Mechanism of Iodine Migration during the Nitrodeiodination of 4-Iodoanisole [1]

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The conversion of 4-iodoanisole into 2-iodo-4-nitroanisole by nitric acid has been shown to occur by rapid nitrodeiodination and iodination to give 2,4-di-iodoanisole and 4-nitroanisole, gradual nitrodeiodination of the former compound at the 4-position with the production of free iodine, and then very slow iodination of the latter compound at the 2-position. Nitrous acid acts as a catalyst and the preliminary step is thought to be nitrosodeiodination. The *ortho*:*para* ratio for the methoxy-group in nitrosodeiodination is very low. The *ipso* factors of Perrin and Skinner are discussed in detail in the light of this and other work.

EARLY work by Reverdin [2] showed that, although nitration of 2-iodoanisole proceeds normally with nitration at the 4-position, nitration of 4-iodoanisole results in formation of 2-iodo-4-nitroanisole in high yield, and thus there is an unexpected migration of the iodine from the 4- to the 2-position. Later work by Robinson [3] indicated that 2,4-di-iodoanisole is an intermediate in this reaction but some details of the mechanism of rearrangement were not clarified. As part of a general study of electrophilic aromatic substitution involving replacement of groups other than hydrogen, an investigation of this reaction is now reported.

Reverdin's original work involved the use of fuming nitric acid and high concentrations of 4-iodoanisole, conditions unsuitable for a kinetic investigation. We used much lower concentrations of substrate (*ca.* 5×10^{-3}M) and a mixture of equal parts (v/v) of nitric and acetic acids containing sodium nitrite (*ca.* 0·025M). The significance of the added nitrite will be discussed later. Because of the low concentration of substrate, the intermediates occurring during the reaction were identified by an isotopic dilution technique.

Starting with [^{14}C]-4-iodoanisole the reaction mixture was quenched 35 s after mixing. Analysis of the product showed that the 4-iodoanisole was converted into an approximately equimolar mixture of 2,4-di-iodoanisole and 4-nitroanisole. Clearly rapid nitrodeiodination of 4-iodoanisole had occurred and the iodine thus released (probably not as free iodine but as some electrophilic iodinating species) had iodinated the most reactive species present, *i.e.*, the unchanged 4-iodoanisole. This part of the reaction is accompanied by formation of a transient yellow colour, the nature of which is unknown.

The above experiment was repeated with the reaction mixture having been allowed to stand for 30 min and analysis of the products showed that the 4-iodoanisole had now been converted into an equimolar mixture of 4-nitroanisole and 2-iodo-4-nitroanisole. Thus, in the second stage of the reaction, the 4-nitroanisole remains unchanged but there is complete nitrodeiodination of the

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[1] A preliminary account of this work was given at the Autumn Meeting of the Chemical Society, York, 1971.

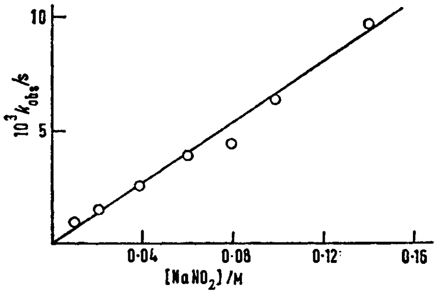
[2] F. Reverdin, *Ber.*, 1896, **29**, 997.

[3] G. M. Robinson, *J. Chem. Soc.*, 1916, **109**, 1078.

2,4-di-iodoanisole at the 4-position. This stage of the reaction is accompanied by the slow formation of molecular iodine which, under our conditions, remained in solution. From spectral studies, the final concentration of iodine equalled approximately half the initial concentration of 4-iodoanisole, the remaining iodine being present as 2-iodo-4-nitroanisole. The appearance of iodine was found to be of the first order in iodine ($k_{obs} = 4{\cdot}14 \times 10^{-3}\ s^{-1}$ at 25 °C; $[NaNO_2] = 0{\cdot}025$M). Under identical conditions the formation of iodine from 2,4-di-iodoanisole occurred at the same rate ($k_{obs} = 4{\cdot}19 \times 10^{-3}\ s^{-1}$), thus confirming its intermediacy in the reaction.

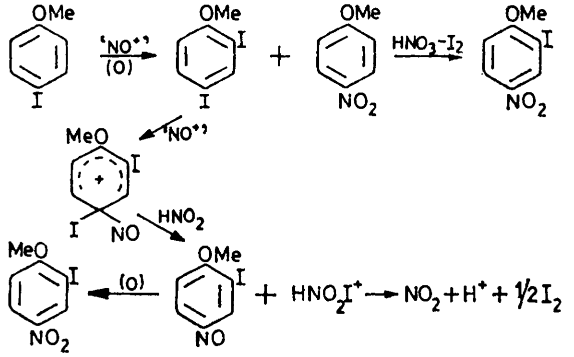
At this stage the reaction mixture contained iodine and nitric acid, a mixture known to effect aromatic iodination.[4] The only susceptible substrate present was 4-nitroanisole, which is much deactivated towards electrophilic attack. However, from 30 min onwards there was slow disappearance of iodine and it seemed probable that this resulted from iodination of 4-nitroanisole at the 2-position, to give a product identical with that obtained from the nitrodeiodination of 2,4-di-iodoanisole. This third stage in the reaction was confirmed by nitrating 4-iodoanisole in the presence of [^{14}C]-4-nitroanisole. After 30 min the 2-iodo-4-nitroanisole isolated from the mixture was found to be essentially inactive but after three days, when all the free iodine had disappeared, the activity of the product was consistent with its partial formation *via* iodination of 4-nitroanisole.

The sequence of events occurring in the formation of 2-iodo-4-nitroanisole from 4-iodoanisole has now been established, but the species responsible for deiodination has not been defined. In the presence of urea, which destroys nitrous acid, there is no reaction, while sodium nitrite acts as a catalyst, so that the species responsible for deiodination is probably a nitrosating agent and there is oxidation of the resulting nitroso-compound to the corresponding nitro-compound. The effect of added sodium nitrite on the rate of formation of iodine from 2,4-diodoanisole and nitric acid is shown in the Figure.



Plot of k_{obs} against $[NaNO_2]$ for the nitrodeiodination of 2,4-di-iodoanisole: $[\text{di-iodoanisole}]_0 = 2 \times 10^{-3}$M, $[HNO_3] = 8{\cdot}05$M

The nitrosating species will be referred to as 'NO^+' although we have no knowledge of the exact nature of this species. It seems improbable that I^+ will be expelled from the Wheland intermediate in a unimolecular process, but will be removed by some nucleophile present in the reaction mixture and, as is shown by the rapid iodination of 4-iodoanisole in the first stage of the reaction, the resulting species must be able to act as an iodinating agent. With these conditions in mind we tentatively suggest nitrous acid as the nucleophile which removes I^+ to give HNO_2I^+, which has been postulated as the species responsible for aromatic iodination by iodine and nitric acid.[5] The suggested mechanism for the complete reaction is shown in Scheme 1.



SCHEME 1

One of the puzzling features of the reaction is the selectivity of the 2- and 4-positions of anisole towards nitrodeiodination. It has been assumed throughout that no reaction occurs at the 2-position because 2-iodoanisole nitrates to give the expected product with no evidence of deiodination. Also, 4-iodo-2-nitroanisole is readily nitrodeiodinated by concentrated nitric acid containing sodium nitrite to give 2,4-dinitroanisole, identified by comparison with an authentic sample, while 2-iodo-4-nitroanisole is quite stable in that medium. The very low *ortho* : *para* ratio has been confirmed directly by studying the nitration of [^{14}C]-2,4-di-iodoanisole under the same conditions as in the nitration of 4-iodoanisole. Dilution of the product with the two possible isomers indicated that there is 92% attack at the 4-position and only 8% at the 2-position. This parallels exactly the isomer ratio observed by Hoggett *et al.*[6] for nitration *via* nitrosation of anisole in 65% sulphuric acid, and is consistent with our view that the initial reaction is nitrosation. Why a nitrosating species should displace iodine so readily is not clear, but an identical situation has been reported by Eaborn *et al.*[7] who found that little or no nitrodesilylation occurred when *p*-tolyltrimethylsilane was treated with nitric acid in acetic anhydride in the absence of lower nitrogen oxides, but when such oxides were present

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[4] R. L. Datta and N. R. Chatterjee, *J. Amer. Chem. Soc.*, 1917, **39**, 435.

[5] A. R. Butler and A. P. Sanderson, *J. Chem. Soc.* (*B*), 1971, 2264.

[6] J. G. Hoggett, R. B. Moodie, and K. Schofield, *Chem. Comm.*, 1969, 605.

[7] C. Eaborn, Z. S. Salih, and D. R. M. Walton, *J.C.S. Perkin II*, 1972, 172.

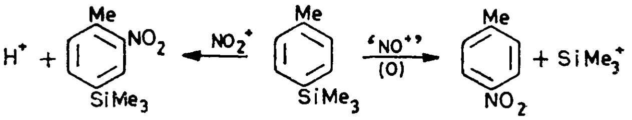
nitrodesilylation products were readily formed, apparently *via* nitrosodesilylation.

As this work was being prepared for publication a paper by Perrin and Skinner [8] appeared which used the nitration of halogenoanisoles to measure *ipso* partial rate factors, *i.e.*, the effect of a substituent on electrophilic attack at the carbon atom to which the substituent is attached. A discussion of this closely argued paper, on a topic not previously considered explicitly, is appropriate in view of our study of the mechanism of one one of the reactions used.

Using nitric acid in acetic anhydride as the nitrating agent these workers obtained, with 4-iodoanisole, 4-nitroanisole and 2,4-di-iodoanisole but no rearranged product. The reason for this is now clear. Nitrodeiodination of 2,4-di-iodoanisole to give the rearranged product is much slower than the initial processes and occurs only if the reaction mixture is allowed to stand for some time.

Although the specifying of the nitrating agent is not crucial to the measurement of *ipso* factors, it was assumed to be NO_2^+. This is open to question. This was the conclusion of Paul,[9] but later workers have preferred protonated acetyl nitrate [10,11] and this has been confirmed by some recent MINDO calculations.[12] Hartshorn *et al.*[13] have reported that the relative reactivities of benzene and toluene towards nitration are very different with nitric acid in acetic anhydride from those obtained with nitrating agents in which the reactive species is known to be NO_2^+, indicating a different mechanism. Also, there is evidence [6] for two distinct pathways in nitration by nitric acid in acetic anhydride, one of which is nitrosation followed by oxidation, and a consideration of this reaction is crucial in any study of the nitration of anisole. Bordwell and Garbisch [10] have shown that the reactivity of anisole towards nitration depends upon the temperature and manner in which the nitric acid and acetic anhydride were mixed and in a more recent study by Eaborn *et al.*[14] it was found that the *ortho* : *para* ratio for the nitration of anisole is influenced by the presence of nitrogen oxides. The *ortho* : *para* ratio for the nitration of anisole is, therefore, subject to some uncertainty. Perrin and Skinner attempted to deal with this by the addition of urea, which removes nitrous acid and so prevents nitrosation, but it is difficult to be certain that this is completely effective. Such doubts were raised by Hoggett *et al.*[15] and confirmed in a recent study of the nitration of thiophen.[16] The extreme susceptibility of anisole to nitrosation, and the fact that more nitrous acid may be produced autocatalytically, makes the complete eradication of nitrosation questionable.

The possibility of even a small amount of nitrosation occurring raises another difficulty. Our work indicates that deiodination by nitric acid in acetic acid is due to nitrosation rather than nitration, but nitration at the 2-position of a 4-halogenoanisole may not involve preliminary nitrosation. This is exactly the situation occurring in the desilylation of *p*-tolyltrimethylsilane by nitric acid in acetic anhydride.[7] The C–Si bond is readily cleaved by the nitrosating species present (not specified) but NO_2^+ (or whatever nitrating species is present) appears to leave the C–Si bond intact and nitrates the substrate at the 2-position (see Scheme 2). So, in comparing the relative reactivities of the 2- and 4-positions in 4-halogenoanisoles towards nitration, it is possible that two different electrophiles are involved: deiodination may, in part, be due to nitrosation. However, the constant value for the product ratio reported by Perrin and Skinner under a variety of conditions argues against this as the extent of nitrosation should vary from run to run, depending on the amount of nitrogen oxides present. On the other hand, the report of erratic results in kinetic studies could result from some nitrosation due to nitrous acid produced autocatalytically. It is not certain that the presence of urea prevents this complication as reaction of the nitrosating species with the halogenoanisole may be faster than the reactions of nitrous acid with urea.



SCHEME 2

The situation would be less uncertain if it was known that NO_2^+ could effect deiodination, even if with less facility than 'NO⁺'. This has been found to be the case. Reaction of 4-iodoanisole with nitronium tetrafluoroborate, where the nitrating species is known to be NO_2^+, in anhydrous acetic acid results mainly in nitration at the 2-position, but iodine is released and some 4-nitroanisole is obtained. Direct comparison with the results of Perrin and Skinner is not possible as the nitrating agent and solvent are different but some doubts concerning their determination of *ipso* factors are removed. The problem remains, however, of deciding whether nitrosation plays any part in the dehalogenation reaction under their conditions. Such doubts must remain until the mechanism of nitration by nitric acid in acetic anhydride is more clearly understood. The measurement of *ipso* factors by use of some other nitrating agent is required but it is surprisingly difficult to find a powerful one not involving a strong acid, which

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[8] C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 1971, **93**, 3389.

[9] M. A. Paul, *J. Amer. Chem. Soc.*, 1958, **80**, 5329.

[10] F. G. Bordwell and E. W. Garbisch, *J. Amer. Chem. Soc.*, 1960, **82**, 3588.

[11] A. Fischer, A. J. Read, and J. Vaughan, *J. Chem. Soc.*, 1964, 3691.

[12] N. Bodov and M. J. S. Dewar, *Tetrahedron*, 1969, **25**, 5777.

[13] S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1971, 1256.

[14] C. Eaborn, Z. S. Salih, and D. R. M. Walton, unpublished observations.

[15] J. C. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1969, 1.

[16] A. R. Butler and J. B. Hendry, *J. Chem. Soc.* (*B*), 1971, 102.

might cause protodeiodination, for which the mechanism of reaction is known with certainty. Nitronium salts appear as likely reagents but the problem there is the possibility of a diffusion-controlled reaction rate. The opposing views on this subject have been given in reviews by Olah[17] and Ridd[18] and, until the matter is fully resolved, the measurement of *ipso* factors by use of these reagents would be subject to considerable ambiguity. The idea of *ipso* partial rate factors is important and, as Perrin and Skinner point out, much work needs to be done for an understanding of them to develop.

EXPERIMENTAL

Materials.—AnalaR acetic acid, nitric acid, and sodium nitrite were used without further purification. Other materials were all reagent grade and distilled or recrystallised before use. 2,4-Di-iodoanisole was prepared by adding iodine (7·5 g) to a mixture of 2-iodoanisole (10 g), conc. nitric acid (15 ml), 0·05M-sodium nitrite solution (5 ml), and acetic acid (80 ml) and stirring for 24 h. After pouring into water the excess of iodine was removed by adding sodium bisulphite and the product, recrystallised from ethanol, had m.p. 68 °C (lit.,[2] 69 °C). 2-Iodo-4-nitroanisole was prepared by an identical procedure but required stirring for four days and had m.p. 96 °C (lit.,[2] 96 °C). 4-Iodo-2-nitroanisole was prepared by the iodination of 2-nitroanisole with iodine and nitric acid[3] and had m.p. 96 °C (lit., 98 °C). Nitration of anisole with a mixture of fuming nitric acid and sulphuric acid gave 2,4-dinitroanisole.[19]

$[^{14}C]$Anisole was prepared from $[^{14}C]$phenol (The Radiochemical Centre, Amersham; 50 μCi mol^{-1}) by methylation with dimethyl sulphate[20] and converted into the 4-iodo-compound by the method of Blicke and Smith.[21] $[^{14}C]$-4-Nitroanisole was prepared by nitration of $[^{14}C]$phenol[22] and subsequent methylation of 4-nitrophenol.[20] $[^{14}C]$-Anisole was converted into the di-iodo-compound by iodination with iodine and iodic acid.[23]

Isotopic Dilution Experiments.—All these experiments followed the same basic procedure and the identification of 2,4-di-iodoanisole as an intermediate will be given as an example. $[^{14}C]$-4-Iodoanisole (50 μCi mol^{-1}; 2×10^{-3} mol) in acetic acid (150 ml) was added to nitric acid (50 ml) containing sodium nitrite ($2{\cdot}5 \times 10^{-3}$ mol). After 35 s the mixture was poured into water (150 ml) and inactive 2,4-di-iodoanisole (8×10^{-3} mol) added. The resulting mixture was extracted with ether (3 × 50 ml) and the other extracts washed with water, sodium carbonate solution, sodium bisulphite solution (to remove a trace of iodine), and finally water. After being dried (Na_2SO_4), the ether was evaporated and the residue recrystallised from ethanol to constant activity ($17{\cdot}8 \times 10^6$ counts min^{-1} mol^{-1}). The activity was measured on a Beckman LS100 Liquid Scintillation Counter with a Fluoralloy cocktail in toluene.

Kinetic Method.—The appearance of iodine was followed by monitoring the absorbance at 475 nm by the use of a Unicam SP 500 spectrophotometer with a thermostatted cell holder. The runs were of the first order during three half lives.

Reaction of 4-Iodoanisole and Nitronium Tetrafluoroborate.—The nitronium salt (3 g) was added to 4-iodoanisole (2 g) in anhydrous acetic acid (100 ml) and stirred for 5 h. After being poured into water (250 ml), the product was extracted with ether (2 × 50 ml). The ether extract was washed with water, sodium carbonate solution, sodium bisulphite solution to remove iodine, and water, and dried ($MgSO_4$). Ether was evaporated and the residue recrystallised from ethanol. The main product was identified as 4-iodo-2-nitroanisole by elemental analysis, m.p., and n.m.r. A small quantity of another product was obtained which had an i.r. spectrum identical with that of 4-nitroanisole.

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[17] G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240.

[18] J. H. Ridd, *Accounts Chem. Res.*, 1971, **4**, 248.

[19] R. Meldola, G. H. Woolcott, and E. Wray, *J. Chem. Soc.*, 1896, **69**, 1321.

[20] H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1930, 2166.

[21] F. F. Blicke and F. D. Smith, *J. Amer. Chem. Soc.*, 1928, **50**, 1229.

[22] A. I. Vogel, ' A Textbook of Practical Organic Chemistry,' Longmans, Green and Co., London, 1961, p. 677.

[23] H. O. Wirth, O. Königstein, and W. Kern, *Annalen*, 1960, **634**, 84.