Nitrodeiodination of Some Alkyl-substituted Iodoanisoles and Iodobenzenes. Discussion of Mechanism

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It has been found that nitrodeiodination of 2,6-diiodo-3,5-dimethyl-4-nitroanisole and 2,4,6-triiodo-3,5-dimethylanisole in nitric acid-nitromethane medium is not catalyzed by nitrite while nitrodeiodination of 2-iodo-4,6-dineopentylmesitylene is. This indicates "true" nitrodeiodination in the first two cases and nitrosodeiodination followed by oxidation in the third. The kinetic orders give evidence that the nitrodeiodination follows much the same mechanistic pattern as the nitrodeprotonation. A low *ortho/para* ratio is found with the triiodoanisole derivative which is unexpected when the mechanism is "true" nitrodeiodination. The reason might be steric factors and/or the paraquinonoid structure of the transition state being more stable than an orthoquinonoid structure.

The existence of nitrodehalogenation of halobenzenes as an "anomalous nitration" process accompanying the well-known aromatic nitrodeprotonation has been known for many years.[1,2] Little work on the mechanistic aspects of this reaction has been done until recently.[3-8] Schofield *et al.* have been working systematically in this field, covering mostly nitrodebromination.[9,10] They have concentrated on "true" nitrodehalogenation and as much as possible avoided nitrodehalogenation *via* nitrosation followed by oxidation. Rather little is known, however, concerning "true" nitrodeiodination. Investigations have been made on the nitrodeiodination of two types of compounds, iodoanisoles with different substitution patterns [5-7] and iodoalkylbenzenes.[3,4] So far it has been claimed that the mechanism for the first class of compounds is nitrosodeiodination followed by oxidation and that true nitrodeiodination occurs

in the other cases.[3-7] Among proposed explanations of this difference are

(a) different *ortho/para* ratios for the two mechanisms,[4]

(b) specific properties of the methoxy substituent,[7]

(c) difference in the Hammett reactivity parameter for the two reactions.[5] Explanation (a) was excluded by the experiments comparing 2,4-diiodomesitylene with 2,4-diiodo-3,5-dimethylanisole,[5] which gave nitro- and nitrosodeiodination, respectively, in spite of the similarity in substitution pattern around the iodine atoms. Explanation (b) could still be of some importance but was abandoned by Olsson [5] for the broader concept that the general reactivity of the compound towards electrophiles is the crucial point which determines which reaction mechanism will be most favoured in each case. If that were true, it would be possible to find anisoles, which are deactivated enough to undergo true nitrodeiodination, and reactive alkylbenzenes, which undergo nitrosodeiodination.
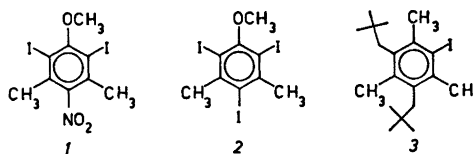
In order to confirm this idea the present investigation of two anisoles, 2,6-diiodo-3,5-dimethyl-4-nitroanisole, *1*, and 2,4,6-triodo-3,5-dimethylanisole, *2*, and one alkylbenzene, 2-iodo-4,6-dineopentylmesitylene, *3*, was made.

RESULTS

The substrates were nitrated at 0 °C in a medium consisting of 90 % aqueous nitric acid, free from nitrous acid, and nitromethane in different proportions. From *1* two components were detected, mainly 2-iodo-3,5-dimethyl-4,6-dinitroanisole and traces of 3,5-dimethyl-2,4,6-trinitroanisole. From *2* two products were obtained: 2,4-diiodo-3,5-dimethyl-6-nitroanisole and 2,6-diiodo-3,5-dimethyl-4-nitroanisole. Half the ratio between the amounts of *ortho* and *para* products was 0.15. The substrate *3* gave mainly the nitrodeiodinated product, 2,4-dineopentyl-6-nitromesitylene, but also a few percent of oxidation products which were identified by GLC/MS as iododineopentyldimethylbenzylalcohols and -benzaldehydes. Whether these products were formed by pyrolysis of the corresponding benzyl nitrates [11] in the gas chromatograph or were present as such in the reaction mixture was not investigated, as the available amounts were inconveniently small.

The three substrates were also treated with the same 90 % nitric acid/nitromethane solution, now containing nitrous acid. The same products in the same relative amounts were formed.

The experimental conditions were not identical for the three substrates. Their reactivities towards electrophiles differ too much for a determination of the reaction rates to be possible with the same concentration of nitric acid. The concentration of nitric acid in the reaction medium decreased in the order *1 > 2 > 3*.

The reaction rates were determined by analysis of the composition of the reaction mixtures

at proper time intervals. Aliquots were withdrawn, quenched in water, extracted with chloroform, and then analyzed by means of GLC. The nitrodeiodination of the iodoalkylbenzene was also followed by running NMR spectra of the reaction mixture at proper time intervals. This gave the same kinetics, qualitatively as well as quantitatively. As the substrates were sparingly soluble in the reaction medium, the NMR measurements were only carried through with the most soluble substrate, *3*.

The material balances were checked by using added internal standards in the GLC determinations. The internal standards used were 1-fluoro-2,4-dinitrobenzene with the anisole derivatives and 1,3,5-trineopentylbenzene with the alkylbenzene derivative. The balance showed no deficit with respect to the aromatic compounds within an accuracy of 2 %.

The reaction rates for the nitrodeiodination of the two anisoles decreased when nitrous acid, added as sodium nitrite, was present in the reaction mixture. In a parallel experiment it was found that the reactions slowed down in much the same way when corresponding amounts of nitrate instead of nitrite were added.

The reactions followed first-order kinetics with respect to the aromatics.

The alkylbenzene derivative behaved quite differently. The reaction rate was increased by the presence of nitrous acid. When a nitric acid sample, freed from nitrous acid as carefully as possible, was used, the kinetics were of zeroth-order in the substrate. When nitrite was added the reaction followed first-order kinetics instead.

The results are summarized in Table 1 and Figs. 1a and 1b.

Table 1. Nitration of *1*, *2* and *3*. The rate constants k and k_0 are pseudo first-order and zeroth-order rate constants, respectively, of the total reaction of the substrate. Each rate constant corresponds to two or three independent runs with the GLC analytical technique. Except the solutes indicated the solutions contained nitromethane. Temperature 0 °C.

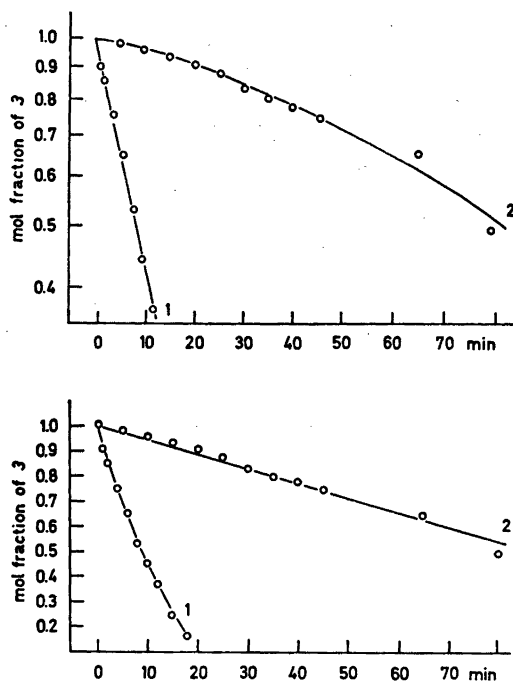| Substrate	[Substrate]/M	[HNO$_3$]/M	[H$_2$O]/M	[NaNO$_2$]/M	[NaNO$_3$]/M	$k/10^{-3}$ s^{-1}	$k_0/10^{-7}$ M s^{-1}
1	0.0025	15	6	0	0	(1.50 ± 0.10)	
	0.0025	15	6	0.21	0	(0.38 ± 0.05)	
	0.0025	15	6	0	0.21	(0.68 ± 0.05)	
2	0.0061	7.6	3	0	0	(1.70 ± 0.10)	
	0.0061	7.6	3	0.11	0	(0.56 ± 0.02)	
	0.0061	7.6	3	0	0.11	(1.30 ± 0.05)	
3	0.0045	1.5	0.7	0	0		(4.80 ± 1.50)
	0.0045	1.5	0.7	0.02	0	(1.90 ± 0.40)	

Fig. 1. Nitrodeiodination of 2-iodo-4,6-dineopentylmesitylene with (1) and without (2) addition of nitrite; (a) logarithmic, (b) linear ordinate.

DISCUSSION

The results indicate that two different mechanisms operate: true nitrodeiodination with the anisole derivatives and nitrosodeiodination followed by oxidation with the alkylbenzene derivative. This indicates that explanation (b) is incorrect. The reaction pathway followed has nothing specific to do with the methoxy group.

A comparison with what is known about nitrodeprotonation and nitrosodeprotonation [11] might help to explain our results. The electrophile arising from nitric acid under the present conditions is believed to be the nitronium ion, which is formed in a relatively slow process, and is present in very low concentration.[12a] When the aromatic molecule is sufficiently deactivated, its reaction with nitronium ion becomes slower than the production of nitronium ion, and the reaction becomes first-order in the aromatic substrate. Even in the presence of excess nitrosonium ion, the more strongly electrophilic nitronium ion will effect most of

the substitution. In the absence of nitrosonium ion, increasing the reactivity of the substrate will result in a gradual change from first- to zeroth-order kinetics. In the case of a very reactive substrate, increasing the concentration of the nitrosonium ion will result in concurrent nitrosation and nitration. The consumption of the aromatic substrate will then follow a superposition of first- and zeroth-order kinetics in which the former may dominate. These considerations account for the kinetics observed in the nitrodeiodination of *3*, where the reaction was zeroth-order without and first-order with added nitrite. A comparison of the zeroth-order rate constant given in Table 1 with those given by Benford and Ingold,[13] which are quoted and corrected by Schofield *et al.*,[12b] shows that the order of magnitude is the same, which ought to be the case since both measure the rate of the production of nitronium ion. The data given by Schofield *et al.* have 3.5 M as the lowest nitric acid concentration ($k_0 = 5.8 \times 10^{-6}$ M s^{-1}), and an extrapolation to our value 1.5 M must be made. The initial water concentration in our experiment was 0.7 M compared to zero in Benford and Ingold's experiments. This water content should approximately halve the reaction rate.[14] A corrected value of k_0 in our case would then be about $(1.0 \pm 0.4) \times 10^{-6}$ M s^{-1}. A plot of log k_0 against the logarithm of the concentration of the nitric acid (see Fig. 2) indicates a behaviour analogous to that in sulfolane.[15] In 5 − 7 M nitric acid k_0 seems to be proportional to the sixth power of the nitric acid concentration and at lower concentrations the dependence seems to be of second to third power. As the nitrodeiodination of *3* is catalyzed by nitrous acid, traces of this acid can make the total reaction faster by parallel nitrosodeiodination, but the dominating reaction must be the true nitrodeiodination as the reaction rate follows zeroth-order kinetics rather well.

Consequently it is not necessary to presume, as was first done [5] [see point (c) above], that the Hammett reactivity parameters are different for the two reactions, nitrodeiodination and nitrosodeiodination, in order to explain the choice of the weaker electrophile, but it is merely an effect of the power of the medium to supply a particular electrophile rapidly enough. A plot of the logarithm of the rate *versus* σ^+ would look like Fig. 3. It is doubtful whether
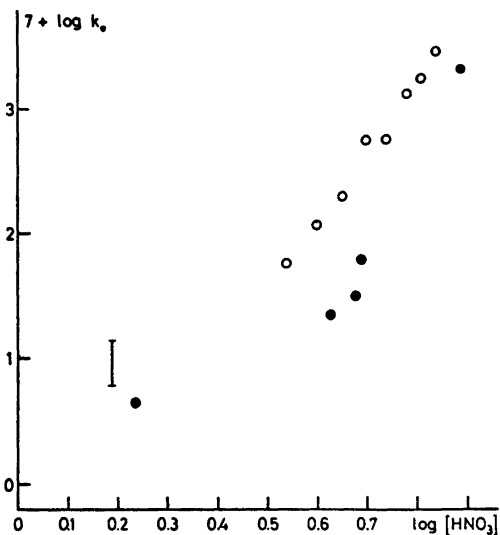
Fig. 2. A plot of log k_0 against the logarithm of the concentration of the nitric acid. The values indicated with a circle (solvent nitromethane) are taken from Ref. 12b and those indicated with a filled circle (solvent sulfolane) from Ref. 15. The bar indicates the present result, corrected and with experimental error (cf. the text).

the phenomenon of "crossing" Hammett plots ever may occur,[16,17] but this is not the place to discuss that question.

The half ortho/para ratio, r, (0.15) found for compound 2 with respect to the methoxy group is quite low. Different opinions have been expressed concerning ortho/para values observed with nitrodeprotonations of anisole. Griffiths et al.[18] and Bunton et al.[19] have found r values around 0.2 for nitration of anisole with nitric
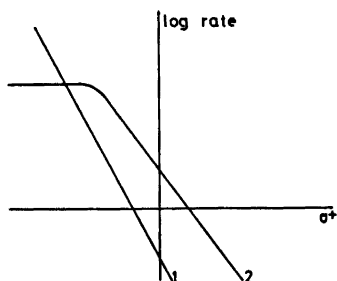

Fig. 3. An imaginary plot of the logarithm of the rate of nitrosodeiodination (1) and nitrodeiodination (2) versus σ^+ under certain conditions (cf. the text).

acid in different media. On the other hand, Schofield et al.[20] found r values around the statistically expected value 1 with nitration of anisole in media of the same type but carefully freed from nitrous acid. When sodium nitrite was added the ratio decreased dramatically. The reported values give an r value of 0.03. The rather low value reported earlier might then have been caused by intervening nitrosation. Butler and Sanderson[6] found a value of 0.04 for the nitrosodeiodination of 2,4-diiodoanisole and pointed out that it is of the same order of magnitude as for nitrosodeprotonation of anisole. Olsson[5] found an r value of 0.3 in the nitrosodeiodination of 2,4-diiodo-3,5-dimethylanisole, which does not seem to be quite comparable to the extremely low values found earlier. As we have found the mechanism with 2 to be a true nitrodeiodination and still giving a low r value the explanation in our case cannot be analogous to that of Schofield. According to Norman and Taylor[21] the para position is favoured with substituents of -I,+M type if the transition state is either reactant-like (a fast reaction) or close to the Wheland intermediate. Compound 2 is deactivated which could make the transition state late and increase the amount of para attack. This would tend to decrease the ortho/para ratio. There may also be some steric acceleration because the para iodine has a more crowded position than the ortho iodine.

Further information may be found from the possible dinitrations of 1 and 2. There were traces of 3,5-dimethyl-2,4,6-trinitroanisole in the case of 1 emanating from a second nitrodeiodination. With 2 no 2-iodo-3,5-dimethyl-4,6-dinitroanisole, which would have been the result from a second nitrodeiodination, was found. Compounds 1 and 2 were nitrated in media of different concentrations of nitric acid as mentioned earlier. Why 1, the more deactivated compound, and not 2 was nitrodeiodinated twice may be explained in the following way. In 1 both the first and the second nitrodeiodinations involve a Wheland intermediate which partakes of an ortho-quinonoid structure and the difference in reactivity is due to an iodine having been replaced by a nitro group before the second nitrodeiodination. In 2, on the other hand, the more important reaction path involves para attack and thus a para-

quinonoid-like intermediate, which makes the first step easier. When the product from this step is further nitrodeiodinated, however, *ortho* attack and an *ortho*-quinonoid-like intermediate are involved. Thus, a greater difference in rates between the first and second step is expected for *2* than for *1*. A basic assumption is, of course, the additivity of the substituent effects.

No demethylation of the anisole derivatives (within 2 % according to the material balance measurements) resulting in phenols was observed. This is consistent with the observation [22] that such demethylation does not occur when the anisole is substituted in both *ortho* positions.

EXPERIMENTAL

The NMR analyses were performed on a Varian A60 NMR spectrometer and a Bruker WH 270 NMR spectrometer. GLC analyses were made on a Perkin-Elmer 900 and/or a Perkin-Elmer 3920-B instrument fitted with 3 mm × 2 m SE-30 columns. The peak areas were determined with a Hewlett Packard 3380 A integrator. Melting points were determined with a Reichert melting point microscope. The mass spectra were determined either on an LKB 9000 instrument (electron energy 70 eV) fitted with a gas chromatograph (at the department of Medical Chemistry of Göteborg), or an AEI 902 mass spectrometer (electron energy 70 eV, accelerating voltage 8 kV, emission 100 μA). Only peaks with an intensity of more than 10 % of the base peak are reported together with the isotope peak corresponding to the base peak.

The fuming nitric acid used was obtained according to Bennett *et al.*[23] The concentration was adjusted to 90 % by mixing with the proper amount of concentrated nitric acid of analytical grade.

2,4,6-Triiodo-3,5-dimethylanisole, *2*, was obtained in two steps. 3,5-Dimethylphenol was triiodinated according to Keefer and Andrews.[24] *2* was prepared from 2,4,6-triiodo-3,5-dimethylphenol according to a method described by Brändström and Junggren [25] and also used by Olsson.[5] The physical properties were identical with those reported.[5] M.p. 139 – 140 °C.

2,6-Diiodo-3,5-dimethyl-4-nitroanisole, *1*, was made by nitrodeiodination of *2*. 2,4,6-Triiodo-3,5-dimethylanisole, 9.9 g (19 mmol), was dissolved in 700 ml of nitromethane by warming. Nitric acid (90 %), 70 ml, was added. The solution was held at about 60 °C for 2 h and was then poured into ice water. The resulting mixture was extracted with hexane. The organic layer was washed with an aqueous solution of sodium sulfite until the iodine colour had

disappeared and then with water. The solution was dried with magnesium sulfate and the solvent was evaporated yielding 5.7 g (68 %) of crude product. This consisted mainly of the two isomers resulting from nitrodeiodination in the *ortho* and *para* position, respectively. The product was recrystallized from hexane giving the *para* isomer (99.3 % pure) which was used for the kinetic measurements, m.p. 124 – 125 °C. The ^{1}H NMR spectrum of the mixture of the *ortho* and *para* isomers in chloroform made it possible to determine the ratio between the two isomers. Comparison between that ratio and the corresponding figure found with GLC allowed the assignment of the proper mass spectrum to each isomer.

^{1}H NMR of *1* (60 MHz, CDCl$_3$): δ 2.39 (6 H, s), 3.88 (3 H, s). ^{1}H NMR of 2,4-diiodo-3,5-dimethyl-6-nitroanisole (60 MHz, CDCl$_3$): δ 2.39 (3 H, s, methyl at C-5), 2.96 (3 H, s, methyl at C-3), 3.88 (3 H, s). MS of *1*: 434(12), 433(100), 416(63), 372(24), 261(21), 134(13), 103(21), 90(36), 89(36), 77(29), 67(20), 64(17), 63(33), 51(21), 39(28). MS of 2,4-diiodo-3,5-dimethyl-6-nitroanisole has been published.[5]

2-Iodo-3,5-dimethyl-4,6-dinitroanisole (for calibration purposes) was made by nitrodeiodination of *1*. Compound *1*, 0.20 g (0.46 mmol), was dissolved in 50 ml of nitromethane and the solution was allowed to stand for 1 h at 0 °C. It was then poured out into ice water and the mixture was extracted with chloroform. The organic layer was washed with aqueous sodium sulfite and then with water and was dried with magnesium sulfate. The solvent was evaporated, yielding 0.15 g (92 %) of a crude product, which according to GLC contained 96 % of the desired product. The byproduct was found (MS) to be 3,5-dimethyl-2,4,6-trinitroanisole. Recrystallization from nitromethane gave 0.10 g (yield 62 %) of pure 2-iodo-3,5-dimethyl-4,6-dinitroanisole, m.p. 135 – 136 °C.

^{1}H NMR of 2-iodo-3,5-dimethyl-4,6-dinitroanisole (60 MHz, CDCl$_3$): δ 2.18 (3 H, s, methyl at C-5), 2.48 (3 H, s, methyl at C-3), 3.96 (3 H, s). MS of 2-iodo-3,5-dimethyl-4,6-dinitroanisole: 353(11), 352(100), 335(65), 318(18), 104(15), 91(15), 90(16), 89(24), 78(16), 77(27), 68(19), 64(24), 51(16), 43(18), 39(16).

2,4-Dineopentylmesitylene was made from mesitylene according to Reuvers *et al.*[26] though the neopentyl substituents were introduced one by one.

2-Iodo-4,6-dineopentylmesitylene, *3*, was made by iodination [24] of 2,4-dineopentylmesitylene, which after recrystallization from ethanol gave the product in 53 % yield, m.p. 85 – 86 °C.

^{1}H NMR (270 MHz, CDCl$_3$): δ 0.93 (18 H, s), 2.30 (3 H, s), 2.56 (6 H, s), 2.89 (4 H, s). MS: 387(6), 386(26), 330(37), 329(100), 274(41), 273(48), 204(12), 203(56), 147(33), 128(14), 57 (70), 41(37), 29(13).

2,4-Dineopentyl-6-nitromesitylene (for calibration purposes) was made by preparative nitrodeiodination of *3*. Compound *3*, 0.25 g (0.6 mmol),

was dissolved in 200 ml of nitromethane and cooled to 0 °C. Nitric acid (90 %), 20 ml, was added and the reaction mixture was allowed to stand at 0 °C for 2 h. The work-up procedure was the same as the one earlier described for the nitrodeiodination of *1*. The yield was 0.15 g (76 %) after recrystallization from nitromethane. Traces of other products were seen by means of GLC. The byproducts were found (MS) to be oxidation products, substituted benzyl alcohols and/or benzaldehydes. M.p. for 2,4-dineopentylmesitylene: 117 – 118 °C. ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.94 (18 H, s), 2.21 (6 H, s), 2.34 (3 H, s), 2.76 (4 H, s).

MS: 306(4), 305(18), 290(23), 250(11), 249(58), 248(14), 233(11), 232(57), 193(24), 176(10), 146(15), 57(100), 41(20), 29(13).

The kinetic measurements were made under the following conditions in the three different series, each of which contained experiments with a certain concentration of sodium nitrite or nitrate in the nitric acid; see Table 1.

(a) Nitrodeiodination of *1*:1 ml of a 0.0100 M solution of *1* in nitromethane was mixed with 3 ml of 90 % nitric acid and kept at 0 °C.

(b) Nitrodeiodination of *2*:5 ml of a 0.0097 M solution of *2* in nitromethane was mixed with 3 ml of 90 % nitric acid and kept at 0 °C.

(c) Nitrodeiodination of *3*:6 ml of a 0.0049 M solution of *3* in nitromethane was mixed with 0.5 ml of 90 % nitric acid and kept at 0 °C.

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