celerated by electron-withdrawing substituents in aqueous solutions above 6*M* in perchloric acid ($\rho = +1.2$),[11] while in weakly acidic solutions the reaction is relatively insensitive to substituent effects ($\rho = +0.118$).[5]

Acknowledgment. The authors are grateful to The Research Corporation, and to the Committee on Research, University of California at Santa Barbara, for research grants which supported this work.

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[11] J. A. Leisten, *J. Chem. Soc.*, 765 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Applicability of the Hammett Equation to the Indole System: Acidity of Indole-3-carboxylic Acids[1]

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Received August 14, 1961

The acidities of six 5- and 6-substituted indole-3-carboxylic acids were determined in aqueous ethanol and their *pK*'s were plotted against the Hammett substituent constants of the respective substituents. A good correlation was obtained using the one term Hammett equation ($\log K/K° = \rho\sigma$) using σ_m for groups in the 5- position and σ_p for groups in the 6- position. These results are taken to indicate that electronic effects are transmitted to the acid center through the carbon para to the 6- position and that virtually no transmission occurs through the indole nitrogen atom. It was also found that the 5-bromoindole-3-carboxylic acid is somewhat less acidic than expected, an effect attributed to steric and electronic factors. Infrared data indicate that whereas the 6-aminoindole-3-carboxylic acid exists as the free acid, the 5-amino isomer exists in its zwitterionic form.

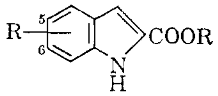
A vast amount of literature has been as accumulated relating to the applicability of the Hammett equation to monocyclic compounds. Much less is known regarding the transmission of electrical effects from one ring to a site on an adjacent ring of a fused ring system. Pioneer work in this problem area has been done by Jaffé.[3]

An additional feature that has not been extensively studied is the transmission of electrical effects through such a fused ring system wherein one of the rings contains a hetero-atom. One such study involved the application of the Hammett equation to the quinoline system.[4] In order to study the transmission of electrical effects from sites within a benzene ring to a site on a fused heterocyclic ring, the author chose for study the indole-3-carboxylic acid system. Previous work in these laboratories concerned the indole-2-carboxylic acid system and the coumarilic acid system.[5] The previous work showed that in the indole-2-carboxylic system I (acid *pK*'s and ester hydrolysis rate constants being used in the $\log k/k°$ term of the equation) there is a good qualitative agreement with the following equation for groups in the 5- position

$$\log k/k° = \rho_{CH}\sigma_m + \rho_{NH}\sigma_p \qquad (1)$$

and for groups in the 6- position

$$\log k/k° = \rho_{CH}\sigma_p + \rho_{NH}\sigma_m \qquad (2)$$



I

The ratio of ρ_{CH}/ρ_{NH} was found to be close to unity.[5] Thus transmission to the 2- position occurs both through the nitrogen and through the carbon joined to the benzene ring. This is in accord with the previous study.[3]

Another interesting study relating to the transmission of electrical effects in the indole system was made by Hall and co-workers.[6] These authors studied the rates of reaction of the enzyme tryptophanase using 5- and 6-substituted tryptophans. They found that groups (chloro and methyl) in these positions gave a very good agreement with the equation:

$$\log k/k° = \rho\sigma \qquad (3)$$

when σ_p values were used for groups in the 5- position σ_m values were used for groups in the 6- position. From these results they conclude that the reaction with the enzyme occurs at the 1- position (the indole nitrogen atom).

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[1] This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

[2] Present address: Chemistry Department, St. Procopius College, Lisle, Ill.

[3] H. H. Jaffé, *J. Am. Chem. Soc.*, **76**, 4261 (1954).

[4] E. Baciocchi and G. Illuminati, *Gazz. Chim. Ital.*, 87, 981 (1957).

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[6] A. N. Hall, J. A. Leeson, H. N. Rydon, and J. C. Tweedle, *Biochem. J.*, **74**, 209 (1960).

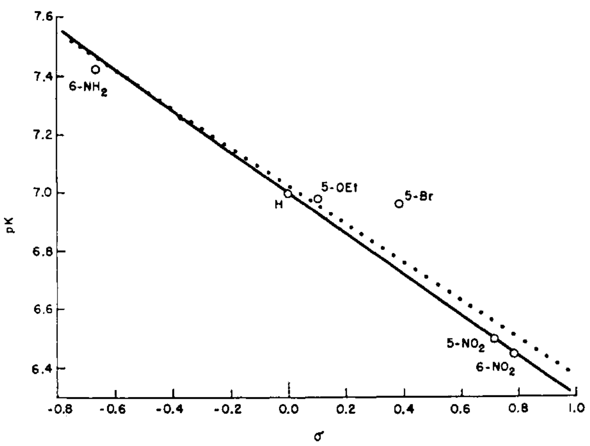

Figure 1. Correlation of acid dissociation constants of indole-3-carboxylic acids with Hammett substituent constants. Measurements made in 50% ethanol at 26±1°.

Solid line = curve without 5-bromo value

Dotted line = curve with bromo value

EXPERIMENTAL

pK measurements: All pK measurements were made by dissolving the samples in the appropriate solvents (50% and 95% by volume of ethanol) and measuring the pH using a Beckman meter (calomel and glass electrodes). A number of measurements were made at intervals between initial solution and the end-point region. The validity of the titrations was checked each time by titrating carefully to the end point and determining the neutralization equivalent.

Materials. All melting points were determined on a Fisher melting point hot stage. No attempts were made to maximize the yields since no more than a gram of material was required for each set of pH measurements.

Indole-3-carboxylic acid was obtained by the method of Majima and Kotake,[7] involving treatment of indole with methylmagnesium iodide followed by treatment with carbon dioxide. The only modification of the procedure[7] was that carbonation was achieved by pouring the ethereal mixture directly onto Dry Ice. The material obtained has a m.p. of 214° dec., reported,[7] m.p. 216–218° dec.

5-Ethoxyindole-3-carboxylic acid. A generous sample of this material (as well as a good amount of the unsubstituted acid) was kindly supplied by Dr. Oskar Süs of Kalle and Co., A.G., in Wiesbaden-Biebrich, Germany.[8] The material had a neutralization equivalent of 209. The formula weight of the material is 205.

5-Nitroindole-3-carboxylic acid. An ethereal solution of 5 g. of 5-nitroindole (Aldrich Chemical Co.) was treated with excess oxalyl chloride. The mixture was allowed to stand in a refrigerator for approximately a day. Filtration from the ethereal mixture yielded 5 g. of presumably 5-nitroindole-3-glyoxylyl chloride, m.p. 310° dec.[9] This material was, in part, refluxed with potassium hydroxide (1:1 molar ratio of acid chloride to base) to yield 3.5 g. of presumably 5-nitroindole-3-glyoxylic acid, m.p. 270–272° dec. Neut. equiv. calcd. 234; found, 246 $pK = 6.30 \pm 0.034$. The acid was yellow in color and had infrared absorption peaks at 5.75 and 6.00 microns. 3.5 g. (0.149 mole) of the 5-nitroindole-3-glyoxylic acid was refluxed 3 hr. in boiling 30% hydrogen peroxide. From the hot solution, there was filtered a green insoluble material, which was washed quickly with hot water. This gave 2.5 g. (98% yield based on the 5-nitroindole glyoxylic acid) of 5-nitroindole-3-carboxylic acid, m.p. 276–278° dec.

Anal. Calcd.: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.54; H, 2.99; N, 13.50.

A portion of the 5-nitroindole-3-glyoxalyl chloride reacted directly with refluxing 30% hydrogen peroxide solution. It yielded 0.5 g. of a material, m.p. 283° dec., whose infrared spectrum closely resembled that of the 5-nitro-indole-3-cariboxylic acid. The over-all yield was 3.0 g. or 47%.

The 5-nitroindole-3-glyoxalyl chloride failed to undergo decarbonylation in refluxing tetrachloroethane, which is reported to occur with the unsubstituted indole 3-glyoxalyl chloride.[10] The free 5-nitroindole-3-glyoxylic acid failed to undergo cleavage on treatment with lead tetraacetate in boiling acetic acid.

5-Bromoindole-3-carboxylic acid was obtained by treating 5-bromoindole (Aldrich Chemical Co.) with methylmagnesium iodide (prepared from 5 moles each of methyl iodide and magnesium per mole of 5-bromoindole used) followed by carbonation with powdered Dry Ice. Upon filtration of the acidified aqueous layer (after hydrolysis of the ethereal mixture) a material melting at 238–240° dec. was obtained which analyzed for 5-bromoindole-3-carboxylic acid.

Anal. Calcd. for 45.02; H, 2.52; N, 5.84; Br, 33.29; Neut. equiv., 240. Found: C, 45.17; H, 2.64; N, 5.74; Br, 33.13; Neut. equiv., 246.

6-Nitroindole-3-carboxylic acid was obtained by the general method of Majima and Kotake.[7] Indole-3-carboxylic acid was dissolved in acetic acid and treated with nitric acid. Filtration of the above mixture after dilution with water yielded 6-nitroindole-3-carboxylic acid, m.p. 280–281° dec., reported,[7] m.p. 275–278° dec. Its neutralization equivalent was 213; formula weight 206.

6-Aminoindole-3-carboxylic acid was obtained by reduction of 6-nitroindole-3-carboxylic acid in methanol with Raney nickel under a hydrogen pressure of 35 p.s.i. at room temperature. These conditions prevailed for approximately a day. The catalyst was removed by filtration. Evaporation of the methanolic filtrate to small volume and dilution with water yielded a material having infrared peaks at 2.93 and 3.00 μ; corresponding to the amino and indole NH absorption. Its neutralization equivalent was 179.5. The formula weight of the desired 6-aminoindole-3-carboxylic acid is 176. Another preparation, using the same procedure, yielded a small amount of material, m.p. 197–199°; reported,[11] m.p. 207–209°.

5-Aminoindole-3-carboxylic acid. Approximately 500 mg. of 5-nitroindole-3-carboxylic acid in methanol was shaken for 8 hr. with Raney nickel under hydrogen atmosphere of 50 p.s.i. On concentrating the filtered methanol solution and addition of water there was obtained a small quantity of dark brownish material, which, on recrystallization using charcoal, yielded 65 mg. of gray material, m.p. 177–179° dec. The infrared spectrum of this material in Nujol failed to show the NH and the COOH (6.0 μ) stretching frequency. However peaks at 4.7 and 6.55 μ as well as a strong absorption at 7.15 μ were present. This strongly suggests that the material is the zwitterionic form of the reduction product, 5-aminoindole-3-carboxylic acid.

Anal. Calcd. for C, 61.35; H, 4.58; N, 15.90. Found: C, 59.00; H, 4.76; N, 15.64. After drying in vacuo: C, 61.17; H, 4.76; N, 16.20.

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(7) R. Majima and M. Kotake, *Ber.*, **63**, 2237 (1930).

(8) The author would like to express his gratitude to Dr. Süs and Kalle and Co. for their graciousness.

(9) The general method of preparation of the indole-3-glyoxalyl chloride was adapted from that of K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).

(10) P. E. Peterson, J. P. Wolf, III, and C. Nieman, *J. Org. Chem.*, **23**, 303 (1958).

(11) R. K. Brown, R. F. Snider, and M. D. Stevenson, *J. Org. Chem.*, **21**, 261 (1956).

TABLE I

pK's of Indole-3-carboxylic Acids at 26 ± 1°

Compound	*pK* in 50% Ethanol	n^b	*pK* in 95% Ethanol	*n*	σ Used^a	NH (Cm.$^{-1}$)
Indole-3-carboxylic acid	7.00 ± 0.05	9	8.92 ± 0.05	3	0.00	3247
6-Nitroindole-3-carboxylic acid	6.45 ± 0.024	3	8.06 ± 0.02	2	0.78	3425
5-Nitroindole-3-carboxylic acid	6.50 ± 0.04	6	8.15 ± 0.035	3	0.71	3333
5-Bromoindole-3-carboxylic acid	6.96 ± 0.036	7	8.72 ± 0.025	3	0.391	3310
5-Ethoxyindole-3-carboxylic acid	6.98 ± 0.035	6	8.91 ± 0.03	2	0.10	3226
6-Aminoindole-3-carboxylic acid	7.43 ± 0.03	2	—		−0.66	3312

[a] See ref. 12 in text. [b] Number of determinations.

RESULTS AND DISCUSSION

The results of the *pK* measurements and their correlation with the Hammett substituent constants[12] are given in Table I and Table II.

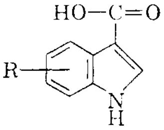
TABLE II

Reaction Constants and Precision of Correlation of *pK*'s of Indole-3-carboxylic Acids with Hammett Substituent Constants.[a]

	With 5-Bromo Value	Without 5-Bromo Value
	50% Ethanol Results	
ρ	−0.670	−0.686
r	0.952	0.987
s	0.120	0.126
s_ρ	0.102	0.109
log $K°_{calcd.}$	−7.030	−6.996
	95% Ethanol Results	
ρ	−1.277	−1.246
r	0.966	0.998
s	0.125	0.033
s_ρ	0.231	0.062
log $K°_{calcd.}$	−9.05	−9.00

[a] See ref. 13 in text.

From these results it is seen that in the indole-3-carboxylic acid system, II, electronic effects from groups in the 5- and 6- positions are transmitted to the acidic center through the benzenoid carbon attached to the 3- position and that virtually no transmission occurs through the nitrogen atom. This conclusion is arrived at by considering the fact that the results give an excellent agreement to Equation 3 wherein groups in the 5- position are treated as *meta* groups and groups in the 6- position are treated as *para* groups. Application of Equations 1 and 2 does not improve the situation. At best, an almost vanishing ρ_{NH} would be obtained. The results herein obtained are quite reasonable, inasmuch as transmission through the carbon atom *meta* to the 5- position and *para* to the 6- position is much more direct (involving transmission through less atoms) than the route through the nitrogen atom.



II

The values obtained for the 5-ethoxyindole-3-carboxylic acid are probably better than Figure 1 or Table II would suggest. A substituent constant of 0.1 was used. However, it was reported by Jaffé[13] that substituent constants of a group such as hydroxyl in aqueous ethanol vary considerably with solvent, decreasing as the proportion of ethanol increases.

The values obtained for the 5-bromoindole-3-carboxylic acid, however, are considerably at variance with the curves drawn excluding the 5-bromo value. Using $\rho = -0.686$ in 50% ethanol and -1.246 in 95% ethanol, the following *pK*'s would be predicted for the 5-bromo compound: 6.728 and 8.513, respectively (assuming $\sigma = 0.391$ and by log $K°_{calcd.}$ −6.996 and −9.000, respectively). Converting the pK's to dissociation constants, one obtains the following results: $K_{found}/K_{calcd.} \times 100$ in 50% ethanol, 59.2; in 95% ethanol 62.0.

Application of Equations 1 and 2 would not materially remedy this deviation, since it would require the *pK* of the 6-amino compound to be substantially lower than that which was found. One possible explanation for the deviation is suggested by Dippy *et al.*[14] who proposed the concept of steric inhibition of solvation of the carboxylate ion to explain the findings that alpha substituted acetic acids and alpha and beta substituted propionic acids are somewhat weaker acids than would be predicted. Dippy[14] stated the principle as follows: "The energy of solution of the carboxylate ion is greater than that of the undissociated acid molecule, so steric compression of the carboxyl group in hindered acids preferentially inhibits solvation of the anion thus diminishing the ionic concentration in the dissociation equilibrium, *i.e.*, the acid strength falls . . ."

The 5-bromoindole-3-carboxylate ion is presumably solvated to a large extent by interaction of the ion with the solvent at the carboxylate group. The 5-nitroindole-3-carboxylate ion could receive much of its solvation by interaction of the solvent

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(12) D. A. McDaniel and H. C. Brown, *J. Org. Chem.*, **23,** 420 (1958).

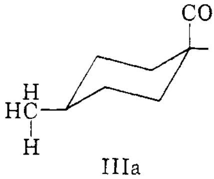
(13) H. H. Jaffé, *Chem. Revs.*, **53,** 191 (1953).

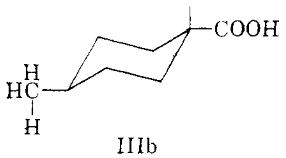
(14) J. F. J. Dippy, S. R. C. Hughes, and A. Rozanski, *J. Chem. Soc.*, 1441 (1959).

with the highly polar nitro group, which would minimize any deviations from that predicted from the Hammett equation due to solvent-solute interactions at the carboxylate group.

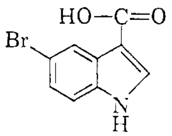
The study reported in the literature which is most germane to the present work is the study of Dippy of the cyclohexanecarboxylic acids.[15]

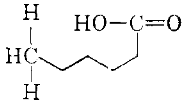
In this study dissociation constants of the two diastereoisomeric 4-methylcyclohexanecarboxylic acids were reported. The *cis* compound IIIa has a value of 0.92×10^{-5} and the *trans* compound IIIb has a value of 1.30×10^{-5}. Thus the *cis* compound is 70% as acidic as the *trans*. This difference in acidity was attributed to steric interference with solvation of the carboxylate ion.[16]


IIIa


IIIb

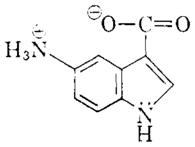
When one considers the compound 5-bromoindole-3-carboxylic acid (IV), it is possible to see a connection between the two studies since the bromo and carboxylate groups of the indole acid are approximately in the same steric relationship as the methyl and carboxylate groups of the *cis* cyclohexane carboxylic acid IIIa. The darkened part of the indole molecule IV below describes somewhat the profile of the cyclohexane molecule in its chair form.


IV


profile of IIIa

It is true that the distance between the carboxyl and methyl groups in Dippy's study is approximately 2Å less than the distance between the bromo and carboxyl groups in the present study. However, Dippy used water while the present author used ethanol-water as solvent. Participation of ethanol in the solvation of the indole carboxylate could impose considerably more steric requirements for the solvation, compared with a system wherein water is the only solvent.

Another possible explanation for the deviation found in the case of the 5-bromo compound is one based on electronic considerations. It is quite conceivable that there may be some specific resonance interaction between the carbon at the 5- position and indole nitrogen (which is *para* to the 5- position). This may serve to decrease the normally expected electron-withdrawing effect of the bromine atom on the carboxylic acid group. That there may be some such specific electronic effect between the indole nitrogen atom and the 5- position is suggested by the fact that while the 6-amino indole-3-carboxylic acid exists as the free carboxylic acid, the 5-amino compound exists in its zwitterionic form, V.


V

It is quite possible that both the steric and electronic factors contribute to the decreased acidity of the 5-bromo compound.

Acknowledgment. The author would like to express his deep gratitude to Professor H. H. Jaffé of the University of Cincinnati for his kind encouragement, support, and extremely helpful advice during the course of this research. The author also wishes to convey his appreciation to the laboratories of Alfred Bernhardt of the Max-Planck Institute für Kohlenforschung in Mülheim (Ruhr), Germany, for the elemental analyses reported in this paper. Generous supplies of indole compounds, other than those mentioned in this paper, were made available by Dr. J. Szmuszkovic of the Upjohn Co. for which the author is appreciative.

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(16) C. W. Bird and R. C. Cookson, *Chem. and Ind.*, 1479 (1955).