BASICITY AND STRUCTURE OF α,β-UNSATURATED KETONES OF THE HETEROCYCLIC SERIES

VI. Pyrrole and Indole Analogs of the Chalcones*

S. V. Tsukerman, L. A. Kutulya, and V. F. Lavrushin

The protolytic equilibrium constants of five pyrrole and three indole analogs of the chalcones in the H_2SO_4–CH_3COOH system have been determined spectrophotometrically. The electronic influences of the 2-pyrryl, N-methyl-2-pyrryl, indol-3-yl, and N-methylindol-3-yl groups have been evaluated quantitatively by means of their σ^+ parameters which are, respectively: −2.10, −2.07, −2.25, and −2.28. It has been shown that in α,β-unsaturated ketones the nitrogen-containing heterocyclic radicals 2-pyrryl and indol-3-yl, and also their N-methyl derivatives, exhibit a positive dynamic conjugation effect considerably exceeding that for 2-furyl, 2-thienyl, and 2-selenienyl.

There is a limited amount of literature information concerning the electronic influence of nitrogen-containing heterocyclic radicals—pyrryl and, in particular, indolyl. Only recently, in a study of the dissociation constants of pyrrole-2- and -3-carboxylic acids and the kinetics of the alkaline hydrolysis and the frequencies of the stretching vibrations of the carbonyl groups of their esters was a considerable electron-donating influence of the pyrrole nucleus shown [1]. The substantial decrease in acidity on passing from benzoic acid (pK_a = 4.20) to indole-3-carboxylic acid (pK_a = 5.25 [2]) shows the electron-donating nature of the indole nucleus.

Two of us, with colleagues, have shown on the basis of a study of the electronic and vibrational spectra and dipole moments [3] of the pyrrole and N-methylpyrrole analogs of the chalcones and also in an investigation of the hydrogen bond of N-methylpyrrole chalcones with phenol by IR spectroscopy [4] that in the static state the electron-donating effect of the 2-pyrryl and N-methyl-2-pyrryl radicals is considerably greater than that for the phenyl, 2-furyl, 2-thienyl, and 2-selenienyl radicals.

We decided to measure the protonation constants of the pyrrole (I–III) and indole (IV, V) analogs of the chalcones and also their N-methyl derivatives (VI–VIII) in the H_2SO_4–CH_3COOH system with the aim of obtaining quantitative information on the electronic influence on the 2-pyrryl and indol-3-yl radicals in the dynamic state. The selection of these radicals is due to the fact that they possess a greater electron-donating influence than their isomers.

An investigation carried out previously [3] showed that with strong acids the pyrrole analogs of the chalcones form strongly-colored salts with a 1 : 1 composition through the addition of a proton to the carbonyl

group. The structure of the conjugate carbonium cation of these salts may be represented by means of two limiting structures: the carbonium structure (A) and the immonium structure (B):
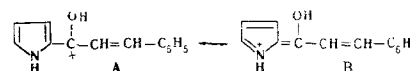

It follows from this that the subsequent addition of a proton even to the pyrrole ring must be considerably hindered. A spectroscopic study of the behavior of the
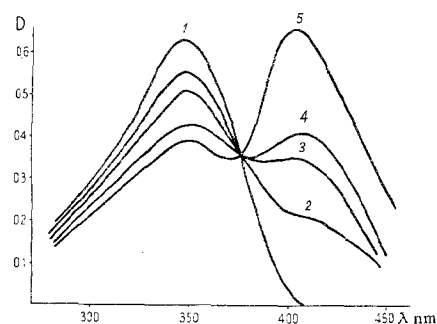
Absorption curves of 1-(2-pyrryl)-3-phenyl-propen-1-one: 1) in glacial acetic acid; 2) in 0.5% H_2SO_4; 3) 0.8% H_2SO_4; 4) 1.4% H_2SO_4; 5) 2.5% H_2SO_4 in glacial acetic acid.

indole chalcones in a strongly acid medium showed that they behave similarly to ketones of the pyrrole series. Because of this, the process of protonation of the pyrrole and indole chalcones, as for the furan, thiophene and selenophene analogs studied previously [5–7] can be represented in simplified form by the equation:

$$B + H^+ \rightleftarrows BH^+$$
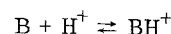
In glacial acetic acid the compounds studied exist in the molecular form, but with even small additions of sulfuric acid (0.1–1.5%) the formation of the corresponding deeply-colored cations takes place. The dynamic equilibrium between the molecular and ionic forms of compounds I–VIII is confirmed by the presence of an isobestic point on their absorption curves measured at various concentrations of sulfuric acid in glacial acid (see, for example, the figure).

The proteolytic equilibrium constants of the pyrrole and indole chalcones that we measured are given in Table 1. Table 1 also gives for comparison the figures for the chalcone IX and its 4'-chloro derivative X. It

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*For part V, see [12].

Table 1

Basicity Constants of the Pyrrole and Indole Analogs of the Chalcones

No.	Ketone	$K \cdot 10^3$	$-pK_a$
I	1-(2-Pyrryl)-3-phenylpropen-3-one	118 ± 2	0.93
II	1-(2-Pyrryl)-3-propen-1-one	9.9 ± 0.3	2.00
III	1-(2-Pyrryl)-3-(4-chlorophenyl)propen-3-one	73 ± 3	1.14
IV	1-(Indol-3-yl)-3-propen-3-one	198 ± 8	0.70
V	1-(Indol-3-yl)-3-(4-chlorophenyl)propen-3-one	100 ± 4	1.00
VI	1-(N-Methyl-2-pyrryl)-3-propen-3-one	106 ± 4	0.98
VII	1-(N-Methyl-2-pyrryl)-3-phenylpropen-1-one	4.6 ± 0.3	2.37
VIII	1-(N-Methylindol-3-phenylpropen-3-one	225 ± 3	0.65
IX	Chalcone	0.062	4.21
X	4'-Chlorochalcone	0.049*	4.31*

*This data was supplied by V. F. Lavrushin, V. N. Tolmachev, and N. D. Trusevich.

follows from a comparison of the basicity constants of IX and X with the corresponding constants for ketones of the pyrrole and indole series that the replacement of a phenyl by a 2-pyrryl or indol-3-yl group leads in all cases to a marked increase in basicity (by 2–3 orders of magnitude) (compare I, II, and IV with IX, and III and V with X).

Table 2

σ^+-Parameters of Heterocyclic Radicals

Radical	σ^+
Phenyl	0
2-Furyl	−0.512
2-Thienyl	−0.377
2-Selenienyl	−0.429
2-Pyrryl	−2.10
N-Methyl-2-pyrryl	−2.07
Indol-3-yl	−2.25
N-Methylindol-3-yl	−2.28

This unconditionally shows the high electron-donating capacity of nitrogen-containing heterocyclic radicals. Since the basicity of the indole chalcones is somewhat higher than that of the analogous pyrrole derivatives (compare I and IV and III and V), the electron-donating effect of the indol-3-yl group is somewhat greater than that for the 2-pyrryl group. In the ketones I, III, IV, and V, the heterocyclic nucleus is separated from the carbonyl group by a vinylidene group, in consequence of which the electron-donating action of the 2-pyrryl and indol-3-yl groups in these compounds is due mainly to their positive dynamic conjugation effect. The somewhat greater donor influence of indol-3-yl as compared with 2-pyrryl is probably due to the possibility of some additional delocalization of the positive charge on the carbon atoms of the benzene nucleus condensed with the heterocyclic nucleus.

As for the furan, thiophene, and selenophene chalcone analogs studied previously [5–7], the basicity of these pyrrole ketones depends to a considerable extent on the position of the carbonyl group in a chain of conjugation. Thus, of the two isomeric pyrrole chalcones I and II, the one in which the carbonyl group is adjacent to the pyrrole ring has the greater basicity (by a factor of about 10). This can be ascribed to the fact that, in addition to the positive conjugation effect, the pyrrole nucleus possesses a negative induction effect.

The appearance of the latter is due to the greater electronegativity of the nitrogen (3.0) as compared with carbon (2.5). The negative induction effect of the 2-pyrryl group naturally affects the basicity to a greater extent when the carbonyl group is adjacent to a pyrrole nucleus. The fact that even in this case when a phenyl group in chalcone is replaced by a 2-pyrryl group the basicity increases more than 100-fold (compare II and IX) permits the statement that for 2-pyrryl the positive conjugation effect considerably exceeds the negative induction effect.

In studying the basicity of the furan, thiophene, and selenophene analogs of chalcone [5–7], we put forward a hypothesis on the existence of steric hindrance to the solvation of the carbonium ions from the direction of the heterocyclic nuclei adjacent to the carbonyl group, especially those containing sulfur and selenium. However, it is hardly appropriate to ascribe a large influence to this in the case of 1-(2-pyrryl)-3-phenylpropen-1-one in view of the considerably smaller size of the nitrogen atom as compared with the atoms of the elements of the sixth group of the periodic system.

As was to be expected, the proton-accepting capacity of the chalcones containing chlorine as substituent is considerably reduced (compare I and III and IV and V). The protolytic equilibrium constants of these compounds have been included to give a more convincing confirmation of the electron-donating capacity of the nitrogen containing heterocyclic radicals.

A comparison of the protolytic equilibrium constants of ketones I and VI and IV and VIII shows that the introduction of a N-methyl group into a pyrrole or indole nucleus remote from the carbonyl group causes practically no change in basicity. At the same time, methylation at the nitrogen of a pyrrole nucleus adjacent to the carbonyl group in a chalcone (cf. II and VII) is accompanied by a marked decrease in basicity. This fact can be explained by steric hindrance to the process of solvation of the conjugate carbonium ion of VII from the direction of the voluminous methyl group, which to a considerable extent screens the atoms upon which the positive charge is delocalized and, consequently, around which solvation must predominantly take place (the carbonium carbon atom, the α-carbon atom, and the nitrogen atom of the pyrrole ring). At the same time, the energies of solvation of the molecular forms of ketones II and VII cannot differ appreciably, since,

Table 3

Results of Spectrophotometric Measurements and Calculated Basicity Constants* of Pyrrole and Indole Analogs of the Chalcones in the H_2SO_4–CH_3COOH System (Initial Concentration of the Ketones, $c \times 10^5$ mole/l: for I) 2.61; for II) 2.57; for III) 2.18; for IV) 1.89; for V) 1.66; for VI) 2.18; for VII) 2.32; for VIII) 1.97).

Compound	Percentage of H_2SO_4 in acetic acid; H_0 of the solutions	Measured optical densities at several wavelengths, D/λ, nm.					Calculated values of ε/λ	$(K \pm K) \cdot 10^3$
I	0.094; −0.47	0.275/460	0.280/465	0.280/470				
	0.19; −0.73	0.420/460	0.425/465	0.425/470			41500/460	
	0.30; −0.94	0.555/460	0.555/465	0.565/470			41500/465	116±2
	0.49; −1.24	0.705/460	0.715/465	0.715/470			42200/470	
	0.77; −1.52	0.860/460	0.870/465	0.880/470				
II	0.79; −1.54	0.335/400	0.340/405	0.335/410	0.325/415			
	1.17; −1.71	0.455/400	0.470/405	0.465/410	0.450/415		49800/400	
	2.12; −1.93	0.650/400	0.660/405	0.670/410	0.655/415		52600/405	9,3±0.7
	3.21; −2.24	0.800/400	0.830/405	0.840/410	0.830/415		55800/410	
	4.18; −2.43	0.890/400	0.930/405	0.960/410	0.950/415		56200/415	
III	0.09; −0.47	0.155/460	0.155/465	0.155/470	0.150/475	0.145/480	38200/460	
	0.19; −0.73	0.255/460	0.255/465	0.250/470	0.245/475	0.235/480	41300/465	
	0.30; −0.94	0.340/460	0.350/465	0.355/470	0.355/475	0.340/480	42100/470	68±5
	0.49; −1.24	0.470/460	0.490/465	0.490/470	0.490/475	0.475/480	43800/475	
	0.77; −1.52	0.590/460	0.615/465	0.630/470	0.625/475	0.620/480	42800/475	
IV	0.09; −0.47	0.275/470	0.295/475	0.305/480	0.300/485			
	0.19; −0.73	0.410/470	0.425/475	0.440/480	0.435/485		42400/470	
	0.30; −0.94	0.510/470	0.520/475	0.545/480	0.540/485		42200/475	194±9
	0.49; −1.24	0.595/470	0.610/475	0.640/480	0.640/485		44500/480	
	0.77; −1.52	0.660/470	0.680/475	0.710/480	0.710/485		42900/485	
V	0.09; −0.47	0.160/480	0.165/485	0.165/490	0.160/495			
	0.19; −0.73	0.255/480	0.260/485	0.260/490	0.255/495		42800/480	
	0.30; −0.94	0.360/480	0.370/485	0.370/490	0.365/495		43600/485	
	0.49; −1.24	0.430/480	0.445/485	0.445/490	0.435/495		43600/490	98±4
	0.77; −1.52	0.520/480	0.530/485	0.530/490	0.520/495		43400/495	
	1.26; −1.74	0.600/480	0.605/485	0.605/490	0.600/495			
VI	0.08; −0.43	0.200/470	0.205/475	0.205/480	0.195/485			
	0.16; −0.70	0.335/470	0.340/475	0.340/480	0.325/485		42400/470	
	0.32; −0.97	0.455/470	0.475/475	0.470/480	0.455/485		42700/475	
	0.45; −1.19	0.570/470	0.580/475	0.570/480	0.540/485		41500/480	106±4
	0.71; −1.49	0.650/470	0.660/475	0.650/480	0.615/485		39300/485	
	1.03; −1.65	0.780/470	0.795/475	0.770/480	0.720/485			
VII	0.92; −1.60	0.220/405	0.220/410	0.215/415	0.205/420			
	1.44; −1.80	0.360/405	0.360/410	0.350/415	0.335/420		56900/405	
	2.12; −1.93	0.460/405	0.470/410	0.460/415	0.440/420		59800/410	4.8±0.3
	3.20; −2.24	0.600/405	0.610/410	0.605/415	0.580/420		59800/415	
	4.18; −2.43	0.680/405	0.690/410	0.680/415	0.655/420		58400/420	
VIII	0.09; −0.47	0.360/470	0.370/475	0.375/480	0.375/485	0.375/490	45200/470	
	0.19; −0.73	0.500/470	0.515/475	0.520/480	0.515/485	0.505/490	46800/475	
	0.30; −0.94	0.610/470	0.630/475	0.640/480	0.635/485	0.620/490	47500/480	232±8
	0.49; −1.24	0.710/470	0.730/475	0.740/480	0.735/485	0.720/490	46700/485	
	0.77; −1.52	0.770/470	0.800/475	0.810/480	0.800/485	0.770/490	44700/490	

*For each ketone 2 or 3 independent measurements of the basicity constant were carried out; the results of only one of them are given in the table.

according to dipole moment data, in 1-(N-methyl-2-pyrryl)-3-phenylpropen-1-one the carbonyl group is turned in the direction opposite to the N-methyl group [3] and, consequently, is not subject to the steric influence of the latter. For the same reason no appreciable steric hindrance whatever can exist to the process of protonation of the ketone VII.

We have shown previously [8] that the pK_a values of the 4-substituted chalcones $X-C_6H_4-CH=CH-CO-C_6H_5$ in the $H_2SO_4-CH_3COOH$ system correlates well with the σ^+ parameters of the substituents which characterize their increased capacity for conjugation with an electronegative reaction center. This has permitted us to make a quantitative evaluation of the electronic influence of the nitrogen-containing heterocyclic radicals with the aid of the σ^+ parameters calculated from the experimental values of pK_a of the 1-heteryl-3-phenyl-propen-3-one and of the reaction constants ρ^+ for a series of 4-substituted chalcones ($\rho^+ = -1.56$). In this process we regarded these heterocyclic radicals as phenyls with substituents in the para position.

The value of the σ^+ constant that we found for the 2-pyrryl group (-2.10) correlates well with the value $\sigma^+ = -2.0$ obtained by Kahn and Morgan [1] on the basis of analogous premises using the characteristic frequency of the vibration of the carbonyl group of the methyl ester of pyrrole-2-carboxylic acid and the value of ρ^+ for the correlation relationship between ν_{CO} and σ^+ for substituted methyl benzoates. No information on the σ^+ values for the indol-3-yl, N-methylindol-3-yl, and N-methyl-2-pyrryl radicals is given in the literature.

The values of the σ^+ constants obtained for 2-pyrryl, indol-3-yl, and their N-methyl derivatives, together with the σ^+ parameters for 2-furyl, 2-thienyl, and 2-selenienyl obtained previously are given in Table 2. These figures show the unusually strong electron-donating influence of nitrogen-containing heterocyclic radicals, which is greater than that not only for other five-membered monoheterocyclic radicals but also for p-dimethylaminophenyl ($\sigma^+ = -1.7$).

The considerably greater electron-donating influence of 2-pyrryl as compared with 2-furyl is explained by the fact that, as is well known [9], of two neighboring elements of one period of D. I. Mendeleev's system, the greater positive conjugation effect is possessed by the atom having the lower electronegativity. In addition, again because the electronegativity of nitrogen is lower than that of oxygen, 2-pyrryl possesses a smaller negative induction effect than 2-furyl. For heterocycles containing atoms from the same group, the conjugation effect depends not only on electronegativity but also on the dimensions of the heteroatom, as we have discussed previously [7].

EXPERIMENTAL

The carbonyl compounds studied were obtained by methods described previously [3,10,11] and were carefully purified by repeated recrystallization.

The measurement of the basicity constants was carried out spectrophotometrically in solutions of H_2SO_4 (100%) in glacial acetic acid at 20° C on an SF-4 instrument. The sulfuric acid solutions (0.1-1.5%) were prepared by diluting a more concentrated solution (10-14%) prepared by weighing [6]. The solutions of the ketones for the spectrophotometric measurements were prepared as described previously [12] immediately before measurement in view of their low stability with time. The investigation of the stability of the acid solutions of the ketones and also the choice of the analytical wavelengths (three or four) in the region of the maximum of the absorption band of the ionic form were carried out on an SF-10 recording instrument. The measurement of the optical density was always carried out during a time in which it remained constant, and was checked several times for freshly-prepared solutions. Two or three independent series of measurements were carried out for each compound.

To determine the acidity functions H_0 of the solutions, the quadratic relationship between H_0 and the percentage concentration of H_2SO_4 in glacial acetic acid obtained by treating the experimental figures of previous workers [13-15] by the method of least squares was used. The calculation of the basicity constants ($K = 1/K_a$) was carried out by means of the formula given previously [5]. The molar absorption coefficient of the ionic form, ε, was found from the straight-line equation $1/\varepsilon' = 1/\varepsilon + (1/K \cdot \varepsilon)(1/h_0)$, by treating the experimental results $1/\varepsilon'= c/D$ and $1/h_0$ ($-\lg h_0 = H_0$) by the method of least squares. The results of the spectrophotometric measurements, the calculated molar absorption coefficients of the ionic forms and the basicity constants of the chalcones investigated are given in Table 3.

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