σ Values of Some Nitroimidazoles

N. Blažević (1), F. Kajfež and V. Šunjić

Faculty of Pharmacy and Biochemistry, University of Zagreb

During the synthesis of some imidazolium betaines via 1-substituted imidazoles it was observed (2) that the formation and stability of these compounds depend on the basicity of the *N*-3 atom in the imidazole ring. Generally, the basicity of the imidazoles is affected by the substituents on the *C*-atoms in the ring (3). It is the purpose of the present discussion to describe how substituents affect the basicity of some nitroimidazoles.

Charton (4-6) has developed a method which includes electrical effects of *ortho*-substituents on the basicity of the nitrogen atom in heterocyclic compounds. He has shown that *ortho*-substituents in these compounds manifest an "abnormal" *ortho*-effect in contrast to the "normal" *ortho*-effect due to corresponding substituents in benzenoid aromatics. Additional steric effects of *ortho*-substituents in arenes are included in Taft's σ_o values (7). The "abnormal" effect of the substituents in azaheterocycles was assigned to a localized electrical effect on the short distance of one interatomic bond, operative also in the reactions of *ortho*-substituted benzenes where phenide ion is the intermediate (8).

We have used Taft's σ_o and Hammett's σ_m values to determine statistical $\epsilon\sigma^*$ values in some nitroimidazole derivatives (see Table I). These values should include all effects of the substituent on the protonation and deprotonation of the nitrogen atoms in the ring. The unsubstituted imidazole ring, as well as those substituted in the positions 2 and 4 or 5 possess a plane of symmetry which passes through the *C*-2 atom and the middle of the bond between *C*-4 and *C*-5 atoms. This symmetry element is retained in their conjugated acids and bases (see formulae in Figure 1.), as was confirmed by extended Hückel calculations of σ- and π-electron densities in the imidazole ring (9).

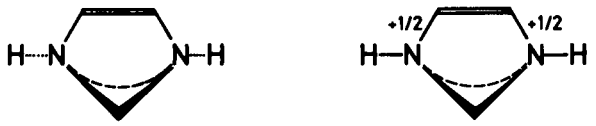

Figure 1.

It is supposed that effects of the substituents on the deprotonation of the conjugate acids with rate constants K_a will be characterized in the case of 2 and 4 substituted imidazoles as pure *ortho*-effect with Taft's σ_o values. For the 4 or 5 substituted imidazoles $\sigma_{4(5)}$ is obtained as a statistical average of σ_o values and classical Hammett's σ_m values. If more than one substituent is present in the ring $\epsilon\sigma^*$ are obtained by summing σ_o, σ_m and $\sigma_{4(5)}$ values in accordance with their additive nature (11).

$$\epsilon\sigma^* = \sigma_2 + \sigma_4 + \sigma_5 [+ \sigma_{4(5)}]$$

where

$\sigma_2 = \sigma_4 = \sigma_o$ Taft's σ_o values (12)

$\sigma_5 = \sigma_m$ Hammett's σ_m values (13)

and for the 4(5) substituents $\sigma_{4(5)}$ is expressed as:

$$\sigma_{4(5)} = 0.5\ (\sigma_o + \sigma_m)$$

The plot of pK_a vs. $\epsilon\sigma^*$ (Figure 2) suggests that substituted nitroimidazoles satisfy a linear relationship of free energy, unless the substituent is at one of the nitrogen atoms (position 1). So the 1-substituted-5-nitroimidazoles (points 8,10,12,14 and 15) clearly fall out from the regression line showing higher pK_a values than predicted. For the other substituted nitroimidazoles the $\epsilon\sigma^*$ values include the additional effects of the substituents on protonation

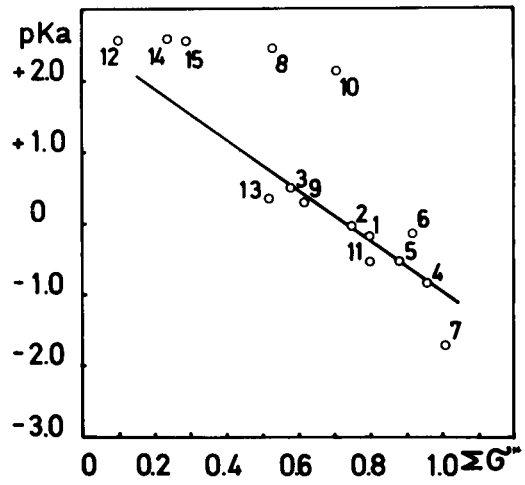

Figure 2.

TABLE I

pKa and $\epsilon\sigma^*$ Values of Some Nitroimidazoles

No.	Compound	$\epsilon\sigma^*$	pKa
1	2-Nitroimidazole	+0.80	−0.20 (a)
2	4(5)-Nitroimidazole	+0.755	−0.05 (b)
3	2-Methyl-4(5)-nitroimidazole	+0.58	+0.50 (c)
4	2-Iodo-4(5)-nitroimidazole	+0.96	−0.85 (d)
5	2-Methyl-4(5)-nitro-5(4)-bromoimidazole	+0.88	−0.55
6	1-Methyl-2-iodo-5-nitroimidazole	+0.92	−0.14 (d)
7	1-Methyl-2-iodo-4-nitroimidazole	+1.01	−1.70 (d)
8	1- Subst. (e) alkyl-2-methyl-5-nitroimidazole	+0.54	+2.39 (c)
9	1-Subst. (e) alkyl-2-methyl-4-nitroimidazole	+0.63	+0.30 (c)
10	1-Methyl-5-nitroimidazole	+0.71	+2.13 (b)
11	1-Methyl-4-nitroimidazole	+0.80	−0.53 (b)
12	1,2-Dimethyl-4-amino-5-nitroimidazole	+0.10	+2.50
13	1,2-Dimethyl-4-nitro-5-aminoimidazole	+0.53	+0.33
14	1,2-Dimethyl-4-methoxy-5-nitroimidazole	+0.24	+2.65
15	1,2-Dimethyl-4-ethoxy-5-nitroimidazole	+0.28	+2.60

(a) E. Laviron, *Bull. Soc. Chim. France*, 2840 (1963). (b) A. Grimison, J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1352 (1960). (c) Ref. 10. (d) M. Hoffer, V. Toome and A. Brossi, *J. Heterocyclic Chem.*, 3, 454 (1966). (e) The substituents were: $-CH_2CH_2OCH_2CH_2Cl$, $-CH_2CH_2Br$, $-CH_2CH_2OH$. We have taken average pKa values for these compounds.

of *N*-1 and *N*-3 protons. Substitution on the nitrogen atom in nitroimidazole seems to have a great effect on its basicity. The reason may be in losing the plane of symmetry by substitution as shown in formulae (Figure 1). The effect of a 4-nitro group in these compounds results in a slight decrease in basicity (points 7,9,11 and 13) caused by the "abnormal" *ortho*-effect described earlier (4,5). The 5-nitro isomers show a much stronger increase in basicity (points 6,8,10,12,14 and 15) attributable to the interaction of the nitro group with *N*-1 atom, since the 5-nitro group decreases the electron withdrawing activity of *N*-1 atom on one hand and also influences the interaction of *N*-1 atom with *N*-3 atom, on the other. Hüther *et al.*, showed (14) that this interaction can be observed from the NMR spectra of protonated forms of 1-substituted-2-methyl-4(5)-nitroimidazoles where the protons on the *N*-3 atom of protonated 5-nitro derivatives have chemical shifts about 1 ppm lower than those of 4-nitro isomers. Such behaviour could also be predicted by simple HMO calculations (14).

EXPERIMENTAL

Compounds prepared by the authors were described earlier (15,16).

All pK_a values were determined spectrophotometrically, on a Perkin-Elmer UV-VIS Spectrophotometer M 129. The accuracy of the measurements was ±0.06 pK_a units. The experimental conditions for the spectroscopic measurements, as well as the method of evaluation of the results were the same as mentioned in ref. 10. The *N*-3 atom and not an amino group was proposed as the site of protonation in compounds **12** and **13** on the basis of the general similarity of their spectra with those of other *N*-3 protonated compounds (10).

TABLE II

Ultraviolet Spectra of Compounds **12** and **13**: (a) in 2 *M* HCl, (b) in 0.1 *M* NaOH

	λ max	mμ (ε)	λ min	mμ (ε)
Compound **12**:				
(a)	220	(6740)	278	(460)
	355	(9150)		
(b)	228	(2780)	219	(2470)
	282	(7130)	240	(2380)
	376	(1470)	352	(1160)
Compound **13**:				
(a)	220	(7650)	278	(540)
	355	(9820)		
(b)	230	(4320)	216	(3160)
	275	(4860)	251	(2850)
	366	(9490)	310	(860)

Acknowledgment.

The authors are indebted to Dr. L. Klasinc for his helpful discussion.

REFERENCES

(1) Correspondence should be addressed to this author.
(2) V. Šunjić, T. Fajdiga and M. Slamnik, to be published.
(3) K. Hoffman, "Imidazole and Its Derivatives", Interscience Publishing Co., New York, N. Y., 1953, pp 13-15.
(4) M. Charton, *Can. J. Chem.*, 38, 2493 (1960).
(5) M. Charton, *J. Am. Chem. Soc.*, 86, 2033 (1964).
(6) M. Charton, *J. Org. Chem.*, 30, 3346 (1965).
(7) R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.
(8) A. I. Shatenshtein, *Tetrahedron*, 18, 95 (1966).

(9) W. Adam and A. Grimison, *ibid.*, 12, 835 (1966).
(10) F. Kajfež, D. Kolbah, T. Fajdiga, M. Oklobdžija, M. Slamnik and V. Šunjić, *Croat. Chem. Acta*, 39, 199 (1967).
(11) L. P. Hammett, "Physical Organic Chemistry," McGraw Hill Book Co., Inc., New York, N. Y., 1940, Chapters 3,4 and 7.
(12) F. W. Taft, Jr., M. S. Newman and F. H. Verhoek, *J. Am. Chem. Soc.*, 72, 4511 (1950).
(13) H. H. Jaffe, *Chem. Rev.*, 53, 191 (1953).
(14) H. Hüther, F. Kajfež, L. Klasinc and V. Šunjić, *J. Mol. Structure*, 4, 108 (1969).
(15) F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga and M. Oklobdžija, *J. Med. Chem.*, 11, 167 (1968).
(16) V. Šunjić, T. Fajdiga, M. Japelj and P. Rems, *J. Heterocyclic Chem.*, 6, 53 (1969).

Received July 3, 1969 Zagreb, Yugoslavia