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Field and Inductive Effects on the Base Strengths of Amines

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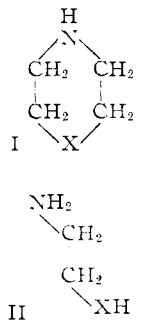
A plot of pK_a values for cylic amines I against those of the corresponding compounds $XCH_2CH_2NH_2$ was linear. The pK_a values of the cyclic amines are more markedly affected by changes in X than are those of the acyclic amines, pointing to the operation of a direct field effect. Plots of these pK_a values against Pauling electronegativity values of X were linear, and electronegativity values for a number of substituents X were deduced from their pK_a values. Finally, plots of pK_a values against the Hammett m-σ-value of the group X were also linear.

Recently Roberts and Moreland[1] showed by a comparison of 4-bromobicycloöctanecarboxylic acid and δ-bromovaleric acid that the inductive effect could account for at most one-half of the effect of the 4-bromo substituent in the bicyclic acid on its pK_a value. The remainder was attributed to a direct field effect.

It is the purpose of the present article to present similar comparisons for the following two series of amines



I

II

Ia, IIa, X = CH_2
Ib, IIb, X = NH
Ic, IIc, X = NH_2^+
Id, IId, X = O
Ie, IIe, X = S
If, IIf, X = $NCOCH_3$
Ig, IIg, X = $NCOC_6H_5$
Ih X = $NCOOC_2H_5$
Ii X = $NSO_2C_7H_7$

The pK_a values for these amines in water solution were either collected from the literature or were determined by potentiometric titration. The data are summarized in Table I. Qualitatively, it is clear that a substituent X in the piperidine ring influences the base strength of the parent amine much more than does the same substituent in the 2-position of ethylamine.

TABLE I

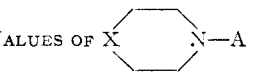
Substituent X	Compound	pK_a	Compound	pK_a
CH_2	Ia	11.13[a]	IIa	10.67[a]
NH	Ib	9.81	IIb	10.08[b]
NH_2^+	Ic	5.55	IIc	6.99[b]
O	Id	8.36	IId	9.45
S	Ie	9.00	..	...
CH_3CON	If	7.94	IIf	9.28
C_6H_5CON	Ig	7.78	IIg	9.13
C_2H_5OCON	Ih	8.28	..	....
p-$CH_3C_6H_4SO_2N$	Ii	7.44	..	....

[a] N. F. Hall and M. R. Sprinkle, THIS JOURNAL, 54, 3469 (1932). [b] D. H. Everett and B. R. W. Pinsent, *Proc. Roy. Soc.* (*London*), 215A, 416 (1952).

A quantitative comparison was made by plotting the pK_a values of the cyclic amines against the corresponding values for the acyclic amines (Fig. 1). A straight line of slope +2.33 can be drawn through all the points except that representing the diammonium ions. Perhaps the mutual repulsions of the positive charges within the molecules deform the acyclic ions more than the cyclic ions, so that the latter are not comparable with the other members of the series. The fact that substituents influence the strength of the cyclic bases so much more strongly than those of the acyclic ions is strong evidence for the operation of a direct field effect. For the bicycloöctane case cited above, the corresponding slope is only 0.50. The smaller distance between substituent group and reactive center in the present cyclic compounds can reasonably be expected to favor an enhanced direct field effect.

A correlation appears to exist between the electronegativity of the substituent and its inductive and field effects. The values for carbon, nitrogen, oxygen, sulfur and positively charged nitrogen were available. When these were plotted against the data for the substituted piperidines and ethylamines, straight lines were obtained for the first three substituents, but not for sulfur or positively charged nitrogen (Fig. 2). The NH_2^+ deviation is in the same direction as in the previous plot, while the former deviation may be due to the relatively larger size of sulfur. It was found that amines of the type XNH_2 (X = CH_3, NH_2, OH) described a similar line of even steeper slope.

TABLE II

pK_a VALUES OF 

X	A = H	A = CH_3	Δ
$C_6H_5CON<$	7.78	6.78	1.00
$C_2H_5OCON<$	8.28	7.31	0.97
$O<$	8.36	7.41	.95
$CH_2<$	11.20	10.19	.99
		Av.	0.97

TABLE III

ELECTRONEGATIVITIES OF SUBSTITUENTS

Substituent	Electronegativity
CH_3CON	3.6
C_6H_5CON	3.7
$C_6H_5SO_2N$	3.8
C_2H_5OCON	3.5
O=N—N	4.0

Values of the electronegativity of the amido groups were extrapolated from these lines and are collected in Table III. Harfenist[2] has shown that

(1) J. D. Roberts and W. T. Moreland, Jr., THIS JOURNAL, 75, 2167 (1953); see also C. A. Grob, E. Renk and A. Kaiser, *Chemistry and Industry*, 1222 (1955).

(2) M. Harfenist, THIS JOURNAL, 76, 4991 (1954).

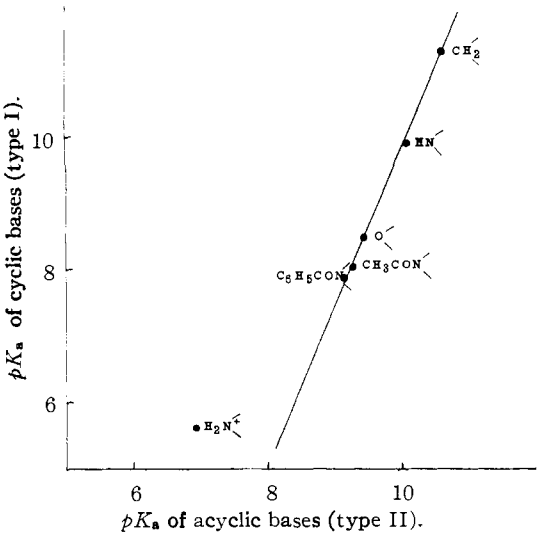
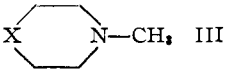


Fig. 1.—Correlation of pK_a values of cyclic and acyclic bases.

similar large effects of substituents occur in the 1-methylpiperazine series



III

It was noted that for four substituents the difference in pK_a between I and III was almost precisely 1.0 pK_a unit (Table II). Revising Harfenist's datum by this quantity to make it comparable with those from the unalkylated piperazines and reading the electronegativity from Fig. 2 gave an electronegativity value for the nitrosoamino group (Table III).

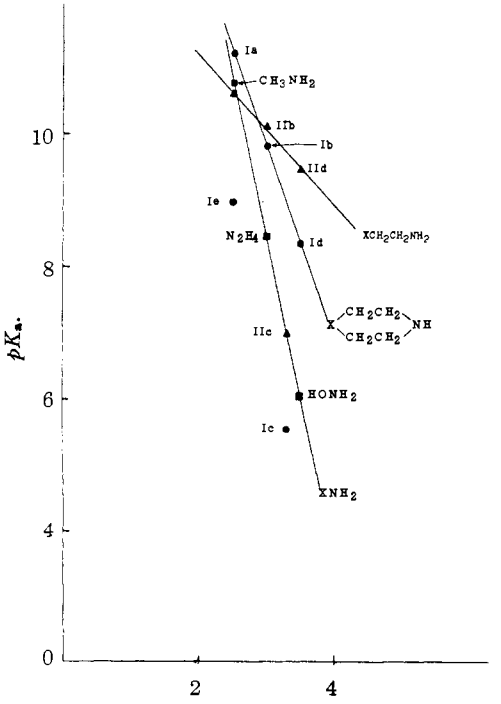


Fig. 2.—Correlation of pK_a values with electronegativities of substituents.

Since the Hammett σ-value for *meta* substituents has also been taken as an indication of inductive effects, a comparison of these constants with the above data was also made. Plotting the pK_a values of the cyclic amines (Ia-i) against the σ-values of the corresponding substituents gave the straight line plot shown in Fig. 3. It easily can be shown from the slope of this line and the known ρ-values for the acidity of anilinium ions that the effect of a substituent on the dissociation constant of a piperazinium ion is just twice as great as the effect of the same substituent on the dissociation of an anilinium ion. For an ethylenediaminium ion, the effect is somewhat less. The deviations from the line are serious for *m*-SCH_3 and *m*-CH_3. No explanation is apparent for these deviations.

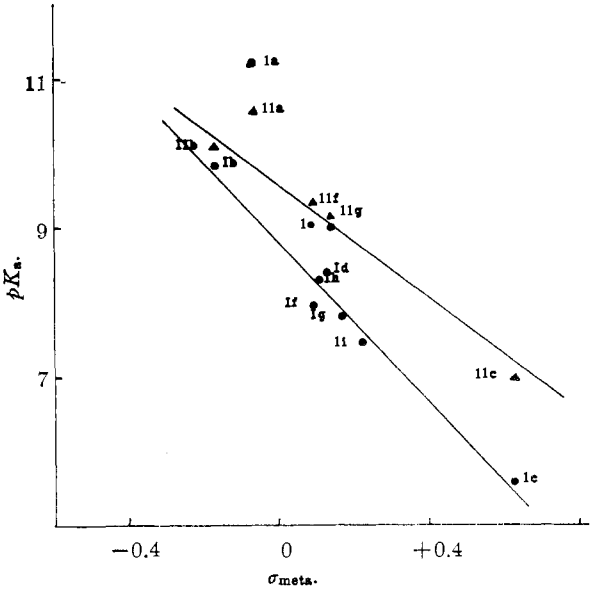


Fig. 3.—Correlation of pK_a values with *meta*-sigma values.

The σ-values of both the *m*- and *p*-amido substituents were determined from the pK_a values of the corresponding substituted benzoic acids in 50% aqueous ethanol, as determined by the method of Roberts, *et al.*[3] The σ-values of the substituents are collected in Table IV along with previous values compiled by Jaffe.[4] The values are in general accord with expectations based on an inductive and field effect only for the *meta* substituents and a combined inductive, field, and resonance effect for the *para* substituents.

Acknowledgments.—We are indebted to Dr. P. W. Morgan for helpful advice and to Mr. Donald G. Preis for invaluable technical assistance.

Experimental

Substituted Benzoic Acids.—The *m*- and *p*-amidobenzoic acids were prepared by acylation of *m*- and *p*-aminobenzoic acids with the appropriate acid chloride in pyridine solution. The products were purified by crystallization or sublimation at 1 mm. pressure. The melting points are given in Table IV.

Monoacylpiperazines.—The directions of Jacobi[5] for the preparation of 1-carbethoxypiperazine were followed ex-

(3) J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2923 (1949).
(4) H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).
(5) K. R. Jacobi, *Ber.*, **66**, 113 (1933).

TABLE IV

Substituent	M.p. °C.	M.p. Lit.	pK_a	σ	Lit.[i] value of σ
m-CH_3CONH	246–247	248[a]	5.58	+0.09	....
p-CH_3CONH	259–260	256[b]	5.81	− .07	−0.02
m-C_6H_5CONH	252–253	278[c]	5.47	+ .17	+ .22
p-C_6H_5CONH	367 dec.	278[d]	Insol.	....	+ .08
m-$C_6H_5SO_2NH$	206–207	[e]	5.42	+0.20	....
p-$C_6H_5SO_2NH$	208–209	212[f]	5.72	− .01	....
m-C_2H_5OCONH	199	189[g]	5.55	+ .11	....
p-C_2H_5OCONH	215–216	208–209[h]	Insol.	....	....

[a] B. Pawlewski, *Ber.*, **35**, 113 (1902). [b] F. Ullmann and J. B. Uzbachian, *ibid.*, **36**, 1801 (1903). [c] G. Pellizzari, *Ann.*, **232**, 150 (1886). [d] A. Brüchner, *ibid.*, **205**, 127 (1880). *Anal.* Calcd. for $C_{14}H_{11}O_3N$: C, 69.69; H, 4.60. Found: C, 68.97, 69.03; H, 4.23, 4.34. [e] *Anal.* Calcd. for $C_{14}H_{13}O_4NS$: C, 56.31; H, 4.00. Found: C, 56.24 56.49; H, 3.69, 3.81. [f] G. Schroeter, *Ber.*, **40**, 1615 (1907). [g] P. Griess, *ibid.*, **9**, 797 (1876). [h] H. King and W. O. Murch, *J. Chem. Soc.*, **125**, 2602 (1924). [i] Collected in ref. 4.

actly on a 20-fold larger scale. The indicator was cresol red. Working up the mixture gave 10.89 g. (66.8%) of mono-N-carbethoxypiperazine, b.p. 114–119° (9 mm.), $n^{25}D$ 1.4760.

The directions of Jacobi[5] for the preparation of 1-benzoylpiperazine were followed exactly on a 20-fold larger scale. The indicator was 4 ml. of a 0.01% solution of cresol red (*p*H range 2–3), since the *p*-benzenesulfonic acid–azobenzylaniline used by Jacobi (*p*H range 2.0–3.3) was not available. There was obtained 10.19 g. (52.0%) mono-N-benzoylpiperazine, b.p. 197° (9 mm.), which crystallized in the receiver, m.p. 65.6–68.0°.

In the preparation of 1-*p*-toluenesulfonylpiperazine, a solution of 25.0 g. of piperazine hexahydrate (0.129 mole) in 100 ml. of H_2O and 200 ml. of acetone was made acidic to brom cresol green with 45 ml. of 3 *N* HCl. A solution of 23.0 g. (0.121 mole) of *p*-toluenesulfonyl chloride in 50 ml. of acetone was used in the reaction. Di-N-*p*-toluenesulfonylpiperazine, 8.0 g., m.p. 292°, precipitated from solution. The filtrate was made strongly basic and was extracted with CH_2Cl_2. Evaporation of the dried methylene chloride extract gave mono-N-*p*-toluenesulfonylpiperazine, 5.0 g., m.p. 101°, and 1.9 g., m.p. 95° (combined yield 23.7%).

Monoacetylpiperazine was prepared as follows: To a solution of 100 g. (0.517 mole) of piperazine hexahydrate in 250 ml. of acetonitrile at 40° was added with stirring a solution of 77.0 g. (0.567 mole) of phenyl acetate in 100 ml. of acetonitrile. The reaction appeared to be rapid, but the solution was refluxed for 2 hours. To it was added with stirring a solution of 96.0 g. (0.505 mole) of *p*-toluenesulfonic acid monohydrate in 250 ml. of acetonitrile. No precipitate formed on cooling. Evaporation of the acetonitrile left a heavy oil, which soon crystallized after adding 500 ml. of methylene chloride. The precipitate was filtered and rinsed with six 100-ml. portions of ether. It weighed 138.4 g. (89%) and melted at 137–138°. An analytical sample was crystallized from 1:16 ethanol–ethyl acetate, m.p. 148–149°.

Anal. Calcd. for $C_{13}H_{20}O_4N_2S$: C, 51.97; H, 6.71; N, 9.32. Found: C, 52.41, 52.19; H, 6.55, 6.48; N, 9.26, 9.22.

An attempt to extract the free base with methylene chloride from an aqueous alkaline solution was unsuccessful.

Monoacylethylenediamines.—Monoacetylethylenediamine, b.p. 132–135° (4 mm.), was prepared exactly as described by Hill and Aspinall.[6] Its salt with *p*-toluenesulfonic acid was also prepared by the reaction of phenyl acetate with ethylenediamine as described above.

Monoacetylethylenediammonium *p*-toluenesulfonate was crystallized from 1:8 ethanol–ethyl acetate, m.p. 125–126°.

Anal. Calcd. for $C_{11}H_{16}O_4N_2S$: C, 48.15; H, 6.61; N, 28.02. Found: C, 48.06, 48.05; H, 6.48, 6.64; N, 9.58, 9.72.

The free base could not be extracted from an aqueous alkaline solution of the salt with methylene chloride. Monobenzoylethylendiamine was also prepared by the directions of Hill and Aspinall.[6] The crude material was freed of diacyl material as follows: 42.3 g. was dissolved in 169 ml. of water. To this was added 100 ml. of 1.2 *N* hydrochloric acid. The mixture was filtered. To the filtrate was added with cooling 105 ml. of 5.2 *N* sodium hydroxide solution. A heavy oil which separated was taken up in 100 ml. of methylene chloride. The water layer was separated and extracted twice with 100-ml. portions of methylene chloride. The organic layers were dried with magnesium sulfate and evaporated to give 18.1 g. of monobenzoylethylenediamine.

Determination of Strengths of Acids and Bases.—Since the amide-substituted benzoic acids were insoluble in water, their strengths were determined in "50%" aqueous ethanol. The method of Roberts, *et al.*,[3] was used. "Pharmco" U.S.P. absolute ethanol and water were purified by distillation from barium oxide and hydroxide, respectively. Aqueous 0.5 *N* carbonate-free sodium hydroxide was mixed with an equal volume of ethanol and standardized. The electrodes were a calomel and a Beckman No. 1190-42 black glass electrode, which was found to be superior to the No. 1190-80 model. A Beckman model G *p*H meter was used. The pK_a value was obtained as the *p*H at the half-neutralization point. One redetermination of pK_a for benzoic acid gave a value of 5.75 (lit. value[3] 5.75). The values of pK_a of aliphatic amines were obtained similarly using purified water at 25.00°. Standard 0.1 *N* HCl was used as the titrant and desired values determined graphically as above.

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(6) A. J. Hill and S. R. Aspinall, THIS JOURNAL, **61**, 822 (1939).