Tetrahedron, 1966, Vol. 22, pp. 2703 to 2710. Pergamon Press Ltd. Printed in Northern Ireland

STERIC EFFECTS IN 1-PHENYL-5-SUBSTITUTED PYRAZOLES

S. TABAK,* I. I. GRANDBERG and A. N. KOST
Moscow State University

(*Received* 9 *December* 1965; *in revised form* 19 *January* 1966)

Abstract—The UV absorption spectra and dissociation constants of some 1-phenyl-5-substituted pyrazoles are studied. An attempt is made to measure the steric effects of the substituents in position 5 of the pyrazole ring from the UV spectra, by known methods; the dissociation constants of the compounds are determined and discussed in the light of these results.

WHILE studying the UV absorption spectra of 1-phenyl-pyrazoles with substituents at positions 3, 4 and 5 of the pyrazole nucleus (Table 1) a very great similarity between the spectra of 3- and 4-substituted pyrazoles (1-phenyl) and a considerable difference between these and the spectra of the 5-substituted isomers was found. 3- and 4-substitution in 1-phenylpyrazole always produces a bathochromic shift (as compared with the spectrum of 1-phenylpyrazole) while 5-substitution always produces hypsochromic and hypochromic effects.

Such a hypochromic shift in the spectrum (with or without a simultaneous hypsochromic effect) is characteristic of conjugated systems, especially in aromatic or heteroaromatic compounds, in which two substituents, one of them conjugated with the aromatic nucleus, *ortho* to each other, interact sterically with a reduction in resonance because of the impossibility of coplanarity of the groups in the conjugated molecules.[1]

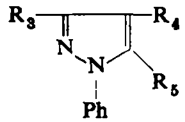
This effect is very clear in the pyrazole series (Table 1) for different substituents, and even for NH_2 and OH groups, the steric effects of which are so small in polycyclic aromatic hydrocarbons that they are not usually seen in the spectra.[2]

In the pyrazole series, Burness[3a] attributed the hypsochromic and hypochromic shifts in the UV spectrum of 1-*p*-nitrophenyl-5-ethylpyrazole to steric hindrance of resonance of the *p*-nitro-phenyl group with the pyrazole nucleus. The same explanation was given by Dal Monte *et al.*[3b] for similar effects in the spectra of several 1-phenyl-pyrazoles with methyl groups in position 5 of the pyrazole ring or 2 of the phenyl ring.

* Visiting Fellow from Brazil. Present address: Whiffen Laboratory, Department of Chemistry, Imperial College, London S.W.7.

[1] L. W. Pickett, G. F. Walter and H. France, *J. Amer. Chem. Soc.* **58**, 2296 (1936); see also the review by H. H. Jaffe and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy* pp. 384–449. Wiley, New York and London (1962).
[2] R. N. Jones, *J. Amer. Chem. Soc.* **67**, 2127 (1945).
[3a] D. M. Burness, *J. Org. Chem.* **21**, 97 (1956); [b] D. Dal Monte, A. Mangini and R. Passerini, *Gazz. Chim. Ital.* **86**, 797 (1956).

TABLE 1. UV SPECTRA OF SUBSTITUTED 1-PHENYLPYRAZOLES, IN METHANOL



No	R_3	R_4	R_5	λ_{max} (Å)	E_{max}	f
1	H	H	H	2530	15100	0·365
2	H	H	CH_3	2400	10000	0·238
3	CH_3	H	CH_3	2440	11500	0·360
4	CH_3	H	H	2560†	14100	—
5	H	H	Cl	2380	7240	0·151
6	CH_3	H	Cl	2420	10500	0·240
7	Cl	H	H	2580	17000	0·432
8	H	H	NH_2	2400	14800	0·349
9	CH_3	H	NH_2	2450	16700	0·416
10	H	NH_2	H	2820	14500	0·381
11	NH_2	H	H	2840	20900	0·492
12	H	H	$NHCOCH_3$	2380	12300	0·352
13	CH_3	H	$NHCOCH_3$	2460	18200	0·431
14	H	$NHCOCH_3$	H	2750	16700	0·384
15	$NHCOCH_3$	H	H	2740	27550	0·594
16	H	H	OH	2410	15900	0·344
17	CH_3	H	OH	2420	12900	0·349
18	H	OH	H	2760	15900	0·364
19	OH	H	H	2710	20900	0·485
20	H	H	COOH	(2500)*	6600	—
21	CH_3	H	COOH	2570	12300	0·294
22	COOH	H	H	2620	14790	—
23	H	H	C_6H_5	2460†	17800	—
24	C_6H_5	H	H	2780†	25100	—

* There is no maximum in the interval studied.
† See Ref 6.

In the Tables to follow, the numeration of the positions of the substituents in the pyrazole ring will be the same.

There are two simple methods* for calculating the *ortho* effect of the substituent in the 5-position from the intensity of the absorption bands. In previous work[4] the Braude equation[5] was used: $E = E_0 \cos^2 \theta$ (I) in which E_0 is the value of the absorption coefficient of a reference, unhindered, parent compound and θ is the spectroscopic angle of twist to be calculated. In this instance,[4] the E value for 1-phenylpyrazole found before[6] was used as reference. This E value was later found to be incorrect and in Table 1 (compound No 1)† the value found after careful purification is given.

In the present work, the Braude equation (I) and the calculation based on the integral intensity of the absorption bands, expressed by the oscillator strength

* Not including quantum mechanical ones, as used in Ref. 22.
† See also Ref. 7.

[4] I. I. Grandberg, S. Tabak and A. N. Kost, *Khim. Geter. Soed.* **1**, 901 (1965).
[5] E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature, Lond.* **173**, 117 (1954).
[6] I. I. Grandberg, *Zh. Obshch Khim.* **33**, 519 (1963).
[7] A. Mangini and D. Dal Monte, *Atti Acad. Naz. Lincei, Rend. Sci. Fis., Mat. e Nat.* **13**, 46 (1952).

$f = 4{\cdot}32 \times 10^{-9}E\nu d\nu$,[8] applying the equation $f = f_0 \cos^2 \theta$ (II) have been used. In this equation f and f_0 are the oscillator strengths for the hindered and the unhindered parent compound, respectively, and θ the spectroscopic angle of twist. With both equations, the reference spectrum for each compound is the spectrum of the unhindered isomer with the same substituent in position 3 of the pyrazole nucleus. This gives a better account of the electronic effects should there be no steric hindrance.

The results of the calculations with Eqs. (I) and (II) are shown in Table 2. It is seen that both results for each compound, within the limits of the experimental errors, are the same. Therefore, the angles for 1-phenyl-5-methylpyrazole and 1,5-diphenylpyrazole may be calculated using data collected before[6] and for 1-phenylpyrazole-5-carboxylic acid, a compound whose spectrum has no maximum in the investigated interval, the E value at 2500 A may be used, employing in both cases Eq. (I). This type of calculation is found in works of Wepster *et al.*[9,10]

TABLE 2. ANGLE OF TWIST OF THE PHENYL GROUP IN 5-SUBSTITUTED 1-PHENYLPYRAZOLES

No	Substituent	θ_1*	θ_2*	θ_3*
1	CH_3	33°	—	47°
2	COOH	48°	—	—
3	NH_2	33°	33°	36°
4	$NHCOCH_3$	—	39°	—
5	OH	29°	33°	24°
6	Cl	49°	54°	43°
7	C_6H_5	33°	—	—

* θ_1—"Spectroscopic angle", calculated by the Braude equation $E = E_0 \cos^2 \theta$.
θ_2—"Spectroscopic angle", calculated by the equation $f = f_0 \cos^2\theta$.
θ_3—Minimum geometrical angle of twist.

Calculation of the minimum geometrical angles of twist

The actual angle of twist in conjugated systems with steric hindrance of coplanarity depends on several factors[8] and the minimum angle, calculated on the basis of geometrical considerations is only an approximation. A comparison of the "spectroscopic" and geometrical angles is nevertheless, interesting.

The minimum geometrical angles can be calculated only if a good geometrical model of the molecule, based on the determination of atomic angles and distances by known physical methods is available. As this is not the case for the derivatives of 1-phenylpyrazole, a model based on a reasonable hypothesis was constructed.

Values for angles and interatomic distances for the pyrazole nucleus in 1-phenylpyrazole were taken from the work of Erlich[11] for pyrazole itself. Values for the phenyl group were taken from Ref. 12. The C_1'—N distance (between the pyrazole

[8] H. B. Klevens and J. R. Platt, *J. Amer. Chem. Soc.* 71, 1714 (1949).
[9] B. M. Wepster, *Rec. Trav. Chim.* 76, 335 (1957).
[10] J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Visser and B. M. Wepster, *Rec. Trav. Chim.* 77, 491 (1958).
[11] H. W. W. Ehrlich, *Acta Cryst* 13, 946 (1960).
[12] B. P. Stoicheff, *Canad. J. Phys.* 32, 339 (1954).

and phenyl rings) was assumed to be the same as the $C_1—C_1'$ distance in biphenyl (1·48 A).[13]

The van der Waals radius for the substituents and the literature references were those given by Pauling[14] and Sutton.[15]

As the calculations of the radius for COOH and $NHCO.CH_3$ substituents would be too arbitrary to be reliable, the geometrical angles for these substituents were not calculated.

The approximate coincidence, in many cases, of the "spectroscopic" and the geometrical angles given in Table 2, was taken as confirmation of the validity of the methods.

Influence of a Me *in position* 3 *on the oscillator strength*

The introduction of a Me group in the *para*-position of benzene derivatives showing an *ortho* effect generally gives bathochromic and hyperchromic effects.[16–18] But in 2,4,6-trimethylacetophenone the intensity of absorption falls.[19] As seen in Table 3,

TABLE 3. INFLUENCE OF THE GROUP CH_3 IN POSITION 3 ON THE SPECTRA OF 5-SUBSTITUTED 1-PHENYLPYRAZOLES

No	R_5	R_3	λ_{max} (Å)	$\Delta\lambda_{max}$	f	Δf
1	CH_3	H	2400		0·238	
				40		0·122
2	CH_3	CH_3	2440		0·360	
3	NH_2	H	2400		0·349	
				50		0·067
4	NH_2	CH_3	2450		0·416	
5	$NHCOCH_3$	H	2380		0·352	
				80		0·079
6	$NHCOCH_3$	CH_3	2460		0·431	
7	OH	H	2410		0·344	
				10		0·005
8	OH	CH_3	2420		0·349	
9	Cl	H	2380		0·151	
				40		0·089
10	Cl	CH_3	2420		0·240	

the introduction of a Me group at position 3 is always accompanied by the expected bathochromic and hyperchromic effects, but its value is dependent on the nature of the substituent at position 5.

Validity of the method of calculation of the "spectroscopic" angle of twist

Both Braude[5] and Klevens and Platt[8] calculate only steric effects that lead to a change in intensity (transition probability) of the characteristic absorption band but

[13] J. Dahr, *Indian J. Phys.* 7, 43 (1932).
[14] L. Pauling, *The Nature of the Chemical Bond* (3rd Edition) Ithaca, New York, Cornell University Press (1960).
[15] L. E. Sutton, *Tables of Interatomic Distances and Configurations in Molecules and Ions*, Special Publication No 11 of the Chemical Society, London (1958).
[16] G. D. Hedden and W. G. Brown, *J. Amer. Chem. Soc.* 75, 3744 (1953).
[17] R. F. Rekker and W. Th. Nauta, *Rec. Trav. Chim.* 73, 969 (1954); 80, 747 (1961).
[18] B. M. Wepster, *Rec. Trav. Chim.* 76, 357 (1957).
[19] E. A. Braude and F. Sondheimer, *J. Chem. Soc.* 3754 (1955).

not in the position of the absorption maximum (transition energy). In this work, changes in both λ_{max} and ε_{max} have been observed and hence the phenyl and parazole rings in both the ground and the excited states cannot be coplanar. This is also the case for biphenyls. In the literature, calculations of "spectroscopic" angles of twist for compounds showing considerable shifts in the λ_{max} are given, e.g. benzophenone[17] and nitroaniline[20] derivatives.

As the UV absorption curves of the phenylpyrazole derivatives resemble one another and are also similar to the spectrum of 1-phenylpyrazole itself, it follows that similar electronic transitions must be involved.

The results themselves, do not differ much from those obtained by the geometrical calculation or from those obtained for the same substituents in other compounds,[21,22] and, therefore, the method used is justified.

In verification, if the geometrical model constructed is representative of the real molecule, protonation in position 2 of the pyrazole nucleus should lead to steric hindrance and produce a twist of the phenyl ring. 1-Phenylpyrazole protonates only in concentrated solutions of strong acids; its UV spectrum in EtOH (λ_{max} 2530 A, ε_{max} 15100) suffers no change when it is dissolved in 10% perchloric acid. In 70% perchloric acid, there are considerable hypsochromic (λ_{max} 2400 A) and hypochromic (ε_{max} 12300) effects. This *ortho* effect probably explains the difficulty of protonation and, consequently, the fall in basicity of the pyrazole nucleus produced by the presence of a phenyl substituent in position 1.

The influence of the *ortho* effect on the fluorescence of the pyrazoles is also interesting. In the fluorescence of about 300 compounds of the pyrazole series,[23] it was observed that derivatives having substituents at both positions 1 and 5 do in general not fluoresce. This is reasonable since steric interaction would reduce conjugation of the substituent with the ring.[24]

*Dissociation constants of isomeric hydroxy-, amino- and carboxy-*1*-phenylpyrazoles, substituted in the pyrazole nucleus*

The pK_a for 1-phenylpyrazoles containing hydroxy-, amino- and carboxyl groups in positions 3, 4 and 5 of the pyrazole nucleus was determined. A comparison of these values obtained should reveal the effect of the nucleus on the substituent, depending upon its position.

As the extrapolation of pK_a values in non-aqueous solutions to the pK_a in water is not always reliable,[25] the pK_a values were determined in water-alcohol mixtures with diminishing concentration of alcohol from 50% to 0% using as many intermediate concentration as possible. The pK_a values obtained are given in Table 4 and they show that the dependence of pK_a upon the concentration of alcohol in the solvent differs for each of the three 1-phenyl-X-aminopyrazole isomers.

[20] H. H. Jaffé and M. Orchin, Ref. 1, page 414.
[21] O. Bastiansen, *Acta Chem. Scand.* 3, 408 (1949).
[22] R. Suzuki, *Bull. Chem. Soc. Japan* 32, 1340 (1959) and previous works by Suzuki.
[23] I. I. Grandberg, S. Tabak and A. N. Kost, *Zh. Obshch Khim.* 33, 525 (1963).
[24] W. West, *Chemical Applications of Spectroscopy* Vol. 9 of the *Technique of Organic Chemistry* (Edited by A. Weissberger) pp. 707 et seq. Wiley, New York (1956).
[25] A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*. Methuen, London and New York (1962).

In the case of 1-phenyl-3-aminopyrazole, the pK_a value decreases as the alcohol concentration falls from 50% to 20%, but after 20% it rapidly increases again, so that the value for pure water is equal to the value for 50% alcohol. For 1-phenyl-4-amino-pyrazole the pK_a value continues to increase as the alcohol concentration becomes less. For both 1-phenyl-5-aminopyrazole and 1-phenyl-3-methyl-5-aminopyrazole the pK_a values do not change significantly with a change in the alcohol concentration from 50% to 0%. The pK_a values for some hydroxypyrazoles and pyrazole-carboxylic acids with change in the composition of the solvent are also given in Table 4.

In all cases, 7, 8 or 9 points were measured on the titration curve and the pK_a calculated by the appropriate formulas, For 1-phenylpyrazole-4-carboxylic acid, a 10^{-3} M solution in 50% alcohol (sparingly soluble compound) was used; 8 pH values were measured on the titration curve and the 8 pK_a values calculated from these were continuously diminishing. From these values, the true pK_a value was extrapolated graphically using the Debye-Hückel equation $f_{\pm}^{1:1} = A\sqrt{I}$, where $f_{\pm}^{1:1}$ is the mean ionic activity coefficient for the uni-univalent electrolyte (the carboxylic acid) and I is the ionic strength. The equation $pK_a = pK_a^T - A\sqrt{I}$ then permits the calculation of the thermodynamic dissociation constant (in water) or, in this case, the true pK_a value in

TABLE 4. pK_a VALUES FOR 1-PHENYL-X-SUBSTITUTED-PYRAZOLES IN ETHYL ALCOHOL-WATER SOLUTIONS

Substituent and position	Concentration % of the alcohol in the alcohol–water solution					
	50	40	30	20	10	0
$3NH_2$[a]	2·97	2·71	2·54	2·50	2·59	2·96 ± 0·04
$4NH_2$[a]	4·38	4·44	4·49	4·54	4·60	4·80 ± 0·07
$5NH_2$[a]	3·11	3·12	3·14	3·14	3·14	3·14 ± 0·05[b]
$3CH_3$; $5NH_2$[a]	3·91	3·91	3·92	3·93	3·93	3·95 ± 0·05
3OH	—	—	8·28	—	7·79	7·57 ± 0·04
4OH	10·20	9·88	9·50	9·21	9·05	9·05 ± 0·06
5OH	—	—	—	—	—	6·56 ± 0·04
$3CH_3$; 5OH	—	—	—	—	—	7·16 ± 0·05
3COOH	—	—	—	—	—	3·60 ± 0·08
4COOH	5·60[c]	—	—	—	—	4·40 – 4·80[d]
5COOH	—	—	3·39	—	2·80	2·70 ± 0·06
$1C_5H_{11}$; $3CH_3$; $5NH_2$[a]	—	—	—	—	—	4·83 ± 0·07

[a] pK_a value of conjugated acid.

[b] Compound insoluble in water; the pK_a value in water is the result of extrapolation from the 5 preceding values.

[c] Result of graphical extrapolation.

[d] Result approximately calculated, on the assumption that the rate of change of the pK_a with the alcohol concentration is the same as for the 4-hydroxypyrazole.

50% alcohol (Table 4). The pK_a in water (4·40–4·80) was then calculated assuming that the rate of change of the pK_a with the change in alcohol concentration for the 1-phenyl-4-pyrazole carboxylic acid is approximately the same as for the 1-phenyl-4-hydroxypyrazole. This latter was determined with a sufficient degree of accuracy.

All further reasoning was based on the assumption that all the aminopyrazoles as well as 1-phenyl-3- and 1-phenyl-4-hydroxypyrazole exist in the hydroxy and amino forms and not in the imino or oxo forms, as was demonstrated by IR spectroscopy.[26]

Carboxylic acids. It is well established that position 4 in the pyrazole nucleus has a greater electron density than the corresponding 3 and 5 positions.[27,28] As the reactivity of the different positions in the pyrazole nucleus of 1-phenylpyrazole does not differ from that in pyrazole itself, the distribution of electron density between the positions 4 and 3 (or 5) is approximately maintained. Consequently, a greater +T effect of the pyrazole nucleus in 1-phenyl-4-pyrazole carboxylic acid, should lead to a decrease in the acidity as compared with the acidity of the 3 and 5 carboxylic acids.

In order to compare the acidities of the 3 and the 5 carboxylic acids, the *ortho* effect of the phenyl substituent in position 1 of the 1-phenyl-5-pyrazole carboxylic acid must be considered. As the carboxyl group on the phenyl ring causes a twist out of coplanarity, the presence of an *ortho* substituent (phenyl) in the 5-carboxylic acid decreases resonance in the free acid (the +T-effect of the aromatic system diminishes the acidity of the carboxyl directly bonded to it), and increases its acidity. This factor is less important for the anion, because of the negative charge of the carboxyl group.

Hence the 5-carboxylic acid must be a stronger acid than the 3-carboxylic acid. As we see from Table 4, the acidity increases in the order $4 < 3 < 5$.

Hydroxypyrazoles. Applying this reasoning to compounds like 1-phenyl-X-hydroxypyrazoles it follows that 1-phenyl-4-hydroxypyrazole should be less acidic (greater +I — effect of the nucleus) that the 3 and 5 isomers. Protons, as Hammond remarks, have very low steric requirement, but it is probably a steric factor that determines the relative acidity of the 5 isomer as compared to the 3 isomer. The molecule of 5-hydroxypyrazole will tend to become planar and will therefore lose a proton more easily that the 3 isomer; this leads to an increase in the acidity, and hence the same order of acidities as for pyrazole-carboxylic acids: $4 < 3 < 5$.

Aminopyrazoles. 1-Phenyl-4-aminopyrazole should be the more basic (less acidic) because of the +I — effect of the pyrazole nucleus. Comparing the basicity of the 3 and 5 isomers, it is seen that the *ortho* effect increases the basicity of the 1-phenyl-5-amino-pyrazole, probably not only by twisting the phenyl ring out of coplanarity (decrease in the conjugation of the system) but also, in part, by a similar twisting of the amino group. This can explain the order of decrease of basicity of the 1-phenyl-X-amino-pyrazoles: $4 > 5 > 3$.

The phenyl substituent decreases the basicity of the amino-group in the pyrazole nucleus by a resonance effect. This can be seen from Table 4, for 1-amyl-3-methyl-5-aminopyrazole, the pK_a value of which (in water; 4·83) is 1 unit greater than the pK_a value of the corresponding 1-phenyl compound (pK_a 3·95). As the steric effect of an alkyl group is very near to that of a phenyl group this decreased basicity is probably due to the resonance between the pyrazole and the phenyl rings, increasing the overall resonance with the amino-group. This fact confirms the possibility of increasing the basicity by twisting the phenyl ring out of coplanarity with the pyrazole ring.

EXPERIMENTAL

All substances were purified by recrystallization until chromatographically pure; liquids were redistilled under red. press until the physical constants corresponded to those in the lit.

[26] V. G. Vinokurov, V. S. Troitskaia, I. I. Grandberg and Iu. A. Pentin, *Zh. Obshch Khim.* **33**, 2597 (1963).

[27] L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

[28] R. D. Brown and L. Heffernan, *Austral J. Chem.* **13**, 49 (1960).

Spectra. All spectra were measures in a spectrophotometer SF-4 (USSR) in MeOH.

Dissociation constants. The pH values were determined in a potentiometer LP-58 (USSR) with glass-calomel electrodes, under a N_2 stream, at 20°.

All substances were titrated in 0·0025M solutions, except 1-phenylpyrazole 4-carboxylic acid, as indicated before.

In titration, 0·05N HCl was used for the amines and NaOH for hydroxypyrazoles and pyrazole carboxylic acids. The technique of calculation was based on Ref. 25.