

The Effect of Nitrous Acid on the Nitrodeiodination of 2,4-Diiodomesitylene and of 2,4-Diiodo-3,5-dimethylanisole

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It has been found that the rate of nitrodeiodination of 2,4-diiodo-3,5-dimethylanisole increases with the concentration of nitrous acid in the reaction medium. This fact indicates a two-step mechanism for the nitrodeiodination reaction. The first step is a nitrosodeiodination, followed by an oxidation of the nitroso group to a nitro group. In the case of 2,4-diiodomesitylene, however, the nitrodeiodination is somewhat retarded by nitrous acid. This gives evidence for a direct nitrodeiodination.

It has been demonstrated that two different mechanisms can operate when an electrophilic aromatic nitrodeiodination takes place. One of them is composed of an exchange of the iodine atom for a nitroso group, followed by an oxidation of the nitroso group to a nitro group. Butler and Sanderson¹ have demonstrated this mechanism in the case of 4-iodoanisole. The other mechanism is a direct exchange of the iodine atom for a nitro group in complete analogy with the well-known mechanism of the nitrodeprotonation reaction. The latter mechanism has been shown to operate in the case of 2-iodo-1,3,5-trineopentylbenzene.²

The reasons why one, and not the other of the two mechanisms operates in a particular case are not clear. It has been suggested² that the two mechanisms have different *ortho:para* ratios, leading to the dominance of one or the other depending on the substrate. It could also be an effect caused by the specific properties of a methoxy substituent in the aromatic iodo compound.

The present paper deals with questions concerning which properties of the aromatic com-

pound are responsible for the realization of a particular mechanism.

In order to test the idea of different *ortho:para* ratios for the two mechanisms, the two compounds 2,4-diiodomesitylene (I_2M) and 2,4-diiodo-3,5-dimethylanisole (I_2Me_2A) were investigated. These compounds are very similar; if one of the methyl groups of I_2M is replaced by a methoxy group, I_2Me_2A is obtained. The iodine atoms of both compounds have two *ortho* substituents and, moreover, the iodine atoms at position 4 in both compounds have identical surroundings.

RESULTS

Qualitative results. The substrates were treated with 90 % nitric acid in nitromethane solution at 0 °C. From I_2M three different products were obtained: 2-iodo-4-nitromesitylene from nitrodeiodination, 2,4-diiodo-6-nitromesitylene from nitrodeprotonation, and 2,4,6-triiodomesitylene from iodination of unreacted starting material by the iodine liberated during the nitrodeiodination. Four products from I_2Me_2A could be detected: 2-iodo-3,5-dimethyl-4-nitroanisole and 4-iodo-3,5-dimethyl-2-nitroanisole from nitrodeiodination, 2,4,6-triiodo-3,5-dimethylanisole (I_3Me_2A) from iodination, and traces of 2,4-diiodo-3,5-dimethyl-6-nitroanisole ($I_2Me_2NO_2A$) from nitrodeprotonation.

The relative amounts of the different products were constant throughout the course of the reactions, which means that the competing reactions all followed the same kinetics.

The substrates were also treated with nitric

acid containing nitrous acid. This was done by dissolving sodium nitrite in the nitric acid before the latter was added to the nitromethane solution of the aromatic substrate. In the case of I_2M the same products were obtained in the same proportions whether nitrous acid was present or not. In the case of I_2Me_2A , however, there was a difference. I_3Me_2A appeared only in the absence of nitrous acid. I_3Me_2A is probably formed as a result of a reaction in which I_2Me_2A acts as a nucleophilic species which accepts the positive iodine expelled in the nitrodeiodination reaction. When nitrous acid is present, other species are possibly more prone to react with positive iodine, and thus no I_3Me_2A is formed. Another reason may be that the nitrous acid present catalyses a nitrodeiodination of the I_3Me_2A that is formed, and thus no detectable amount of this compound accumulates. The latter explanation cannot be the only one, however, because the observed amount of $I_2Me_2NO_2A$ did not correspond to the lost amount of I_3Me_2A . The fact that no similar dependence of the composition of the product mixture on the presence of nitrous acid could be detected with I_2M may be explained if nitrous acid has no catalyzing effect on nitrodeiodination of I_3M .

The conditions were not identical for the two substrates. As I_2Me_2A is much more reactive towards electrophiles than I_2M and reasonable reaction rates were desired in order to make possible determinations of the rate constants, it was necessary to use a reaction solution with a lower concentration of nitric acid in the case of I_2Me_2A than in the case of I_2M . This means also that the water concentrations had to be different, if the relation between the concentrations of nitric acid and water was to be the same for both substrates.

Quantitative results. The reaction rates were determined by measuring photometrically the increasing amount of liberated molecular iodine. All the iodine expelled in the nitrodeiodination reactions does not appear as molecular iodine, but the amount of free iodine is proportional to the molar amount of aromatic reaction products. This was shown by comparing the rate of appearance of iodine with the rate of consumption of substrate. The material balance with respect to aromatic compounds showed no deficit.

Table 1. Nitration of 2,4-diiodomesitylene (I_2M) and of 2,4-diiodo-3,5-dimethylanisole (I_2Me_2A) with an excess of nitric acid containing varying amounts of sodium nitrite. For conditions, see Experimental section. The rate constants k are the pseudo first-order rate constants of the total reaction of the substrate.

Substrate	mol NaNO ₂ / mol HNO ₃	mol NaNO ₂ / mol of substrate	$k \times 10^3$ (s ⁻¹)
I_2M	0	0	2.0
	0.003	130	1.8
	0.007	260	1.4
	0.011	440	1.1
	0.016	650	1.0
I_2Me_2A	0	0	0.3
	0.003	8	1.2
	0.007	16	2.1
	0.011	27	2.9
	0.016	40	3.6

The dependence of the rate of reaction on addition of nitrous acid was determined for both substrates. It was found that the reaction rate for I_2Me_2A increased with increasing amounts of nitrous acid, while the rate for I_2M decreased. The results are summarized in Table 1.

In a separate experiment, it was found that sodium nitrate causes a decrease of the rate of reaction for I_2M of the same order of magnitude as that caused by the addition of sodium nitrite. It is thus impossible to state whether the decrease of the rate of reaction for I_2M , with increasing concentrations of nitrous acid, is analogous to the decrease found for the rate of nitrodeprotonation under the same circumstances,³ or if it is merely an effect of the nitrate ions which are formed when sodium nitrite is added.

DISCUSSION

The results found indicate a difference in mechanism between the nitrodeiodination reactions of the two compounds. In the case of I_2Me_2A , a nitrosodeiodination is apparently the first step, followed by an oxidation, giving altogether a nitrodeiodination. In the case of I_2M , a direct nitrodeiodination is operating. Thus two different mechanisms seem to operate for two substrates which are sterically very similar but which differ widely in electronic

properties. The idea that different *ortho:para* ratios are responsible for the operation of different reaction mechanisms can be ruled out since the two substrates used in the present investigation have similar patterns of substitution around the reacting iodine atoms.

One possible explanation of the difference in mechanism is that the methoxy group has some special properties which favour the nitrodeiodination reaction. In such a case, the oxygen atom may play a key role, but its action is not limited to the neighbouring positions since both iodines were affected similarly (*cf.* Experimental section).

Another explanation is based on the fact that the two substrates differ widely in their reactivity towards electrophiles. In such a case, one of the two competing reactions, nitrodeiodination and nitrosodeiodination, may dominate for the most reactive species and the other for the less reactive one. The Hammett equation⁴ is assumed to be applicable to the two different reactions (ni = nitro; no = nitroso):

$$\log (k^{\text{ni}}/k_0^{\text{ni}}) = \rho^{\text{ni}}\sigma \quad (1)$$

$$\log (k^{\text{no}}/k_0^{\text{no}}) = \rho^{\text{no}}\sigma \quad (2)$$

The symbols have the following meanings: k^{ni} is the rate constant for the nitrodeiodination reaction of a substrate of interest, k_0^{ni} is the corresponding constant for a standard substrate, ρ^{ni} is the reaction parameter of the nitrodeiodination reaction and σ is the substituent parameter of the substrates at hand. The symbols of eqn. (2) have the corresponding meanings.

If eqn. (2) is subtracted from eqn. (1), the following expression is obtained:

$$\log (k^{\text{ni}}/k^{\text{no}}) = \log (k_0^{\text{ni}}/k_0^{\text{no}}) + (\rho^{\text{ni}} - \rho^{\text{no}})\sigma \quad (3)$$

As $\log (k_0^{\text{ni}}/k_0^{\text{no}})$ is a constant, it can be seen from eqn. (3) that $\log (k^{\text{ni}}/k^{\text{no}})$ can be either positive or negative, *i.e.* either nitrodeiodination or nitrosodeiodination is dominating, depending on the value of σ , provided that the difference between the values of ρ^{ni} and ρ^{no} is sufficiently large.

A necessary condition for a change in σ to result in a change of sign, from positive to negative, of $\log (k^{\text{ni}}/k^{\text{no}})$ can be expressed in the following way:

$$(\rho^{\text{ni}} - \rho^{\text{no}})\sigma_1 > -\log (k_0^{\text{ni}}/k_0^{\text{no}}) > (\rho^{\text{ni}} - \rho^{\text{no}})\sigma_2 \quad (4)$$

where σ_1 is the substituent parameter for the compound which mainly undergoes nitrodeiodination (in the present case I₂M) and σ_2 has the corresponding meaning for the other compound (I₂Me₂A).

In the present case, the standard compound corresponding to k_0^{ni} and k_0^{no} is 2,4-diiodo-1,3-dimethylbenzene. This means that σ_1 is the substituent parameter for a methyl group and σ_2 that for a methoxy group. Both groups have an activating effect on electrophilic aromatic substitutions and thus σ_1 and σ_2 are negative, and since the methoxy group has the strongest activating effect, σ_2 has the largest absolute value. From eqn. (4) it can thus be concluded that the expression $(\rho^{\text{ni}} - \rho^{\text{no}})$ is positive, *i.e.* $\rho^{\text{ni}} > \rho^{\text{no}}$. As ρ^{ni} and ρ^{no} both refer to electrophilic aromatic substitutions, their values are negative, and thus ρ^{no} has a larger absolute value than ρ^{ni} .

The difference in reactivity parameters for the two reactions may explain the difference in behaviour of the two compounds studied. If this assumption is correct, the methoxy group, as such, would not be crucial for the dominant operation of the nitrosodeiodination. The effect of the methoxy group in such a case is merely a general activation of the substrate towards electrophiles. It might thus be possible to find substrates with a methoxy group which are not reactive enough to undergo nitrosodeiodination, and substrates without methoxy groups which undergo this reaction because they are sufficiently activated towards electrophiles for some other reason.

EXPERIMENTAL

The NMR analyses were performed on a Varian A 60 NMR spectrometer. About 10 % (by weight) solutions in carbon tetrachloride were used. The probe temperature was 35 °C. The chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard. The peaks were all singlets, indicated by (s). No other peaks than those reported could be detected, which indicates that the compounds prepared were free from isomers.

Gas chromatographic (GLC) analyses were made on a Perkin-Elmer 900 instrument fitted with columns packed with SE-30 silicon gum rubber. Photometric measurements were made on a Beckman DB UV spectrophotometer using a thermostatted cuvette holder.

The mass spectra (MS) were determined (at the Department of Medical Chemistry, University of Göteborg) on an LKB 9000 instrument fitted with a gas chromatograph. The electron energy used was 70 eV. The intensities of the peaks are reported in parentheses as percentage of the base peak. Only peaks with an intensity of more than 10 % of the base peak are reported, together with the isotope peaks corresponding to the base peaks.

The melting points were determined on a Koffler micro hot stage. The purity of the substances prepared was checked by gas chromatography and was found to be at least 99.5 % as estimated from the peak heights.

The fuming nitric acid used was obtained according to Bennett *et al.*⁵ The concentration was adjusted to 90 % by mixing with a proper amount of concentrated nitric acid. The acid did not contain nitrous acid within an experimental accuracy of 1 mol %.³

2,4-Diiodomesitylene was obtained from mesitylene *via* reaction with iodine monochloride in acetic acid with zinc(II) chloride as catalyst. The reaction has been described by Keefer and Andrews.⁶ The physical properties were identical with those reported previously.⁷

3,5-Dimethylanisole was prepared from 3,5-dimethylphenol according to a method described by Brändström and Junggren.⁸ Tetrabutylammonium hydrogen sulfate (34 g, 0.1 mol) and 8 g (0.2 mol) of sodium hydroxide were dissolved in 100 ml of water, and 150 ml of dichloromethane was added. 3,5-Dimethylphenol (12.2 g, 0.1 mol) and 14.2 g (0.1 mol) of iodomethane were added. The mixture was stirred vigorously at room temperature for 15 min. The two layers were separated and 400 ml of diethyl ether was added to the organic layer. Tetrabutylammonium iodide precipitated and the crystals were filtered off. Small amounts of unreacted starting material were present in the solution and were removed by washing with an aqueous sodium hydroxide solution, water, aqueous acetic acid and water, in that order. The solution was dried with magnesium sulfate and the solvent was evaporated yielding 7.5 g (55 %) of 3,5-dimethylanisole. NMR: δ 6.37 (s, 3 H, aromatic), 3.67 (s, 3 H, methoxy), 2.24 (s, 6 H, methyl).

2,4-Diiodo-3,5-dimethylanisole was obtained from 3,5-dimethylanisole according to the method described by Keefer and Andrews.⁶ NMR: δ 6.49 (s, 1 H, aromatic), 3.82 (s, 3 H, methoxy), 2.86 (s, 3 H, methyl), 2.46 (s, 3 H, methyl). MS: 39(15), 51(13), 63(13), 65(12), 91(35), 104(13), 119(17), 127(10), 246(37), 388(100), 389(9). M.p. 124–125 °C, reported⁹ 125 °C.

Nitration of 2,4-diiodomesitylene (I₂M). A solution of 42 mg of I₂M in 50 ml of nitromethane was prepared. In a cuvette 1.25 ml of the solution (containing 2.8×10^{-3} mmol of substrate) was placed and cooled to 0 °C. Then 0.50 ml (11 mmol) of 90 % nitric acid (cooled to 0 °C) was added. The concentration of I₂M

was 1.6×10^{-3} M, that of nitric acid 6.3 M, and that of water 2.4 M in the reaction solution. (The volume of the reaction solution was assumed to be equal to the sum of the volumes of the nitromethane solution and the nitric acid.)

The absorption of iodine (at 477 nm) was measured as a function of time. Approximately half of the expelled iodine could be detected in the form of molecular iodine. The appearance of the iodine was found to follow a first-order rate equation, and the rate constant (estimated accuracy ± 10 %) was calculated using the Guggenheim method.¹⁰ The experiment was repeated with differing amounts of sodium nitrite added to the nitric acid. The results are presented in Table 1.

In separate experiments under conditions similar to the above-mentioned (both with and without sodium nitrite added to the nitric acid) it was proved that the appearance of iodine and the consumption of I₂M follow pseudo first-order kinetics and have the same rate constant. Since no aromatic material was lost (see below), the latter must apply also to the formation of total aromatic product. The iodine content was measured photometrically as described above, and the consumption of I₂M was monitored by taking aliquots, quenching with a small amount of water, and analyzing by means of GLC. The gas chromatograms also show that the relative ratios between the products were constant during the course of reaction.

The dependence of the rate constant on the addition of sodium nitrate was checked in one experiment with conditions similar to those used in the experiments concerning addition of sodium nitrite. A decrease in the rate of reaction by one third was found when 16 mmol of sodium nitrate was added per mol of nitric acid. As can be seen from Table 1, a decrease by one half was found in the case of sodium nitrite.

The products obtained were identified by means of mass spectrometry. For this purpose I₂M was nitrated as described above (no nitrite was added), and after completion of the reaction, a small amount of water was added to the solution. The new solution was extracted with cyclohexane, and the organic phase was washed with water and dried with magnesium sulfate. After evaporation of the solvent, the product was analyzed by means of combined gas chromatography and mass spectrometry. The products were identified as 2-iodo-4-nitromesitylene (INO₂M), 2,4-diiodo-6-nitromesitylene (I₂NO₂M) and 2,4,6-triiodomesitylene (I₃M) in the approximate relative ratio 85:11:4, as determined from the peak heights of the gas chromatogram. (When the reaction was carried out with nitrous acid present, the same product ratio was obtained.) No other products could be found by means of GLC or NMR studies of the crude product mixture.

The material balance was checked by weighing the crude products after completed reaction.

The molar yield of aromatic products was quantitative in the presence, as well as in the absence, of nitrous acid.

MS for INO_2M : 30(16), 39(33), 50(16), 51(37), 52(14), 63(23), 65(26), 75(12), 77(37), 78(19), 89(12), 91(77), 92(14), 103(30), 104(19), 115(46), 116(21), 117(79), 118(79), 119(81), 120(12), 127(35), 137(40), 274(100), 291(95), 292(9).

MS for $\text{I}_2\text{NO}_2\text{M}$: 89(10), 91(16), 115(21), 116(14), 117(32), 118(26), 127(12), 207(10), 244(25), 245(21), 273(14), 400(77), 417(100), 418(9).

MS for I_3M : 51(12), 105(27), 107(33), 117(25), 244(25), 371(23), 498(100), 499(11).

Nitration of 2,4-diiodo-3,5-dimethylanisole ($\text{I}_2\text{Me}_2\text{A}$). This substrate was nitrated as described for I_2M with the exception that 2.00 ml of a nitromethane solution containing 7.2×10^{-3} mmol of $\text{I}_2\text{Me}_2\text{A}$ was placed in the cuvette. The 90% nitric acid added amounted to 0.080 ml (1.7 mmol). The concentration of $\text{I}_2\text{Me}_2\text{A}$ was 3.5×10^{-3} M, that of nitric acid 0.82 M, and that of water 0.32 M in the reaction solution. The temperature was kept at 0 °C and the rate constants were determined in the same manner as for I_2M . The results are summarized in Table 1. As in the case of I_2M , it was checked (both with and without nitrite added) that the same rate constant applied to the formation of free iodine and to the formation of total aromatic product. The relative ratios of the different products were also constant during the course of reaction in the presence, as well as in the absence, of nitrous acid, as seen from the gas chromatograms.

The products obtained were identified in the following way. $\text{I}_2\text{Me}_2\text{A}$ was nitrated under the conditions just described, and the reaction mixture was then worked up as described for the nitration of I_2M . The mass spectra were determined by means of combined GLC and MS, and the different compounds could be identified as 2-iodo-3,5-dimethyl-4-nitroanisole, 4-iodo-3,5-dimethyl-2-nitroanisole, and 2,4,6-triiodo-3,5-dimethylanisole ($\text{I}_3\text{Me}_2\text{A}$) which were the main products. Traces (less than 1%) of 2,4-diiodo-3,5-dimethyl-6-nitroanisole ($\text{I}_2\text{Me}_2\text{NO}_2\text{A}$) could also be detected. When sodium nitrite had been added to the nitric acid used, no $\text{I}_3\text{Me}_2\text{A}$ could be detected in the product mixture.

In order to make possible an identification of the two isomers of iodo-3,5-dimethyl-nitroanisole, the $\text{I}_3\text{Me}_2\text{A}$ was removed from the mixture of reaction products by means of column chromatography (silica gel, cyclohexane as eluent). A good separation of the two isomers was not achieved, however, and the NMR spectrum of the mixture of them was determined. From this spectrum it was possible to deduce the NMR spectrum of each compound, determine the relative abundance of the two compounds, compare this figure with the corresponding one obtained from GLC and then

assign the proper mass spectrum to each isomer.

The relative amounts of 2-iodo-3,5-dimethyl-4-nitroanisole, 4-iodo-3,5-dimethyl-2-nitroanisole and $\text{I}_3\text{Me}_2\text{A}$ were found to be 72:24:4 as determined from the NMR spectrum of the product mixture before any separation of the products had been done. The nitric acid used contained no nitrite in this case. When nitrite was present, the relative amounts of the two isomers of iodo-3,5-dimethyl-nitroanisole were the same as in the case just mentioned.

The crude product was weighed and the yield of aromatic products was found to be quantitative after completed reaction in the presence, as well as in the absence, of nitrous acid.

Spectral characteristics of 2-iodo-3,5-dimethyl-4-nitroanisole. NMR: δ 6.46 (s, 1 H, aromatic), 3.89 (s, 3 H, methoxy), 2.41 (s, 3 H, methyl), 2.26 (s, 3 H, methyl). MS: 39(13), 51(10), 65(18), 77(12), 91(19), 119(10), 135(16), 246(16), 290(100), 307(75), 308(9).

Spectral characteristics of 4-iodo-3,5-dimethyl-2-nitroanisole. NMR: δ 6.74 (s, 1 H, aromatic), 3.85 (s, 3 H, methoxy), 2.49 (s, 3 H, methyl), 2.37 (s, 3 H, methyl). MS: 39(20), 51(16), 63(16), 65(28), 77(19), 78(13), 91(37), 104(23), 107(20), 119(17), 135(14), 246(22), 290(55), 307(100), 308(11).

Spectral characteristics of $\text{I}_3\text{Me}_2\text{A}$. NMR: δ 3.81 (s, 3 H, methoxy), 2.94 (s, 6 H, methyl). MS: 63(10), 89(12), 90(11), 245(16), 372(34), 499(15), 514(100), 515(11).

MS of $\text{I}_2\text{Me}_2\text{NO}_2\text{A}$: 39(13), 41(22), 43(41), 51(11), 53(35), 57(38), 63(17), 67(13), 69(22), 71(15), 77(17), 81(11), 83(15), 89(22), 90(17), 97(15), 103(13), 217(11), 372(51), 416(39), 433(100), 434(11).

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