# Kinetics and Mechanism of Nitration of Indazole

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The rate profile for the nitration of indazole at acidities below 90% sulphuric acid shows that the reaction involves the conjugate acid of indazole; this is supported by the Arrhenius parameters.

THE kinetics of nitration of indazole have not been studied previously. The rate profile for the structurally related compound pyrazole at acidities $>90\%$ w/w sulphuric acid shows[1] that reaction involves the conjugate acid. At acidities $<90\%$ w/w the slope of the rate profile is considerably less than that for glyoxaline and it is unlikely that nitration involves the conjugate acid.[1-3] The object of this work was to determine whether indazole is nitrated as its neutral molecule or its conjugate acid and to check whether the rate profile is normal or whether it resembles that for pyrazole at lower acidities.

*Products of Nitration.*—The mononitration of indazole is known[4] to produce 5-nitroindazole and under more

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[1] M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1965, 1051.

[2] M. W. Austin, Ph.D. Thesis, London 1964.

[3] M. W. Austin, unpublished data.

[4] K. Von Auwers and H. Kleiner, *J. prakt. Chem.*, 1928, **2**, 75, 118.

forcing conditions 5,7-dinitroindazole can be obtained.[5] Preparative scale experiments (Table 1) were carried out to check the nature and yield of isolated nitration products. The yields quoted are minimum estimates based on the amounts actually isolated. No attempts were made to recover unchanged indazole or to isolate nitro compounds other than those quoted.

TABLE 1

Nature and yield of nitro compounds obtained by nitration of indazole or 5-nitroindazole under various reaction conditions

| Substrate | Substrate (mol) | $HNO_3$ (mol) | $H_2SO_4$ (%) | $T$/°C | $t$/h | Yield (%) [a] |
|---|---|---|---|---|---|---|
| Indazole | 0.42 | 0.42 | 83 | 20 | 1.00 | 80 (m) |
| Indazole | 0.1 | 0.3 | 83 | 17.5 | 1.5 | 91 (m) |
| Indazole | 0.54 | 5.00 | 83 | 30 | 24.00 | 100 (m) |
| Indazole | 0.39 | 1.40 | 98 | 23 | 0.05 | 80 (m) |
| Indazole | 0.39 | 2.90 | 80 | 23 | 22.00 | 75 (m) |
| Indazole | 0.14 | 0.71 | 98 | 100 | 2.50 | 70 (d) |
| 5-Nitroindazole | 0.24 | 6.00 | 98 | 25 | 1.00 | 60 (d) |

[a] m, product 5-nitroindazole; d, product 5,7-dinitroindazole.

TABLE 2

Dependence of the rate of nitration at 25.0 °C in the concentration of reactants

| $H_2SO_4$ (%) corrected | $10^3$[Indazole]/M | $10^3$[Nitric acid]/M | $k_2$ [a]/l mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|
| 80.21 | 9.09 | 10.6 | $0.61_3$ |
| 80.22 | 12.1 | 7.6 | $0.60_8$ |
| 80.20 | 6.07 | 14.1 | $0.56_3$ |

[a] Mean of two determinations.

The results in Table 1 show that 5-nitro- or 5,7-dinitro-indazole can be obtained in high yield from nitration of indazole. The use of higher temperatures and longer reaction times favour dinitration but mono- and di-nitro products are easily separated. Under the conditions used for the kinetic studies no evidence of dinitration was obtained even after 100 mononitration half-lives. Spectrophotometric studies of the product showed that mononitration is essentially quantitative. No evidence for the formation of products other than 5-nitro- or 5,7-dinitro-indazole was obtained.

TABLE 5

Nitration of indazole in 74.27% sulphuric acid at 25.0 °C. [Indazole] 0.00697M; [Nitric acid] $0.0754_5$M

| $t$/min | Optical * density | $10^3k_2$/ l mol$^{-1}$ s$^{-1}$ | $t$/min | Optical * density | $10^3k_3$/ l mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|---|---|
| 0 | 0 | | 29.33 | 0.398 | 6.21 |
| 10.20 | 0.166 | 5.72 | 43.33 | 0.495 | 5.92 |
| 15.23 | 0.244 | 5.94 | 52.75 | 0.545 | 5.91 |
| 20.22 | 0.305 | 5.98 | ∞ (22 h) | 0.735 | |
| 25.05 | 0.350 | 5.84 | ∞ (calc.) | 0.738 | |

* Measured in 10 mm cells at 325 nm after dilution by a factor of 58.8.

*Kinetics*.—The kinetics of mononitration were determined by a spectrophotometric technique described elsewhere[6] for quinoline. With the concentration of sulphuric acid effectively constant the equation rate = $k_2$[indazole][nitric acid] is obeyed. Values of $k_2$ for different reactant concentrations are in Table 2; apart from small variations $k_2$ is constant. The corrected values of $H_2SO_4$ in Table 2 allow for the water introduced with the 70% nitric acid used.

The dependence of the stoicheiometric, second-order rate coefficients upon solvent composition is in Table 3. The variation of the rate of nitration of indazole with temperature and the corresponding Arrhenius parameters are shown in Table 4.

TABLE 3

Dependence of the rate of nitration at 25 °C upon the medium composition

| $H_2SO_4$ (%) corrected) | $k_2$/l mol$^{-1}$ s$^{-1}$ |
|---|---|
| 70.9 | $0.000\ 43_3$ |
| 74.27 | $0.0061_2$ |
| 75.6 | $0.022_5$ |
| 80.2 | $0.61_0$ |

*Mechanism*.—Indazole [p$K_a$ 1.2[7]] is nearly completely protonated in the reaction media used; nitration could therefore occur either *via* reaction of the neutral molecule or of the conjugate acid. Over the acidity range studied in this work the rate profile is linear and the value of the slope [d $\log_{10} k_2$/d $H_2SO_4$ (%) 0.34] is similar to that for quinoline,[6] glyoxaline,[1] 1,2-dimethylpyrazolinium ion,[3] isoquinoline,[8] $N$-methylquinolinium ion,[8] and trimethylphenylammonium ion;[9] this shows that indazole is nitrated as its cation.

TABLE 4

Dependence of the rate of nitration upon temperature

| $H_2SO_4$ (%) (corrected) | $T$/°C | $k_2$/l mol$^{-1}$ s$^{-1}$ | $E$/kJ mol$^{-1}$ | $\log_{10}$ ($A$/s$^{-1}$) | $\Delta S^{\ddagger}$/J mol$^{-1}$ K$^{-1}$ |
|---|---|---|---|---|---|
| 74.27 | 25.0 | $0.0061_2$ | 57.6 | 7.7 | −105.8 |
| 74.27 | 35.1 | $0.012_9$ | | | |
| 74.17 | 13.8 | $0.0017_5$ | 58.7 | 7.9 | −102.7 |
| 74.17 | 25.1 | 0.004 43 | | | |

The temperature dependence of the nitration rate also indicates reaction *via* the conjugate acid; the stoicheiometric entropy of activation is close to the expected[10] value of −83.8 J mol$^{-1}$ K$^{-1}$ for reaction between two positively charged ions and is similar to reported[11]

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[5] R. R. Davies, *J. Chem. Soc.*, 1955, 2412.

[6] M. W. Austin and J. H. Ridd, *J. Chem. Soc.*, 1963, 4204.

[7] A. Usert, 'Heterocyclic Chemistry,' Athlone Press, 1968, p. 441.

[8] R. B. Moodie, K. Schofield, and M. J. Williamson, *Chem. and Ind.*, 1963, 1283.

[9] R. J. Gillespie and D. G. Norton, *J. Chem. Soc.*, 1953, 971.

[10] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1953, p. 132.

[11] C. D. Johnson, A. R. Katritzky, N. Shakir, and M. Viney, *J. Chem. Soc.* (*B*), 1967, 1212.

values for pyridine 1-oxides which have been shown to nitrate as their cations.

The encounter rate criterion[1] provides supporting evidence for the conjugate acid mechanism. The calculated encounter rate in 80% sulphuric acid at 25 °C is $9.7 \times 10^{8}$ l mol$^{-1}$ s$^{-1}$.[11] In 80% sulphuric acid $H_0 = -9.44$ (assuming that the protonation of indazole follows $H_0$ as measured for tertiary amines), so that the calculated encounter rate coefficient for nitration of indazole as the free base is $2 \times 10^{-2}$ l mol$^{-1}$ s$^{-1}$; this is only *ca.* 3% of the observed value of $k_2$ and rules out reaction *via* the neutral molecule.

## EXPERIMENTAL

*Materials.*—Commercial samples of indazole were purified by repeated recrystallisation. Nitric and sulphuric acids of AnalaR quality were used. The compositions of reaction media were determined as described elsewhere.[6] Concentrated nitric acid (*d* 1.42) was used and the water added to reaction media was allowed for in calculating the percentage of sulphuric acid. Samples of 5-nitroindazole and 5,7-dinitroindazole were prepared as described elsewhere [4,5] and purified by repeated recrystallisation.

*Spectroscopic Measurements.*—The kinetics were studied by measurement of the strong adsorption of the neutral molecule of 5-nitroindazole ($\varepsilon$ $6.22 \times 10^{3}$ at 325 nm) in 0.4N-acid solution at 325 nm. At and above this wavelength the absorption of indazole is not significant even in concentrations ten times greater than those used for the kinetic studies.

*Kinetics.*—The technique used was exactly as described elsewhere.[6] Samples (1 ml) of reaction mixture were quenched in water (*ca.* 40 ml) contained in a calibrated flask and the resulting solution was made up to 50 ml. The calculation of rate constants was carried out as described previously.[6] Details of a typical kinetic run are shown in Table 5.

Analysis of the kinetic runs at wavelengths in the range 280—350 nm gave results very similar to those which were obtained at 325 nm but at wavelengths below 315 nm the absorption of the indazolinium ion was perceptible and had to be taken into account. The spectra of the quenched solutions corresponded exactly with that expected for 5-nitroindazole and over the range of acidities studied (71—80% sulphuric acid) the observed values of $D_\infty$ were always between 95 and 102% of those calculated theoretically for complete reaction.

*Preparative Scale Experiments.*—The substrate (either indazole or 5-nitroindazole) was dissolved in sulphuric acid and nitric acid was added to the stirred solution. After a suitable time for reaction the cooled mixture was poured into ice–water and left overnight. The precipitated nitro compound was then filtered off, washed with a little water, dried, and weighed to determine the yield. I.r. and u.v. spectra were used to characterise the products. Sodium carbonate was added to the mother liquor to check whether any further solids could be obtained.

Part of this work was performed during the tenure of a NATO Fellowship awarded by the S.R.C.

[7/1277 *Received*, 18*th July*, 1977]