The Addition of Nitrotoluenes to Aldehydes

A Comparison of Steric Inhibition of Resonance and Steric Hindrance in Mononitrotoluenes

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The decreased reactivity of o-nitrotoluene (ONT) in the reaction with formaldehyde compared with the reactivity of p-nitrotoluene (PNT) was shown to be due mainly to steric inhibition of resonance and not to steric hindrance of the o-methyl group by the NO_2 group. The evidence came from the reaction of 4-nitro-m-xylene with formaldehyde.

It was further shown that the product from the reaction between ONT and formaldehyde, 2-(o-nitrophenyl)-ethanol, inhibits further reaction, probably by solvating the basic catalyst.

The successful additions of o- and p-mononitrotoluenes to aldehydes was reported some time ago.[1,2] The reaction has now been further studied and the results are reported here.

Nitrotoluenes are known to be acidic and the acidity increases as the number of nitro groups[3] increases. 2,4- and 2,6-Dinitrotoluenes as well as 2,4,6-trinitrotoluene[4,5] react with aldehydes under basic conditions in conventional solvents. Mononitrotoluenes react only in cation solvating solvents like dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and hexamethyl phosphoric triamide (HMPA).

However, a variation in the reactivity of the methyl group towards aldehydes is found even between o- and p-mononitrotoluene. p-Nitrotoluene (PNT) is thus more reactive than o-nitrotoluene (ONT), as shown by an experiment where ONT and PNT were allowed to react together in DMSO with formaldehyde, competing for "unsolvated" base (see below). At the end of the reaction, 86 % of the PNT had reacted and only 39 % of the ONT.

The reaction between the nitrotoluene and formaldehyde is assumed to be a two step process:
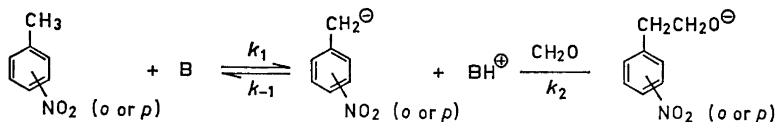
The formation of the carbanion is probably the rate determining step, as shown by Wesslén [6] for the analogous reaction between fluorene and formaldehyde. The reaction rate for that reaction was of zero order in formaldehyde. However, as no kinetic investigation of the reaction between mononitrotoluenes and formaldehyde is known to this author, the term "reactivity of the methyl group towards aldehydes" may include both k_1, k_{-1}, and k_2 in the reaction scheme above.
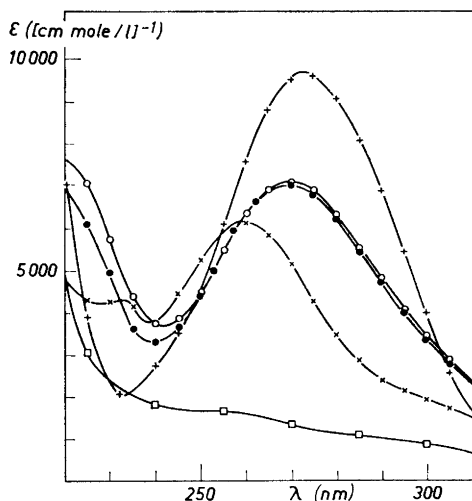

Fig. 1. UV spectra of PNT ($+$), ONT ($\times$), 2-nitro-*m*-xylene ($\square$), I ($\bigcirc$), and II ($\bullet$)·

A study of the UV spectra of ONT and PNT (Fig. 1) indicates the nitro group of ONT on average to be forced out of coplanarity with the benzene ring, thus diminishing the possibility of resonance. This is probably also the case for the *o*-nitrobenzylic anion. As the resonance contribution from the nitro group is assumed to be the main reason for the acidity of the methyl protons, this steric inhibition of resonance [7] may be responsible for the lower reactivity of ONT compared with PNT.

An interesting point in this connection is the possibility that the nitro group in ONT acts as a steric inhibitor for the reactants attacking the *o*-methyl group, or *o*-nitrobenzylic anion. One could argue that this effect is the main reason for the low reactivity of ONT as compared to PNT and that the steric inhibition of resonance is not the most important factor involved. To test this possibility, 4-nitro-*m*-xylene (I) was reacted with formaldehyde in DMSO with base as catalyst. 4-Nitro-*m*-xylene has one methyl group *ortho* and one *para* to the nitro group. If steric inhibition of resonance is the only factor involved, the two methyl groups should be expected to be equally reactive. However, if the nitro group inhibits the approach of the attacking reagent, either by steric hindrance or electrostatic repulsion, the *o*-methyl should be less reactive than the *p*-methyl group.

If the addition of formaldehyde to the carbanion of I is irreversible, one can compare the reactivity of the o- and p-methyl groups by comparing the amounts of o- and of p-addition of formaldehyde.

That the obtained ratio was not a result of an equilibration of II and III was shown by adding base to DMSO solutions of II and III at ratios above and below that experienced in the reaction. No change in the ratios took place after the addition of the base.
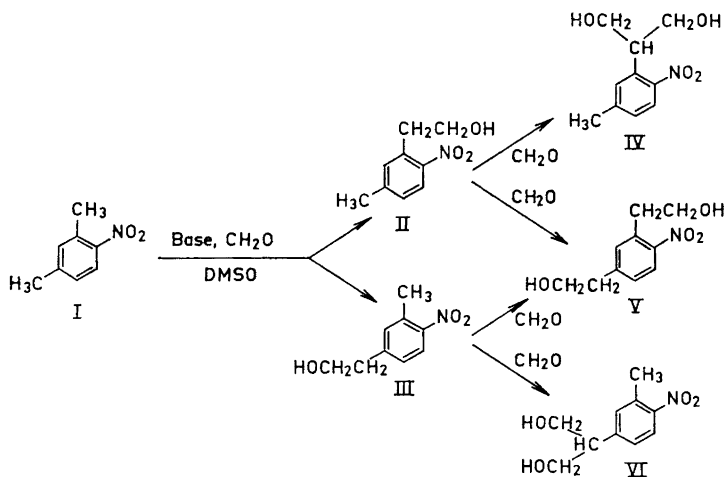
The reaction products were separated by liquid phase chromatography and by preparative VPC. The UV (Fig. 1) and IR spectra of the monoadducts II and III were almost identical, and in agreement with both of the structures II and III. The NMR spectra were different and made it possible to distinguish between them. The structural determination rests upon the fact that ONT has its methyl signal at a higher δ-value than that of PNT. The NMR signals of ONT, PNT, 4-nitro-m-xylene, and the compounds separated by VPC are given in Table 1.

Table 1.

Compound	NMR signals as δ-values		
	$-CH_3$	$Ar-CH_2-$	$-CH_2OH$
ONT	2.53		
PNT	2.43		
4-Nitro-m-xylene	2.53 and 2.36		
VPC Compound 1	2.40	3.13, triplet, $J=6$ cps	3.92, triplet, $J=6$ cps
VPC Compound 2	2.58	2.90, triplet, $J=6$ cps	3.85, triplet, $J=6$ cps

The compound eluted first on the VPC column had its methyl signal at a lower frequency than that which eluted second, indicating that the first compound has its Me-group *para* (*i.e.* II) and the second *ortho* (*i.e.* III) to the nitro group. The first compound had its benzylic methylene signal at a higher δ-value than the corresponding signal in the second compound, as one would expect if the first compound had its benzylic methylene group *ortho* (*i.e.* II) and the second *para* (*i.e.* III) to the nitro group. The first compound is thus assumed to be II and the second III. NMR of the three diadducts showed that the first to be eluted on the vapor phase chromatograph was IV, the second VI, and the third V. These structures were elucidated on the principles used for the monoadducts II and III.

The ratio between the products derived from attack on the *o*-methyl group (*i.e.* II, IV and $\frac{1}{2}$ of V and those from attack on the *p*-methyl group (*i.e.* III, VI and $\frac{1}{2}$ of V) was 45/55 for two parallel runs. This indicates steric hindrance of the reaction of the *o*-methyl by the nitro group to be of only minor importance. Consequently it is reasonable to assume that the difference in reactivity between ONT and PNT towards formaldehyde is mainly due to steric inhibition of resonance in ONT.

The UV spectra of II and III (Fig. 1) indicate no more steric inhibition of resonance in II than in III. The product composition of the diadducts (IV to VI, see Table 2) can therefore be explained as a result of an increased reactivity of the methylene groups of II and III due to the methylol groups, together with a decreased reactivity of the methylene group in II caused by steric crowding by the *o*-nitro group. However, further experiments will be necessary to clarify this point.

The steric inhibition of resonance is shown dramatically both chemically and spectroscopically by 2-nitro-*m*-xylene. In this compound, the nitro group is forced so far out of the plane of the benzene ring that the UV spectrum (Fig. 1) is quite different from that of ONT or PNT. The acidity of the methyl groups is so low that no reaction with formaldehyde in DMSO could be detected. This low acidity also shows that the activation of the methyl group in ONT is not due to the inductive effect of the nitro group but is caused by resonance.

The addition of ONT to aldehydes always stops before 100 % conversion. With formaldehyde as reactant a conversion of 30—40 % is typical. This low conversion was believed to be due to accumulation of byproducts during the reaction, or to the establishment of an equilibrium. However, experiments showed none of these explanations to be valid.

The main feature of solvents like DMSO, DMF *etc.* is the good solvation of cations and the low solvation of small anions, thus making ethoxide and hydroxide ions very reactive. As the addition of ONT to formaldehyde proceeds, more and more 2-(*o*-nitro-phenyl)ethanol (ONPE) is produced. The OH group of ONPE will then solvate the base making it less reactive and thus stopping the reaction. This possibility was tested by running the addition of ONT to formaldehyde in the presence of various concentrations of ONPE and of 2-phenyl-ethanol. The results are shown in Table 4. It is evident that both these alcohols inhibit the reaction of ONT with formaldehyde.

The products from the addition of ONT to aldehydes are valuable intermediates for chemical syntheses. These compounds have earlier been difficult

to obtain. Direct nitration of, *e.g.*, phenylethanol produces isomeric mixtures which are difficult to separate. The products are especially valuable as intermediates for various indole derivatives.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer Model 257. The electronic spectra were recorded in ethanol solution on a Beckman DK-2 spectrophotometer. NMR spectra were recorded in CDCl$_3$ solution on a Varian A 60 spectrometer using tetramethylsilane as internal standard. Gas chromatographic separations were made on a Perkin-Elmer F 11 gas chromatograph, equipped with a hydrogen flame ionisation detector. A Varian Aerograph Model 90-P was used for preparative VPC.

Competitive reaction between ONT and PNT. To ONT (1.9988 g, 14.6 mmoles), PNT (2.0004 g, 14.6 mmoles), and formaldehyde (0.88 g, 29.4 mmoles) in DMSO (50 ml) was added NaOEt (from 25 mg Na in 0.5 ml EtOH). VPC of the reaction mixture showed it to contain ONT (1.21 g, 8.8 mmoles, 61 % of starting material) and PNT (0.27 g, 1.97 mmole, 14 % of starting material).

4-Nitro-m-*xylene and formaldehyde.* Two runs were made. In run 1, KOH (12.5 mg, 0.22 mmole) in EtOH (0.125 ml) was added to 4-nitro-m-xylene (9.45 g, 62.5 mmoles) and formaldehyde (1.875 g, 62.5 mmoles) in DMSO (12.5 ml). VPC of the reaction mixture showed it to contain 4-nitro-m-xylene (6.50 g, 43 mmoles, 68.7 % of starting material), 2-(o-nitro-m-methylphenyl)-ethanol (II) (1.15 g, 6.35 mmoles) and 2-(p-nitro-m-methylphenyl)-ethanol (III) (1.20 g, 6.62 mmoles). The reaction mixture also contained formaldehyde (0.9 g, 47 % of starting material). To determine the amounts of mono- and di-adducts directly, 20.633 g of the reaction mixture was poured into water, extracted three times with ether, the ether phase washed twice with water, dried (Na$_2$SO$_4$) and concentrated, giving 7.75 g (corresponding to 9.55 g for the whole reaction mixture). The concentrate was chromatographed on silica gel, eluted with chloroform.

F$_1$ 5.4 g corresponding to 6.70 g for the whole react. mixt. (4-nitro-m-xylene)
F$_2$ 1.94 g   »   » 2.41 g » »   »   »   (II+III)
F$_3$ 0.50 g   »   » 0.62 g » »   »   »   (IV, V, VI)

F$_2$ was separated by preparative VPC to give II (λ_{max} 268 nm, ε_{max} 6200). IR (liquid) 3330, 2920, 2870, 1610, 1585, 1510, 1440, 1340, 1040, 830 cm^{-1}) and III (electronic and IR spectra near identical to II). The amounts of II and III were determined by analytical VPC. F$_3$ was esterified with Ac$_2$O/pyridine, and the esters separated by preparative VPC. The pertinent NMR data are given in Table 3. The amounts of IV, V, and VI were determined by analytical VPC.

The second run was analogous to the first one, except it was scaled up by a factor of 2. The quantitative results from the two runs are given in Table 2.

Examination of a possible equilibrium in the reaction between 4-nitro-m-*xylene and formaldehyde.* The reaction mixture of the addition products II and III was separated

Table 2. Yields of compounds II—VI in the reaction between 4-nitro-m-xylene and CH$_2$O.

	Yields in percent of reacted 4-nitro-m-xylene				
	II	III	IV	V	VI
Run 1	33.0	34.7	2.6	0.9	9.8
Run 2	28.8	30.3	2.0	2.0	8.3

Table 3.

Compound	NMR signals as δ-values		
	CH_3-	$Ar-CH-$	$-CH_2O-$
Acetate No. 1 from VPC (IV)	2.48	*Ca.* 4.3, multiplet	4.45, doublet, $J = 6$ cps
Acetate No. 2 from VPC (VI)	2.67	3.50, multiplet, $J = 6$ cps	4.42, doublet, $J = 6$ cps
Acetate No. 3 from VPC (V)	—	Two triplets at 3.08 and 3.34, both with $J = 6$ cps	Two triplets at 4.32 and 4.35, both with $J = 6$ cps

by preparative VPC. Two solutions in 1.5 ml DMSO were made. Solution 1 contained 168 mg II and 72 mg III (II/III = 70/30) as determined by VPC. Solution 2 contained 83 mg II and 145 mg III (II/III = 36/64). KOH (1 mg) in EtOH (0.01 ml) was added to each of the solutions. After 5 h at 23°, VPC showed the ratios between II and III to be unchanged in the two solutions.

Reaction of pure ONPE and formaldehyde. To see if accumulation of byproducts was the reason for the low conversion in the reaction between ONT and CH_2O, a typical reaction mixture was produced from pure materials. To ONPE (12.1 g), ONT (20.9 g) and formaldehyde (4.55 g) in DMSO (50 ml) was added NaOEt (2 mmoles) in EtOH (1 ml). VPC of the products showed the concentrations of the reactants (ONT and ONPE) not to have changed after addition of base.

Examination of a possible equilibrium in the reaction between ONT and formaldehyde. To ONPE (25 g) in DMSO (50 ml) (31 % ONPE in DMSO as compared to ca 15 % in a typical run, see above) was added NaOEt (2 mmoles) in EtOH (1 ml). VPC of the products showed that no reaction had occurred.

Reaction of ONT with formaldehyde in presence of alcohols. To eight samples, each containing ONT (10 g, 73 mmoles), formaldehyde (2.2 g, 73 mmoles), DMSO (25 ml), and various amounts of ONPE or 2-phenylethanol was added NaOEt (from 25 mg Na in 0.5 ml EtOH). The amount of unreacted ONT and formed ONPE was determined by VPC. The results are given in Table 4.

Table 4. Results from the reaction between ONT and CH_2O in the presence of added alcohols.

Alcohol added	Amount of alcohol added, mmol	Reacted ONT %	Formed ONPE % of reacted ONT
ONPE	0	60	62
»	27	32	35
»	54	15	5
»	81	5	—
2-Phenylethanol	0	58	67
»	30	10	115
»	60	4	100
»	90	9	100

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