64-6; methyl-C^{14}-triphenylphosphonium bromide, 1560-53-8; 1,1,3,5,5-pentaphenyl-1,4-pentadiene-2,4-C^{14}, 10425-66-8; 1,2,4-triphenyl-1,4-butanedione-4-C^{14}, 10425-679; 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine-4-C^{14}, 10425-50-0.

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Linear Free-Energy Relations for 5- (or 6-) Substituted Benzimidazoles

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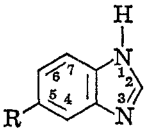
Aqueous p$K_a{}^+$ values at 25° have been measured for a series (H, CH_3, F, Cl, Br, CF_3, NO_2) of tautomeric 5- (or 6-) substituted benzimidazoles. $\Delta pK_a{}^+$ values satisfy the Taft equation $\Delta pK_a{}^+ = (2.61 \pm 0.10)\sigma_I + (2.10 \pm 0.13)\sigma_R{}^0 + 0.05\ (\pm 0.04)$ with $s = 0.06$ and $r = 0.999$. Application of the 6-quinoline bicyclic substituent constants of Jaffé and Jones gives an excellent correlation. $\Delta pK_a{}^+ = (5.62 \pm 0.07)\sigma^{6-1} - 0.01(\pm 0.01)$ with $s = 0.02$ and $r = 1.000$. The correlations show that the relative weighing of inductive (σ_I) and polar resonance ($\sigma_R{}^0$) effects and their ease of transmission in 5- (or 6-) substituted benzimidazoles are nearly the same as in 6-quinolines. Substituent effects for the title compounds are found to be intermediate in composition between those which may be correlated by σ_m and $\sigma_p{}^0$. The excellent correlations and their insensitivity to tautomerism results from the tautomers being nearly equivalent in thermodynamic stability.

Rabiger and Joullié[2] attempted a classical Hammett correlation[3] of the acidity constants of a series of 5- (or 6-) halogenated benzimidazoles. They reported that the correlation was unsuccessful and presumed that the failure was due to tautomerism between forms I and II.



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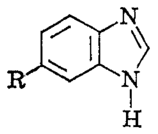

II

In this paper we reexamine the applicability of the Hammett equation to the system in question using a wider range of compounds and a more basic and varied approach. Our major aims were to obtain increased insight into substituent effects on 5- (or 6-) substituted benzimidazoles and to clarify the role of tautomerism as it relates to linear relationships for this heterobicyclic system.

Results and Discussion

Acidity Constants.—Thermodynamic acidity constants determined spectrophotometrically in this study and that of benzimidazole determined earlier by the same method in this laboratory[4] are given in Table I. Our results are in good agreement with thermodynamic values reported for the unsubstituted and 5- (or 6-) methyl compound. The spread of the other values found in Table I indicates the desirability of obtaining a set of values from one laboratory by one method, whereby procedural or systematic errors may to some extent cancel. For 5- (or 6-) nitrobenzimidazole one finds literature values ranging from 3.5 to 4.5. Procedural or systematic errors cannot account for this large range. We judge that the high value of 4.5 involves gross error.

TABLE I

THERMODYNAMIC ACIDITY CONSTANTS OF THE CATIONS OF 5- (OR 6-) SUBSTITUTED BENZIMIDAZOLES IN WATER AT 25 ± 0.2°

Substituent	Registry no.	p$K_a{}^+$	n^a	Mean dev	Scatter^b	Lit. p$K_a{}^{+\,c}$
NH_2	934-22-5		...	...	...	6.06^d
CH_3	614-97-1	5.78	5	0.02	0.04	5.78^e
H	51-17-2	5.55^g	3	0.03	0.04	5.44^e 5.52^{d,l} 5.532^f
F	1977-72-6	4.92	3	0.03	0.04	5.11^h 5.21^i
Cl	4887-82-5	4.70	3	0.01	0.01	4.98^i
Br	4887-88-1	4.66	3	0.01	0.02	4.89^i
CF_3	326-55-6	4.22	6	0.01	0.05	...
NO_2	2672-29-9	3.42	3	0.02	0.02	3.48^j 3.80^k 4.50^l

[a] Number of determinations. [b] Maximum deviation from mean value. [c] Values with superscripts *d*, *e*, and *f* are thermodynamic values obtained by extrapolation to 0 ionic strength or from the simple Debye–Hückel expression for solutions of low ionic strength, others are uncorrected. [d] By titration of hydrochloride: M. T. Davies, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **3**, 420 (1951). [e] By titration of base; see reference in *d*. [f] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940). [g] Reference 4. [h] In water: E. C. Fisher and M. M. Joullié, *J. Org. Chem.*, **23**, 1944 (1958). [i] Reference 2; 5:95 ethanol-water (0.1 *M* in NaCl) at 30 ± 5°. [j] J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1363 (1960). [k] J. L. Rabinowitz and E. C. Wagner, *J. Am. Chem. Soc.*, **73**, 3030 (1951). [l] D. J. Rabiger and M. M. Joullié, *J. Org. Chem.*, **29**, 476 (1964). Same conditions as under *i*.

Data Used in Correlations.—Column 4 of Table II shows aqueous ΔpK^+ values ($\Delta pK_a{}^+ = pK_H - pK_R$) used in the correlations. All but the amino ΔpK^+ value were obtained in this laboratory. A reported[5] unfavorable difference between the spectra of the neutral molecule and the monocation discouraged us from obtaining the amino value. Also shown in Table II are 50:50 alcohol/water $\Delta pK_a{}^+$ values for 1-methyl-

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(1) Work performed as National Science Foundation Undergraduate Research Participants and in partial fulfillment of the requirements for the B.S. degree in chemistry.

(2) D. J. Rabiger and M. M. Joullié, *J. Chem. Soc.*, 915 (1964).

(3) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 184; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(4) H. Walba and R. W. Isensee, *J. Org. Chem.*, **26**, 2789 (1961).

(5) G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. Chim. Ital.*, **85**, 769 (1955).

TABLE II

BENZIMIDAZOLE ΔpK_a^+ [a] AND SUBSTITUENT CONSTANTS USED IN CORRELATIONS

No.	Substituent, R	Registry no. 1-Me-5-R	Registry no. 1-Me-6-R	In H_2O at 25°, 5- (or 6-) R	In 50% (v/v) aqueous EtOH,[b] 1-Me-5-R	In 50% (v/v)aqueous EtOH,[b] 1-Me-6-R	σ_I[d]	σ_R^0[e]	σ^{6-1}[f]
1	H	. . .	. . .	0	0	0	0	0	0
2	CH_3	10394-35-1	10394-40-8	−0.23	−0.34	−0.29	−0.05	−0.10	−0.04
3	F	. . .	. . .	0.63	. . .	. . .	0.52	−0.35	0.12
4	Cl	10394-36-2	10406-94-7	0.86	1.07	1.00	0.47	−0.20	0.15
5	Br	. . .	. . .	0.89	. . .	. . .	0.45	−0.19	0.16
6	CF_3	. . .	. . .	1.33	. . .	. . .	0.41	0.12	. . .
7	NO_2	5381-78-2	5381-79-3	2.13	2.21	(2.3)[c]	0.63	0.19	0.38
8	NH_2	10394-38-4	. . .	−0.54[b]	−0.98	. . .	0.1	−0.48	−0.12
9	OCH_3	10394-39-5	10394-42-0	. . .	−0.19	(−0.1)[c]	0.25	−0.37	−0.04

[a] $\Delta pK_a^+ = pK_R - pK_H$. [b] From reference in footnote *d*, Table I. [c] Calculated values, see text (eq 1). [d] R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davies, *J. Am. Chem. Soc.*, **85**, 709 (1963). [e] $\sigma_R^0 = \sigma_P^0 - \sigma_I$; σ_P^0 values from R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960); σ_R^0 for CF_3 from R. T. C. Brownlee, A. R. Katritzky, and R. D. Topsom, *J. Am. Chem. Soc.*, **88**, 1413 (1966). [f] See text and H. H. Jaffé and H. L. Jones, *Advan. Heterocyclic Chem.*, **3**, 209 (1964), a review article on applications of the Hammett equation to heterocyclic compounds.

5-substituted and 1-methyl-6-substituted benzimidazoles obtained from the work of Davies, *et al.*[6]

The 50% (v/v) aqueous ethanol pK_a^+ values of the 1-methyl-6-nitro and -methoxy group are not known. The values shown are calculated from the easily derived equation that assumes a constant N-methyl effect (eq 1)

$$K_a^{1\text{-Me-6-R}} = aK_E^{5\text{-(or 6-)R}} - K_a^{1\text{-Me-5-R}} \qquad (1)$$

where $K_E^{5\text{-(or 6-)R}}$ is the experimentally obtained macroconstant[6] and a is the enhancement factor of the methyl group estimated by us from the work of Davies, *et al.*,[6] to be 2.2 ± 0.2. Superscripts make the remaining terms self-explanatory. The pK_a^+ values so calculated have an uncertainty of about ±0.2 log unit.

Substituent parameters used as part of this study are the σ_I, σ_R^0, and σ_P^0 constants of Taft.[7,8] The σ_I and σ_R^0 values selected are given in Table II. Taft does not give a σ_R^0 value for CF_3 and the value 0.12 listed is the rounded-off value of 0.115 calculated from infrared data by Brownlee, Katritzky, and Topsom.[9] These workers found good concordance between Taft's σ_R^0 values and their calculated σ_R^0 values. Alternatively for CF_3 we would expect Wepster's[10] σ^n of 0.53 to substitute well for σ_P^0. We obtain $\sigma_R^0 = \sigma^n - \sigma_I = 0.12$, in agreement with the value of Topson, *et al.* Also employed are the recommended σ_m values of McDaniel and Brown.[11] In addition we have applied the 6-quinoline bicyclic substituent constants of Jaffé and Jones[12] labeled as σ^{6-1} in Table II. For this set we have averaged values for quinolines in water, and 4-chloroquinolines in water, 7.7% ethanol, and 10% ethanol. These constants are defined by

$$\sigma^{6-1}{}_{\text{quinolines}} = (pK_H - pK_{6-R})/\rho_{\text{pyridine}} \qquad (2)$$

and serve as a convenient means of comparing substituent effects in 6-quinolines with those in the somewhat structurally akin 5- (or 6-) substituted benzimidazoles.

Correlation Studies.—Bryson has found that the Taft equation

$$\Delta pK = \alpha\sigma_I + \beta\sigma_R + C \qquad (3)$$

satisfactorily reproduces the p*K* data of naphthols and naphthylamines substituted in the ring containing the reaction site[13] and, in selected cases, the second ring.[14] Charton[15] has used eq 3 to obtain the composition of the electrical effect of a substituent in the homocyclic ring of quinolines substituted in the 5 and 6 positions. For this purpose Charton defines the parameter $\epsilon = \beta/\alpha$. The coefficients β and α are pictured as being a measure of the sensitivity of the reaction site to resonance and inductive effects, respectively.

We have applied eq 3 to pK_a^+ data of 5- (or 6-) substituted benzimidazoles using Taft's inductive parameter, σ_I,[8] and the normal reactivity polar resonance parameter, σ_R^0.[7] The choice of $\sigma_R^0 = \sigma_R^0(para)$ over σ_R is preferred since σ_R values may include contributions from direct resonance interactions with the reaction site.[7,10] Such interactions may result in variations in the partial regression coefficient (β). On the other hand, direct resonance interaction of substituents with reaction site is absent or minimal for σ_R^0 values.[7,16] Ridd and Smith[17] have pointed out that there is no direct resonance interaction between substituents in the homocyclic ring and the "pyridine" nitrogen of benzimidazole. Thus this potential source of failure of a Hammett relationship is presumably not present. However, the applicability of σ_R^0 values, based on monocyclic benzene derivatives, to the electronically more complex and tautomeric 5- (or 6-) substituted benzimidazoles, is, *a priori*, certainly not without question.

The results from a least-squares correlation[18] of σ_I and σ_R^0 with our seven aqueous ΔpK^+ values at 25° (excluding NH_2 of Davies, *et al.*[6]) is

$$\Delta pK_a^+ = (2.61 \pm 0.10)\sigma_I + (2.10 \pm 0.13)\sigma_R^0 + 0.05\ (\pm 0.04) \qquad (4)$$

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(6) See footnote *d* in Table I.

(7) See R. W. Taft, Jr., footnote *e*, Table II.

(8) See footnote *d*, Table II.

(9) See R. T. C. Brownlee, *et al.*, footnote *e*, Table II.

(10) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **78**, 815 (1959).

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

(12) See footnote *f*, Table II.

(13) A. Bryson and R. W. Mathews, *Australian J. Chem.*, **16**, 401 (1963).

(14) A. Bryson, *J. Am. Chem. Soc.*, **82**, 4862 (1960).

(15) M. Charton, *J. Org. Chem.*, **30**, 3341 (1965).

(16) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

(17) See footnote *j*, Table I.

(18) A. J. Capato, "Catalog of Programs for IBM 1620 and 1710 Data Processing Systems," IBM, Program Information Department, Hawthorne, N. Y., 1966, p 057, No. 1620-06.0.148.

The plus and minus values are standard errors. The standard deviation from the regression plane is 0.06 and the multiple correlation coefficient is 0.999. Inclusion of NH_2 does not significantly change this excellent correlation. The average deviation between observed and calculated values, excluding the amino compound is 0.04, with a maximum deviation of 0.06. A modified Charton parameter, $\epsilon^0 = \beta^0/\alpha$ where α has the same meaning as previously and β^0 is a measure of the sensitivity of the reaction site to the polar resonance effect, is 0.80 ± 0.08. We also have correlated the six 1-methyl-5 benzimidazoles of Davies, *et al.*,[6] in 50% (v/v) aqueous ethanol at 25° and have obtained

$$\Delta pK_a^+ = (2.94 \pm 0.24)\sigma_I + (2.43 + 0.27)\sigma_R^0 + 0.00\,(\pm 0.10) \quad (5)$$

with $s = 0.14$ and $r = 0.996$. Both this and the previous correlation are above the 99% confidence level. For the 1-methyl-5 compounds $\epsilon^0 = 0.83 \pm 0.19$. Inclusion of the two experimentally obtained values for the 1-methyl-6 compounds causes negligible change in the statistical results.

It is informative to compare the ϵ^0 of 0.8 obtained above with ϵ^0 of 0.5 for σ_m and ϵ^0 of 1 (by definition) for σ_p^0 given by Taft.[16,19] The comparison suggests that substituent effects in the title compounds are intermediate in composition between those which may be correlated by σ_m and σ_p^0.

Satisfactory correlations, according to Jaffé's guidelines,[3b] are also obtained with σ_p^0 ($r = 0.991$, $s = 0.12$) and σ_m ($r = 0.976$, $s = 0.19$) which indicate that acceptable linear correlations for the title compounds are possible over a fairly wide weighting of inductive and resonance parameters. Charton[15] has noted that successful standard Hammett correlations are often the result of a lack of sensitivity of substituent effects to the composition of the substituent constant.

Correlation with σ_m yields a ρ of 2.91, which falls within the range observed by Taft,[20] $\rho_m = 2.8 \pm 0.5$, for benzene derivatives undergoing a change in formal charge of one at the atom attached to the ring. Thus the -NHCH- linkage in benzimidazole is close to acting as a "constant *ortho* substituent." Jaffé[3b] defines a "constant *ortho* substituent" as one which affects the value of the equilibrium constant but has no effect on the reaction constant.

The structural similarity, in terms of the fused benzenoid ring and the nature and position of the reaction site, between benzimidazole and quinoline prompted us to correlate the σ^{6-1} quinoline bicyclic substituent constants of Jaffé and Jones[12] with σ_I and σ_R^0. We find

$$\sigma^{6-1} = (0.47 \pm 0.02)\sigma_I + (0.39 \pm 0.03)\sigma_R^0 + 0.01\,(\pm 0.01) \quad (6)$$

with $s = 0.02$, $r = 0.997$, and $\epsilon^0 = 0.83$. This value of ϵ^0 indicates that substituent effects in 5- (or 6-) substituted benzimidazoles ($\epsilon^0 = 0.80$) and 6-quinolines are of about the same composition. Thus we may expect an excellent correlation of our pK^+ values with σ^{6-1} and in turn compare the ease of transmission of substituent effects in the two systems. We find for substituents 1–5, 7, and 8 of Table II

$$\Delta pK_a^+ = (5.43 \pm 0.13)\sigma^{6-1} + 0.03\,(\pm 0.02) \quad (7)$$

with $s = 0.05$ and $r = 0.999$. Without the amino group, the correlation yields

$$\Delta pK_a^+ = (5.62 \pm 0.07)\sigma^{6-1} - 0.01\,(\pm 0.01) \quad (8)$$

with $s = 0.02$ and $r = 1.000$. Since $\sigma^{6-1} = \Delta pK/5.77$[12] we see that the efficacy of transmission of substituent effects in 5- (or 6-) substituted benzimidazoles is nearly equivalent to 6-substituted quinolines. There is also the suggestion (consistent with the view that -NHCN- is a "constant *ortho* substituent") that the linkages between reaction site and the homocyclic ring in benzimidazole, -NHCH-, and the longer linkage $-CH(CH)_2-$ in quinoline have little effect on the reaction constant since one would otherwise expect $\rho_{\text{benzimidazole}} > \rho_{\text{quinoline}}$.[12]

The Role of Tautomerism.—The application of the Hammett equation to the problem of tautomeric equilibria has been studied extensively by Jaffé[12,21] and Kabachnik.[22] Charton[23] has considered the Hammett equation in relationship to tautomerism in imidazoles and unsymmetrical diazarenes.

Ridd and Smith[17] have pointed out, and the acidity constants of the 1-Me derivatives listed in Table II show, that the 5 and 6 tautomers of 5- (or 6-) substituted benzimidazoles are nearly equivalent in thermodynamic stability. Thus, if we assume that a linear free-energy relationship is separately applicable to each of the tautomers and recognize from the near-equal stability of the tautomers that $\sigma_5\rho_5 \cong \sigma_6\rho_6$, then the experimentally observed macroacidity constants might be expected, and in this paper are demonstrated, to correlate with appropriate sets of substituent constants.

Experimental Section

Preparation of Compounds.—All compounds were prepared according to reported methods and recrystallized to a constant melting point and constant ultraviolet spectrum. For halogen compounds see ref 2, for the methyl and nitro compounds see ref 10, and for 5- (or 6-) trifluoromethylbenzimidazole see ref 24.

Acidity Constants.—The acidity constants of the cations were determined spectrophotometrically in the manner previously described[4] using a Beckman Model 76 Zeromatic pH meter with expanded scale. The temperature of the solution was maintained at 25.0 ± 0.2° by measuring the pH of the solutions in a water-jacketed beaker.

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[19] R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).

[20] R. W. Taft, Jr., and I. C. Lewis, *ibid.*, **80**, 2436 (1958).

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[22] M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov, and T. A. Melentyeva, *Tetrahedron*, **9**, 10 (1960).

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