Pyrazoles. XIII. Ionisation Constants and UV Spectra of Mono- and Dinitropyrazoles (1,2).

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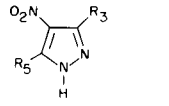
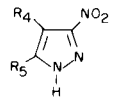
It has been shown previously that the 4-position in pyrazoles possesses a stronger electron releasing capacity than the 3- and 5-positions (4). This is corroborated by the calculated higher π electron density in the 4-position (5,6), and also by the formation of 4-substituted derivatives of pyrazoles upon electrophilic substitution (7). The large discrepancy of behaviour of the 3(5)- and 4-position on electrophilic substitution has been recently confirmed when we demonstrated that nitration of 3(5)-nitropyrazole easily and exclusively afforded 3(5),4-dinitropyrazole (1,8), whereas the latter compound cannot be obtained on further nitration of 4-nitropyrazole. In the same publication we offered a convenient and general method for the preparation of 3(5)-nitropyrazoles, and the synthesis of a series of 3(5)- and 4-nitro-, and of some dinitropyrazoles was reported.

In general the introduction of a *C*-nitro group in azoles strongly increases the ionisation constants (proton loss) and shifts the uv maxima to larger wavelengths, as was shown for nitroimidazoles (9,10) and for 4-nitropyrazoles (11,12). As the newly synthesized nitropyrazoles (compounds IV, VII-XI and XIII-XXI; see Chart I) have nitro groups in the *different* positions of the pyrazole ring, we determined the p*K*a values of these compounds. The spectrophotometric method was used.

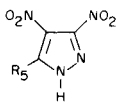
CHART I



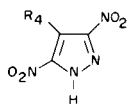
I R_3 H, R_5 H
II R_3 CH_3, R_5 H
III R_3 H, R_5 CH_3
IV R_3 $C(CH_3)_3$, R_5 H
V R_3 CH_3, R_5 $C(CH_3)_3$
VI R_3 H, R_5 $C(CH_3)_3$
VII R_3 C_6H_5, R_5 H
VIII R_3 *p*-NO_2-C_6H_4, R_5 H



IX R_4 H, R_5 H
X R_4 CH_3, R_5 H
XI R_4 C_2H_5, R_5 H
XII R_4 C_6H_5, R_5 H
XIII R_4 H, R_5 CH_3
XIV R_4 H, R_5 $C(CH_3)_3$
XV R_4 H, R_5 C_6H_5
XVI R_4 H, R_5 *p*-NO_2-C_6H_4



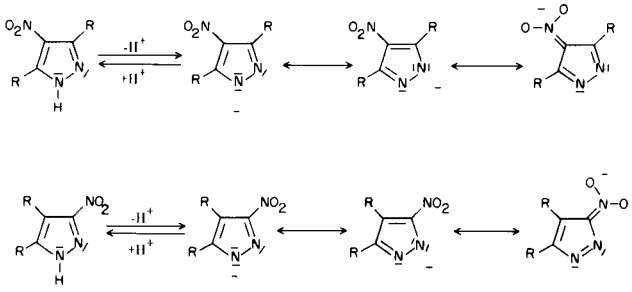
XVII R_5 H
XVIII R_5 CH_3
XIX R_5 C_6H_5



XX R_4 H
XXI R_4 C_2H_5

As was demonstrated previously, the uv spectrum of 4-nitropyrazole (I) consists of a single band with λ max at 275 nm (11). Introduction of additional substituents has but a small influence on the place of this band, whereas proton loss results in a large bathochromic shift. It appears now that the absorption bands of 3(5)-nitropyrazoles (compounds IX-XVI, see Table I), with λ max at 260-270 nm, also shift to larger wavelengths upon dissociation. From the uv spectra of the neutral molecules,

SCHEME I



the conjugate bases, and equilibrium mixtures in buffered solutions, we calculated the p*K*a values of the nitropyrazoles. Although the uv spectra of the dinitropyrazoles (compounds XVII-XXI) were more complex, the same spectrophotometric method could be used. The results, together with values from references 11 and 12, and the more relevant spectroscopic data, are summarized in Table I.

These data show that the p*K*a value found for 3(5)-nitropyrazole (IX) is similar to that of 4-nitropyrazole (9.81 and 9.67, respectively). Identical p*K*a values are also found for the isomer pairs 3(5)-methyl-4-nitropyrazole (II) and 4-methyl-3(5)-nitropyrazole (X) (p*K*a = 10.06 and = 10.10 respectively), and 4-nitro-3(5)-phenylpyrazole (VII) and 3(5)-nitro-4-phenylpyrazole (XII) (p*K*a = 9.11). These identical p*K*a values seem to contrast the aforesaid differences between the 4- and 3(5)-position in the pyrazole ring. Looking at the de-protonation equilibria (see Scheme I) however, provided that the more stable structure for the 3(5)-nitro compound is the 3-, as shown, the nitro groups are situated similarly, spatially as well as electronically, relative to the site of reaction.

TABLE I

pKa Values and Uv Spectra of Nitropyrazoles (λ max in nm)

Number	Pyrazole	in 0.05 N HCl λ max (log ε)		in 0.05 N NaOH λ max (log ε)		pKa	Δ pKa
I (a)	4-Nitro-		274 (3.92)		319 (4.06)	9.67	---
II (a)	3(5)-Methyl-4-nitro-		282 (3.91)		322 (4.08)	10.06	+0.39
III (a)	3,5-Dimethyl-4-nitro-		284 (3.93)		321 (4.10)	10.65	+0.98
IV	4-Nitro-3(5)-*tert*-butyl-		288 (3.86)		326 (4.04)	10.27	+0.60
V (b)	3(5)-Methyl-4-nitro-5(3)-*tert*-butyl-		288 (3.87)		323 (4.03)	10.92	+1.25
VI (b)	4-Nitro-3,5-di-*tert*-butyl-		278 (3.73)		327 (4.06)	11.29	+1.62
VII	4-Nitro-3(5)-phenyl-	±225 (e),	280 (3.83)	±230 (e),	329 (3.95)	9.11	-0.56
VIII (c)	4-Nitro-3(5)-(*p*-nitrophenyl)-	±300 (s,e),	277 (4.0)	307 (4.0, e),	±330 (s)	8.46	-1.21
IX	3(5)-Nitro-		261 (3.79)		316 (3.86)	9.81	---
X	4-Methyl-3(5)-nitro-		266 (3.80)		318 (3.90)	10.10	+0.29
XI	4-Ethyl-3(5)-nitro-		269 (3.77)		319 (3.90)	10.09	+0.28
XII (c,d)	3(5)-Nitro-4-phenyl-	±225 (e),	268 (3.69)	±230 (e),	325 (3.83)	9.11	-0.70
XIII	3(5)-Methyl-5(3)-nitro-		265 (3.82)		321 (3.84)	10.25	+0.44
XIV	3(5)-Nitro-5(3)-*tert*-butyl-		264 (3.86)		324 (3.89)	10.35	+0.54
XV	3(5)-Nitro-5(3)-phenyl-	254 (4.34, e),	±270 (s)	258 (4.23, e),	315 (3.91)	8.75	-1.06
XVI (c)	3(5)-Nitro-5(3)-(*p*-nitrophenyl)-		306 (4.25)		346 (4.27)	7.59	-2.23
XVII	3(5),4-Dinitro-		267 (3.73)		312 (3.77)	5.48	---
XVIII	3(5)-Methyl-4,5(3)-dinitro-		273 (3.77)		317 (3.86)	6.35	+0.87
XIX (c)	3(5),4-Dinitro-5(3)-phenyl-	±225 (e),	±265 (s)	±230 (e),	340 (3.78)	5.09	-0.39
XX	3,5-Dinitro-	244 (4.09),	±270 (s)	280 (4.03),	±305 (s)	3.14	---
XXI	4-Ethyl-3,5-dinitro-	254 (4.10),	±280 (s)	290 (4.10),	±310 (s)	3.80	+0.66

(a) See reference 11. (b) See reference 12. (c) Due to poor solution measured in 2.5% methanol. (d) A freshly prepared solution was measured; the uv spectrum changed upon standing (*cf.* reference 13). (e) Ascribed to a "phenylpyrazole" transition; see text. (s) Shoulder.

Therefore, in the case of this acid-base equilibrium the effects of the two nitro groups may be identical. On the other hand, for the dinitropyrazoles a large difference in p*K*a values is found between the 3,5-dinitro- and the 3(5),4-dinitro derivatives. 3,5-Dinitropyrazole (XX) has a markedly low p*K*a value (3.14), whereas the 3(5),4-dinitro isomer XVII has a p*K*a of 5.48. This difference can be explained in terms of steric interactions. In the case of the 3(5),4-dinitro compound, coplanarity with the pyrazole ring of the two nitro groups, a condition for maximal resonance in the conjugate base, is impeded.

The effect of additional substituents on the ionisation constants of nitropyrazoles can be expressed in Δ p*K*a values, calculated by substraction of the p*K*a value of the corresponding parent nitro- or dinitropyrazole from the p*K*a value of the substituted derivative (see Table I). These Δ p*K*a values express the change in p*K*a value resulting from both the electronic and the steric interactions of the substituent and the nitropyrazole.

It has been shown formerly that the introduction of *ortho* methyl groups, or even of one *ortho tert*-butyl group, has little or no steric effect on the uv spectra and the ionisation constants of 4-nitropyrazoles (11,12). It appears that this does not hold good anymore for the methyl group in 3(5)-methyl-4,5(3)-dinitropyrazole (XVIII), where a much higher Δ p*K*a value (+0.87) is found than for methyl derivatives of 4-nitro- and 3(5)-nitropyrazole (compounds II, X, and XIII; Δ p*K*a = +0.39, = +0.29, and = +0.44 respectively). This enhanced effect of three adjacent substituents in the pyrazole ring is another example of the occurrence in a 5-membered aromatic ring system of the buttressing effect well known from the chemistry of 1,2,3-trisubstituted benzene derivatives (13,14). Comparison of the ionisation constants of 4-nitro-3(5)-*tert*-butylpyrazole (IV) and 3(5)-nitro-5(3)-*tert*-butylpyrazole (XIV) confirms that no appreciable steric hindrance is exercised by one *ortho tert*-butyl group, for similar Δ p*K*a values are found (+0.60 and +0.54, respectively), and these can be ascribed to the inductive effect of the *tert*-butyl group. On the other hand, the large increase in p*K*a value on introduction of two *tert*-butyl groups in 4-nitropyrazole (compound VI, Δ p*K*a = +1.62) does indeed indicate the occurrence of steric hindrance. In this case, the relatively low values of λ max and log ε in the uv spectrum of VI also indicate such a steric effect. With the use of the Braude equation $\epsilon = \epsilon_o \cos^2 \theta$ (15), designed to calculate angles of twist from coplanarity of sterically hindered conjugated systems such as *ortho* substituted nitrobenzenes (16), we found an angle of twist of 37° for the pyrazole ring and the nitro group in 3,5-di-*tert*-butyl-4-nitropyrazole (VI) (17). However, no such steric effect is found for the conjugate base of VI, which has a uv spectrum very similar to the uv spectra of the conjugate bases of the unhindered compounds I-V. Possibly, in the anion of VI a conformation is favored where a maximum of coplanarity of pyrazole ring and nitro group is realized at the expense of the usual bond angles between substituents in pyrazoles.

Analogous to the effect of the introduction of substituents into the *ortho* positions of biphenyl, both Dal Monte (18) and Tensmeyer (19) and their coworkers showed that introduction of substituent groups in the adjacent positions of both rings in phenylpyrazoles results in steric inhibition of resonance between the pyrazole and phenyl rings. It may be expected therefore that in the case of adjacent nitro and phenyl groups in pyrazole, both substituents will, more or less, turn out of the pyrazole plane. The Δ p*K*a values found for 3(5)-nitro-4-phenyl-, 3(5),4-dinitro-5(3)-phenyl-, and 4-nitro-3(5)-phenylpyrazole (compounds XII, XIX, and VII; Δ p*K*a = -0.70, = -0.39, and = -0.56, respectively) do indeed indicate steric hindrance. The steric and electronic effects of the phenyl group have opposite signs, but from the fact that for 3(5)-nitro-5(3)-phenylpyrazole (XV), a compound with no steric effects at all, a much larger Δ p*K*a value is found (Δ p*K*a = -1.06) we may conclude that steric effects do operate in the former compounds. The uv spectrum of XV consists of a high intensity band at 254 nm with a shoulder at *ca.* 270 nm. Upon deprotonation the first band shifts to 258 nm, while the second band shifts to 315 nm. Apart from minor changes in place and intensity, these spectra can be considered as superpositions of the spectra of 3(5)-nitropyrazole (the neutral molecule has λ max at 261 nm, the anion at 316 nm; see Table I) and 3(5)-phenylpyrazole (λ max = 248 nm; log ε = 4.14 (13)). It is known that the uv spectrum of 3(5)-phenylpyrazole is relatively insensitive to the *p*H of the solution (18). A significant hypsochromic shift of the "phenylpyrazole" band is found in both the neutral molecules and conjugate bases of VII and XIX, which in these cases indicates twisting of the bond between the phenyl and pyrazole rings. The 280 nm band in VII can be assigned to the 4-nitropyrazole transition, and the small hypochromic shift of this band as compared to this band in compounds I-V points at a deflection from coplanarity bewteen the nitro group and the pyrazole ring. The idea of both a twisted nitro group and a twisted phenyl group is confirmed by the uv spectrum of 3(5)-nitro-4-phenylpyrazole (XII), where the 225 nm band can be assigned to a blue-shifted 4-phenylpyrazole band (13) and the 268 nm band corresponds with the 261 nm band of 3(5)-nitropyrazole, while the lower intensity of the "nitropyrazole" band, as compared to compounds IX-XI, may be due to a slight twisting of the nitro group. The difference between the Δ p*K*a values of 4-nitro-3(5)-(*p*-nitrophenyl)-pyrazole (VIII) and the isomeric 3(5)-nitro-5(3)-(*p*-nitro-

phenyl)pyrazole (XVI) (-1.21 and -2.23, respectively) can also be explained by assuming steric inhibition of resonance in the first compound. The uv spectrum of VIII consists of a band at 277 nm with a shoulder at *ca.* 300 nm. In view of the behaviour of these bands upon deprotonation (see Table I), the main absorption band can be ascribed to a 4-nitropyrazole transition, while the shoulder is supposedly a blue-shifted 3(5)-(*p*-nitrophenyl)-pyrazole band (20).

In agreement with the behaviour of other azoles (21,22), the ionisation constant of nitropyrazoles appears to be very sensitive upon further substitution. Notwithstanding the limitations of using p*K*a values for interpreting resonance and steric effects, within the series of 3(5)- and 4-nitro pyrazoles the differences found in p*K*a values can be interpreted in terms of electronic and steric interactions. In addition, these interpretations are supported by the uv spectral data.

EXPERIMENTAL

Materials.

The syntheses of compounds IV, VII-XI, and XIII-XXI are described in reference 1; a sample of 3(5)-nitro-4-phenylpyrazole (XII) was kindly provided by Dr. W. E. Parham, University of Minnesota.

Measurements.

All spectra were taken at room temperature with a Perkin-Elmer 137 uv spectrophotometer. The spectra of the neutral molecules were determined in aqueous hydrochloric acid (0.05 *N*), those of the conjugate bases were determined in aqueous sodium hydroxide (0.05 *N*). The spectra of the equilibrium mixtures of the neutral molecule and its conjugate base were measured in buffer solutions. We used buffer solutions as described in "Handbook of Chemistry and Physics," (23) (*p*H 6.0 to 10.5) and in "International Critical Tables" (24) (*p*H 2.9 to 6.0). From the uv spectra p*K*a values were calculated using optical densities at wave lengths near λ max of the neutral molecule and of its conjugate base, depending upon the shape of the spectra. No corrections were applied to obtain thermodynamic ionisation constants.

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