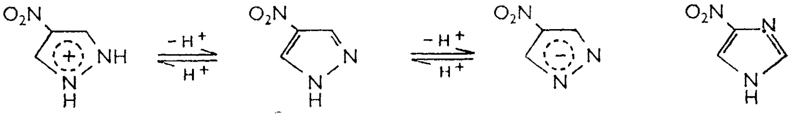
188. *The Kinetics and Mechanism of Heteroaromatic Nitration. Part II.*[1] *Pyrazole and Imidazole.*

By M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith.

The rate-profile for the nitration of pyrazole over the range 90—99% sulphuric acid shows that the reaction involves the conjugate acid of pyrazole; this conclusion is supported by the Arrhenius parameters. Related arguments based on the rate profile and on a comparison with encounter rates show that the nitration of imidazole involves the conjugate acid. The reactivity of these conjugate acids is compared with that of the quinolinium ion and approximate partial rate factors are calculated. A spectrophotometric study of prototropic equilibrium involving 4-nitropyrazole is reported.

The kinetic studies described in this Paper extend those reported in Part I[1] of this series to substrates with five-membered heteroaromatic rings. As before, our aim has been to establish the mechanism of these reactions and then to compare the reaction rates of related substrates.

(1) *Products of Nitration.*—The nitration of pyrazole in strongly acidic media[2] leads only to 4-nitropyrazole (II); unstable *N*-nitropyrazoles can be obtained at lower acidities.[3]



(I) p*K* = −2·0 (II) p*K* = 9·64 (III) (IV)

Our spectrophotometric studies of the reaction product have shown that the nitration is quantitative. The equilibria involved in forming the conjugate acid (I) and conjugate base (III) of 4-nitropyrazole have been studied spectroscopically; the p*K* values obtained are stated above and details of the spectra are given in the Experimental section.

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[1] Part I, Austin and Ridd, *J.*, 1963, 4204.

[2] Buchner and Fritsch, *Annalen*, 1893, **273**, 256.

[3] Hüttel and Büchele, *Chem. Ber.*, 1955, **88**, 1586.

The nitration of imidazole gives 4(5)-nitroimidazole (IV),[4] but the yield depends on the conditions. This is illustrated by the figures below.

H_2SO_4 (%)	83·7	89·6	93·8	98·8	1% SO_3
Yield (%)	46	26	19	19	90

These figures are based on a spectrophotometric estimation of the reaction product in the presence of excess of nitric acid at 25°; the results of preparative experiments are in substantial agreement. With the exception of ammonia, the other products formed have not been identified but they cannot be detected in the absorption spectrum above 2900 Å and presumably result from an oxidative breakdown of the imidazole ring for the reaction is accompanied by a reduction of some of the nitric acid to nitrous acid. With excess of nitric acid, the yield of nitro-compound is not very sensitive to the concentrations of the reactants; this implies that the ring-opening reaction and the nitration have a similar kinetic form. Ring-opening also occurs when imidazole reacts with bromine at lower acidities.[5] We hope to discuss the course of these reactions later and limit the present discussion to the concurrent nitration. The prototropic equilibria involving 4(5)-nitroimidazole have been discussed elsewhere.[6]

(2) *Kinetic Form.*—The kinetics of the nitration of pyrazole were determined spectrophotometrically from the concentration of the conjugate base of 4-nitropyrazole present in basified samples of the reaction media. The same procedure was used for following the nitration of imidazole but the presence of the side reaction implies that the concentration of the reactants can be known accurately only at the start of the reaction; conditions were therefore adjusted to obtain an accurate value for the initial reaction rate. This value was divided by the product of the initial concentrations of imidazole and nitric acid to obtain the corresponding value of the second-order rate coefficient (k_2).

When the concentration of sulphuric acid is effectively constant, both nitration reactions obey the equation (in this equation the concentration terms refer to the stoicheiometric concentrations of the reactants).

$$\text{Rate} = k_2[\text{azole}][\text{nitric acid}]$$

Evidence for the constancy of k_2 with different reactant concentrations is given in Table 1.

The dependence of these stoicheiometric second-order rate coefficients on acidity is given in Table 2 and the combined results from Tables 1 and 2 are compared with those

TABLE 1.

Dependence of the rate of nitration on the concentration of the reactants.

	Pyrazole (80·8°)			*Imidazole* (25°)		
10^2 [Substrate] (M)	0·279	0·349	61·3	0·607	1·53	6·63
10^2 [Nitric acid] (M)	11·9	1·65	0·245	3·98	7·48	5·11
[H_2SO_4] (%)	98·54	98·69	98·72	98·18	98·13	98·17
10^4k_2 (mole^{-1} sec.$^{-1}$ l.)	13·4	13·2	13·0	3·78	4·20	4·30

TABLE 2.

Dependence of the rate of nitration on the composition of the medium.

Pyrazole (80·8°)

H_2SO_4 (%)	83·75	87·51	90·37	92·95	93·95	94·97	95·87	98·72
10^4k_2 (mole^{-1} sec.$^{-1}$ l.)	7·85	52·2	67·5	51·0	44·0	39·3	26·8	13·0

Imidazole (25°)

H_2SO_4 (%)	83·79	86·84	89·60	90·88	93·85	96·08	99·26
10^4k_2 (mole^{-1} sec.$^{-1}$ l.)	2·58	16·7	31·5	27·3	11·4	7·42	3·07

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[4] Fargher and Pyman, *J.*, 1919, **115**, 217.

[5] Ridd, unpublished observation.

[6] Grimison, Ridd, and Smith, *J.*, 1960, 1352.

for quinoline in the Figure. The rate profiles for all three substrates have a similar form. These rate profiles do not include results obtained in oleum because in oleum the yields of nitro-compounds change considerably for reasons which are not yet understood; the yields from pyrrazole and quinoline decrease and that from imidazole increases. Indeed, nitration in oleum provides a higher yield of 4(5)-nitroimidazole than any of the less acidic conditions previously used; however, we do not recommend that this be adopted as the standard preparative technique because of the inconvenience involved.

The variation of the rate of nitration of pyrazole with temperature and the corresponding Arrhenius parameters are given in Table 3.

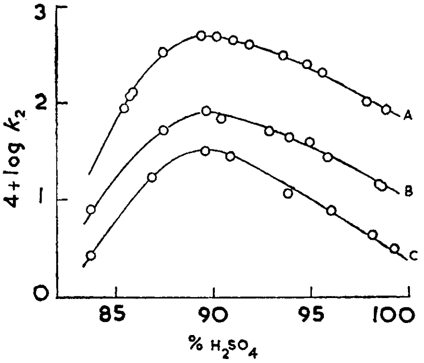
TABLE 3.

Dependence of the rate of nitration of pyrazole on the temperature.

$H_2SO_4 = 98{\cdot}62 \pm 0{\cdot}07\%$.

Temperature	10^4k_2 (mole^{-1} sec.$^{-1}$ l.)	E (cal.)	$\log_{10} A$	$\Delta S\ddagger$ (cal. deg.$^{-1}$)
54·9°	1·87			
80·8	13·4	17,290	7·80	−24·8
100·0	44·8			

(3) *Mechanism.*—Both imidazole and pyrazole are almost completely protonated in the reaction medium; in principle, therefore, the nitration reactions could occur either through the conjugate acids or through the much smaller concentrations of the (presumably more reactive) neutral molecules. In discussing the relative contributions of these reaction paths, it is convenient to consider first the rate profiles for the range 90—99% sulphuric acid as illustrated in the Figure.



Variation of the rate of nitration with the composition of the medium: A = quinoline (25·27°), B = pyrazole (80·8°), C = imidazole (25·0°).

The nitration of quinoline in 90—99% sulphuric acid has been shown in Part I[1] to involve the quinolinium ion, and the work of Moodie, Schofield, and Williamson[7] indicates that the nitration of the neutral quinoline molecule does not contribute significantly to the reaction rate even in acidities as low as 79% sulphuric acid. The whole of the rate profile for quinoline in the Figure can therefore be considered as representative of the direct nitration of a protonated heteroaromatic molecule. The rate profile has the form observed for the nitration of such positive ions as the phenyltrimethylammonium ion and can be interpreted in the same way.[8] If the nitration of quinoline had involved the neutral molecule, then arguments based on the H_0 acidity function suggest that the ratio of the rate in 90% sulphuric acid to that in 99% sulphuric acid should have been >100. The rate profiles for the two mechanisms over this range of acidity therefore differ greatly (see Part I, Fig. 2) and this difference should persist at higher temperatures for neither the (very

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[7] Moodie, Schofield, and Williamson, *Chem. and Ind.*, 1963, 1283.

[8] Cf. de la Mare and Ridd, "Aromatic Substitution," Butterworths, London, 1959, ch. 5.

slight) temperature dependence[9] of the H_0 function nor the activation energies of nitration[10] change greatly over this range of acidity.

The similarity in the rate profiles for the nitration of pyrazole and quinoline over the range 90—99% sulphuric acid therefore provides strong evidence that the nitration of pyrazole involves a rate-determining reaction between a nitronium ion and a pyrazolium ion.

This interpretation is supported by the similarity in the Arrhenius parameters for the nitration of pyrazole and quinoline; for pyrazole, the activation energy is a little higher and the activation entropy a little more negative (compare Table 3 with that in Part I). Both differences could come from the shorter distance between the positive charges in the transition state for the nitration of the pyrazolium ion. The Arrhenius parameters would be more difficult to understand if pyrazole were reacting through the neutral molecule, for the reaction rate is only a little less than the calculated encounter rate between pyrazole molecules and nitronium ions (see below); this interpretation would therefore require that the activation energy for the substitution process were very small. It seems unlikely that the difference between this and the observed activation energy could be made up by the variation in the concentration of neutral pyrazole molecules with temperature.

The variation of the rate coefficient for the nitration of imidazole over the range 90—99% sulphuric acid is somewhat greater than that with pyrazole but still considerably less than that expected for a reaction of the neutral imidazole molecule, providing that this can be treated as a Hammett base. The rate profile may be complicated by the change in the yield of 4(5-)-nitroimidazole (see above), for the rate profiles for the nitration of pyrazole and imidazole over the range 90% sulphuric acid to dilute oleum are more similar when calculated in terms of the total reaction rate (*i.e.*, dividing k_2 by the fractional yield of nitro-compound) than when calculated from the rates of nitration. This provides a hint that nitration and ring-opening may be alternative reaction paths available to an intermediate formed in a common rate-determining step. The interpretation of the rate-profile for nitration alone is therefore more difficult than in the example of pyrazole.

Comparison of the observed reaction rate with the calculated encounter rate for a reaction of the neutral molecule provides a different mechanistic criterion and is particularly helpful in the example of imidazole. In media containing more than 90% sulphuric acid, this encounter rate can be estimated by taking the concentration of nitronium ions as equal to the stoicheiometric concentration of nitric acid and by calculating the concentration of azole molecules from the appropriate dissociation constant and the H_0 acidity of the medium. The rate constant for an encounter reaction in 98% sulphuric acid can be estimated to be about $8{\cdot}5 \times 10^{8}$ mole^{-1} sec.$^{-1}$ l. (cf. Part I). When this value is multiplied by the fraction of azole present as the neutral molecule, the result ($k_2^{\text{calc.}}$) gives a measure of the stoicheiometric second-order rate coefficient that should be observed if nitration were limited to the neutral azole molecules and then occurred on every encounter with a nitronium ion. These calculated rate coefficients are compared with the observed values in Table 4. For

TABLE 4.

Comparison of nitration rates with encounter rates for reaction in 98% sulphuric acid at 25°.

Substrate	pK_a	log k_2 (calc.) *	log k_2 (obs.) *	k_2 (obs.)/k_2 (calc.)
Quinoline	4·94	−5·88	−2·02	7×10^{3}
Pyrazole	2·53	−3·47	−4·88 †	4×10^{-2}
Imidazole	7·03	−7·94	−3·42	3×10^{4}

* k_2 in mole^{-1} sec.$^{-1}$ l. † Extrapolated from the results at higher temperatures given in Table 3.

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[9] Gel'bshtein, Shcheglova, and Temkin, *Doklady Akad. Nauk S.S.S.R.*, 1956, **107**, 108.
[10] Gillespie and Norton, *J.*, 1953, 971.

imidazole, the observed rate of nitration is far greater than that calculated for a reaction of the neutral azole molecules, even if these molecules are assumed to react on every encounter. By implication, therefore, this result points to the imidazolium ion as the reactant. For pyrazole, the encounter criterion is equivocal, but fortunately the evidence from the rate-profile is then more clear-cut. Our conclusion is therefore that both of these azoles undergo nitration essentially through their conjugate acids in 98% sulphuric acid.

For pyrazole, the slope of the rate profile at lower acidities is considerably less than that for quinoline; reaction through the pyrazolinium ion may therefore be effectively limited to concentrations of sulphuric acid above 90%. The lower acidities are now being investigated in detail.

(4) *Partial Rate Factors.*—The values of log k_2 (obs.) in Table 4 permit a direct comparison of the reactivity of these three conjugate acids under similar conditions. Since the partial rate factors for the nitration of the quinolinium ion at the 5- and 8-positions have been given,[1] the partial rate factors for the azole conjugate acids can be calculated. The following results are then obtained.

	Pyrazolium ion (4-position)	Imidazolium ion (4,5-position)
Partial rate factor	$2{\cdot}1 \times 10^{-10}$	$3{\cdot}0 \times 10^{-9}$ *

* Our first estimate of this value [11] was $7{\cdot}8 \times 10^{-9}$. The difference is partly because comparisons were then made at a different acidity and partly because our first experiments led us to overestimate the initial rate of nitration of imidazole in 90% sulphuric acid.

Unfortunately, the concept of a partial rate factor is of limited value unless the rate of nitration of the substrate and of benzene respond in a similar way to changes in the medium. The nitration of the quinolinium ion has been shown to vary in the usual way with the concentration of sulphuric acid,[7] but the nitration of the pyrazolinium ion may be more difficult to check at lower acidities if reaction through the neutral molecule supervenes. A similar check with the imidazolium ion is complicated by the variation in the yield of nitro-compound with acidity. The partial rate factors for the azolium ions are therefore subject to qualification concerning the experimental conditions, but nevertheless they serve to indicate the very low reactivity of these heteroaromatic systems.

The poor correlation between the overall reactivity of heteroaromatic ions and the localisation energies has been pointed out elsewhere [11,12] and is further illustrated by the pyrazolium ion, for the only published calculation (with $\alpha_N = \alpha + 2\beta$) suggests that the ion is somewhat more reactive than benzene.[13] However, there is scope for further variation in the parameters used; these matters will be discussed more fully later.

EXPERIMENTAL

Materials.—Pyrazole and imidazole were commercial samples and were purified by repeated crystallisation. Nitric acid, sulphuric acid, and oleum (Judex) were of AnalaR quality. The composition of the reaction media was determined as described in Part I.[1] The nitric acid was used as concentrated nitric acid (*d* 1·42) but the water thereby introduced into the reaction media has been allowed for in calculating the percentage of sulphuric acid present. Samples of the nitro-compounds were prepared as described elsewhere [2,6] and purified by several crystallisations.

Spectroscopic Measurements.—The analysis of the kinetic results has been based on the strong absorption of the conjugate bases of the nitro-compounds in alkaline solution. Pyrazole and imidazole have no significant absorption above 2350 Å, even in concentrations a hundredfold greater than those used in the kinetics.

The spectroscopic properties of the different forms of 4-nitropyrazole were determined in

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[11] Ridd in "Physical Methods in Heterocyclic Chemistry," ed. Katritzky, Academic Press, New York, 1963, Vol. 1, ch. 2.

[12] Austin, Brickman, Ridd, and Smith, *Chem. and Ind.*, 1962, 1057.

[13] Brown, *Aust. J. Chem.*, 1955, **8**, 100.

the course of the present work. The spectrum of the conjugate base ($\lambda_{max.}$ = 3200 Å, ε_λ = 11·8 × 10³) was determined in aqueous sodium hydroxide (0·1M), that of the neutral molecule ($\lambda_{max.}$ = 2750 Å, ε_λ = 8·13 × 10³) was determined in ethanol and in aqueous buffers, and that of the conjugate acid ($\lambda_{max.}$ = 2380 Å, ε_λ = 7·8 × 10³) was determined in concentrated sulphuric acid (71%). In buffer solutions at about pH 9, the equilibrium between the conjugate base and the neutral molecule gives rise to a set of absorption curves with an isosbestic point at 2900 Å; from these the pK_a of the conjugate base can be calculated in the usual way to be 9·64. Unfortunately, the protonation of the neutral molecule cannot be studied so easily because of a medium effect on the spectrum of the conjugate acid; this leads to a shift of the maximum towards shorter wavelengths accompanied by some increase in the maximum extinction coefficient. We did not find a completely satisfactory way of correcting for this medium effect but it is not important below 13N-sulphuric acid and a detailed analysis of the absorption curves at lower acidities suggests that the pK_a of the neutral molecule is about −2·0. This calculation assumes that 4-nitropyrazole can be treated as a Hammett base.

The estimation of 4(5)-nitroimidazole as the conjugate base was based on the absorption maximum at 3500 Å (ε_λ = 10·19 × 10³).[6]

Nitration of Pyrazole.—Weighed quantities of pyrazole (~0·005M) and nitric acid (~0·1M) in separate volumes of sulphuric acid of the required concentration were mixed and aliquots were sealed in glass tubes and immersed in a thermostat. At suitable times, tubes were removed, cooled to room temperature and samples (~1 ml.) were extracted by a calibrated pipette and run into sufficient dilute sodium hydroxide to give an alkaline medium (reaction mixtures in oleum were diluted with water before neutralisation). The concentration of the conjugate base of 4-nitropyrazole was then calculated from the absorption at 3200 Å.

The majority of the kinetic experiments were carried out with a large excess of nitric acid so that first-order kinetics were obtained. The calculation of the rate coefficients was carried out as described previously[1] except that the time of withdrawal of the first tube was taken arbitrarily as zero. Details of a typical kinetic experiment are shown in Table 5.

TABLE 5.

Nitration of pyrazole in 98·72% sulphuric acid at 80·8°.

Pyrazole = 0·00279M. Nitric acid = 0·119M.

Time (min.)	Optical density *	10^4k_2 (mole⁻¹ sec.⁻¹ l.)	Time (min.)	Optical density *	10^4k_2 (mole⁻¹ sec.⁻¹ l.)
0	0·024	—	98	0·370	13·9
24	0·116	(10·7)	141	0·422	12·5
38	0·195	13·1	193	0·480	12·4
54	0·244	13·1	∞ (24 hr.)	0·580	
76	0·310	13·3	∞ (calc.)	0·599	

Mean k_2 = 13·0 × 10⁻⁴.

* Measured at 3200 Å in 1 cm. cells after dilution of the reaction mixture by a factor of 55.

The spectra of the basified solutions always corresponded exactly with that expected from the formation of 4-nitropyrazole and over the range 83·7—98·7% sulphuric acid the observed values of D_∞ were between 96 and 101% of those calculated theoretically for complete reaction. In oleum media (~1% SO_3), the yield of 4-nitropyrazole was about half that expected and the rate of nitration was about half that in 98% sulphuric acid.

Nitration of Imidazole.—It was first necessary to check that the other products formed did not absorb at the wavelength (3500 Å) used to estimate 4(5)-nitroimidazole as its conjugate base. The spectra of the reaction mixtures above 3000 Å corresponded exactly to that of the

TABLE 6.

Nitration of imidazole in 90·61% sulphuric acid at 25°.

Imidazole = 0·00649M. Nitric acid = 0·0327M.

Time (min.)	1·00	1·46	2·08	3·12	4·85	7·26
Optical density (obs.) *	0·019	0·031	0·046	0·076	0·123	0·180
Optical density (calc.)	0·016	0·030	0·046	0·073	0·118	0·181

Optical density (calc.) = 0·026t — 0·008.

* Measured at 3500 Å in 4 cm. cells after dilution by a factor of 53·6.

conjugate base, but to check the possibility of accidental agreement, the yield from preparative experiments was compared with that determined spectrophotometrically. The agreement was satisfactory [14] in both concentrated sulphuric acid and oleum.

The kinetic studies were carried out as described for pyrazole except that the solutions of nitric acid and imidazole were brought to the required temperature before mixing and were then mixed in a flask. A series of samples were extracted by a calibrated pipette to cover the first 10—15% of reaction. After basification, the plots of optical density versus time were found to be linear: this is illustrated by the agreement between the observed and calculated values in Table 6. The initial rate of formation of 4(5)-nitroimidazole was calculated from the slopes of these plots.

Conventional ammonia estimations on neutralised samples of the reaction mixture indicated that about 5% of the nitrogen initially present in the imidazole is converted into ammonia in the course of the nitration. The amount of ammonia formed appears to vary with the conditions of the nitration, but this point was not investigated in detail.

The amount of nitrous acid formed was determined from the characteristic absorption spectrum at about 3800 Å in diluted samples of the reaction mixture (2M-H_2SO_4); these results were checked by one of the colorimetric methods involving the coupling of diazotised sulphanilic acid with α-naphthylamine.[15] In 96·2% sulphuric acid, the oxidation of each molecule of imidazole involves the reduction of between 3 and 4 molecules of nitric acid to nitrous acid.

William Ramsay and Ralph Forster Laboratories,
University College, London W.C.1.
Chemistry Department, Chelsea College of Science and Technology,
London S.W.3.
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[14] Further details are given in the Ph.D. Thesis of M. W. Austin, London, 1964.

[15] Bunton, Halevi, and Llewellyn, *J.*, 1952, 4916.