1,2-Diaryl-2-imidazolines. A Structure–Basicity Relationship: Application of the Hammett Equation

By **B. Fernández,* I. Perillo,** and **S. Lamdan,** Departamento de Química Orgánica, Facultad de Farmacia y Bioquimica, Universidad Nacional de Buenos Aires, Junin 956, Buenos Aires, República Argentina

The pK_a values of sixteen 1,2-diaryl-2-imidazolines have been determined and the influence of substituents at N-1 and C-2 upon basicity have been studied. The experimental data have been successfully correlated with the Hammett equation, the imidazoline ring being considered a substituent of the benzene ring. Comparisons with aniline and amidine systems have also been made.

CONTINUING our work on 1,2-diaryl-2-imidazolines,[1] we have studied the structure–basicity relationship in these compounds. The mixed ionization constants of various 1,2-diaryl-2-imidazolines were determined potentiometrically. They were denoted as K_a^M [2] and expressed in terms of the equilibrium between the base (I) and its conjugate acid (IH^+) with one solvated proton in the standard solvent, methylcellosolve–water.

$$(IH^+)_{solv} + nH_2O \rightleftharpoons H_3O^+_{solv} + (I)_{solv}$$

2-Imidazolines act as monoprotic bases,[3,4] behaviour which is accounted for by considering them as cyclic amidines, which upon protonation at N-3 give a resonance-stabilized imidazolinium ion (III).[5] This behaviour is similar to that of acyclic amidines [6,7] and other cyclic amidines.[8,9]

TABLE 1

Apparent ionization constants of 1,2-diaryl-2-imidazolines (I) in water at 25 °C

No.	Ar^1	Ar^2	pK_a^M	K_a^M	Ref.
(1)	Ph	Ph	9·26	$5{\cdot}49 \times 10^{-10}$	1,*a*,*b*
(2)	$4\text{-MeO}\cdot C_6H_4$	Ph	9·64	$2{\cdot}29 \times 10^{-10}$	1,*a*
(3)	$3,4\text{-(MeO)}_2\cdot C_6H_3$	Ph	9·55	$2{\cdot}82 \times 10^{-10}$	*a*
(4)	$4\text{-EtO}\cdot C_6H_4$	Ph	9·60	$2{\cdot}51 \times 10^{-10}$	
(5)	$4\text{-HO}\cdot C_6H_4$	Ph	8·86 *	$1{\cdot}38 \times 10^{-9}$	
			9·62	$2{\cdot}40 \times 10^{-10}$	
(6)	4-MeC_6H_4	Ph	9·48	$3{\cdot}31 \times 10^{-10}$	*a*,*b*
(7)	3-MeC_6H_4	Ph	9·36	$4{\cdot}36 \times 10^{-10}$	1,*a*
(8)	4-ClC_6H_4	Ph	8·98	$1{\cdot}05 \times 10^{-9}$	*b* †
(9)	$4\text{-NO}_2\cdot C_6H_4$	Ph	7·65	$2{\cdot}24 \times 10^{-8}$	1,*b*
(10)	$2\text{-NO}_2\cdot C_6H_4$	Ph	7·51	$3{\cdot}09 \times 10^{-8}$	1
(11)	$2,4\text{-(NO}_2)_2\cdot C_6H_3$	Ph	6·65	$2{\cdot}24 \times 10^{-7}$	1
(12)	α-Naphthyl	Ph	8·67	$2{\cdot}14 \times 10^{-9}$	1
(13)	β-Naphthyl	Ph	8·63	$2{\cdot}34 \times 10^{-9}$	1,*b*
(14)	Ph	$4\text{-NO}_2\cdot C_6H_4$	7·66	$2{\cdot}19 \times 10^{-8}$	*c*
(15)	Ph	$3\text{-NO}_2\cdot C_6H_4$	7·75	$1{\cdot}78 \times 10^{-8}$	1
(16)	$4\text{-NO}_2\cdot C_6H_4$	$4\text{-NO}_2\cdot C_6H_4$	6·74	$1{\cdot}82 \times 10^{-7}$	

[a] K. H. Wünsch, H. Dettmann, and S. Schönberg, *Chem. Ber.*, 1969, **102**, 3891. [b] M. W. Partridge and H. A. Turner, *J. Chem. Soc.*, 1949, 1308. [c] H. W. Heine and H. S. Bender, *J. Org. Chem.*, 1960, **25**, 461.

* Corresponds to the phenolic hydroxy-group whose acidity, compared with that of the phenol (pK_a 9·89), is increased by the presence of the cationic imidazolinium portion. † The base in *b* was not isolated. See Table 4 for the analysis.

The experimental pK_a values obtained in our investigation (Table 1), support N-3 protonation, since if the basic character were due to protonation at N-1 [structure (II)] as pointed out by Harnsberger and Riebsomer [10] the values would be close to those of the corresponding arylamines (Table 2). It is observed however that imidazolines are much stronger bases, a fact which can be explained by protonation at N-3 to give the ion (III). As expected a phenyl group at N-1 (pK_a 9·90) decreases

TABLE 2

pK_a Values of some arylamines and 1-aryl-2-phenyl-2-imidazolines at 25 °C

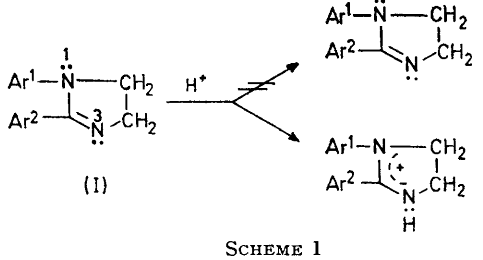
R	$R\cdot C_6H_4\cdot\overset{+}{N}H_3$	$R\cdot C_6H_4\cdot N\cdot C(C_6H_5){:}\overset{+}{N}H\cdot CH_2\cdot CH_2$
H	4·61	9·26
4-MeO	5·33	9·64
4-EtO	5·20	9·60
4-Me	5·08	9·48
4-Cl	4·03	8·98
4-NO_2	1·00	7·65

TABLE 3

Application of the extrapolation method to determination of apparent pK_a values of some organic bases at 25 °C

Base	pK_a^M	pK_a from literature[a]
Aniline	4·72	4·61
p-Anisidine	5·34	5·33
n-Butylamine	10·48	10·63
1-Butylpiperidine	10·36	10·47[b]
Diethanolamine	8·85	8·88
β-Naphthylamine	4·25	4·16
2-Phenyl-2-imidazoline	9·88	9·90[c]
Piperidine	10·96	11·12
m-Toluidine	4·79	4·71
Triethanolamine	7·78	7·77

[a] Average from reliable and approximate values (ref. 20). [b] At 23 °C. [c] At 20 °C (ref. 5).



(I) (II) (III)

SCHEME 1

---

[1] I. Perillo and S. Lamdan, *J. Heterocyclic Chem.*, 1970, **7**, 791.

[2] A. Albert, ' Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, Academic Press, New York, 1963, vol. I.

[3] R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, 1954, **54**, 593.

[4] K. Hofmann, ' The Chemistry of Heterocyclic Compounds; Imidazole and its Derivatives,' Interscience, New York, 1953, part I, p. 219.

[5] J. Elguero, E. González, J. L. Imbach, and R. Jacquier, *Bull. Soc. chim. France*, 1969, **11**, 4075.

[6] R. Mecke and W. Kutzelnigg, *Spectrochim. Acta*, 1960, **16**, 1216.

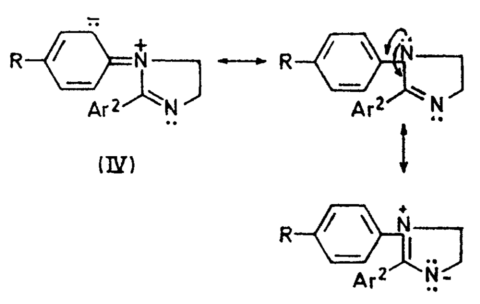
[7] J. C. Grivas and A. Taurins, *Canad. J. Chem.*, 1959, **37**, 1260.

[8] D. J. Brown and R. F. Evans, *J. Chem. Soc.*, 1962, 527.

[9] E. J. Moriconi and A. A. Cevasco, *J. Org. Chem.*, 1968, **33**, 2109.

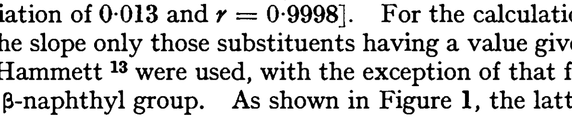
[10] B. G. Harnsberger and J. L. Riebsomer, *J. Heterocyclic Chem.*, 1964, **1**, 188.

the basicity [compound (1)], because of its electron-attracting ability. In contrast aryl substituents having an overall electron-donating effect (negative σ value) should increase the basicity in the same way as alkyl groups.[5] Since, however, their basic strength is diminished [compounds (2)—(7)], it is concluded that an important role is played by competition of the aryl group for the electron pairs of the imidazoline ring (IV). The loss of symmetry in the imidazolinium ion also influences the decrease in the basicity. Taking 1,2-diphenyl-2-imidazoline (1) as a reference, it may be seen (Table 1) that substituents in the benzene ring can either decrease or increase the basicity, depending on whether they are electron acceptors [compounds (8)—(16)] or electron donors [compounds (2)—(7)], respectively; similar behaviour has been observed for acyclic amidines to which 2-imidazolines are structurally related.[11,12]



SCHEME 2

Application of the Hammett Equation.[13,14a]—Although the literature does not report antecedents for application of the Hammett equation to imidazolines, it does so for acyclic amidines. Jaffé,[14b] on the basis of the data obtained by Lorz and Baltzly for *NN*-dibutylbenzamidines,[11] showed that a linear relation holds. When log k/k_0 for 10 imidazolines with substituents in the *meta*- and *para*-positions, were plotted against Hammett σ values [13] a straight line was obtained (Figure 1) by a least-squares procedure [$n = 7$ a slope (ρ) of $+1{\cdot}28$ with a median deviation of 0·013 and $r = 0{\cdot}9998$]. For the calculation of the slope only those substituents having a value given by Hammett [13] were used, with the exception of that for the β-naphthyl group. As shown in Figure 1, the latter group shows the greatest deviation. This is not surprising since deviations for this group have been commonly observed.[15-17] Values based on anilines [13] rather than benzoic acids [15] gave a nearer approach to linearity, a reflection perhaps of the involvement of polar forms (V) which affect, though indirectly, the electronic density at N-3. Although the need to use substituent constants based upon anilinium ions for certain groups such as p-NO_2, β-naphthyl, and p-OH permits comparison between the aniline and the imidazoline systems, in the former compounds the nitrogen which is responsible for the basicity is directly attached to the benzene ring and in the imidazolines it is not.



SCHEME 3

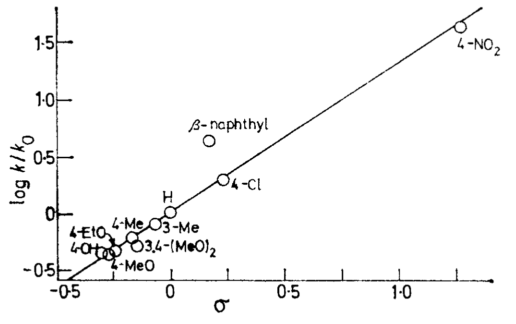
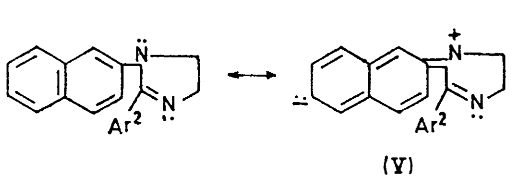


FIGURE 1 Application of the Hammett equation to 1-aryl-2-phenyl-2-imidazolines. The substituent constants used are: p-NO_2: $\sigma = +1{\cdot}27$ (ref. 13); p-OH: $\sigma = -0{\cdot}288$ when the side chain is $-NR_2$ (ref. 14*c*); 3,4-$(MeO)_2$: $\Sigma\sigma = -0{\cdot}153$ that gives a better fit than the σ found (ref. 14*d*). σ values from Hammett's were used for the other groups (ref. 13)



SCHEME 4

In Figure 2 the lower slope obtained for the imidazolines shows that the transmission of the substituents effect is found diluted or attenuated by the presence of two atoms (–N–C–) which separate the benzene ring from the N responsible for the basicity. The comparisons of the slopes supports N-3 protonation since if N-1 protonation were involved $\Delta\rho$ would approach zero. Furthermore, the slope $\rho = +1{\cdot}28$ calculated for the imidazoline system is perfectly logical, if it is compared with that of $+1{\cdot}412$ obtained for the acyclic amidines [14b] where there is one atom less between the phenyl group and the reaction site.

EXPERIMENTAL

Preparation of 1,2-*Diaryl*-2-*imidazolines*.—These compounds were prepared by cyclization of *N*-aroyl-*N'*-arylethylenediamines with ethyl polyphosphate (PPE) in chloroform solution, by the following procedure. *N*-Aroyl-*N'*-arylethylenediamine (1 g) was refluxed for 2 h with a chloroform solution (20 ml) of PPE.[18] The organic layer

---

[11] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992.

[12] D. J. Carswell, J. Cymerman, and L. E. Lyons, *J. Chem. Soc.*, 1952, 431.

[13] L. P. Hammett, 'Physical Organic Chemistry; Reaction Rates, Equilibria and Mechanisms,' McGraw-Hill, New York, 1970.

[14] (*a*) H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191; (*b*) 200; (*c*) 229; (*d*) 244.

[15] C. C. Price and R. H. Michel, *J. Amer. Chem. Soc.*, 1952, **74**, 3652.

[16] E. S. Gould and J. D. McCullough, *J. Amer. Chem. Soc.*, 1951, **73**, 1109.

[17] H. H. Jaffé and G. Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.

[18] W. Pollmann and G. Schramm, *Biochim. Biophys. Acta*, 1964, **80**, 1.

TABLE 4

Analytical data for new 1,2-diaryl-2-imidazolines

No.	M.p. (t/°C) [a]	Cryst. solvent	Analysis: Found (%) C	H	N	Formula	Required (%) C	H	N
(4)	104	n-Heptane	76·5	7·0	10·3	$C_{17}H_{18}N_2O$	76·7	6·8	10·5
(5)	250	Methanol	75·6	5·8	11·6	$C_{15}H_{14}N_2O$	75·6	5·9	11·8
(8) [b]	95	Cyclohexane	70·4	5·4	11·1	$C_{15}H_{13}N_2Cl$	70·2	5·1	10·9
(16)	216	Ethanol	57·5	4·0	17·7	$C_{15}H_{12}N_4O_4$	57·7	3·8	17·9

[a] Uncorrected [b] Cl: found: 13·5, required: 13·8.

was extracted with dilute hydrochloric acid (×4); the acid extract was made alkaline with 20% sodium hydroxide when the imidazoline was generally precipitated. If this failed to occur the suspension was extracted with methylene chloride (4 × 30 ml). The organic solution was washed with water, dried, and then evaporated *in vacuo*.

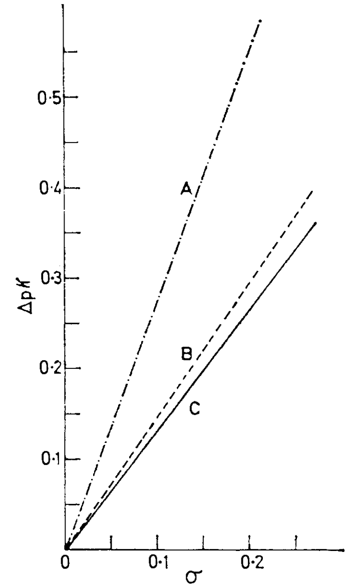


FIGURE 2 Decrease of ρ values with increasing number of atoms separating the substituent from the reaction site: A, aniline system from Hammett's values, ρ = +2·73 (ref. 13); B, amidine system from Lorz and Baltzly's, ρ = +1·412 (ref. 14*b*); C, imidazoline system from our investigation, ρ = +1·28.

Compounds (1)—(5) and (8)—(16) were purified by crystallization from the solvents reported in the literature (see refs. in Table 1) or Table 4 for the new products. Compounds (6) and (7) were purified by dissolution of the crude product in dilute hydrochloric acid. The acid solution was brought to neutral pH and extracted with chloroform to remove basic products. The resulting aqueous solution was made strongly alkaline with 20% sodium hydroxide and then extracted with methylene chloride. The organic extracts were washed, dried, and concentrated *in vacuo* to afford the pure base the purity of which was checked by t.l.c.

pK_a *Determination*.—The pK_a values of the 1,2-diaryl-2-imidazoline hydrochlorides were determined by the extrapolation method to 0% organic solvent.[19] The representation of the experimental values and their extrapolation to 0% organic solvent to obtain the pK_a in pure water at 25° is presented in Figure 3. The selected solvent was methylcellosolve which, since it has a more hydrophilic character than the alcohols, remarkably reduces the error due to the use of solvent mixtures. No thermodynamic corrections were applied because the solutions used never had a higher concentration than 0·01M.

Solutions.—Five 0·1M-HCl solutions were prepared in mixtures of 70, 50, 30, 20, and 10% (w/w) methylcellosolve–water, which were potentiometrically titrated in the presence of anhydrous sodium carbonate dissolved in the corresponding mixture methylcellosolve–water.

In the same way five 0·1M-NaOH solutions were prepared which were also potentiometrically titrated against anhydrous potassium biphthalate, as in the former case. Each pair of 0·1M-solutions was checked weekly by potentiometry. The use of titrated solutions made it possible to control the purity of the imidazolines during each titration. Purity was in no case lower than 99·3%.

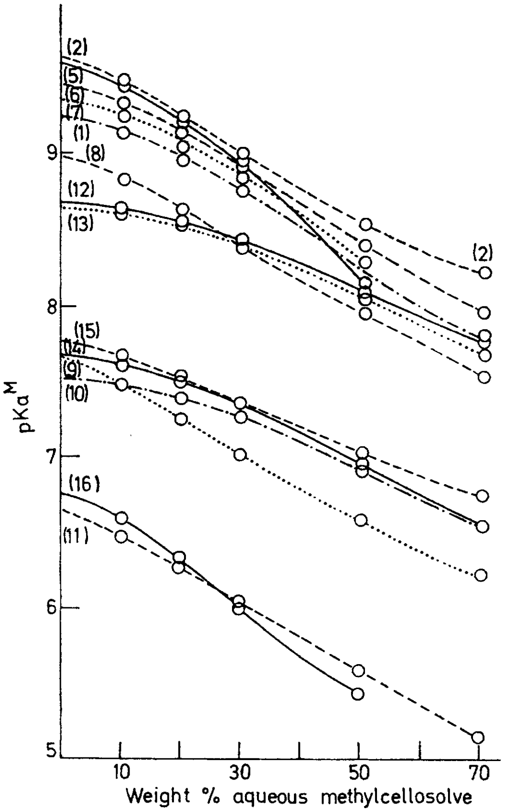


FIGURE 3 Determination of apparent pK_a values of 1,2-diaryl-2-imidazolines (I) by extrapolation to 0% (w/w) organic solvent. Curves for compounds (3) and (4) were not drawn to avoid complicated superposition in the graph

---

[19] N. F. Hall and M. R. Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.

Methylcellosolve was refluxed during 8—12 h over anhydrous potassium carbonate and then fractionally distilled three times; the fraction with b.p. 124·5 °C was collected.

General Procedure.—pK_a Determination were performed potentiometrically with a Beckman Zeromatic II instrument, the electrodes being standardized before each titration at 25 °C with Beckman buffer solutions of pH 4·01, 6·86, and 9·18 and after each titration with a solution of pH 7·413.

An aliquot of 0·005M-solution of each base in the corresponding mixture of methylcellosolve–water was potentiometrically back titrated at 25 °C. The pH scale of the apparatus was used so that the e.m.f. was read in E' units. The region between 0·5 E' units of the equivalence point was covered by spacing the E' values in 0·05—0·1 units. Approximately 15 readings were made in the course of each titration between the 20 and the 80% of the hydrochloride neutralization. Furthermore, each pK_a value was corrected according to the purity of the base. The six values used to determine each pK_a value agreed within ±0·05 pK maximum units. In order to determine the accuracy of the method, the pK_a values of other known organic bases were determined by using the same method, previously described.

The values shown in Table 3 were obtained and compared with the ' best ' value extracted from literature.[20] The pK_a values obtained by natural extrapolation of the curves show that the mixture of methylcellosolve–water worked efficiently in the pK_a range between 6 and 10 there being noticed negative deviations for values higher than 10 and increasing positive deviations for values lower than 6.

We thank Miss M. Esteve for her help in the preparation of some of the compounds.

[2/1214 *Received* 31*st May*, 1972]

---

[20] D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.