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The Addition of Nitroethylbenzenes and Nitroisopropylbenzenes to Formaldehyde. A Comparison of Steric Inhibition of Resonance and Steric Hindrance in Mononitroalkylbenzenes

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The addition of nitroalkylbenzenes to formaldehyde has been studied. The decreased reactivity of *o*-nitroethylbenzene as compared to *p*-nitroethylbenzene was explained by both steric inhibition of resonance and by steric hindrance of the *o*-ethyl group by the nitro group. The evidence came from the reaction of 4-nitro-*m*-diethylbenzene with formaldehyde. Attempts to add *o*-nitroisopropylbenzene and 4-nitro-*m*-diisopropylbenzene to formaldehyde were negative, but indications of addition of *p*-nitroisopropylbenzene to formaldehyde were given.

Recently, a study of the addition of *o*- and *p*-nitrotoluenes to formaldehyde in dimethylsulfoxide (DMSO) was reported.[1] In a competitive reaction, *o*-nitrotoluene was less reactive than *p*-nitrotoluene towards formaldehyde. It was concluded that the lower reactivity of *o*-nitrotoluene was mainly due to the lack of coplanarity of the nitro group with the benzene ring (steric inhibition of resonance), and not to differences in steric hindrance.

The evidence for this conclusion came from the reaction of 4-nitro-*m*-xylene (*1*). In this compound, the effect of the steric inhibition of resonance was assumed to be approximately the same for both methyl groups. Attack on the *o*-methyl group, however, could also be subject to sterical hindrance by the nitro group.

The formation of the anions of the nitroalkylbenzenes was assumed to be the rate determining step in the reaction.[2] These anions, and probably also the transition states in their formation, will approach coplanarity with the phenyl ring to obtain maximum resonance stabilization.[3]

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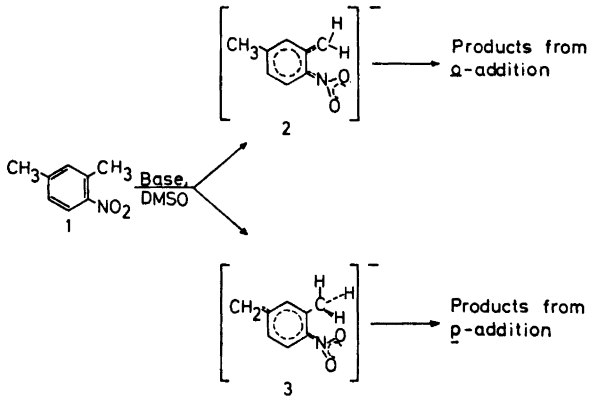
In the reaction of the 4-nitro-*m*-xylene with formaldehyde, the steric inhibition of the resonance might thus be slightly larger for the reaction at the *o*-methyl than at the *p*-methyl group; the *o*-methylene group (from the reaction at *o*-methyl) (*2*) might be more space consuming than the *o*-methyl group staggered with the nitro group (when the reaction occurs at the *p*-methyl) (*3*):

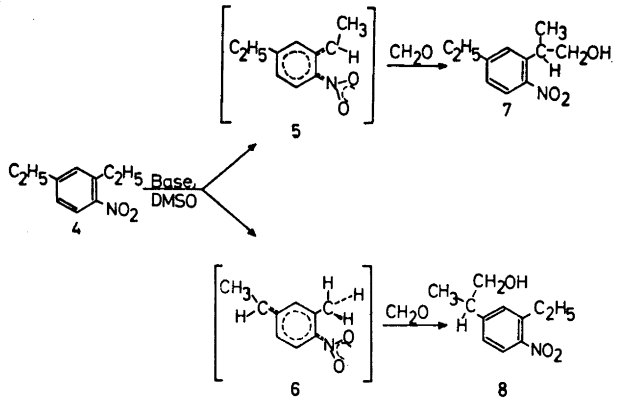


The observed ratio of the *o*-addition to *p*-addition of 4-nitro-*m*-xylene (*1*) was 82:100. It is not possible to say if the small difference in the reactivity of the *o*- and *p*-methyl groups was due to a small difference in steric inhibition of resonance for reaction at the *o*- and *p*-methyls, or if the reaction at the *o*-methyl was sterically hindered by the nitro group. However, the result clearly indicated steric hindrance, if present, to be of only minor importance in the addition of *o*-nitrotoluene to formaldehyde.

By substituting larger groups for the hydrogens of the methyl group of *o*-nitrotoluene, *e.g.* methyl, one would expect both the steric hindrance of the attack at the α-carbon and the steric inhibition of resonance of the nitro group to increase. It was considered of interest to investigate the addition of formaldehyde to *o*- and *p*-nitroethylbenzene, to 4-nitro-*m*-diethylbenzene and to *o*- and *p*-nitroisopropylbenzene as well as 4-nitro-*m*-diisopropylbenzene to obtain an idea of the importance of the two effects, as the group *ortho* to the nitro group increased in size.

In a competitive reaction between *o*-nitroethylbenzene and *p*-nitroethylbenzene with formaldehyde, the ratio of reacted *o*-nitroethylbenzene to reacted *p*-nitroethylbenzene was 20:100. The analogous ratio for the reaction with *o*-nitrotoluene and *p*-nitrotoluene was 45:100,[1] suggesting a greater hindrance of the reaction in *o*-nitroethylbenzene than in *o*-nitrotoluene.

Formaldehyde was then added to 4-nitro-*m*-diethylbenzene (*4*). In this compound, as in 4-nitro-*m*-xylene, the effect of the steric inhibition of resonance would be approximately the same for reaction at the *o*- and the *p*-methylene group. Coplanarity of the *o*-group with the benzene ring in the transition state should be about the same as in 4-nitro-*m*-xylene (see above), as the methyl of the *o*-ethyl probably will be *trans* to the nitro group (*5*):



Therefore, if there was no steric hindrance to reaction at the *o*-ethyl, a ratio of *o*-addition to *p*-addition close to 100:100 as in the 4-nitro-*m*-xylene case would have been expected. However, the ratio of *o*-addition to *p*-addition (*i.e.* 7:8) was found to be 26:100, thus indicating the reaction at the *o*-ethyl to be sterically hindered by the nitro group.

The importance of steric hindrance to attack at the α-carbon had thus increased by substitution of one hydrogen in the *o*-methyl with a methyl group. The decreased reactivity of *o*-nitroethylbenzene as compared to *p*-nitroethylbenzene is therefore probably due to both steric hindrance and to steric inhibition of resonance. In the *o*-nitrotoluene/*p*-nitrotoluene case, the steric hindrance was found to have only minor importance.

Attempts to add formaldehyde to *o*- and to *p*-nitroisopropylbenzene and to 4-nitro-*m*-diisopropylbenzene were successful only with *p*-nitroisopropyl benzene. As the size of the *o*-alkyl group increases from ethyl to isopropyl, both steric hindrance and steric inhibition of resonance (see Table 1) apparently become so severe that the last hydrogen at the α-carbon practically looses its activity.

Table 1. UV absorption maxima for nitroalkylbenzenes (in ethanol, 95 %).

Alkyl group	Position relative to NO_2				2,4-disubstituted	
	o		*p*			
	λ_{max} (nm)	ε (l mol^{-1} cm^{-1})	λ_{max} (nm)	ε (l mol^{-1} cm^{-1})	λ_{max} (nm)	ε (l mol^{-1} cm^{-1})
Methyl	260	6200	272	9700	268	6800
Ethyl	256	5200	273	9900	268	6500
Isopropyl	252	4300	273	10800	265	4000
H	251	9000	251	9000		

Experimental. Nitration of *m*-diisopropylbenzene to 4-nitro-*m*-diisopropylbenzene, was carried out as described by Hansch and Helkamp [4] for isopropylbenzene. The additions of nitroalkylbenzenes to formaldehyde were performed by making a 5 mM solution of the nitroalkylbenzene in DMSO, adding an equimolecular amount of paraformaldehyde, and then, under stirring, 2 mol % of KOH in EtOH. After 1 h, the amounts of product and starting materials were determined by GLC (internal standard method). The products were isolated by pouring the reaction mixture on to water, extracting the water phase three times with ether, washing the ether phase twice with water, drying (Na_2SO_4) and evaporating the ether. The products were separated from the starting materials by column chromatography on silica gel, with chloroform as eluent.[1]

The products from the reaction with 4-nitro-*m*-diethyl-benzene [5] (yield 17 %; 73 % of reacted 4-nitro-*m*-diethylbenzene) were separated by preparative GLC (column: SE 30, 3 feet). The first eluted compound (*7*) contained 5 % of *8* and had IR absorption (5 %, $CHCl_3$) at 3600, 3400, 2960, 2920, 2870, 1610, 1590, 1350, 1030, 840 cm^{-1}. IR of the second compound (*8*) (contaminated with 1.5 % *7*) had identical spectrum. The NMR spectra of the two compounds (Table 2) showed the second compound to be *8*. This assignment rests on the fact that protons in methyl, methylene, or methine groups *ortho* to the nitro group have their NMR signals at slightly higher δ-value than the protons in the corresponding *para* groups (Table 2). The position of the compound on the gas chromatogram and TLC, the IR spectrum, and the NMR spectrum (low intensity due to lack of material) identified *7*.

Table 2. NMR data for nitroalkylbenzenes (in $CDCl_3$).

Compound	NMR signals as δ-values		
	Ar–CH_2– or Ar–CH<	R–CH_2OH	Me
o-Nitroethyl-benzene	2.81 (quartet)	–	1.18 (triplet)
p-Nitroethyl-benzene	2.70 (quartet)	–	1.21 (triplet)
4-Nitrodiethyl-benzene	2.87 (quartet, *o*) and 2.65 (quartet, *p*)	–	1.20 (triplet)
Compound *8*	2.92 (quartet, *o*)	3.70 (doublet)	1.26 (triplet) 1.29 (doublet)
Compound *7* (weak spectrum)	Multiplet, 2.75	Multiplet, 3.75	Multiplet, 1.30
o-Nitroisopropyl-benzene	3.39 (heptet)	–	1.25 (doublet)
p-Nitroisopropyl-benzene	2.99 (heptet)		1.25 (doublet)
4-Nitro-*m*-diiso-propylbenzene	3.50 (5 signals recognized, *o*) and 2.97 (5 signals recognized, *p*)		1.23 (doublet) and 1.28 (doublet)

*Addition of formaldehyde to nitroisopropylbenzene and to 4-nitro-*m*-diisopropylbenzene.* The addition to *o*-nitroisopropylbenzene and to 4-nitro-*m*-diisopropylbenzene was unsuccessful as judged by TLC. The addition of paraformaldehyde (0.18 g) to *p*-nitro-

isopropylbenzene (1.00 g) in DMSO (2.5 ml) (base: KOH, 30 mg/0.33 ml of ethanol) gave unreacted nitroisopropylbenzene (0.82 g) and 2-methyl-2-(*p*-nitrophenyl)-propanol (0.05 g) (isolated by chromatography on silica gel column, eluted with chloroform). 2-Methyl-2-(*p*-nitrophenyl)-propanol had IR bands (liq.) at 3400, 2960, 2940, 2880, 1605, 1520, 1350, 1110, 1095, 1050, 960, 850, 760, 730, 700 cm^{-1}.

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