Kinetics and Mechanism of Hydrolysis of the Amidinating Agent, 1-(N^1-Benzoylamidino)-3,5-dimethylpyrazole

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The kinetics of hydrolysis of 1-(N^1-aroylamidino)-3,5-dimethylpyrazoles (3) have been studied at high and low pH in 24·5% methanol at 30°. At high pH (>11) a specific base catalysed elimination occurs with the formation of *N*-cyanoarenecarboxamides (which, stabilized as the anions, do not undergo further reaction) and 3,5-dimethylpyrazole. Variation of the *N*-aroyl substituent (in 1·0M-HO^- in water) gave $\rho = +0·45$. In neutral solution (3) is unreactive but acid hydrolysis results in direct formation of aroylureas. This reaction is specifically acid catalysed and the apparent pK_a required to fit the kinetic data [1·40 in 24·5% methanol for the unsubstituted compound (3; X = H)] is the same as the measured spectrophotometric pK_a. Data for the variation of the *N*-aroyl substituent are also presented and are consistent with a mechanism involving water attack on protonated (3). Kinetic data are also presented for *N*-benzoyl-*S*-methylisothiourea which also shows a rapid base-catalysed elimination (reflecting the improved leaving group, MeS^-, relative to pyrazole anion) to give *N*-cyanobenzamide.

A NUMBER of structurally related reagents have been used for the amidination of the terminal amino-group of the amino-acids ornithine, lysine, and glutamic acid, *e.g.* *O*-methylisoureas (1; Y = OMe), *S*-methylisothioureas (1; Y = SMe), and amidino-3,5-dimethylpyrazole (1; R^2 = H, Y = 3,5-dimethylpyrazol-1-yl).[1-4]

Under certain conditions, the α-amino-group of amino-acids which have no aliphatic side chain is also readily converted to a guanidino-group using these reagents. The related nitro-derivative 3,5-dimethyl-1-(N^1-nitroamidino)pyrazole (1; $R^2 = NO_2$, Y = 3,5-dimethylpyrazol-1-yl) has also been used to introduce a protected

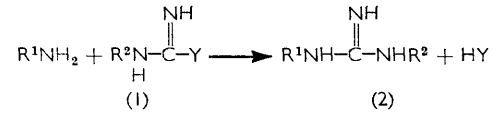
[1] L. C. Allen and T. Viswanatha, *Canad. J. Biochem.*, 1970, **48**, 1189; Y. Fujita, *Bull. Chem. Soc. Japan*, 1959, **32**, 439.

[2] W. H. Johnson, H. D. Law, and R. O. Studer, *J. Chem. Soc.* (*C*), 1971, 748; S. N. Vinogradov and H. A. Harbury, *Biochemistry*, 1967, **6**, 709.

[3] A. F. S. A. Hubeeb, *Biochem. Biophys. Acta*, 1964, **93**, 533; R. A. Henry, R. C. Makosky, and G. B. L. Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4743.

[4] L. A. Cohen, *Ann. Rev. Biochem.*, 1968, **37**, 695.

arginine function during peptide synthesis.[2] Such nitroamidination has proved a useful technique to modify chemically protein structures since it replaces a



positively charged ammonium group by a non-basic nitroguanidino-group.

While it has been suggested [1] that *O*-methylisourea is the least reactive of the reagents (and thus most selective) there is little kinetic evidence available to distinguish between the possible modes of reaction, *e.g.* substitution may occur *via* an addition–elimination mechanism or by a prior elimination. It is of interest to discover the optimum conditions (pH, *etc.*) for the reaction and whether the various reagents (1) utilize a common reaction pathway. As standard substrates we have initially chosen the benzoyl derivatives (R^2 = ArCO, Y = 3,5-dimethylpyrazol-1-yl), since their reactions are amenable to study over a wide pH range and the products of hydrolysis do not undergo subsequent reaction.

TABLE 1

Pyrazoles (3)

X	M.p. (°C)	Found (%) C	H	N	Formula	Requires (%) C	H	N
H	113—114	64·9	5·95	23·15	$C_{13}H_{14}N_4O$	64·4	5·8	23·1
p-Br	144—145	48·9	4·2	17·8	$C_{13}H_{13}BrN_4O$	48·6	4·05	17·45
p-Cl	140—141	56·8	4·8	20·1	$C_{13}H_{13}ClN_4O$	56·4	4·7	20·3
p-MeO	115—117	61·3	5·8	20·2	$C_{14}H_{16}N_4O_2$	61·8	5·9	20·6
p-NO_2	188—189	54·0	4·5	24·0	$C_{13}H_{13}N_5O_3$	54·35	4·5	24·4
p-Me	130·5—131·5	65·15	6·45	22·3	$C_{14}H_{16}N_4O$	65·6	6·25	21·9
3,5-$(NO_2)_2$	244—245	46·6	3·55	25·2	$C_{13}H_{12}N_6O_5$	47·0	3·6	25·3
o-Me	93—94	65·25	6·2	21·8	$C_{14}H_{14}N_4O$	65·6	6·25	21·9
m-NO_2	164—164·5	54·5	4·6	24·0	$C_{13}H_{13}N_5O_3$	54·35	4·5	24·4
m-Br	109·5—110	48·5	4·2	17·0	$C_{13}H_{13}BrN_4O$	48·6	4·05	17·4

TABLE 2

Cyanamides (4)

X	M.p. (°C)	Found (%) C	H	N	Formula	Requires (%) C	H	N
H	143—144	65·6	4·1	19·3	$C_8H_6N_2O$	65·75	4·1	19·2
p-Br	168—169	42·4	2·25	12·3	$C_8H_5BrN_2O$	42·7	2·2	12·4
p-Cl	157—158 (decomp.)	53·3	2·9	15·3	$C_8H_5ClN_2O$	53·2	2·8	15·5
m-Br	129—130	42·8	2·4	12·6	$C_8H_5BrN_2O$	42·7	2·2	12·4
p-Me	149—150 (decomp.)	67·8	5·0	17·35	$C_9H_8N_2O$	67·5	5·0	17·5

EXPERIMENTAL

1-(N^1-*Benzoylamidino*)-3-5-*dimethylpyrazole* (3; X = H).—4N-Nitric acid (125 ml) was added to a slurry of aminoguanidinium hydrogen carbonate (68 g) in water (150 ml) over 30 min with stirring. The mixture was heated to 60° to obtain a solution and complete the evolution of carbon dioxide. On cooling (ice); aminoguanidinium nitrate (61 g, 90%) crystallised, m.p. 137—140°. On recrystallization from ethanol it had m.p. 143—144° (lit.,[5] m.p. 144°). The nitrate (13·7 g) was dissolved in 80% aqueous ethanol (90 ml), acetylacetone (10 g) was added, and the solution refluxed for three hours. On cooling, 1-amidino-3,5-dimethylpyrazole nitrate (9·1 g, 90%) separated, m.p. 160—164°. Recrystallization from ethanol–diethyl ether raised the m.p. to 167—168° (lit.,[6,7] 168°). The pyrazole nitrate (20·1 g) was dissolved in 10% aqueous sodium hydroxide (80 ml) and benzoyl chloride (14·0 g) in diethyl ether (20 ml) was added. The mixture was stirred for 30 min until the ether had evaporated and an oily solid (21·8 g, 90%) had separated. On recrystallization from absolute ethanol this yielded 1-(N^1-benzoylamidino)-3,5-dimethylpyrazole, m.p. 113—114° (lit.,[7] 111—112°). The other 1-(N^1-aroylamidino)pyrazoles were prepared by the same general method. Analytical and m.p. data are summarised in Table 1.

3,5-Dimethylpyrazole was prepared by the method of Wiley and Hexner [8] and had m.p. 103—105°.

N-*Cyanobenzamide*.[9]—Cyanamide (4·2 g) was dissolved in 10% aqueous sodium hydroxide solution and benzoyl chloride (14·0 g) in diethyl ether (20 ml) was added. The solution was stirred for 30 min and then acidified with hydrochloric acid at 0°. The *benzoyl derivative* (90%) separated, m.p. 137—138°, and on recrystallisation from water had m.p. 142·5—143° (Found: C, 65·6; H, 4·1; N, 19·3. $C_8H_6N_2O$ requires C, 65·75; H, 4·1; N, 19·2%). The same material was also prepared by the method of Ambelang and Johnson.[10] Several substituted *N*-cyanobenzamides were also prepared in a similar manner (see Table 2 for analytical and m.p. data).

Hydrolysis of 1-(N^1-*Benzoylamidino*)-3,5-*dimethylpyrazole*.—(*a*) *Under acidic conditions*. The benzoylamidinopyrazole (2·42 g, 0·01 mol) was dissolved in ethanol (20 ml) and 5N-hydrochloric acid (10 ml) was added. The solution

[5] J. Thiele, *Annalen*, 1892, **270**, 26.
[6] J. Thiele and E. Dralle, *Annalen*, 1898, **302**, 294.
[7] F. L. Scott and J. Reilly, *J. Amer. Chem. Soc.*, 1952, **74**, 4562.
[8] R. H. Wiley and P. E. Hexner, *Org. Syntheses*, 1951, **31**, 43.
[9] W. Buddeus, *J. prakt. Chem.*, 1890, **42**, 84.
[10] J. C. Ambelang and T. B. Johnson, *J. Amer. Chem. Soc.*, 1939, **61**, 632.

was refluxed for 1 h and on cooling benzoylurea (1·43 g, 87%), m.p. 206—208° (lit.,[7] m.p. 208—210°) separated. On evaporation of the filtrate *in vacuo* the solid which remained was extracted with diethyl ether to give a further crop (0·14 g) of benzoylurea. The residue was dissolved in water (5 ml), basified with sodium hydroxide, and the solvent was removed *in vacuo*. Extraction of the solid which remained gave 3,5-dimethylpyrazole (0·88 g, 92%).

Hydrolysis under acidic conditions of other aroylamidinopyrazoles also yielded the corresponding aroylureas in good yield. M.p. and analytical data for these compounds are listed in Table 3.

TABLE 3

Ureas (5)

		Found (%)				Requires (%)		
X	M.p. (°C)	C	H	N	Formula	C	H	N
H	207—208	58·4	4·9	17·05	$C_8H_8N_2O$	58·5	4·9	17·1
p-Br	259—260	39·3	2·9	11·4	$C_8H_7BrN_2O_2$	39·5	2·9	11·5
p-Cl	252—253	48·3	3·7	14·5	$C_8H_7ClN_2O_2$	48·4	3·5	14·1
p-MeO	226—227	55·5	5·4	14·4	$C_9H_{10}N_2O_3$	55·7	5·15	14·4
p-NO_2	251—252	45·8	3·4	20·4	$C_8H_7N_3O_4$	45·9	3·35	20·1
p-Me	245—246	60·8	5·7	15·9	$C_9H_{10}N_2O_2$	60·7	5·6	15·7
o-Me	214—215	60·6	5·4	15·9	$C_9H_{10}N_2O_2$	60·7	5·6	15·7
m-NO_2	195	46·0	3·4	19·95	$C_8H_7N_3O_4$	45·9	3·35	20·1
m-Br	202—203	39·4	2·7	11·7	$C_8H_7BrN_2O_2$	39·5	2·9	11·5

(*b*) *Under basic conditions.* The benzoylamidinopyrazole (2·42 g, 0·01 mol) was dissolved in ethanol (20 ml) at 60°. 1N-Sodium ethoxide (10 ml) was added and the solution refluxed for 3 h. The solvent was evaporated *in vacuo*; extraction with ether of the solid which remained gave 3,5-dimethylpyrazole (0·89 g, 93%). The residue was dissolved in water and acidified with concentrated hydrochloric acid to precipitate *N*-cyanobenzamide (1·30 g, 90%).

N-Benzoyl-S-methylisothiourea.— *S*-Methylthiouronium-sulphate (2·78 g) was dissolved in 5% sodium hydroxide solution (32 ml) and benzoyl chloride (2·8 g) in ether (20 ml) was added. The mixture was stirred vigorously for 30 min until the ether had evaporated. The *isourea* (2·33 g, 60%) obtained was recrystallized from ethanol, m.p. 111—112° (Found: C, 56·1; H, 5·3; N, 14·4. $C_8H_{10}N_2O_5$ requires C, 55·7; H, 5·15; N, 14·4%). The *hydrochloride* (prepared by the addition of concentrated hydrochloric acid to a ethanolic solution of *N*-benzoyl-*S*-methylisothiourea) had m.p. 222—223° (Found: C, 47·0; H, 4·9; N, 12·2. $C_9H_{11}ClN_2OS$ requires C, 46·85; H, 4·8; N, 12·0%).

Kinetic Measurements.—The solvent used for the kinetic experiments was (unless otherwise stated) 24·5% AnalaR methanol prepared by diluting 250 ml methanol to 1 l with twice distilled water at 30°. The ionic strength was maintained at 1·0 throughout using potassium chloride. Standard solutions of 1·0M-potassium hydroxide and 1·0M-hydrochloric acid in 24·5% methanol were prepared using M and B Volucon standard ampoules, and the buffer solutions were prepared by mixing appropriate amounts of these solutions.

In all cases the rates of hydrolysis were followed spectrophotometrically by recording the decrease in optical density with time at a suitable wavelength. In the pH regions where the solutions were self-buffered by the presence of acid or base a Unicam SP 800 instrument was used, while a Cary 14 machine combined with a Radiometer pH-stat (which has been previously described) [11] was used otherwise. Reaction was initiated by the addition of one drop of a concentrated solution (5×10^{-3}—10^{-2}M) of the substrate in dioxan or acetonitrile. In all cases good pseudo-first-order plots were obtained and rate constants were obtained from these graphically using either experimental infinity values or by the method of Guggenheim.

pK_a *Determinations.*—The acid and base dissociation constants of 1-(N^1-benzoylamidino)-3,5-dimethylpyrazole and of *N*-cyanobenzamide were determined at 30° in 24·5% methanol [μ = 1·0 (KCl)] spectrophotometrically at suitable wavelengths (see Figures 1—3). The buffer solutions were the same as used in the kinetic experiments. Theoretical titration curves were plotted using equation (1), and the observed optical density *vs.* pH plot was compared with the theoretical titration curve to give the pK_a. At each optical density measurement at high and at low pH, some hydrolysis of the substrate (3) took place during a determination. In these cases the optical density *vs.* time curve was extrapolated back to zero time to give the optical density of the unhydrolysed substrate.

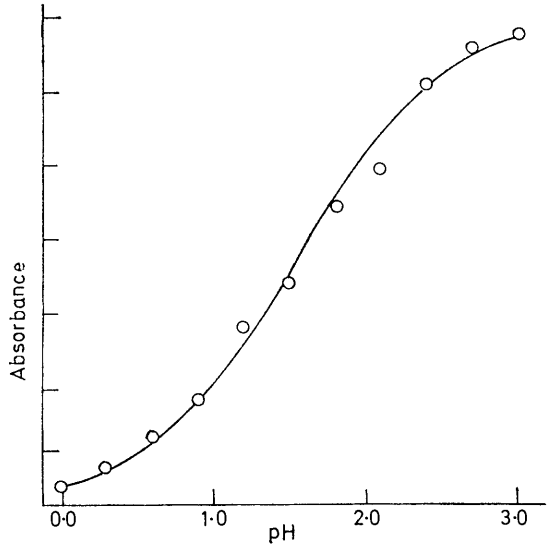


FIGURE 1 Plot of the observed optical density of pyrazole (3; X = H) at 290 nm *vs.* pH in 24·5% methanol at 30°

$$O.D._{obs} = O.D._{max.} \frac{K_a}{a_H + K_a} \quad (1)$$

[11] F. Kurzer, *J. Chem. Soc.*, 1951, 1258.

RESULTS AND DISCUSSION

The rates of hydrolysis of the pyrazole (3; X = H) have been investigated at low pH (<3·0) and at high pH (>11·0). At intermediate pH values the rate of hydrolysis was too slow to permit convenient measurement. The solvent used was 24·5% methanol; this was the highest aqueous concentration which permitted

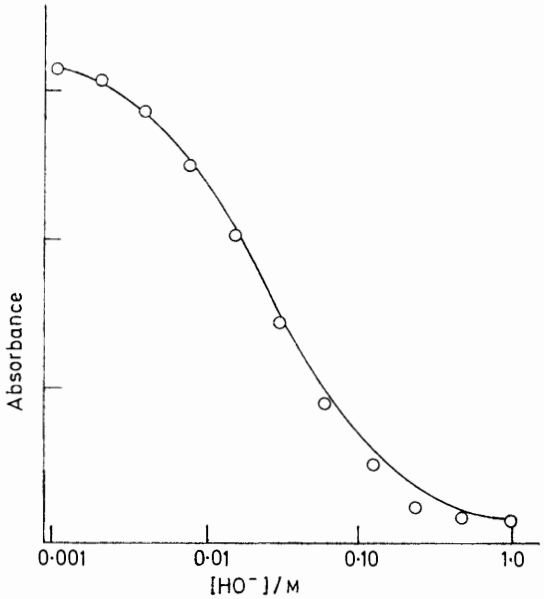


FIGURE 2 Plot of the observed optical density of pyrazole (3; X = H) at 290 nm *vs.* pH in the basic region in 24·5% methanol at 30°

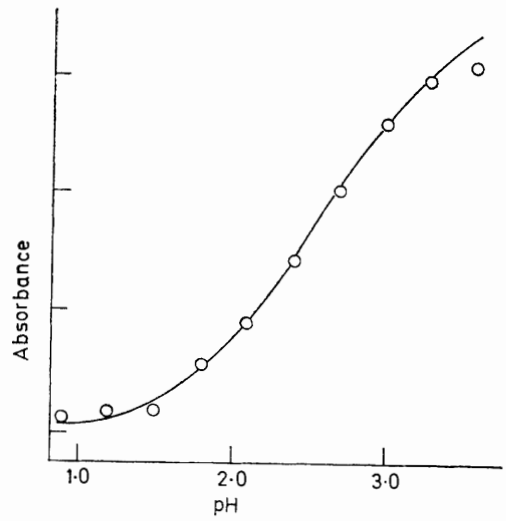
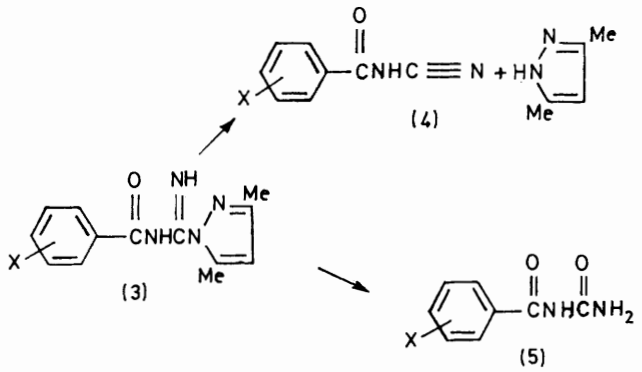


FIGURE 3 Plot of the observed optical density of cyanamide (4; X = H) at 250 nm *vs.* pH in 24·5% methanol at 30°

the complete solution of the substrates over the entire pH range.

Acid Hydrolysis.—The rate constants obtained for the hydrolysis of (3; X = H) over the pH range 0—3 at 30° are listed in Table 4. It is seen that at higher pH the rate increases rapidly with decreasing pH but eventually forms a pH-independent plateau at pH *ca.* 0. These kinetic data are best correlated in terms of an



empirical equation (2) (*i.e.* specific acid catalysis of hydrolysis). The value of pK_a which best fits these

TABLE 4

Observed pseudo-first-order rate constants for the hydrolysis at 30° of pyrazole (3; X = H) in acidic solution

pH	$10^4 k_{obs}/s^{-1}$	pH	$10^4 k_{obs}/s^{-1}$
0·00	5·12	1·80	1·81
0·30	5·39	2·10	1·19
0·60	5·20	2·40	0·68
0·90	4·08	2·70	0·34
1·20	3·97	3·00	0·16
1·50	2·82		

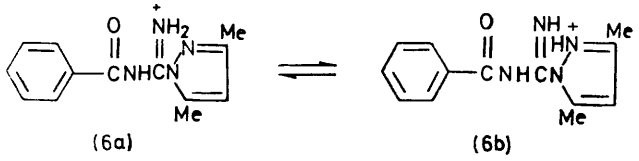
data at 30° is 1·40 (=pK_{a_1}); $k_1 = 3{\cdot}0 \times 10^{-4}$ s^{-1}. The product formed in this region is the corresponding

$$k_{obs} = k_1 a_H/(K_{a_1} + a_H) \qquad (2)$$

N-benzoylurea (5; X = H). This was shown both by the identity of the spectra obtained on hydrolysis of (3) in acidic solution with an authentic sample of (5) and by the isolation of (5) in good yield on the hydrolysis of (3) on a larger scale (but under the same conditions as used for the kinetic experiments). An initial elimination reaction [to form *N*-cyanobenzamide (4)] followed by rapid hydration was ruled out as an alternative pathway by the following observations. (a) The hydration of (4; X = H) was relatively slow at 30° in 24·5% methanol in acidic solution. Thus repetitive scans of the u.v. spectrum of the cyanamide (4) were unchanged under these conditions at pH 2 after 12 h. (b) Conversion of (3) to (5) in the acidic pH region was characterised by tight isosbestic points at 240 and 310 nm. The cyanamide (4; X = H) has a characteristic absorption at 241 nm of sufficient intensity to disturb these isosbestic points if it was an intermediate product of hydrolysis. Therefore conversion of (3) to (5) is direct.

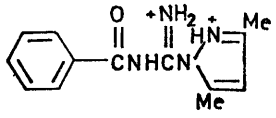
In the same pH region (*i.e.* between 3 and 0) the u.v. spectrum of the unchanged starting material (3) shows a change with pH. By measuring the variation in optical density with pH over the range 0·0—3·0 (see Figure 1) the sigmoid shaped curve obtained which best fits the data has pK_a 1·40, *i.e.* exactly the same

value as used to correlate the kinetic data. This provides good evidence that the protonated species which gives rise to the change in spectrum at low pH is also the reactive form of (3). This is most likely the monoprotonated species (6). The rate-determining step



(6a) (6b)

would then involve attack by water [on (6b)] with the neutral pyrazole as the leaving group. The spectral change at low pH could also conceivably be the result of the formation of a reactive diprotonated species [as (7)]. This however is unlikely since the monoprotonated



(7)

form should have a pK_a value somewhere between 1·40 and the pK_a of guanidine itself (*i.e.* 13·6 at 25°). Repetitive scans of the u.v. spectrum over the pH range 11—3 show no change in the spectrum of (3). Moreover since the pK_a for the second protonation of guanidine has been calculated [12] as −11 it is extremely unlikely that (3) should be diprotonated at pH 1·0. Therefore the measured pK_a of 1·40 is best associated with (6). It is interesting to note the profound effect that the combined presence of the benzoyl group and the incorporation of one of the nitrogens in a heterocyclic ring have on lowering the pK_a of the guanidino-group in (3) from *ca.* 13·6 (for guanidine itself) to 1·40. The pK_a of 1-amidino-3,5-dimethylpyrazole under the same conditions is 5·0. Therefore the major base weakening effect on the guanidino-group is caused by the involvement of one of the (guanidino) nitrogen atoms in the heterocycle.

At pH 0·0, a plot of the observed rate constants (Table 5) for (3; X = *p*-Me, -MeO, -H, -NO_2, and -Br and *m*-Br and -NO_2) *vs.* the corresponding σ values [13] is distinctly curved (Figure 4). Electron-donating substituents Me and MeO have a relatively larger deactivating effect (ρ for *p*-MeO, *p*-Me, and H *ca.* +0·95), while the rates of hydrolysis of the electron-withdrawing substituted compounds are almost independent of the substituent (ρ = +0·33 for X = H, *p*-Br, *m*-Br, *p*-NO_2, *m*-NO_2). This is readily explicable in terms of the pH profile for (3; X = H) (Table 5). At $[H^+]$ = 1·0M, the rate of hydrolysis is almost in the ' plateau ' region. Electron-donating substituents would tend to increase the pK_a of the conjugate base of (3), with the result that at $[H^+]$ = 1·0M, the measured rate of hydrolysis for these compounds would also be decomposition of the protonated species. When (3) carries an electron-withdrawing substituent (*e.g.* *p*-NO_2) the pK_a of the protonated substrate is lowered; this has the result that the hydrolytic rate at $[H^+]$ = 1·0M is no longer the plateau rate [k_1 in equation (2)], but a composite factor involving the pK_a of the substrate and k_1. Since a given substituent would be expected to act in opposite ways on k_1 and pK_a (an electron-withdrawing substituent would tend to increase k_1 and decrease pK_a), the resultant effect of these substituents on the overall rate is small.

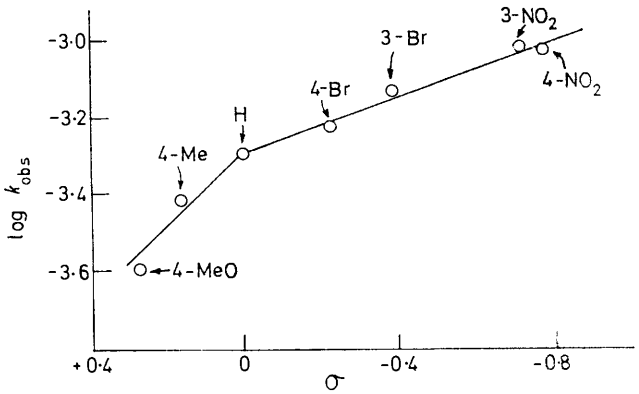


FIGURE 4 Plot of log of the observed rate constants *vs.* σ for the hydrolysis of (3) in 24·5% methanol containing 1·0M-hydrochloric acid at 30°

TABLE 5

Observed pseudo-first-order rate constants for the hydrolysis of pyrazoles (3) at 30° in 24·5% methanol (μ = 1·0) at (a) $[H^+]$ = 1·0M, (b) $[HO^-]$ = 1·0M

	X	H	4-Br	3-Br	3-NO_2	4-NO_2	4-MeO	4-Me
(a)	$10^4k_{obs}/s^{-1}$	5·12	6·02	7·35	9·60	9·60	2·56	3·87
(b)	$10^4k_{obs}/s^{-1}$	2·53	3·73	3·65	5·79	3·62	2·26	2·54

TABLE 6

Observed pseudo-first-order rate constants for the hydrolysis at 30° of pyrazole (3; X = H) and of *N*-benzoyl-*S*-methylisothiourea in basic solution

$[HO^-]$/M	10^4k_{obs}(3; X = H)/s^{-1}	10^3k_{obs}(9)/s^{-1}
1·0	4·71	
5 × 10^{-1}	5·14	79
2·5 × 10^{-1}	6·91	48
1·25 × 10^{-1}	7·90	25
6·25 × 10^{-2}	8·08	14
3·12 × 10^{-2}	7·83	6·6
1·56 × 10^{-2}	3·55	2·5
7·81 × 10^{-3}	1·84	
3·91 × 10^{-3}	0·81	
1·95 × 10^{-3}	0·43	
9·76 × 10^{-4}	0·40	

Base Hydrolysis.—The hydrolysis of (3) also occurs at high pH but the dependence of observed rate constants on pH (see Table 6) in this region is more complex.

[12] G. Williams and M. C. Hardy, *J. Chem. Soc.*, 1953, 2560.
[13] A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J.C.S. Perkin II*, 1972, 44.

The observed rate of hydrolysis rises rapidly with pH between pH 11 and 12, then levels out and finally decreases with increasing [HO^-]. However the observed ' bell ' shape of the curve is not symmetrical (the decrease in k_{obs} at high pH is slower than that towards low pH) and thus the data do not fit the normal ' bell-shaped ' curve, without the addition of several other terms.

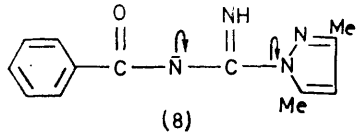
The observed rate constants can be rationalised qualitatively however. The substrate (3; X = H) is converted to the corresponding anion in alkaline solution. From the variation of the observed optical density of (3; X = H) at 294 nm with pH (Figure 2) a pK_a value (= pK_{a_2}) can be calculated for the substrate. At pH = pK_{a_2}, it is seen (Table 6) that the observed rate of hydrolysis of (3; X = H) is approximately half its maximum value. This is expected if the anion of (3; X = H) is the reactive species. In the absence of other factors. the rate constants would tend to a pH-independent plateau at high pH, *i.e.* equation (3) for a specific base catalysed process would be followed.

$$k_{obs} = k_2 K_{a_2}/(a_H + K_{a_2}) \qquad (3)$$

The observed rate constants (in 24·5% methanol) however decrease as the pH is raised in the region 13—14. The magnitude of the decrease appears to be dependent on the solvent composition. Thus when the methanol content of the solvent is increased to 50% (v/v) the rate constant at 1·0M-[HO^-] is *ca.* one-fifth of that observed at [HO^-] = 0·1M. In purely aqueous solution [in which the substrate (3; X = H) was soluble above pH 13] the decrease in k_{obs} at high pH was entirely eliminated; k_{obs} = 2·54 (±0·10) × 10^{-4} s^{-1} at pH 13·1, 13·4, 13·7, and 14·0 [μ = 1·0 (KCl)]. The decrease in k_{obs} in methanol–water is therefore most likely due to a specific salt effect in changing the counter-ion from chloride to hydroxide; in purely aqueous solution this effect is, as expected, less marked.

The product formed in this pH range is the anion of *N*-cyanobenzamide (4), which is resistant to further hydrolysis under the conditions used for the kinetic experiments. This is presumably due to the fact that (4) exists entirely as the anion [pK_a of (4) at 30° in 25% MeOH is 2·46] and is therefore resistant to direct HO^- attack. Under more vigorous conditions however (reflux for 12 h in 1·0M-[HO^-]) hydration of (4) to (5) could be forced.

It is therefore apparent that the pyrazoles (3) react at high pH by an elimination mechanism (of the *E*lcB type). The rate enhancement observed in the presence of added methanol at pH 13—14 is explicable in these terms; in this pH region (3) is present almost entirely as the anion (8) and the rate-determining step is consequently the unimolecular decomposition of this anion. A decrease in the ion-solvating power of the medium will therefore tend to aid a process which involves charge dispersal in the transition state. No evidence for solvent attack by methanol or by hydroxide ion [which would have given the stable urea (5)] on the neutral substrate (3) was observed.



(8)

At [HO^-] = 1·0M the rates of hydrolysis (3; X = H, *p*-MeO, *p*-Me, *p*-Br, *m*-Br, and *m*-NO_2) (Table 6) were correlated by the Hammett equation to give $\rho = +0.45$ (see Figure 5). The datum point for the *p*-nitro-substituted compound which lies well below the line used to correlate the other compounds was arbitrarily omitted. Use of ' exalted ' σ values for the *p*-NO_2 group in fact increased the deviation from the line.

At this [HO^-] the unsubstituted material (3; X = H) exists largely as the anionic species (since pK_{a_2} 12·4). This is equally true for the compounds with electron-withdrawing substituents. However the small positive

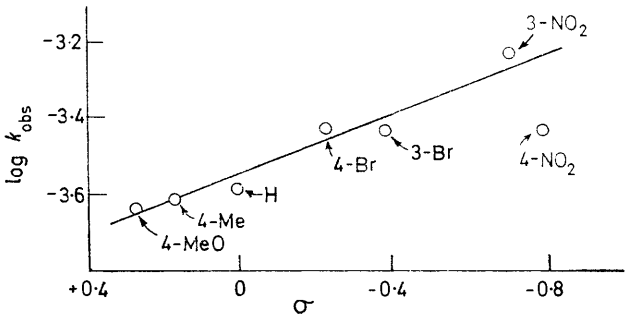
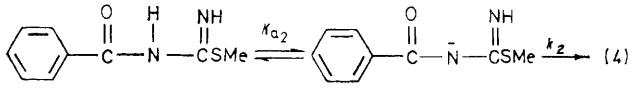


FIGURE 5 Plot of log of the observed rate of hydrolysis of pyrazoles (3) in the presence of 1·0M-hydroxide ion in water *vs.* the σ value of the corresponding substituent X

ρ value indicates that during elimination further negative change is localised on the benzoyl group. It is difficult to visualize how this might occur except through some contribution due to the formation of the stabilized *N*-cyanobenzamide anion.

Variation of the leaving group from 3,5-dimethylpyrazole anion (pK_a of conjugate acid 15) to mercaptide (pK_a of MeSH 10) caused a large increase in the rate of elimination. The rate of hydrolysis of *N*-benzoyl-*S*-methylisothiourea (9) to *N*-cyanobenzamide was



(9) (10) (4)

proportional to [HO^-] over the range 1·56 × 10^{-2}—5 × 10^{-1}M (Table 6). Since even at the highest [HO^-] used the rate constants were directly proportional to [HO^-], the substrate is present in this pH region largely as the neutral species (9) [rather than as the anion (10)]. The observed rate constants therefore represent composite values with $k_{obs} = k_2 K_{a_2}/a_H$ [from equation (3) with $a_H \gg K_{a_2}$]. Assuming that K_{a_2} is 10^{-15} (a maximum value), then k_2 *ca.* 1·5 s^{-1} (which is

thus a minimum estimate). The $^{-}$SMe leaving group is therefore at least three orders of magnitude more effective than 3,5-dimethylpyrazole anion. Unlike the pyrazole analogues (3), however, (9) does not undergo acid catalysed conversion to ureas at 30°.

It thus appears that in basic solution the hydrolysis of the amidino-derivatives (3) and (9) involves an elimination–addition pathway with the formation of substituted *N*-cyanobenzamides, which may then undergo further reaction. Because of stabilization of the cyanamide (4) as the anion, further reaction with nucleophiles in basic solution is inhibited, contrary to the reported results for other less acidic cyanamides and carbodi-imides.[14,15] In acidic solution the conjugate acid of (3) undergoes nucleophilic attack by water whereas (9) which does not have a basic site on the leaving group is inert in acidic solution.

[3/794 *Received*, 12*th April*, 1973]

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