Two-Phase Nitration of Phenols, Part 3:
The Nitration of Anisole

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Abstract: The two-phase nitration procedure previously described for phenols can be modified to lead to successful nitration of anisole but through a different mechanism. The addition of N(III) species is unnecessary and the reaction is not supressed by nitrous acid traps , the presence of which alters the ortho:para ratio.

In our earlier reports[1,2] we outlined the two-phase nitration of phenols by a mechanism proceeding through the phenoxy radical after an initial electron transfer between the aromatic and NO^+. One of the key indicators to the mechanism of the nitration was the inability of anisoles to nitrate using the same procedure. Various studies on the nitration of anisole[3-6] have found a variable ortho:para ratio depending on the reaction medium and a catalytic role for the lower oxides of nitrogen.

Recently Germain [7] demonstrated the successful nitration of anisole by a modification of the two-phase procedure. The method consists of the use of 65% nitric acid in the presence of 0.14 molar equivalents of added $NaNO_2$ and an organic solvent. The nature of the solvent was shown to be of paramount importance for the success of the procedure and also in determining the ortho:para ratio of the nitrated products. No nitration was observed when diethyl ether was the solvent. As our earlier work had failed to show any nitration for anisole by our procedure, further investigation was warranted.

Contrary to the findings of Germain, we find diethyl ether is the most active solvent, but not the best, for the mono nitration of anisole . Using 1ml of 65% nitric acid to 5ml of diethylether as described by Germain, and in the presence of added nitrite(0.02 molar equivalents) no nitration was evident. Using this ratio of acid to ether, no phase separation was evident. The nitric acid has protonated the ether resulting in a homogeneous mixture, in effect reducing the acidity of the medium. This prompted an investigation into the relative amount of acid and diethyl ether solvent necessary to effect successful nitration.

Nitration in the presence of diethyl ether was accomplished by the use of a volume of 70% nitric acid equal to the volume of ether and 0.02 molar equivalents of $NaNO_2$. An induction period was evident during which there was a build up of a violet colouration. When the nitration proper started, the reaction was rapid and exothermic and required external cooling. After 1 hour the reaction was quenched by the addition of cold water which resulted in a dark blue-green organic phase and a green aqueous phase. GLC, ^{1}H-NMR and ^{13}C-NMR analysis of the organic phase showed the main product to be 2,4-dinitroanisole [8] (52%). The other products were 4-nitroanisole and 2-nitroanisole, with an ortho:para ratio of 0.52. A similar result was found using 50% nitric acid

in the presence of 0.02 molar equivalents $NaNO_2$. In this instance the reaction required 5 hours for complete nitration of starting material and dinitrated products made up 30% of the total product. Using 30% nitric acid no nitration was evident after 24 hours. Under identical conditions using 30% nitric acid m-cresol was completely nitrated within minutes.

The addition of $NaNO_2$, in a catalytic amount, was found to give a marked rate enhancement in the two-phase nitration of phenols. It has been argued in our earlier study that the role assigned to the nitrite is as a source of NO^+ which in turn acts as an electron transfer (ET) agent. Similarly it has been shown that the presence of N(III) species is rate accelerating in general for reactive aromatics such as phenols and anilines[12].

Using the nitration procedure as described below, the role of added $NaNO_2$ was investigated for the nitration of anisole in 70% HNO_3 / CCl_4. Figure 1 shows the relationship between the amount of added $NaNO_2$ and the ortho:para ratio. With no added nitrite this ratio is 0.45, but as the amount of nitrite increases, the ortho:para ratio decreases. As this implies that the relative amount of the 4-nitro isomer is increasing, it is further implied that at least part of this product is derived from oxidation of the corresponding nitroso compound. Addition of nitrite is unnecessary for successful nitration but a small amount is effective in accelerating the reaction, but any such addition alters the ortho:para ratio. When nitrous acid traps are used the nitration is still successful but a very different ortho:para ratio is obtained and is dependent on the effectiveness of the trap to remove N(III) species.

Figure 1
A plot of the relationship between the amount of added $NaNO_2$ and the ortho:para ratio for the nitration of anisole with 70% HNO_3 / CCl_4
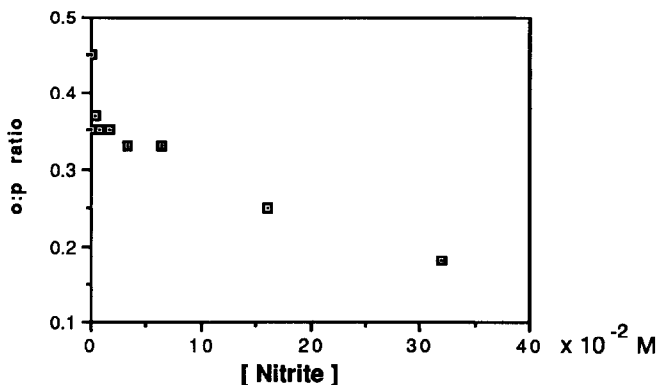
Various nitrous acid traps[9] have been used to eliminate the "special" nitration mechanism as described by Ingold[3]. Further studies [2,10,11,12] have since shown that N(III) species have a role in nitration in addition to that of the nitrosation of the substrate. In our earlier study it was shown that the addition of urea effectively removed the N(III) species in the two-phase nitration of phenols, thus preventing the initiation of the reaction. The addition of urea (0.01-0.50 molar equivalents of anisole) did not suppress the nitration of anisole using 70%HNO_3 / CH_2Cl_2. Table 1 shows the relationship between the amount of added urea and the ortho:para ratio. As the amount of urea increases so the ortho:para ratio increases, but not to the extent that it does in the presence of more effective nitrous acid traps. Table 1 shows that at a concentration of 5.0×10^{-2} M, both NaN_3 and

sulphanilic acid are more effective nitrous acid traps than urea, in the presence of 70% HNO$_3$. For both azide and sulphanilic acid a longer reaction time was required but the reaction was very clean, no coloured by-products were formed and the yield of mono-nitrated products was virtually quantitative. The ortho:para ratio found in the presence of these two nitrous acid traps (1.10 and 1.20 respectively) is comparable to the ratio calculated by the AM1-MO procedure[13] using the coefficient of the HOMO in the ground state (ortho:para =1.30) or the spin density in the radical cation (ortho:para =1.20)

Table 1

The effect of nitrous acid traps on the nitration of anisole, using 70% HNO$_3$ / CH$_2$Cl$_2$, as determined by GLC after 1 hour unless otherwise stated.

[urea]	ortho:para ratio
0	0.45
1.0×10^{-2} M	0.45
5.0×10^{-2} M	0.48
1.0×10^{-1} M	0.55
2.5×10^{-1} M	0.60
5.0×10^{-1} M	0.69
[NaN$_3$]	
5.0×10^{-2} M	1.10 (6 hours)
[Sulphanilic acid]	
5.0×10^{-2} M	1.20 (6 hours)

Figure 2

A plot of the relationship between the degree of nitration of anisole and nitric acid concentration, as determined by GLC after 30 minutes
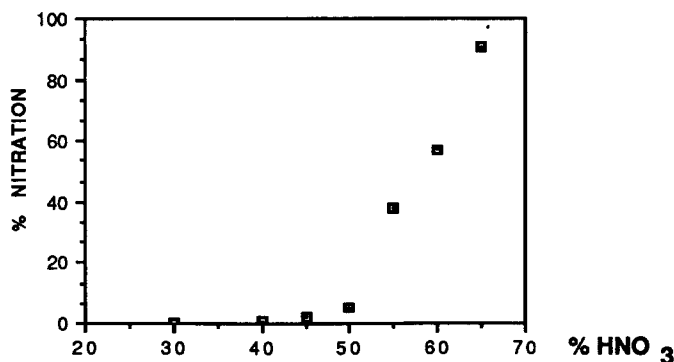
As the nitration of anisole failed in the normal two-phase nitration procedure but was successful using 70% nitric acid , it was decided to investigate the role of the concentration of the nitric acid. The reaction was set up using CCl$_4$ solvent and a range of nitric acid concentrations each containing 0.02 molar equivalents of NaNO$_2$.

After 30 minutes the reaction was quenched by the addition of 3 volumes of ice cold water. The phases were separated and the organic layer analysed by GLC and ^{1}H-NMR. Figure 2 shows a plot of nitric acid concentration and the % nitration as determined by GLC. Nitration was rapid at a nitric acid concentration of 55% or greater but fell sharply below this concentration. At 40% nitric acid only a trace amount of nitrated product was detected and no product was found at a concentration of 30% nitric acid, even after 12 hours. The ortho:para ratio was found to be in the range 0.31-0.35 for these six experiments.

These results help to reinforce two aspects of our earlier nitration study. Firstly it highlights the difference in reactivity of phenol and the corresponding methyl ether (anisole). Phenols show a markedly increased reactivity toward nitration by the two-phase procedure. Secondly it highlights the extremely mild nature of the nitration procedure as outlined in detail in earlier work. It may further be implied that it shows the existence of two or more nitration mechanisms each of which may act independently or in unison, depending on the reaction conditions. We believe these findings show that while phenols can undergo a nitration via the phenoxy radical under extremely mild conditions, that the nitration described here for anisole does not proceed via this mechanism but by electrophilic nitration assisted by N(III)species.

Experimental:

Nitric acid (5ml of the required concentration, containing added nitrite or nitrous acid trap) was added to a stirred mixture of anisole (0.54g, 5mmol.) in organic solvent (10 ml) and the resulting two-phase system stirred at room temperature for the required reaction time. Three volumes of ice cold water were added and the phases separated. The organic layer was washed with bicarbonate, water and then dried over anhydrous MgSO$_4$. The organic solution was then analysed by capillary GLC or the solvent was removed and the residue analysed by ^{1}H and/or ^{13}C-NMR.

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