Electrical Effects of *ortho* Substituents in Imidazoles and Benzimidazoles

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A previous investigation has shown that *ortho*-substituted pyridines, quinolines, and isoquinolines show an "abnormal" electrical substituent effect. This work has been extended to 2-substituted imidazoles, benzimidazoles, and naphthimidazoles and related compounds. Values of pK_a extant in the literature have been correlated with the Hammett equation by means of the σ_I, σ_m, and σ_p constants. Best correlation is generally with the σ_m constants, in accord with the results obtained for 2-substituted pyridines and their benzologs. The "abnormal" electrical effect observed in these compounds is in sharp contrast to the "normal" electrical effect generally observed in *ortho*-substituted benzene sets free of steric effects. Sets which show the "normal" *ortho* electrical effect are best correlated by the σ_p constants. The Hammett equation has been applied to the problem of annular nitrogen tautomerism in imidazoles. Generally applicable equations for the estimation of the tautomeric equilibrium constants K_T have been derived.

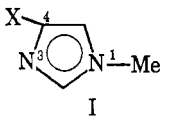
We have recently shown that most *ortho*-substituted benzene sets in the absence of serious steric effects or intramolecular hydrogen bonding, obey the Hammett equation[1] using σ_p constants as a measure of the electrical effect.[2] Sets in which eq. 1 is obeyed were considered representative of the "normal" electrical effect of *ortho* substituents. We have also shown that in *ortho*-substituted pyridines and quinolines the electrical effects are "abnormal" in that the resonance contribution to the over-all effect is about 0 to 0.5 times that in the "normal" set. This abnormal effect has also been observed in benzenoid sets in which an *ortho* proton is reacting.[3,4] In an attempt to determine the extent to which this abnormal effect is general, we have investigated *ortho* effects in a number of sets of 2-substituted imidazoles, benzimidazoles, naphthimidazoles, and related compounds. Values of pK_a for these compounds (taken from the literature) were correlated with the Hammett equation (2) using the σ_I, σ_m, and σ_p constants. Data used in the correlations are given in Table I. The σ_m and σ_p values used were generally taken from the compilation of McDaniel and Brown.[5] The σ_I values were generally from our recent compilation.[6] Values of σ from other sources are given in Table II. We have included the points for X = NH_2 in those sets for which they are available (sets 1, 2, 5, and 8–11), although no direct evidence for predominance of the amino form is available except in the case of 5-aminotetrazole. In their review, Katritzky and Lagowski[7] state that the great majority of compounds containing potential amino groups exist in the amino form. Further evidence is supplied by the close agreement between pK_a values for the 2-amino- and 2-dimethylaminobenzimidazoles (sets 5 and 6, Table I) and the 2-amino- and 2-dimethylamino-5,6,7,8-tetrahydronaphth[2,3]imidazoles (set 10).

$$Q_{o,X} = \rho_o\sigma_{p,X} + Q_H \quad (1)$$

$$Q_X = \rho\sigma_X + Q_H \quad (2)$$

The correlations were made as described by Jaffé.[1] The results are presented in Table III.

Imidazoles.—The 2-substituted imidazoles were correlated with the inclusion (set 1a) and exclusion (set 1b) of the value for X = NH_2. Set 1a gave excellent results with σ_m, σ_p, and σ_I although σ_m gave somewhat better results than did the other constants. The results with set 1b are clearcut: correlation with σ_m is far superior. The ρ values obtained for sets 1a and 1b are about the same, as are the values of Q_H. We consider this to be evidence for the predominance of the 2-amino tautomer. The results obtained for the 2-substituted 1-methylimidazoles (set 2) are in accord with those obtained for the 2-substituted imidazoles, σ_m clearly giving the best results. The 4-substituted 1-methylimidazoles (set 3), I, which are also capable of exhibiting an "*ortho* effect" gave best results with σ_m. The 5-substituted 1-methylimidazoles (set 4) gave, as expected, best correlation with σ_m.



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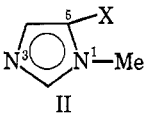


II

Benzimidazoles and Naphthimidazoles.—The results obtained for the data in water (sets 5 and 6) clearly show best correlation with σ_m. The data in 5% ethanol–water (set 7) do not permit any distinction to be made between σ_I, σ_m, and σ_p. This is due to the fact that for the substituents in this set, σ_I is linear in σ_m and to a lesser extent in σ_p. Thus, this set does not provide a legitimate test of electrical effects in benzimidazoles. The data in 50% aqueous ethanol (set 8) do not distinguish between σ_m and σ_p. This is probably due to seven of the eight substituents lying in a range of 0.2 σ unit. The two series of naphthimidazoles studied (sets 9 and 10) both show best results with σ_m. Correlations of the data for the 5,6,-7,8-tetrahydronaphth[2,3]imidazoles were made with (set 10a) and without (set 10b) the value for MeS = X, as this value is only approximate. No significant difference in the results was obtained.

5-Substituted Tetrazoles.—Correlations of this set were made excluding (set 11a) and including (set 11b) the value for X = AcNH as this group is capable of imino–amino tautomerism (see below). Although cor-

(1) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956; V. Palm, *Russ. Chem. Rev.*, **31**, 471 (1961); P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); in particular, see the recent excellent review by H. H. Jaffé and H. L. James, *Advan. Heterocyclic Chem.*, **3**, 209 (1964).

(2) M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964).

(3) A. I. Shatenshtein, "Isotopic Exchange and the Replacement of Hydrogen in Organic Compounds," Consultants Bureau, New York, N. Y., 1962; A. I. Shatenshtein, *Tetrahedron*, **18**, 95 (1962).

(4) R. Huisgen, W. Meek, K. Herbig, N. Ott, and E. Anneser, *Chem. Ber.*, **93**, 412 (1960).

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

(6) M. Charton, *ibid.*, **29**, 1222 (1964).

(7) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 339 (1963); **2**, 27 (1963).

TABLE I

DATA USED IN CORRELATIONS[a]

1. Ionization constants of 2-substituted imidazoles in water at 25°

X	H	Me	Et	Ph	NO_2	NH_2
pK_a	6.95	7.86	8.00	6.39	−0.81	8.46
Ref.	*b*	*b*	*b*	*b*	*c, d*	*e*

2. Ionization constants of 2-substituted 1-methylimidazoles in water at 25°

X	H	NO_2	NH_2
pK_a	7.33	−0.44	8.65
Ref.	*b*	*c, d*	*e*

3. Ionization constants of 4-substituted 1-methylimidazoles in water at 25°

X	H	NO_2	Cl	Ph
pK_a	7.25	−0.60	3.10	5.78
Ref.	*f*	*c, d*	*c*	*b*

4. Ionization constants of 5-substituted 1-methylimidazoles

X	H	Cl	NO_2
pK_a	7.25	4.75	2.08
Ref.	*e*	*c,g*	*c,d*

5. Ionization constants of 2-substituted benzimidazoles in water at 25°

X	H	Me	Et	CH_2OH	EtO	Ph	NH_2
pK_a	5.58	6.29	6.27	5.40	4.18	5.23	7.54
Ref.	*h*	*h*	*h*	*h*	*i*	*j*	*k*

6. Ionization constants of 2-substituted benzimidazoles in water at 25°[l]

X	H	Me	Ph	$PhCH_2$	Cl	Me_2N	$HOCH_2$	$AcOCH_2$	$PhCH_2CH_2$	PhC_2H_2
pK_b	8.6	8.3	9.2	8.9	11.4	6.6	8.4	9.4	7.9	8.8

7. Ionization constants of 2-substituted benzimidazoles in 5% (v./v.) ethanol–water at 30°[m]

X	Me	Et	*i*-Pr	$PhCH_2$	Ph	Ac	CF_3	H
pK_a	6.10	6.15	6.08	5.70	5.33	4.61	4.51	5.52

8. Ionization constants of 2-substituted benzimidazoles in 50% ethanol–water at 25°[n]

X	H	Me	Et	Pr	*i*-Pr	*t*-Bu	Ph	NH_2
pK_a	4.98	5.77	5.69	5.66	5.79	5.76	4.51	7.39

9. Ionization constants of 2-substituted naphth[2,3]imidazoles in water at 20°[b]

X	H	NH_2	Me	Et
pK_a	5.24	7.01	6.11	6.14

10. Ionization constants of 2-substituted 5,6,7,8-tetrahydronaphth[2,3]imidazoles in water at 20°[b]

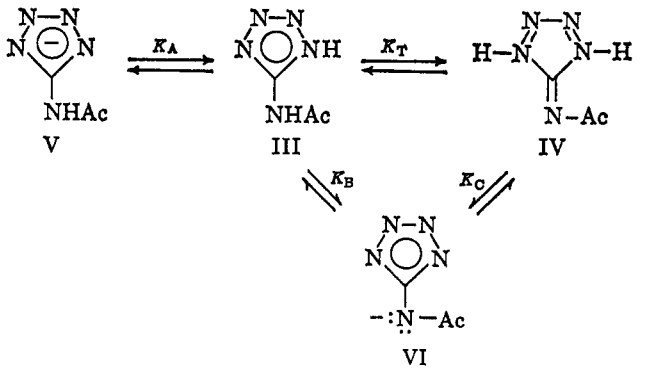
X	H	Et	Cl	NH_2	Me_2N	MeS
pK_a	5.98	6.64	2.68	7.69	7.65	5

11. Ionization constants of 5-substituted tetrazoles in water at 25°

X	H	Cl	Br	I	NH_2	AcNH	Me	Et	Pr	*i*-Pr
pK_a	4.89	2.07	2.13	2.85	6.00	4.49	5.562	5.592	5.607	5.553
Ref.	*b*	*b*	*b*	*b*	*b*	*o*	*p*	*p*	*p*	*p*

[a] pK_a values are of cations except for set 11 for which anionic pK_a values are given. [b] A. Albert, "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter I. [c] Ref. 10. [d] Average value. [e] B. T. Storey, W. W. Sullivan, and C. L. Meyer, *J. Org. Chem.*, **29**, 3118 (1964). [f] K. Hofmann, "Imidazole and Its Derivatives," part I, Interscience Publishers, Inc., New York, N. Y., 1963. [g] In 1:3 methanol–water. [h] T. J. Lane and K. P. Quinolan, *J. Am. Chem. Soc.*, **82**, 2995 (1960). [i] L. S. Efros and A. V. El'tsov, *Zh. Obsch. Khim.*, **27**, 684 (1957); *Chem. Abstr.*, **51**, 16437*f* (1957). [j] H. Walda and R. W. Isensee, *J. Org. Chem.*, **26**, 2789 (1961). [k] At 20°. [l] L. S. Efros and B. A. Porai-Koshits, *Zh. Obsch. Khim.*, **23**, 697 (1953); *Chem. Abstr.*, **48**, 7603*h* (1953). [m] D. J. Robiger and M. L. Jouillie, *J. Org. Chem.*, **29**, 476 (1964). [n] M. T. Davis, P. Mammalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **3**, 420 (1951). [o] E. Lieber and E. Oftedahl, *Trans. Illinois State Acad. Sci.*, **51**, 41 (1958); *Chem. Abstr.*, **56**, 4151*a* (1963). [p] J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

relation in both 11a and 11b is decidedly better with σ_m, the results for 11a are very much better than those for 11b. The tautomerism involved may be represented as follows since evidence has been presented to show that N-1 bears the proton.[7] Now the macroconstant K_M reported for 5-acetylaminotetrazole must



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be equal to the sum of the microconstants K_A, K_B, and K_C. Lieber and Oftedahl[8] have reported a value of pK_a for 1-benzyl-5-acetylaminotetrazole of 8.49. From this value we obtain K_R which is approximately equal to $K_B + K_C$. Then $K_A = K_M - K_R = 3.24 \times 10^{-5}$ corresponding to pK_a = 4.49. The value of K_A obtained by calculation from set 11a is 3.09×10^{-4} corresponding to pK_a 3.51. Thus amino–imino tautomerism does not explain the large discrepancy between the value of pK_a calculated from the Hammett equation and that obtained from the work of Lieber and Oftedahl.[8] Furthermore, although the available data do not permit the calculation of K_T ($K_T = C_{III}/C_{IV} = K_C/K_B$), it has been shown for other acetylamino heterocycles that the amino form predominates.[7]

The "Normal" *ortho* Electrical Effect.—We have previously demonstrated that the σ_o constants pro-

(8) E. Lieber and E. Oftedahl, *Trans. Illinois State Acad. Sci.*, **51**, 41 (1958).

TABLE II

SUBSTITUENT CONSTANTS

X	σ_I	σ_m	σ_p	X	σ_I	σ_m	σ_p
CH_2OH		0.03[a]	−0.01[b]	$PhCH_2$		−0.01[a]	−0.10[b]
CH_2OAc	0.14[c]	0.12[a]	0.09[d]	$PhCH_2CH_2$		−0.05[a]	−0.14[d]
NH_2	0.10[e]			*trans*-PhC_2H_2	0.06[f]	0.025[g]	−0.05[g]
Me_2N	0.10[e]			*i*-Pr		−0.07[a]	
NO_2	0.63[e]			Pr		0.06[a]	

[a] Estimated from $\sigma_m = (2\sigma_I - \sigma_p)/3$: R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958). [b] O. Exner and J. Jonas, *Collection Czech. Chem. Commun.*, **27**, 2296 (1962). [c] Estimated from $\sigma_{I,CH_2X} = m\sigma_{I,X} + c$ [M. Charton, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 56-V], using the value 0.43 for $\sigma_{I,OAc}$ obtained from $\sigma_I = (3\sigma_m - \sigma_p)/2$. [d] From $\sigma_{p,CH_2X} = n\sigma_{I,X} + d$. [e] P. R. Wells, ref. 1. [f] From the equation in footnote *c*. [g] J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3542 (1953).

TABLE III

RESULTS OF CORRELATION

Set		ρ	r[a]	s[b]	t[c]	Q_H	n[d]
1a	I	−12.8	0.9975	0.300	24.50	7.29	5
	m	−11.1	0.9997	0.112	65.97	7.08	
	p	−9.36	0.9972	0.319	23.08	6.51	
1b	I	−12.9	0.956	1.15	6.496	7.71	6
	m	−10.9	0.9987	0.198	39.36	7.00	
	p	−6.92	0.924	1.48	4.865	5.90	
2	I	−13.9	0.960	1.94	3.439	8.57	3
	m	−10.6	0.9992	0.270	25.73	7.12	
	p	−6.43	0.942	2.33	2.814	5.43	
3	I	−11.2	0.972	0.998	5.810	7.25	4
	m	−10.5	0.995	0.434	13.68	6.88	
	p	−9.00	0.964	1.12	5.154	6.12	
4	I	−7.55	0.957	1.07	3.282	7.46	3
	m	−7.27	0.9988	0.176	20.71	7.39	
	p	−6.31	0.977	0.787	4.536	6.81	
5	I	−6.73	0.983	0.161	10.66	5.83	6
	m	−10.9	0.964	0.233	7.222	5.58	
	p	1.22	0.162	0.861	0.327	5.61	
6	I	6.26	0.747	0.860	3.174	8.19	10
	m	7.92	0.977	0.278	12.83	8.54	
	p	3.69	0.850	0.680	4.571	9.12	
7	I	−3.58	0.960	0.196	8.416	5.82	8
	m	−3.08	0.968	0.177	9.402	5.75	
	p	−2.14	0.965	0.185	8.954	5.62	
8	I	1.30	0.105	0.890	2.598	5.70	8
	m	−12.0	0.947	0.288	7.199	4.99	
	p	−3.85	0.957	0.258	8.124	4.99	
9	I	5.90	0.577	0.723	1.000	6.13	4
	m	−11.0	0.996	0.0823	15.14	5.31	
	p	−2.33	0.939	0.304	3.861	5.54	
10a	I	−8.10	0.810	1.24	2.761	7.11	6
	m	−8.69	0.994	0.225	18.75	6.06	
	p	−3.95	0.867	1.06	3.475	5.01	
10b	I	−8.03	0.797	1.44	2.284	7.12	5
	m	−8.87	0.996	0.203	20.24	6.01	
	p	−3.95	0.858	1.22	2.889	5.01	
11a	I	−6.78	0.951	0.538	8.163	5.41	9
	m	−7.18	0.993	0.202	22.67	5.02	
	p	−4.75	0.844	0.936	4.163	4.19	
11b	I	−6.50	0.931	0.596	7.204	5.47	10
	m	−6.90	0.974	0.373	12.04	5.09	
	p	−4.72	0.842	0.881	4.411	4.22	

[a] Correlation coefficient. [b] Standard deviation. [c] Student's t test. [d] Number of points in the set.

posed by a number of authors as a measure of the electrical effect of an *ortho* substituent fit eq. 3. Thus

$$\sigma_{o,X} = m\sigma_{p,X} + c \quad (3)$$

we consider the "normal" electrical effect of an *ortho* substituent to be proportional to that of the same substituent in the *para* position. Little and his co-workers[9] have recently reported an extensive set of σ_o values defined from the chronopotentiometric quarter-wave potentials for 2-substituted phenylferrocenes. Their values are given in Table IV. We have correlated these σ_o values with the σ_I, σ_m, and σ_p constants to provide a further test of eq. 3. The results are in Table V. They clearly show that eq. 3 is obeyed.

(9) W. F. Little, C. N. Reilley, J. D. Johnson, K. N. Lynn, and A. P. Sanders, *J. Am. Chem. Soc.*, **86**, 1376 (1964).

TABLE IV

σ_o CONSTANTS FROM CHRONOPOTENTIOMETRIC QUARTER-WAVE POTENTIALS[a]

MeO	−0.39	F	0.12	I	0.36	CO_2Me	0.29
EtO	−0.38	Cl	0.31	NO_2	0.79	CH_2OH	0.09
Me	−0.03	Br	0.34	CO_2H	0.23	Ph	−0.03

[a] See ref. 9.

TABLE V

CORRELATION OF σ_o

σ	m	r[a]	s[a]	t[a]	C
I	1.00	0.614	0.271	2.462	−0.172
m	1.25	0.820	0.197	4.526	−0.179
p	0.971	0.928	0.128	7.903	−0.000486

[a] See the corresponding footnotes to Table III.

The "*ortho*" Electrical Effect in Imidazoles and Their Derivatives.—It is convenient to characterize the electrical effect of a substituent in terms of the parameter[2] ϵ where

$$\epsilon = \delta/\lambda \quad (4)$$

and eq. 5 defines λ and δ. For the "normal" *ortho*

$$\sigma_X = \lambda\delta_{I,X} + \delta\sigma_{R,X} \quad (5)$$

electrical effect ϵ has a value of 1; for the "abnormal" *ortho* electrical effect observed in 2-substituted pyridines and quinolines the value of ϵ is 0 to 0.4. The results obtained there for 2-substituted imidazoles and their derivatives (sets 1, 2, 5, 6, and 8–10) show generally best correlation with σ_m. This corresponds to a value of ϵ of 0.3 to 0.6 in accord with the results obtained previously for pyridines and quinolines. The 4-substituted 1-methylimidazoles are also an *ortho*-substituted set; they too are best correlated by σ_m (set 3). This is the case with the analogous 5-substituted tetrazoles (set 11). Thus the *ortho* electrical effect in all of these sets is of the type we have described as "abnormal." It would be very desirable to study substituent effects in imidazoles which do not involve an *ortho* reaction site. The only available set of this type is the 5-substituted 1-methylimidazoles (set 4). By comparison with 3-substituted pyridines and with 4-substituted furanoic and thenoic acids this set would

be expected to give best results with σ_m. This is in fact the case.

Magnitude of ρ.—The ρ values obtained for the 2-substituted imidazoles and the 4-substituted 1-methylimidazoles are in accord with those obtained for 2-substituted pyridines (ρ values are given in Table VI). The values for the benzimidazoles are in fairly good agreement with ρ for 2-substituted quinolines with the exception of the set in 5% aqueous ethanol (set 7). The value obtained for this set is about 0.5 to 0.25 of the expected value.

TABLE VI

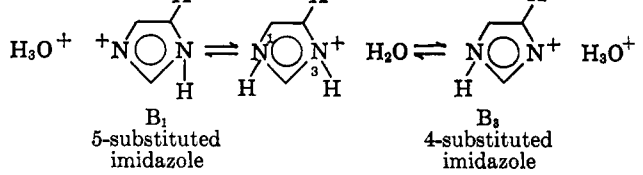
ρ VALUES

Set	Solvent	Temp., °C.	ρ_m
2-Substituted pyridine[a]	H_2O	25	−11.8
2-Substituted pyridine[a]	H_2O	20	−9.04
2-Substituted pyridine[a]	50% EtOH–H_2O	25	−8.69
2-Substituted imidazoles (1)	H_2O	25	−11.1
2-Substituted 1-methylimidazoles (2)	H_2O	25	−10.6
4-Substituted 1-methylimidazoles (3)	H_2O	25	−10.5
2-Substituted quinolines[a]	H_2O	25	−10.4
1-Substituted isoquinolines[a]	H_2O	25	−13.7
2-Substituted benzimidazoles (5)	H_2O	25	−10.9
2-Substituted benzimidazoles (7)	5% EtOH–H_2O	30	−3.08
2-Substituted benzimidazoles (8)	50% EtOH–H_2O	25	−12.0
2-Substituted naphth[2,3]imidazoles (9)	H_2O	25	−11.0
2-Substituted 5,6,7,8-tetrahydronaphth[2,3]imidazoles	H_2O	25	−8.69
3- or 4-Substituted pyridines	H_2O	20	−5.70
5-Substituted 1-methylimidazoles	H_2O	25	−7.27

[a] From ref. 2.

The ρ values observed for sets 1–3, 5, and 7–10 are in accord with the short distance between the reaction site and the substituent. The ρ value for the 5-substituted 1-methylimidazole is surprisingly large when compared with ρ for 3- or 4-substituted pyridines.

Annular Nitrogen Tautomerism in Imidazoles.—4- (or 5-) substituted imidazoles can exist in two tautomeric forms (B_1, B_3) depending on which nitrogen atom is the site of proton transfer.[7,10] These tautomers are in equilibrium with a common conjugate acid (BH^+).



B_1 5-substituted imidazole — B_3 4-substituted imidazole

The application of the Hammett equation to the problem of tautomerism has been studied by Jaffé[11] and by Kabachnik and his co-workers.[12] We find that the imidazole system lends itself readily to a new simple relationship.

From the observation that both the 4-substituted and 5-substituted 1-methylimidazoles (sets 3 and 4) are best correlated by σ_m, we may write eq. 6 for proton transfer at N-1 and N-3, respectively, in 4- (or 5-) substituted imidazoles. Now $pK_{a_1,H} \equiv pK_{a_3,H}$ as when X = H, $B_1 \equiv B_3$.

$$pK_{a} = \rho_1\sigma_{m,X} + pK_{a_1H};\ pK_{a_3} = \rho_3\sigma_{m,X} + pK_{a_3,H} \quad (6)$$

Then

$$pK_{a_1} - pK_{a_3} = (\rho_1 - \rho_3)\sigma_{m,X} \quad (7)$$

and as

$$pK_{a_1} = (-1)\log\frac{C_{H_3O^+}C_{B_1}}{C_{BH^+}};\quad pK_{a_3} = (-1)\log\frac{C_{H_3O^+}C_{B_3}}{C_{BH^+}} \quad (8)$$

we obtain

$$\log\frac{C_{B_3}}{C_{B_1}} = (\rho_1 - \rho_3)\sigma_{m,X} \quad (9)$$

Let us define

$$K_T = \frac{C_{B_3}}{C_{B_1}} \quad (10)$$

Then

$$\log K_T = (\rho_1 - \rho_3)\sigma_{m,X} \quad (11)$$

As both sets 3 and 4 have an N-methyl group, its effect on ρ can be assumed to be about the same in both sets and the difference in their ρ values can be taken as a measure of $(\rho_1 - \rho_3)$ in eq. 11. This gives a value of 3.2 for $(\rho_1 - \rho_3)$. Thus B_1 predominates with strong donor groups and B_3 predominates with strong acceptor groups. As a crude check on our assumption that the N-methyl group in set 3 does not greatly change the value of ρ, we may estimate ρ_3 from the pK_a of 4- (or 5-)nitroimidazole (for which log K_T = 2.30) and that of imidazole, which must include a statistical factor of 0.5 as there are two equivalent nitrogens in this compound. The pK_a values are −0.05 and 7.25, respectively, corresponding to a value of ρ_3 of about 10 in good agreement with ρ for set 3.

The above results represent a special case of a more general situation. For any unsymmetrical diazaarene, capable of the equilibrium

$$B_1 + H_3O^+ \rightleftharpoons BH^+ + H_2O \rightleftharpoons B_n + H_3O^+$$

we may write

$$pK_{a_1,X} = \alpha_1\sigma_{IX} + \beta_1\sigma_{RX} + pK_{a_1,H};$$
$$pK_{a_n,X} = \alpha_n\sigma_{IX} + \beta_n\sigma_{RX} + pK_{a_n,H} \quad (12)$$

Then $pK_{a_1,H} \equiv pK_{a_n,H}$ as when X = H, $B_1 \equiv B_n$. Therefore

$$pK_{a_1,X} - pK_{a_n,X} = (\alpha_1 - \alpha_n)\sigma_{IX} + (\beta_1 - \beta_n)\sigma_{RX} \quad (13)$$

and from eq. 8 and 13

$$\log\frac{C_{B_n}}{C_{B_1}} = (\alpha_1 - \alpha_n)\sigma_{IX} + (\beta_1 - \beta_n)\sigma_{RX} \quad (14)$$

Defining

$$K_T = \frac{C_{B_n}}{C_{B_1}} \quad (15)$$

we obtain

$$\log K_T = (\alpha_1 - \alpha_n)\sigma_{IX} + (\beta_1 - \beta_n)\sigma_{RX} \quad (16)$$

Now

$$\alpha = \rho\lambda;\ \beta = \rho\delta \quad (17)$$

where λ and δ are defined by eq. 5.

Values of λ and δ for some common substituents are σ_I, $\lambda = 1$, $\delta = 0$; σ_m, $\lambda = 1$, $\delta = 0.3$–0.6; σ_p, $\lambda = 1 = \delta$. Thus, if ρ values can be estimated for the ionization of each tautomer, and the type of substituent constant required for correlation is known or can be predicted, it should be possible to estimate log K_T for this system. The same technique can be applied to diazaarenes undergoing the equilibrium

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$$B_1H^+ + H_2O \rightleftharpoons H_3O^+ + B \rightleftharpoons B_nH^+ + H_2O$$

Now

$$pK_{a_1,x} \cong (-1) \log \frac{C_{H_3O^+}C_B}{C_{B_1H^+}}; \quad pK_{a_n,x} \cong (-1) \log \frac{C_{H_3O^+}C_B}{C_{B_nH^+}} \tag{18}$$

Then

$$\log \frac{C_{B_1H^+}}{C_{B_nH^+}} = (\alpha_1 - \alpha_n)\sigma_{IX} + (\beta_1 - \beta_n)\sigma_{RX} \tag{19}$$

Defining

$$K_T = \frac{C_{B_nH^+}}{C_{B_1H^+}} \tag{20}$$

we obtain eq. 21. An example of this type of tautomeric equilibrium is the ionization of a 4-substituted pyrimidine. We hope to discuss this system in a following paper.

$$\log K_T = (\alpha_n - \alpha_1)\sigma_{IX} + (\beta_n - \beta_1)\sigma_{RX} \tag{21}$$

Neighboring-Group Effects in the Hydrolysis of 1-Silylpropyl-2-imidazolines

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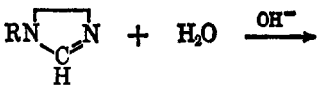
The hydrolysis of the imino bond in a group of 1-(3-silylpropyl)-2-imidazolines was shown to be first order in imidazoline in aqueous alkaline solution. With one exception, the series gave a pseudo-first-order rate constant, $k_{obsd} = k_A[OH]/(1 + K[OH])$. One example, 1-(3-trimethylsilylpropyl)-2-imidazoline (V), gave $k_{obsd} = (k_A[OH] + k_B[OH]^2)/(1 + K[OH])$. This was interpreted as a neighboring-group interaction with the silyl group of V which assists direct attack of the nucleophile on the free base of V.

Participation of the trimethylsilyl group in the transition state has been invoked to explain the enhanced rate of displacement of chloride from chloromethyltrimethylsilane.[1] The importance of such effects for other organofunctional silicon compounds is largely unknown. The synthesis of 1-(3-silylalkyl)-2-imidazolines provided an opportunity to search for effects of the silyl group during hydrolysis of an imidazoline ring according to eq. 1. The rate-controlling step



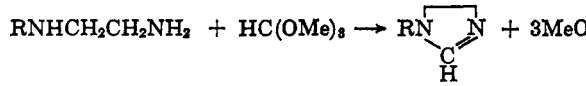
$$RNHCH_2CH_2NH(CHO) + RN(CHO)CH_2CH_2NH_2 \quad (1)$$

A B

I, R = n-C_3H_7
II, R = $Me_3Si(CH_2)_3$
III, R = $(MeO)Me_2SiCH_2CHMeCH_2$
IV, R = $(MeO)_2MeSiCH_2CHMeCH_2$
V, R = $(MeO)_3Si(CH_2)_3$

for similar reactions in alkaline solution has been pictured as an attack of hydroxide ion on the protonated imino group.[2] Any interactions between the imidazoline ring and silicon which might facilitate the attack of the nucleophile would then be apparent in the kinetics of the system.

2-Imidazolines were prepared according to eq. 2.[3] The products of hydrolysis of compounds II and III were isolated and identified as being mostly A, R = $Me_3Si(CH_2)_3$ and $O_{0.5}Me_2SiCH_2CHMeCH_2$, respectively. The other 2-imidazolines were assumed to give analogous products.



Experimental Section

1-(3-Silylalkyl)-2-imidazolines were prepared by a modification of the method reported by Hill and Johnston.[3] A mixture of the N-propyl- or N-(silylpropyl)-1,2-ethylenediamine and a 5–10% molar excess of methyl orthoformate was heated in a stainless steel bomb at 180–200° until no further increase in pressure was noted. About 1.5–3 hr. were required to reach a maximum pressure of about 20 atm. In certain cases the reaction became noticeably exothermic (see Table I) before a temperature of 200° was reached. In these examples, although the external heating was discontinued as soon as an exothermic reaction was observed, the temperatures rose well beyond 200°. The products were isolated by vacuum distillation. The results are summarized in Table I. Physical properties and analyses are given in Table II. The infrared spectra of the 2-imidazolines showed a strong absorption at 6.1–6.2 μ (in CCl_4 solution) characteristic of C=N stretching.[4] They all showed the strong absorption at 229–234 mμ (in isooctane) in the ultraviolet characteristic of 2-imidazolines.[5]

Hydrolysis of 1-(3-Trimethylsilylpropyl)-2-imidazoline.—A mixture 10 g. of 1-(3-trimethylsilylpropyl)-2-imidazoline (II) and 10 g. of water was saturated with potassium carbonate. Two layers separated. The aqueous phase was extracted with ether and the extracts were combined with the organic phase. The solution was evaporated. The residue was kept in a vacuum at room temperature for 96 hr. A 93% yield, 10.7 g., of N-[2-(3-trimethylsilylpropylamino)ethyl]formamide [A, R = $Me_3Si(CH_2)_3$] hydrated with 0.5 mole of water resulted.

The infrared spectrum (in dilute CCl_4 solution) showed a broad single absorption at 3.01, a strong absorption at 5.94 for carbonyl, and a single sharp absorption at 8.01 μ for methyl on silicon. The lack of a doublet in the 3-μ region and the absence of significant absorption in the 6.0–6.3-μ region indicated the absence of significant amounts of primary amine B.

Anal. Calcd. for $C_9H_{23}N_2O_{1.5}Si$: neut. equiv., 211. Found: neut. equiv., 211.8.

The above formamide (3.22 g.) was treated with 2.46 g. phenylisothiocyanate in 25 ml. of benzene. The benzene solution was mixed with 50 ml. of pentane and the resulting crystals, 3.12 g., 56% yield, were filtered. Recrystallization of the solid from ethanol water and drying gave the phenylthiourea derivative of A [R = $Me_3Si(CH_2)_3$], m.p. 116.5–118.0°.

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(3) A. J. Hill and J. V. Johnston, *ibid.*, **76**, 922 (1954).
(4) F. H. Suydam, *Anal. Chem.*, **35**, 193 (1963). The absorption was shifted by about 30 cm.$^{-1}$ to lower frequencies than those reported above. This was attributed to the strain in the five-membered ring system.
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