridine	4-H	4-NH_2	4-NHMe	4-NMe_2	Aniline	B. p.
	B. p.	M. p.	M. p.	M. p.	*o*-H	183—184°
3-H	114—115°	157—158°	124—125°	108—109°	*o*-Me	199—200°
				B. p./mm.	*oo'*-Me_2	216—218
3-Me	144—145	108—109	125—126	68—69°/0·9 mm.	*o*-Pr^i	108—110°/20 mm.
3-Et	164—166	73—74	117—118	82—84°/0·8 mm.	*o*-Bu^t	107—108°/12 mm.
3-Pr^i	179—180	52—53	95—96	53—54°/0·1 mm.		
3,5-Me_2	171—172	83—84	120—121	50—52°/0·1 mm.		
3-Br	169—171	69—70	92·5—93·5	78—80°/0·1 mm.		
	M. p.					
2,3,5,6-Me_4	77—78°	197—198	118—119	—		

The ionisation constants were determined in the manner described earlier [3] in thermostat baths held at 20° ± 0·05°, 35° ± 0·05°, and 5·4° ± 0·1°, the last temperature being obtained by stirring an equilibrium mixture of solid and liquid benzene in a large beaker surrounded by a bath of ice-water. The pK_a values were converted into " thermodynamic values " by applying a correction calculated from the usual approximate Debye–Hückel equation $\log_{10} \gamma_{BH^+} = -AZ^2\sqrt{I}/(1 + \sqrt{I})$. The values of A used were those quoted for water by Gold.[37] The ionic

[36] Trotman-Dickenson, *J.*, 1949, 1293.
[37] Gold, " pH Measurements," Methuen and Co. Ltd., London, 1956.

strength I of the solution, taken to be that given by the initial concentration of the base, lay between 0·0008 and 0·0057 in the present work. The " thermodynamic " pK_a values so determined, with the maximum deviations observed in the titrations, are given in Table 9.

TABLE 9. *Thermodynamic* pK_a *values of substituted pyridines in aqueous solution.*

Substituent	Temp.	4-H	4-NH_2	4-NHMe	4-NMe_2
3-H	5·4°	5·44 ± 0·01	9·71 ± 0·02	10·10 ± 0·02	10·14 ± 0·02
	20	5·28 ± 0·02	9·29 ± 0·02	9·65 ± 0·01	9·70 ± 0·01
	35	5·11 ± 0·02	8·89 ± 0·02	9·27 ± 0·01	9·33 ± 0·01
3-Me	5·4	5·96 ± 0·02	9·88 ± 0·01	10·25 ± 0·02	9·03 ± 0·02
	20	5·80 ± 0·02	9·45 ± 0·01	9·84 ± 0·02	8·69 ± 0·02
	35	5·61 ± 0·01	9·00 ± 0·01	9·43 ± 0·02	8·35 ± 0·02
3-Et	5·4	6·00 ± 0·02	9·94 ± 0·02	10·35 ± 0·02	9·02 ± 0·01
	20	5·81 ± 0·02	9·49 ± 0·01	9·89 ± 0·01	8·67 ± 0·02
	35	5·60 ± 0·02	9·12 ± 0·01	9·48 ± 0·01	8·33 ± 0·01
3-Pr^i	5·4	6·10 ± 0·02	9·98 ± 0·01	10·42 ± 0·01	8·62 ± 0·01
	20	4·88 ± 0·01	9·59 ± 0·02	9·98 ± 0·01	8·26 ± 0·02
	35	5·68 ± 0·02	9·13 ± 0·02	9·52 ± 0·01	7·96 ± 0·01
3,5-Me_2	5·4	6·42 ± 0·01	9·95 ± 0·01	9·89 ± 0·02	8·55 ± 0·01
	20	6·25 ± 0·01	9·53 ± 0·02	9·96 ± 0·01	8·12 ± 0·01
	35	6·02 ± 0·01	9·16 ± 0·02	8·98 ± 0·01	7·81 ± 0·02
2,3,5,6-Me_4	5·4	8·19 ± 0·01	10·99 ± 0·02	10·46 ± 0·01	
	20	7·90 ± 0·01	10·57 ± 0·02	10·07 ± 0·02	
	35	7·58 ± 0·01	10·21 ± 0·02	9·70 ± 0·02	
3-Br	5·4	2·99 ± 0·02	7·34 ± 0·01	7·82 ± 0·01	6·77 ± 0·02
	20	2·91 ± 0·02	7·05 ± 0·01	7·49 ± 0·02	6·53 ± 0·01
	35	2·85 ± 0·01	6·76 ± 0·01	7·14 ± 0·01	6·29 ± 0·02

For each compound the values of pK_a were plotted against $1/T$, and the method of least squares was applied to obtain the straight line which best fitted the results. From this line were obtained the values $pK_a(292{\cdot}3°)$, and thence of $\Delta G(292{\cdot}3°)$. The slope of the line gave $\Delta H/2{\cdot}3026\boldsymbol{R}$. From such plots the values $pK_a(292{\cdot}3°)$ were obtained, and it is these which are quoted in Table 2. The relation between pK_a and $1/T$ can be written $pK_a = a/T + b$. The standard errors in " a " and " b," δa and δb, were calculated [23] and used to find the standard errors in ΔH, etc. [$\delta(\Delta H) = 2{\cdot}3026\boldsymbol{R}\delta a$; $\delta(\Delta G) = 2{\cdot}3026\boldsymbol{R}T\{(\delta a/T)^2 + (\delta b)^2\}^{\frac{1}{2}}$, and $\delta(T\Delta S) = -2{\cdot}3026\boldsymbol{R}T(\delta b)$].

The ultraviolet absorption data were obtained in the way described earlier.[3] The oscillator strengths, $f = 4{\cdot}32 \times 10^{-9} \int \varepsilon dv$, were estimated by graphical summation, between the limiting values mentioned in the Discussion.

The infrared data were obtained with a Mervyn N.P.L. grating spectrophotometer. The region was calibrated by using the spectrum of ammonia vapour, two bands in the water vapour spectrum being used as markers. The spectra were determined for 4×10^{-4}M-solutions in carbon tetrachloride, and 2×10^{-2}M in chloroform. The solvents were " AnalaR " reagents, which were dried over and distilled from phosphorus pentoxide. A cell of path length 5·0 cm., and possessing windows of sodium chloride, was used. Intensities were calculated [38] from the equation $I = (\pi/2)\varepsilon\Delta v_{\frac{1}{2}}$, an effective slit-width less than 0·4 of the band half-width being used.

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[38] Ramsey, *J. Amer. Chem. Soc.*, 1952, **74**, 72.