of each flask held a silver–silver chloride electrode. This was a length of 22-gage silver wire, wrapped around an 8 mm. glass rod, which had been coated by using it as the anode while electrolyzing *ca.* 0.5 N hydrochloric acid for 10 minutes using two dry cells in series. Through the third neck of the titration flask was placed the tip of a Gilmont 1-ml. micropipet-buret containing 0.5304 N HCl. The third neck of the reaction flask was used to introduce the acyl halide. The standard taper central neck carried a blade-type stirrer driven by an electric motor of adjustable speed. Piperidine, 4.9226 g., was weighed into a 50-ml. volumetric flask and made up to the mark with CO_2-free distilled water; 20 ml. of this solution was added by pipet to both the reaction and the titration flask. Glass and calomel electrodes were placed in one flask and the pH was lowered to 5.40 by the addition of 19.270 ml. of 1.87 N nitric acid from a Koch 5-ml. automatic microburet. The process was repeated on the other flask. The glass and calomel electrodes were replaced by the salt bridge and silver–silver chloride electrodes (the latter were damaged if introduced into the solution containing piperidine prior to neutralization). The electrodes were connected to a Leeds and Northrup type K-2 potentiometer, set at zero. This in turn led to a Leeds and Northrup type 2430-d galvanometer. Stirring was begun. Several drops of ethyl chloroformate were placed in a 2-ml. weight buret and the weight was determined. To the reaction flask were added two drops of the chloroformate, and the weight buret was set aside for subsequent weighing. The time at which the galvanometer needle crossed zero was noted, after which just sufficient standard hydrochloric acid was added from the pipet to bring the needle back. The process was repeated until the volume added was 2.000 ml. (68.2% of the calculated amount). The final pH was 5.22. Reactions were, in general, not carried to completion because the electrodes did not last indefinitely. For some of the faster reactions, the quantities of chloride ion formed after 10 half-lives were found to be in good agreement with the theoretical values.

Precipitation of amine salts of the buffers was noted in several instances. V formed precipitates with cyclohexylamine and benzylamine, though, in the latter case, at least one kinetic run could be made at a lower buffer concentration.

Intermittent titration runs were performed in the same flasks. The amine, 2–3 g., was weighed into 250 ml. of

water and was brought to the proper pH by 2 N hydrochloric acid. With stirring, the ethyl chloroformate was added. With the pH meter locked in the "on" position, the pH could be held fairly constant by the progressive addition of 0.5 N sodium hydroxide solution from a Gilmont 1-ml. pipet.

Calculations.—First-order rate constants were calculated as previously described.[2b] If necessary, they were extrapolated to zero time. They were corrected for hydrolysis by subtracting 2.28×10^{-4} sec.$^{-1}$ [2b] from the observed rate constant. The corrected constant was then divided by the concentration of free amine to give the second-order rate constant.

The rate constants obtained by the method of intermittent titration exceeded those obtained by the concentration cell method by factors of 2–3. This is attributed to a higher concentration of alkali, and hence of amine, in the vicinity of the pipet tip.

Product Isolation.—It was deemed unnecessary in general to isolate the products. The reaction is firmly established as one of preparative value.[12] Since *cis*-2,6-dimethylpiperidine gave unusual kinetics behavior, however, it was necessary to verify that amidation was actually occurring.

To a solution of 200 g. of VII and 34.0 g. of *cis*-2,6-dimethylpiperidine in 3.5 l. of water at 25° was added 5.0 ml. of ethyl chloroformate with stirring. After two days at room temperature, the mixture was acidified with a solution of 40 ml. of concentrated sulfuric acid in 150 ml. of water and was continuously extracted overnight with methylene chloride. The organic extract was dried over magnesium sulfate, the solvent was distilled and the residue was distilled in a small Claisen flask to give 1.00 g. (11.7%) of 1-carbethoxy-*cis*-2,6-dimethylpiperidine, b.p. 123° (34 mm.), $n^{30}D$ 1.4552.

Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.82; H, 10.33. Found: C, 65.33, 65.14; H, 9.95, 10.00.

Therefore, at least part of the observed reaction consists of amidation.

(12) (a) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929); (b) K. R. Jacobi, *Ber.*, **66**, 113 (1933); (c) H. W. Stewart, N. Q. Quinones, E. G. Lee and J. J. Denton, *J. Org. Chem.*, **18**, 1878 (1953).

WILMINGTON 98, DEL.

Correlation of the Base Strengths of Amines[1]

BY H. K. HALL, JR.

The base strengths of primary, secondary and tertiary non-aromatic amines were plotted against the Taft σ^*-values Each class of amine lay on a different line. This indicates that solvation of the ammonium ion through the N^+–H bonds plays an important role in determining base strength. All the *tertiary* amines gave an excellent correlation with the sum of the σ^*-values, irrespective of their degree of steric hindrance. This suggests that B-strain is not a factor determining the pK_a value. For *secondary* and *primary* amines, only those amines with a low degree of steric hindrance gave a linear plot against σ^*-values. This is also incompatible with the B-strain theory (for the primary amines), but in good agreement with the solvation theory if solvation of the ammonium ion is regarded as subject to hindrance. These correlations permit the prediction of the pK_a values of new amines.

Introduction

The Taft equation[2] $\log k/k_0 = \sigma^*\rho^*$ has enjoyed outstanding success in correlating rate and equilibrium data for many reactions of aliphatic com-

(1) This is the third in a series of papers on base strengths. For paper II, see THIS JOURNAL, **78**, 2570 (1956).

(2) In this equation k and k_0 are the rate or equilibrium constants for the substituted and the reference compound, respectively, σ^* is a constant which expresses the polar effect of the substituent, and ρ^* is a constant measuring the susceptibility of the reaction in question to polar effects. The treatment is summarized by R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

pounds. No correlation of the σ^*-values with the pK_a values of amines has been reported, however. This omission is striking in view of the excellent correlation which exists between the former and the pK_a values for carboxylic acids. The only report on this topic is that of Hansson,[3] who showed that the pK_a values of a limited group of tertiary amines could be correlated with structural parameters similar to those of Taft. In the present communication, we describe an extension of this

(3) J. Hansson, *Svensk Kem. Tidskrift*, **67**, 256 (1955); "A Kinetic Study of the Addition of Amines to Propylene Oxide," Lund, 1955.

correlation to a wide variety of tertiary, and also to secondary and primary, amines.

Results

In Table I have been assembled the pK_a and $\Sigma\sigma^*$-values for all the non-aromatic amines which we have found in the literature.[4] The plots of the data are given in Fig. 1. It can be seen that the
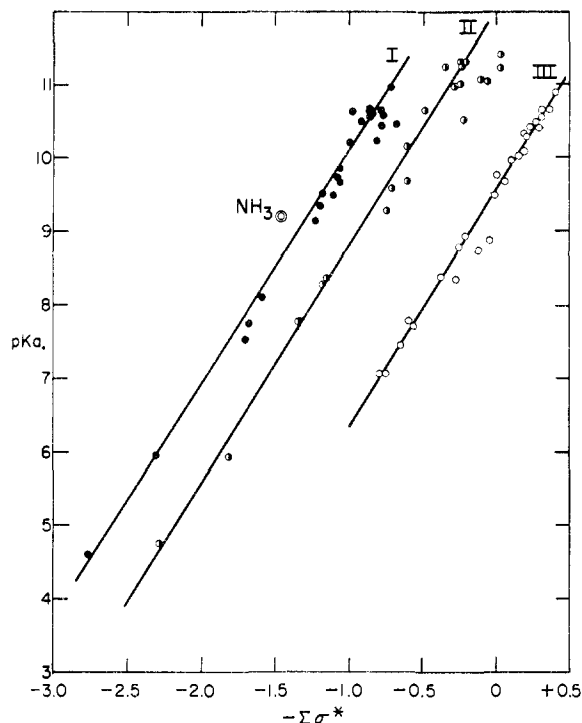

Fig. 1.

data for each class of amines fall on a different line. The equations of the lines and their probable errors are given in Table II. These lines will be discussed separately.

The pK_a values of *tertiary* amines give an excellent correlation with their pK_a values (line III). The relation discovered by Hansson is thereby fully confirmed and extended. As a test of the use of the relation in predicting new pK_a values, the data for the N-methyl-, and N-ethyl-, and N-allyl-derivatives of piperidine and morpholine were utilized. The pK_a value for N-methylpiperidine was used in equation IIc to calculate a σ^*-value for the cyclopentamethylene group. This value was then used in calculating $\Sigma\sigma^*$-values for N-ethyl-piperidine and N-allylpiperidine. The points for these two amines lay on line III. An exactly analogous procedure with the morpholine derivatives gave equally good results. These results serve to check the validity of the correlation.

The data for all *secondary* or for all *primary* amines could not be correlated with single lines. For these classes, lines were drawn through the points corresponding to amines of minimum steric requirements. These were amines containing methyl, allyl or cycloalkylene groups. In this way, lines II and I were drawn and equations IIb

(4) The investigation was limited to groups containing five or fewer carbon atoms.

and IIa were obtained. Values for piperidine, morpholine, N-benzoylpiperazine, N-carbethoxypiperazine, hydroxylamine, methoxyamine and the mono-N-methyl derivatives of the latter two were calculated from the pK_a values of the N-methyl derivatives in the manner already described. It can be noted that amines with branched or hindering groups deviate from the line and that the deviation is greater for the more hindered amines. It is significant that the derivations were all such as to make the base *weaker* than its σ^*-value would predict.

Discussion

The salient features of the above results are as follows.

(1) The amines fall into four groups, depending on the number of hydrogens attached to nitrogen. This is strong evidence in favor of the solvation theory as proposed by Trotman-Dickenson[5] (but see below). In his view, solvation occurs by hydrogen-bonding between N^+-H groups in the ammonium ions and water molecules The more N^+-H bonds, the more such hydrogen-bonding can occur.

(2) The tertiary amines are all correlated by a single line, irrespective of their degree of steric hindrance. This again agrees with Trotman-Dickenson's proposal, if the proviso is made that the single hydrogen bond of a tertiary ammonium ion cannot be sterically hindered. However, it is in direct contrast to the B-strain theory[6] which predicts that tertiary amines should become weaker bases as they become more hindered.

(3) Primary and secondary amines are correlated by single lines only in cases where the amine groups are of low steric requirements. The deviations for the larger groups must be a steric effect because electronic effects are accounted for in the σ^*-values. As the degree of steric hindrance increases, the base strengths become lower relative to the predicted value. This steric weakening of base strength cannot be ascribed to B-strain, because (1) the tertiary amines should show the same effect to a greater degree; (2) primary amines are incapable by definition of exhibiting B-strain. Steric hindrance of solvation can, however, explain the result.

Modification of the Solvation Theory.—One may wonder why the single hydrogen bond of a tertiary ammonium ion should be insensitive to steric hindrance, but one of the two hydrogen bonds in a secondary ammonium ion should be sensitive. To overcome this reasonable objection, we believe that the simple viewpoint of Trotman-Dickenson must be modified in either of two ways.

It may be that only one water molecule can hydrate a tertiary ammonium ion, but that much larger numbers may hydrate the secondary and primary ammonium ions. These larger aggregates may have appreciable steric requirements. Alternatively, we may suggest that a tertiary ammonium ion is not hydrated at all. More experimentation will be required to decide among these possibilities.

(5) A. F. Trotman-Dickenson, J. Chem. Soc., 1293 (1949). A number of other investigators, notably R. G. Pearson. have offered similar interpretations and supporting evidence.

(6) H. C. Brown, Rec. Chem. Progr., 14, 83 (1953).

TABLE I

Compound	$-\Sigma\sigma^*$	pK_a	Ref.
Ammonia	−1.47	9.21	f
Primary amines			
Methyl	−0.98	10.62	f
Ethyl	− .88	10.63	f
n-Propyl	− .86	10.53	f
n-Butyl	− .85	10.59	f
Isopropyl	− .79	10.63	g
n-Butyl	− .79	10.43	g
t-Butyl	− .68	10.45	g
sec-Butyl	− .77	10.56	g
neo-Pentyl	− .81	10.21	h
Cyclohexylmethyl	− .92	10.49	i
Cyclohexyl	− .83	10.64	g
Allyl	−1.11^a	9.49	g
Benzyl	−1.20	9.34	j
Trimethylsilylmethyl	−0.72	10.96	h
β-Phenylethyl	−1.06	9.83	j
γ-Phenylpropyl	−1.00	10.20	j
β-Difluoroethylamine	−1.71	7.52	k
Glycine ester	−1.69	7.75	l
Hydrazine	−1.60	8.10^e	m
β-Alanine ester	−1.23	9.13	l
Ethanolamine	−1.18	9.50	n
γ-Amino-n-butyric acid ester	−1.07	9.71	l
Ethylenediamine	−1.06	9.98^e	m
Hydroxylamine	−2.32	5.97	o
Methoxyamine	−2.79	4.60	o
Secondary amines			
Dimethyl	−0.49	10.64	g
Diethyl	− .29	10.98	g
Di-n-propyl	− .25	11.00	i
Di-n-butyl	− .23	11.25	i
Diisopropyl	− .11	11.05	g
Diisobutyl	− .23	10.50	p
t-Butylcyclohexyl	+ .04	11.23	i
Allylmethyl	− .62	10.11	p
Benzylmethyl	− .71	9.58	j
Benzylethyl	− .61	9.68	j
Piperidine	− .35^b	11.22	q
Morpholine	−1.16^b	8.36	r
N-Carbethoxypiperazine	−1.19^b	8.28	r
N-Benzoylpiperazine	−1.35^b	7.78	r
Dietrimethylsilylmethyl	+0.03	11.40	h
Di-sec-butyl	−0.08	11.01	p
Diallyl	−0.75	9.29	i
N-Methylhydroxylamine	−1.83	5.96	o
N-Methylmethoxyamine	−2.30	4.75	o
Pyrrolidine	−0.23^b	11.27	q
Trimethyleneimine	−0.25^b	11.29	q
Tertiary amines			
Trimethyl	0	9.76	s
Dimethylethyl	+0.10	9.99	s
Methyldiethyl	+ .20	10.29	s
Triethyl	+ .30	10.65	s
Dimethyl-n-propyl	+ .12	9.99	s
Dimethyl-n-butyl	+ .13	10.02	s
Dimethyl-isobutyl	+ .13	9.91	s
Dimethyl-isopropyl	+ .19	10.30	s
Dimethyl-sec-butyl	+ .21	10.40	s
Dimethyl-t-butyl	+ .30	10.52	s
Tri-n-propyl	+ .35	10.65	g
Tri-n-butyl	+ .39	10.89	t
Triallyl	− .39	8.31	i
Diallylmethyl	− .26	8.79	p
Allyldimethyl	− .13	8.72	u
Benzyldimethyl	− .22	8.93	g
Benzyldiethyl	− .02	9.48	g
N-Allylpiperidine	+ .05^b	9.68	v
N-Ethylpiperidine	+ .28^b	10.40	g
N-Allylmorpholine	− .80^b	7.05	v
N-Ethylmorpholine	− .57^b	7.70	v
Propargyldimethyl	− .76^c	7.05	u
Propargylmethyldimethyl	− .28^c	8.33	u
Propargylethyldimethyl	− .05^c	8.88^d	u
N-Methylpiperidine	+ .14^b	10.08	q
N-Methylmorpholine	− .67^b	7.41	v
N-Methyltrimethyleneimine	+ .24^b	10.40	q
N-Methylpyrrolidine	+ .26^b	10.46	q
Triethanolamine	− .60	7.77	w
N,N-Dimethylhydroxylamine	−1.34^b	5.20	o
N,N-Dimethylmethoxyamine	−1.81^b	3.65	o

^{a} The σ^*-value of the crotyl group was used. ^{b} These σ^*-values were obtained from the σ^*-values of the corresponding N-methylamines, which in turn were obtained from the $\Sigma\sigma^*$-pK_a correlation for tertiary amines. The σ^*-values were
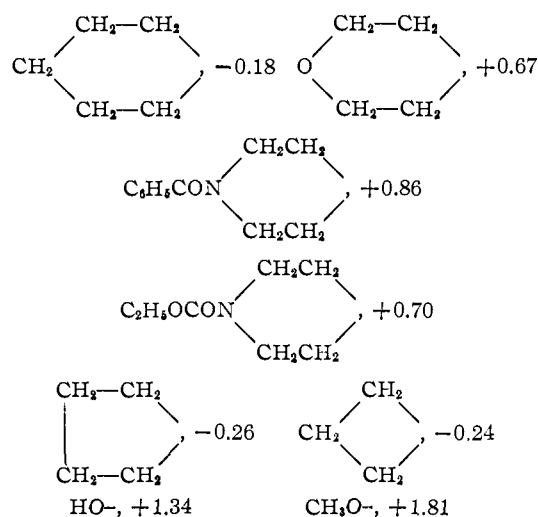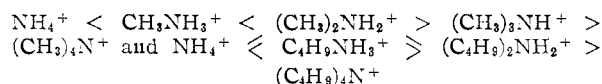

They apply only to water solution (cf. ref. v).
^{c} These σ^*-values were calculated from the pK_a values of the corresponding carboxylic acids (G. H. Mansfield and M. C. Whiting, J. Chem. Soc., 4761 (1956)) and the equation relating pK_a of carboxylic acids to σ^* (Taft, p. 607). The σ^*-values were: HC≡C—CH₂-, +0.76; HC≡C—(CH₂)₂-, +0.28; HC≡C—(CH₂)₃, +0.08. ^{d} The deviations for these compounds may be due to quasi-5 or 6-membered rings. ^{e} A statistical correction of −0.30 was applied to these values. ^{f} D. H. Everett and B. R. W. Pinsent, Proc. Roy. Soc. (London), 215, 426 (1952). ^{g} N. F. Hall and M. R. Sprinkle, THIS JOURNAL, 54, 3469 (1932). ^{h} L. H. Sommer and J. Rockett, ibid., 73, 5130 (1951). ^{i} G. Girault-Vexlearschi, Bull. soc. chim. France, 577, 1710 (1956). ^{j} W. H. Carothers, C. F. Bickford and G. J. Hurwitz, THIS JOURNAL, 49, 2908 (1927). ^{k} "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., p. 259. ^{l} A. Neuberger, Proc. Roy. Soc. (London), A158, 68 (1937). ^{m} G. Schwarzenbach, Helv. Chim. Acta, 16, 522 (1933); 19, 178 (1936). ^{n} R. G. Bates and G. D. Pinching, J. Research Natl. Bur. Standards, 46, 349 (1951). ^{o} T. C. Bissot, R. W. Parry and D. H. Campbell, THIS JOURNAL, 79, 799 (1957). ^{p} Present investigation. ^{q} S. Searles, M. Tamres, F. Block and L. A. Quarterman, THIS JOURNAL, 78, 4917 (1956). ^{r} H. K. Hall, Jr., ibid., 78, 2570 (1956). ^{s} J. Hanson, Svensk Kem. Tidskrift, 67, 256 (1955). ^{t} R. G. Pearson and F. V. Williams, THIS JOURNAL, 76, 258 (1954). ^{u} K. N. Campbell, F. C. Fatora, Jr., and B. K. Campbell, J. Org. Chem., 17, 141 (1952). ^{v} H. K. Hall, Jr., J. Phys. Chem., 60, 63 (1956). ^{w} "Landolt-Bornstein," Vol. III, p. 2120.

TABLE II

EQUATIONS CORRELATING pK_a WITH $\Sigma\sigma^*$

Class of amine	Equation
Primary	(a) $pK_a = -3.14\Sigma\sigma^* + 13.23$
Secondary	(b) $pK_a = -3.23\Sigma\sigma^* + 12.13$
Tertiary	(c) $pK_a = -3.30\Sigma\sigma^* + 9.61$

Steric Effect of the Solvent.—As we have seen, the hydration of the primary or secondary ammonium ion decreases as the bulkiness of the alkyl groups increases. One might expect that increasing steric requirements of the solvent might prevent solvation of a secondary ammonium ion. This effect has been demonstrated by conductimetric studies in N-methylacetamide,[7] in which solvent the limiting ionic conductances are

$$NH_4^+ < CH_3NH_3^+ < (CH_3)_2NH_2^+ > (CH_3)_3NH^+ >$$
$$(CH_3)_4N^+ \text{ and } NH_4^+ \lessgtr C_4H_9NH_3^+ \gtrless (C_4H_9)_2NH_2^+ >$$
$$(C_4H_9)_4N^+$$

A preliminary potentiometric study of the base strengths of amines in organic solvents[8] gave an order of base strengths in agreement with that in water. It therefore appears that solvation plays an important role in these solvents as well.

Hydration of the Amine.—In the above discussion, the hydration of the ammonium ions has been emphasized at the expense of the hydration of the amine. The latter is by no means negligible. However, Briegleb[9] has calculated that, while the heat of hydration of typical amines is in the range 10–12 kcal. per mole, those of the ammonium ions are in the range 83–85 kcal. per mole. Moreover, the former quantities are similar for primary, secondary and tertiary amines. They are therefore taken to be constant in our comparisons.

(7) L. R. Dawson, E. D. Wilhoit and P. G. Sears, THIS JOURNAL, 78, 1571 (1956).

(8) H. K. Hall, Jr., J. Phys. Chem., 60, 63 (1956).

(9) G. Briegleb, Z. Elektrochem., 53, 350 (1949). See also D. Pressman and M. Siegel, THIS JOURNAL, 79, 994 (1957).

Dipole Moments.—One other circumstantial bit of evidence in favor of the hydration theory may be mentioned. Taft[2] found that the dipole moments of amines in benzene, in which no solvation occurs, were correlated very well by his equation. Moreover, primary, secondary and tertiary amines all fell on the same straight line. This circumstance again indicates that the division into three lines noted above is concerned in some way with interaction with the solvent.

B-Strain.—Our interpretation has favored the solvation theory at the expense of the B-strain theory. However, it must not be thought that the latter effect will not be found in very highly branched tertiary amines. Indeed, the present investigation will give a useful method for determining the presence of B-strain, inasmuch as the observed pK_a value of a new tertiary amine can now be compared with a predicted value.

Conclusions.—The base strengths of primary, secondary and tertiary amines have been examined with the aid of the Taft equation. A marked base strengthening effect, which is identified with hydration of N^+–H groups, occurs in the following order: ammonia > primary amines > secondary amines > tertiary amines. A high degree of steric hindrance in the primary or secondary amines depresses their base strengths toward those of the tertiary amines.

The correlation equations derived in the course of this work can be used to predict the pK_a value of any tertiary amine or of secondary and primary amines of low steric size. Conversely, deviations from the equations for primary or secondary amines can be used as a gauge of steric requirement.

Steric Effects on the Base Strengths of Cyclic Amines[1]

BY H. K. HALL, JR.

A series of 1- and 2-methyl derivatives of piperidine exhibiting a wide variation in degree of steric hindrance was prepared. Their base strengths in water and in acetonitrile were measured. Those of the tertiary amines rose markedly as the degree of substitution increased, but those of the secondary amines rose only slightly. Our interpretation is that the methyl groups interfere with hydration of the secondary ammonium ions, thus offsetting the polar effects of the former.

In an earlier article of this series, polar effects on the base strengths of cyclic amines were studied.[2] In the present article steric effects on the base strengths of such amines have been examined and interpreted in light of a recent theory of base strength.[1]

Preparation of Secondary Amines.—Piperidine (I) and 2-methylpiperidine (III) were commercially available.

(1) This is the fourth paper of a series on amine base strengths. For the third paper, see THIS JOURNAL, 79, 5441 (1957).

(2) H. K. Hall, Jr., ibid., 78, 2570 (1956).

cis-2,6-Dimethylpiperidine was prepared readily by the hydrogenation of 2,6-lutidine,[3] but attempts to obtain the pure trans-isomer were unavailing by this reaction. The electrolytic[4] and sodium[5] reductions of 2,6-lutidine also

(3) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, ibid., 77, 4101 (1955).

(4) E. V. Zappi, Anal. Soc. Quim. Argentina, 3, 433 (1915); C. A., 10, 1523 (1916).

(5) A. Marcuse and R. Wolffenstein, Ber., 32, 2525 (1899). Other investigators have shown that sodium often fails to reduce completely pyridine rings. See S. Wawzonek, M. F. Nelson, Jr., and P. J. Thelen, THIS JOURNAL, 74, 2894 (1952); R. F. Feldkamp, U. S. Patent 2,657,211.