ELECTRONIC TRANSMISSION OF SUBSTITUENT EFFECTS THROUGH THE PYRROLE RING

IONIZATION CONSTANTS OF SOME 4 AND 5-SUBSTITUTED-2-PYRROLCARBOXYLIC ACIDS

F. FRINGUELLI, G. MARINO* † and G. SAVELLI

Istituto di Chimica Organica, Università di Perugia, Italy

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Abstract—The ionization constants of several 4- and 5-substituted-2-pyrrolcarboxylic acids were determined in water at 25.0°. A good fit in the Hammett equation was found using σ_m and σ_P constants. The ρ value (1.65) has been compared with those for the ionization of benzene-, furane-, thiophene- and seleno-phene-carboxylic acids.

Most of the literature data on the transmission of electronic effects of substituents through the pyrrole ring, are qualitative, the only quantitative study being that reported by Fournari¹ concerning the effects of various substituents in position 5 on the polarographic half-wave potentials of 2- and 3-nitropyrroles.

We have tested the applicability of the Hammett equation to the pyrrole nucleus by determining the ionization constants of several substituted 2-pyrrolcarboxylic acids. The substituents investigated each had a different electronic character: methyl (+I, +M), chloro and bromo (-I, +M) and nitro (-I, -M). Only position 4 (*meta*-like) and 5 (*para*-like) were considered, since they do not involve a vicinal relation with the carboxylic group.

RESULTS AND DISCUSSION

The ionization constants were determined in water at 25.0° using a potentiometric procedure.³ The values of pK_{a}^{T} , obtained by application of the usual activity correction, are reported in Table 1. The values for the unsubstituted and the 5-methyl-2-carboxylic acids are in satisfactory agreement with the literature values.⁴⁻⁶

Two possible complications must be considered when examining the dissociation of pyrrolcarboxylic acids. The first, arises from the acidic character of the proton bound to the N atom of the pyrrole ring when electron-attracting substituents are present.⁷ The pK_a 's for 4- and 5-nitro-2-methoxycarbonyl pyrroles were determined and since the values obtained (7.70 and 7.48) are much higher it may be concluded that the dissociation always refers to the carboxylic group.

^{*} To whom correspondence should be addressed.

[†] For earlier work see Ref. 1.

Substituent	pK ^T		
5-NO ₂	3.22		
4-NO ₂	3.37		
4-Br	4-06		
4-Cl	4.07		
5-Br	4.17		
5-Cl	4.32		
Н	4·50 4·60* 4·88		
4-CH ₃			
5-CH3			

TABLE 1. IONIZATION CONSTANTS OF SUBSTITUTED PYRROL-2-CARBOXYLIC ACIDS

^a Ref 5.

A second complication could be due to the often postulated pyrrole-pyrrolenine tautomerism. However, all the experimental data⁸ seem to exclude the importance of such a prototropic equilibrium and therefore it was ignored. Further, the linearity observed between pK_a 's and σ constants confirmed "a posteriori" the correctness of our assumption.⁹

Inspection of the constants listed in the Table 1, reveals that both inductive and conjugative effects of the substituents examined are operative.

For a deeper insight, the fitness of the data in a free-energy relationship was tested. Following the practice first established by Hammett¹⁰ in treating the furoic acids, many Authors¹¹⁻¹³ applied the Hammett equation to various reactions of thiophene and furan derivatives, by considering the 2-4 and 2-5 relationships as *meta* and *para*-like and using the corresponding σ_m and σ_p constants. Accordingly, the same procedure was used and the log K/K_0 's were plotted against the σ constants¹⁴ (see Fig. 1), yielding a ρ value of 1.65.



FIG. 1 Hammett's plot for the ionization of substituted 2-pyrrolcarboxylic acids in water, at 25-0°.

In Table 2, the ρ values are compared with the dissociations of benzene-, thiophene-, furane- and selenophenecarboxylic acids.

TABLE 2. THE APPLICATION OF THE HAMMETT BQUATION TO 5-MEMBERED HETEROAROMATIC RINGS

	$pK_{a'}$ in water at 25°	ρª	r	Sc	n	Ref
1	Benzoic acids	1		_	_	
2	Thiophen-2-carboxylic acids	1.10	0-988	0.07	5	11 <i>a</i>
3	Selenophen-2-carboxylic acids	1.23	0-998	0-02	7	15
4	2-Furoic acids	1.40	0.988	0-06	6	12
5	Pyrrol-2-carboxylic acids	1.65	0-988	0.09	9	e

" The reaction constant;

^b The correlation coefficient;

^e The standard deviation from the regression line;

⁴ The number of acids entering into the determination of ρ ;

" This work.

The Table reveals that the order of intensity of transmission of electronic effects is -CH=CH - < -S - < -Se - < -O - < -NH. The order is the same as observed by Tirouflet *et al.*^{2, 16} in the polarographic reductions of nitro derivatives of these rings. However, the available data¹⁷ seem to indicate that the situation is different when the electrophillic substitutions at the C atoms are considered.

EXPERIMENTAL

Materials. The following pyrrole carboxylic acids were prepared according to described procedures (original references and m.ps are given): unsubstituted,¹⁸ 207° dec; 5-methyl,¹⁹ 136–137°; 4-nitro,²⁰ 217°; 5-nitro,²⁰ 160–161°.

The four halopyrrolcarboxylic acids were prepared by hydrolysis of the corresponding methyl esters. The halogenated esters were obtained by reaction of 2-carboxymethylpyrrole with bromine²¹ or sulfuryl chloride.²² The 4- and 5-substituted isomers were separated on 20×20 cm chromatoplates coated with a 0-5 mm layer of silica gel (Merck PF₂₅₄). The developing solvent was cyclohexane-ethyl ether 9:1 and two passes of solvent were necessary for adequate band separation.

The ester (2 mmoles) dissolved in 5 ml MeOH was hydrolysed by heating under reflux for 2 hr with 6-7 ml of 20% KOH aq. After cooling, the MeOH was removed by distillation under vacuum; water was added and the mixture was extracted with ether. The aqueous soln was acidified with dil HCl and again extracted with ether. The acid, obtained after removing of the solvent, was purified by crystallization from hexane (5-chloro) or from a mixture of hexane and benzene (7:3) (4-chloro, 4- and 5-bromo) until constant m.p.

4-Chloro-2-pyrrolcarboxylic acid, m.p. 148–150° (Kofler) (Found: C, 41-45; H, 2-73; N, 9-77. C₅H₄O₂NCl requires: C, 41-26; H, 2-77; N, 9-62%).

5-Chloro-2-pyrrolcarboxylic acid, m.p. 124–126° (Kofler) (Found : C, 42-08; H, 2-75; N, 9-71. C₅H₄O₂NCl requires : C, 41-26; H, 2-77; N, 9-62%).

4-Bromo-2-pyrrolcarboxylic acid, m.p. 160° dec. (Kofler) (Found : C, 31·32; H, 2·29; N, 7·30. C₃H₄O₂NBr requires : C, 31·60; H, 2·12; N, 7·37%).

5-Bromo-2-pyrrolcarboxylic acid, m.p. 138° dec (Kofler) (Found: C, 31.41; H, 2.10; N, 7.25. C₅H₄O₂NBr requires: C, 31.60; H, 2.12; N, 7.37%).

The 5-halo-2-pyrrolcarboxylic acids must be used for pK_s measurements soon after preparation since they decompose on standing.

Determination of the ionization constants. The ionization constants were determined by potentiometric titration using an Amel pH meter mod 329 equipped with EA 121X glass electrode and an "Ingold" calomel reference electrode.

Standardization was performed with 005M potassium biphthalate buffer.

A soln of acid (about 0-01M) in CO₂-free water was thermostated at 250°. A 0-1N soln of carbonate-free NaOH was added from a 5 ml microburette. During the addition, the soln was stirred magnetically under a slow stream of O₂-free nitrogen. The pH of the soln was recorded at 0-1 ml intervals in the 40-60% neutralization range; plots of pH versus volume gave smooth curves. The pK_s values were calculated at various points of the titration by using the formula³: pK_s = pH + log([HA] - {H⁺}/[A⁻] + {H⁺}). An average of three titrations was made for each acid. The ionization constants were accurate to ± 0.02 pK_s units.

Termodynamical pK_a^T were then calculated by applying the usual activity correction $30.5\sqrt{(I)}$.

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