Sodium Borohydride as a Reagent for Nucleophilic Aromatic Substitution by Hydrogen: the Role of Hydride Meisenheimer Adducts as Reaction Intermediates

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The reaction of *o*-bromo- and *p*-chloro-nitrobenzenes and of 1,4-dinitrobenzene with sodium borohydride in a dilute solution in dimethyl sulphoxide solution leads to some nitrobenzene. When tritiated borohydride is employed, aromatic hydrogen exchange occurs to a comparable extent.

Under similar conditions 1-X-2,4-dinitrobenzenes mostly undergo either displacement of the 2-nitro-group by hydrogen or ring reduction. With these compounds it is possible to observe the n.m.r. spectra of the unstable cyclohexadienyl anions (hydride Meisenheimer adducts), formed by hydride addition to the 3- and/or the 5-position, which decompose into the final products.

For 2,4-dinitroanisole it is shown by an isotope-labelling experiment that the displacement of the 2-nitro-group is accompanied by intramolecular hydrogen migration from the methylene group of the Meisenheimer adduct (at the 3-position) to the 2-position. This mechanism is the nucleophilic analogue of the mechanism of *ipso*-attack with migration, recognised as one of the reaction paths in electrophilic aromatic substitution. The term ' vicinal attack ' is proposed for this general class of aromatic substitution reactions in which the entering group first attacks and attaches itself to a ring position adjacent to the position that it occupies in the reaction product and from which the leaving group is displaced.

THE action of sodium borohydride (tetrahydridoborate) on nitroaromatic compounds has been reported to lead to a variety of reaction products, their nature depending on the precise substrate and reaction conditions. The products include (*a*) azoxy-[1-3] and azo-compounds[2,3] and amines,[3] and (*b*) compounds in which there is reduction of an aromatic ring,[4-8] or (*c*) displacement of a nitro-[7,9-13] halogeno-,[7,14] or hydroxy-group[10] by hydrogen. Radical anions have been detected in some reaction mixtures,[15] and Severin *et al.* have inferred that unstable salts isolated in reactions of types (*b*) and (*c*) are mono-,[5] di-,[5,6,8] and tri-[4] hydride adducts (*i.e.* hydride Meisenheimer adducts). The isolation of a stable adduct of this type (for 1,3,5-trinitrobenzene)[16,17] and the occurrence of aromatic hydrogen exchange between nitrobenzene and tritium-labelled sodium borohydride in dimethyl sulphoxide (DMSO) solution[18] strongly support at least the formation of monohydride adducts as reaction intermediates.

The present study seeks to provide information on the relative importance of some of the alternative reactions, including aromatic hydrogen exchanges in simple derivatives of nitrobenzene and, by n.m.r. observations during the course of the reactions, to identify and relate reaction intermediates to final products. All measurements refer to solutions in DMSO at temperatures of 25 or 37 °C. The compounds included in this study were 1,4-dinitrobenzene, 2- and 4-chloro- and -bromonitrobenzene, and a series of 1-X-2,4-dinitrobenzenes.

EXPERIMENTAL

Tritium Exchange.—Weighed amounts of the aromatic compound and of sodium boro[^{3}H]hydride (Radiochemical Centre, Amersham, 0.30 Ci mol^{-1}) were dissolved in DMSO (25 cm^3; redistilled under reduced pressure from calcium hydride and subsequently stored over molecular sieve, 4 Å). At the end of the reaction period, a large excess of substrate was added as carrier. The aromatic compound was extracted with benzene, and the solvent was evaporated off. The sample was crystallised to constant activity, as determined by scintillation counting (with correction for the reduction in counting efficiency in the presence of quenching substrates). The experimental details of experiments with different compounds are summarised in Table 1.

Products of Reaction.—The experimental conditions were similar to those for the exchange experiments, except that unlabelled sodium borohydride was used. After a given reaction time, product mixtures were extracted with cyclohexane or benzene. The extracts were dried ($MgSO_4$ or Na_2SO_4), most of the solvent was evaporated off, and the products were analysed by g.l.c. (Varian 1200 gas chromatograph with flame ionisation detector, employing a 10 ft column of 20% S.E. 30 on Chromosorb W). The identification of eluates was based on the comparison of retention times with those of authentic samples. In view of the chemical similarity of the products, analyses were not corrected for differences in detector response: they are accordingly subject to minor uncertainties. Experimental conditions and results are summarised in Table 2. In the case of the two 1-halogeno-2,4-dinitrobenzenes reaction was more extensive than in the case of the corresponding mono-nitro-compounds, and the progress of product formation was

TABLE 1

Summary of exchange experiments with X-$C_6H_4NO_2$ and tritiated $NaBH_4$

X	n [a]	[NC] [b]	[BH] [c]	t [d]/h	A [e]$_{obs}$	A [f]$_{calc}$	% Reaction
4-NO_2	4	52	26	143	1.01	10	10
4-Br	2	56	23	144	3.38	13.5	25
4-Cl	2	116	116	142	1.26	20	6
2-Br	1	64	80	140	0.25	22	1.1
2-Cl	1	72	76	140	0.43	24	1.8

[a] Assumed number of exchanging hydrogen atoms in X-$C_6H_4NO_2$. [b] [NC] = 10^3 [X-$C_6H_4NO_2$]/mol dm^{-3}. [c] [BH] = 10^3 [$NaBH_4$]/mol dm^{-1}. [d] Reaction time. [e] (Activity of X-$C_6H_4NO_2$ after time t)/mCi mol^{-1}. [f] Calculated equilibrium activity of X-$C_6H_4NO_2$/mCi mol^{-1}, assuming random distribution of total activity between 4 hydrogen atoms of borohydride and n hydrogen atoms of X-$C_6H_4NO_2$.

followed. In all cases the identified eluates represent the major reaction products, but some less volatile products were also formed to a minor extent.

In view of a report[12] that nitrobenzene is not formed in the reaction of 1,4-dinitrobenzene in a DMSO–water mixture, the effect of solvent variation on the reaction of this substrate was briefly examined (Table 3).

TABLE 2

Product formation from reactions of $ArNO_2$ with sodium borohydride

Substituents[a] in Ar	[NC]/[BH][b]	t[b]/h	% Halide loss[c]	% Nitro loss[d]
4-NO_2	2.1	146		15
4-Br	2.5	140	2.0	Not detected
		5 000	5	Not detected
4-Cl	0.97	143	3.7	Not detected
2-Br	1.5	144	12	Not detected
2-Cl	0.93	145	7.3	Not detected
2-Br,5-NO_2	1.56	1	<1	23
		3	<1	23
		48	<1	31
		144	<1	44
2-Cl,5-NO_2	1.2	0.03	4	15
		0.08	7	29
		0.17	10	39
		0.67	13	51
		1.0	14	54
		4.0	13	63
		24	15	73
		336	37[e]	57[e,f]

[a] Positions are numbered from nitro-substituent. [b] Symbols defined in Table 1. [c] Percentage of parent compound converted into product resulting from replacement of halogen by hydrogen only. [d] Percentage of parent compound converted into product resulting from replacement of one nitro-group by hydrogen only. [e] Formation of 7% nitrobenzene is additionally observed. [f] Formation of *p*-chloronitrobenzene; *o*-isomer not detectable.

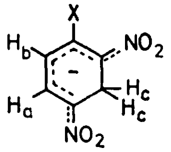
N.m.r. observations on reaction mixtures. Samples were prepared by mixing in an n.m.r. tube 0.5 cm³ portions of stock solutions in [$^2H_6$]DMSO of the aromatic compound and of sodium borohydride so as to produce a solution containing each component at a stoicheiometric concentration of 0.2 to 0.5 mol dm^{-3}, *i.e. ca.* 2—20 times higher than in the experiments on exchange and on product formation. Selected spectra were taken on a Bruker HFX 90 instrument (90 MHz) at room temperature. Other spectra were recorded on a Perkin-Elmer R12B instrument (60 MHz) at 37 °C immediately after mixing and after successive time intervals of 6 min. Typical initial spectra are reproduced in the Figure 1. The signals were assigned on the basis of multiplicities and chemical shifts by comparison with published information on n.m.r. spectra, especially those of Meisenheimer adducts with alkoxides[19,20] and with hydride.[16] Some of the signals of the spectrum in Figure 1(a) are attributed to two isomeric hydride Meisenheimer adducts (1 and 2; X = Br) corresponding to hydride addition at the 3- or 5-positions of 1-bromo-2,4-dinitrobenzene (*i.e.* '3M' and '5M'). The other two spectra are typical of reaction mixtures giving rise to single adducts, at the 3- and 5-positions, respectively. Table 4 lists the signals corresponding to analogous Meisenheimer adducts, for the entire set, together with their assignments. All these signals decreased in intensity with time, all those attributed to the same isomer diminishing at the same rate, as indicated by the column of approximate half-lives ($\tau_{\frac{1}{2}}$) in Table 4. In every case the relative intensities of the signals assigned to H_a, H_b, and H_c were close to the ratio 1 : 1 : 2 required by the formulae of 3M and 5M. In 3M, the H_a and H_b signals were doublets and the H_c signal a singlet, whereas in 5M, H_a gave a singlet, H_b a triplet, and H_c a doublet (see Figure 1). The coupling constants were, for the typical case of

TABLE 3

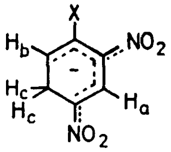
Reaction between 1,4-dinitrobenzene and sodium borohydride in aqueous DMSO

% Water[a]	[NC]/[BH][b]	t[b]/h	% Nitro loss[b]
0	2.1	146	15
5[c]	0.5	144	100
30[c]	0.5	144	72
23[d]	0.5	19	11

[a] x % means x volumes of water + (100 − x) volumes of DMSO. [b] See Tables 1 and 2 for symbols and terms used. [c] 10^{-3}M NaOH used in place of pure water. [d] Solvent composition employed by Bird, Rae, and White[12] who reported no chemical change of 1,4-dinitrobenzene after 1 h.



(1)(3M)



(2)(5M)

TABLE 4

Positions of n.m.r. signals (δ) due to transient hydride Meisenheimer adducts of 1-X-2,4-dinitrobenzenes in [$^2H_6$]DMSO

	3M				5M			
X	H_a	H_b	H_c	$\tau_{\frac{1}{2}}$	H_a	H_b	H_c	$\tau_{\frac{1}{2}}$
H		Not observed			8.20	5.40	3.40	1 day
CN		Not observed			8.12	6.19	3.55	8 min
Br[r]	7.13	5.25	3.94	4 min	8.31	5.68	3.34	15 min
Cl[r]	7.28	5.22	3.95	6 min	8.41	5.46	3.44	40 min
F †[r]	7.3	*ca.* 5	3.84	10 min	8.13	*ca.* 5	3.40	1 day
OMe[v]	7.42	5.01	3.74	20 min		Not observed		
OEt[v]	7.45	5.05	3.77	60 min		Not observed		
NH_2[s]	7.39	5.16	3.57	10 days		Not observed		
$NH{\cdot}NH_2$[s]	7.42	4.97	3.52	7 days		Not observed		
NMe_2[s]	7.34	5.17	3.82	2 h		Not observed		
NHPh[s]	*	5.13	3.68	3 h		Not observed		
NPh_2[s]	*	5.10	3.85	6 min		Not observed		

* Obscured by signal due to phenyl protons. † All signals are F-coupled, those at *ca.* 5 p.p.m. are complex. [r] Final product corresponds to ring reduction. [s] Final product corresponds to displacement of 2-nitro-group. [v] Variable composition of final product; see text.

1-bromo-2,4-dinitrobenzene, J_{ab} (in 3M) 9 Hz and J_{bc} (in 5M) 5 Hz.

In the case of 1,3-dinitrobenzene, the initial spectrum showed very broadened resonances which gradually sharpened before decaying with quite long half-life (*ca.* 1 day). The initial appearance of the spectrum is probably associated with the generation of transient anion radicals [15] from a side reaction, as has also been observed in the reactions of this substrate with base.[21] Similarly broadened resonances were sometimes noticed also with the initial spectra of other reaction mixtures.

Partial deuteriation of 2,4-*dinitroanisole by* $NaBD_4$. A solution of commercial sodium boro[$^2H_4$]hydride(tetrahydridoborate) ($NaBD_4$, 0.11 g, 0.002 6 mol) in [$^2H_6$]DMSO (99.5% D, 1 cm^3) was added dropwise and with cooling, to keep the temperature below 30 °C, to a solution of 2,4-dinitroanisole (0.5 g, 0.002 5 mol) in the same solvent (5 cm^3). After 15 min the blue reaction mixture was poured into water (200 cm^3) acidified with two drops of concentrated sulphuric acid. The precipitate was filtered off, washed with water, and crystallised from ethanol to give a specimen of partially deuteriated 2,4-dinitroanisole (0.15 g), free of 4-nitroanisole. The incorporation of deuterium was confirmed by a mass spectrum but the extent was not determined quantitatively.

Reaction of partially deuteriated 2,4-*dinitroanisole with sodium borohydride*. A solution of sodium borohydride (0.016 g, 0.000 4 mol) in DMSO (1 cm^3) was added, with cooling as before, to a solution in DMSO (5 cm^3) of a sample of partially deuteriated 2,4-dinitroanisole (0.1 g, 0.000 5 mol). After 16 h at room temperature, the reaction mixture was poured into acidified water, as before. The resulting mixture was extracted with diethyl ether (2 × 50 cm^3). After being dried ($MgSO_4$) the extract was concentrated and chromatographed (thin-layer silica gel, eluting with benzene) and the zone corresponding to *p*-nitroanisole was removed and extracted with chloroform. *p*-Nitroanisole was separated (15 mg, 20% yield) and its ^{2}H n.m.r. spectrum at 13.8 MHz was recorded in trichlorofluoromethane solution (Bruker HFX 90 instrument), using an internal standard of [$^2H_6$]acetone (δ 2.067 p.p.m.). Deuteron resonances were observed at *ca.* δ 6.9, 8.2, and 8.6, in the approximate intensity ratio 1 : 2.5 : 0.9. For comparison, the proton n.m.r. spectrum of *p*-nitroanisole contains two multiplets centred at δ 6.89 and 8.11, attributable, in first order, to the aromatic protons at the 2- and 3-positions, respectively. The complex proton n.m.r. spectrum of 2,4-dinitroanisole has the appearance of a doublet (separation 2.6 Hz) centred at δ 8.73 Hz, a double doublet (separations 2.9 and 2.6 Hz, separation of centres of doublets 9.2 Hz) centred at *ca.* δ 8.46, and a doublet (separation 9.4 Hz) centred at δ 7.29. In first order, these groups of signals can be assigned to the aromatic protons at 3-, 5-, and 6-positions, respectively. The deuteron resonances observed in the isolated specimen (of partially deuteriated *p*-nitroanisole) are accordingly assigned to ring positions 2 and 3 (most intense) and the unresolved signal at *ca.* δ 8.6 to contamination by the starting material (2,4-dinitro[3-^{2}H]anisole), or possibly by deuteriated dinitrocyclo-hexene or -hexadiene.

DISCUSSION

The Products.—The product analyses for reactions of 2- and 4-substituted nitrobenzene derivatives with sodium borohydride in DMSO solution show that substitution reactions in which a halogen or nitro-group is displaced by hydrogen occur quite readily (see Tables 2 and 3). These experiments concentrated on the relative ease of displacement of substituents, and the yields of less volatile products, such as cyclohexene derivatives, were not measured. Qualitatively, it seems that reduction of the aromatic ring becomes more important as the concentration of borohydride is increased. For this reason the occurrences of ring reduction in experiments on the preparative scale was firmly established fifteen years ago [4-7] before any extensive study of the substitution reaction had been carried out.

The substitution reactions of nitroaromatic compounds with sodium borohydride in DMSO solution share some of the characteristic features of other nucleophilic aromatic substitution reactions. For example (*cf.* Table 2), in non-hydroxylic solvents a nitro-group is more readily displaced than halogen from a 4-position in a 4-X-nitrobenzene, and a 4-nitro-group generally appears to be less activating than a 2-nitro-group.[22] The comparatively ready displacement of a nitro-group in 1-chloro- and 1-bromo-2,4-dinitrobenzene is more unusual, since solvolysis of these compounds has invariably been considered to lead exclusively to halide loss.

Even under experimental conditions leading predominantly to substitution products (rather than to ring-reduction products) the use of tritiated sodium borohydride with some of the less reactive substrates readily gives rise to ring-labelled starting material (see Table 1). Attack of borohydride on the aromatic ring is therefore competitive with, and possibly the initial step of, the substitution reaction. In comparing the relative progress of hydrogen exchange (Table 1) with that of substituent loss (Table 2) one must allow for an expected intramolecular kinetic isotope effect in a BH_3T^- ion (which will discriminate against loss of tritium relative to protium). The hydride transfer step therefore appears to be a more rapid reaction than tritium exchange for these particular substrates.

Intermediates.—The role and progress of hydride transfer to the aromatic ring in nitroaromatic compounds was more directly investigated by observation of the proton n.m.r. spectra of reaction mixtures as a function of time. The compounds used were twelve 1-X-2,4-dinitrobenzenes. In all cases equimolar mixtures of the nitro-compounds and sodium borohydride in DMSO immediately produced highly coloured solutions from the n.m.r. spectra of which the signals due to the parent aromatic compounds had disappeared. In their place new signals were evident. Some of these signals persisted or grew with time and were therefore attributable to final products; others were transient and hence belonged to unstable reaction intermediates.

The persistent signals were in some cases easily identified as the spectrum of the 1-X-4-nitrobenzene, *i.e.* the product due to elimination of a 2-nitro-group. In other cases, of which the spectrum of 1-bromo-2,4-dinitrobenzene [Figure 1(a)] is typical, the persistent signals were mostly broad and in the positions expected for dinitrocyclohexene derivatives. According to Severin and Adam,[5] the main reaction product for this compound in tetrahydrofuran–formamide solution is a dihydride adduct from which the dinitrocyclohexene (3) is liberated on addition of water or acid. The letters (d)—(h) against various peaks in the spectrum of Figure 1(a) indicate a very tentative interpretation in terms of the hydrogen positions in compound (3). The broad shape of the signals is possibly due to the presence of a mixture of stereoisomers as well as complex spin coupling.

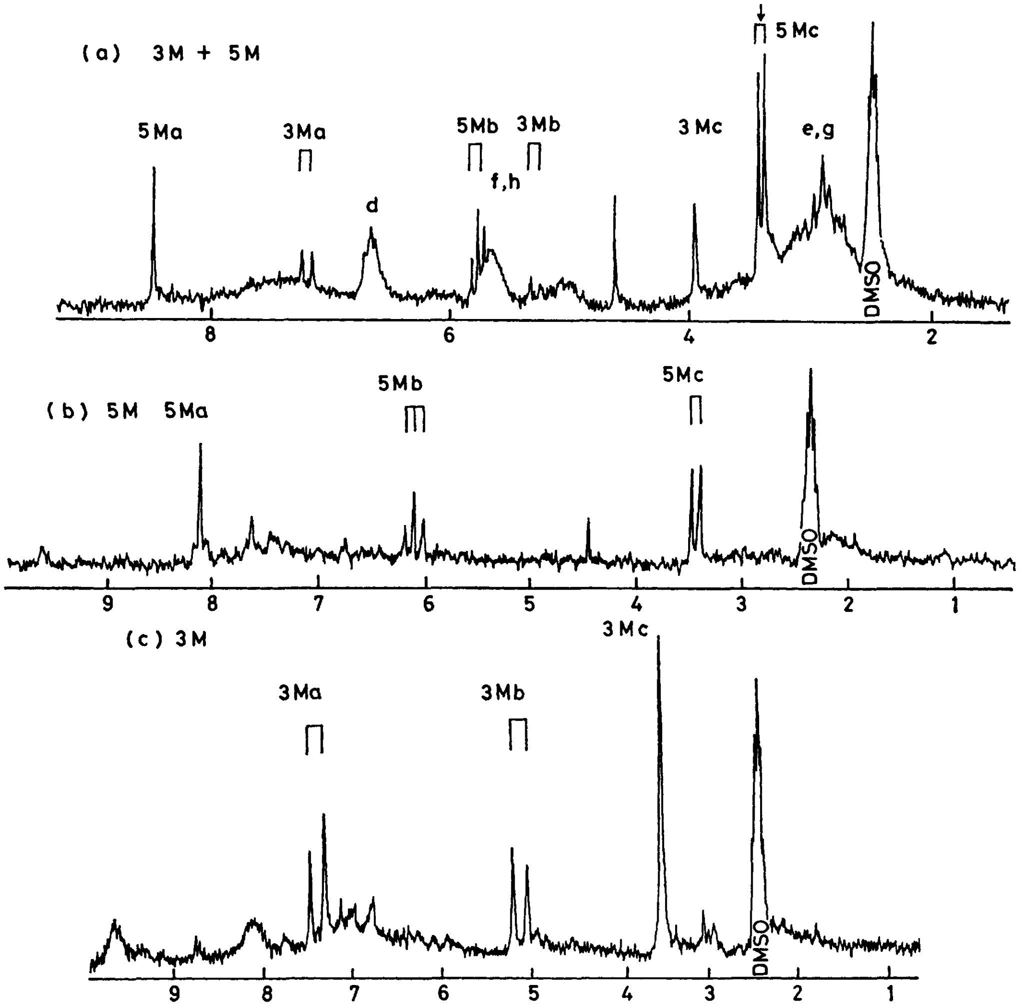
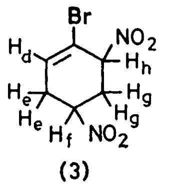


FIGURE 1 N.m.r. spectra of intermediates from reaction of $NaBH_4$ with 2,4-dinitro-compounds: (a) 1-bromo-2,4-dinitrobenzene (90 MHz); (b) 1-cyano-2,4-dinitrobenzene (60 MHz); (c) 2,4-dinitroaniline (60 MHz). For assignments see text



(3)

We note that the observed product in our solutions is the dinitrocyclohexene rather than a precursor salt.

The transient signals were centred at either *ca.* δ 3.7, 5.1, and 7.3 or at *ca.* δ 3.4, 5—6, and 8.3. For the three 1-halogeno-2,4-dinitrobenzenes resonances were observed at all six positions [see Figure 1(a)]. The signals were attributed to the two hydride adducts (1) (3M) and (2) (5M). The letters a—c in the spectra of Figure 1 correspond to the similarly labelled positions in formulae (1) and (2). The chemical shifts observed bear a close resemblance to those previously established for Meisenheimer adducts resulting from methoxide addition to 2,4- and 2,6-dinitroanisoles.[19,20] The correspondence is evident from the chemical shifts indicated in the annotated formulae of Figure 2, where the dotted lines connect structures with similarly placed hydrogen atoms. The multiplicities and relative intensities of signals agree with the assignments summarised in Table 4.

The position of the methylene group resonance depends on the location of the group relative to the nitro-substituents. It varies from δ 3.9 (when there are three symmetrically placed nitro-groups) to δ 3.5—3.8 (when two flanking nitro-groups are present) to δ 3.3—3.5 (when one nitro-group is adjacent and one opposite).

All the spectral features show a regular pattern for the entire set of compounds (Table 4) which indicates a basic similarity (and progression in behaviour) through the series.

The assignment of the transient resonances to structures (1) and (2) was confirmed by repeating the experiment with sodium boro[$^2H_4$]hydride ($NaBD_4$) in place of sodium borohydride, when the signals ascribed to the methylene hydrogens (H_c) became unresolved narrow multiplets (due to CHD) and the triplet due to the b protons in (2) turned into a doublet. When such a reaction mixture (with 2,4-dinitroanisole) was poured into D_2O, partially deuteriated starting material was recovered.

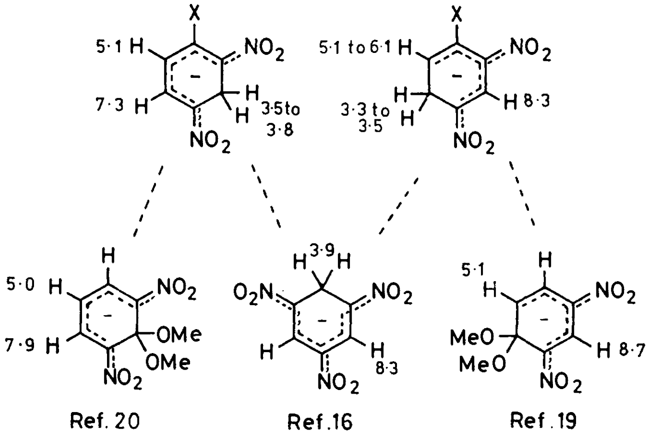
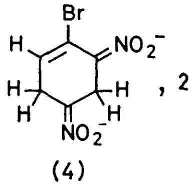


FIGURE 2 Chemical shift comparison for methoxide and hydride Meisenheimer adducts

For the cases in which signals were observed at all six positions the resonances were clearly due to two different chemical species, as indicated by their gradual decay. The group of signals attributed to 3M always disappeared more rapidly than the group ascribed to 5M (see Table 4), and all members of the same group decayed at the same rate. It follows that, for DMSO solutions at the low concentrations of our experiments, there is no evidence for a dihydride Meisenheimer adduct (4), the formula ascribed by Severin and Adam [5] to a salt isolated under very different experimental conditions.

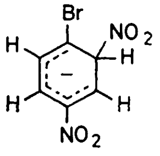


(4)

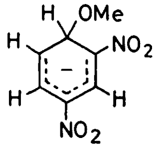
In all spectra of compounds with resonances indicative of two adducts, both groups of signals decayed from the outset (though at different rates). This behaviour is incompatible with the idea that the less stable adduct is converted into the more stable adduct and that this in turn goes to the final product. Such a rearrangement of an adduct is observed in methoxide addition to 2,4,6-trinitroanisole.[23] However, it clearly does not occur at a significant rate in the hydride adducts 3M and 5M, which therefore must be formed in parallel reactions. The relative intensities of the spectra due to these two adducts immediately after mixing them reflect their relative rates of formation from the parent compound.

The final n.m.r. spectra of solutions of all the amines and of the hydrazine, in which the reactions had been allowed to go to completion, indicated clean replacement of the 2-nitro-group (see Table 4). For the two ethers substitution decreased relative to ring reduction as the concentration of borohydride in the solutions was increased. This finding is relevant to the observation of predominant ring reduction found for the 1-halogeno-2,4-dinitrobenzenes in the n.m.r. experiments whereas gas-chromatographic analysis of the products of the same compounds (Table 2) had indicated extensive substitution. The apparent discrepancy is explained by the difference in concentrations of reagents used in the two series of experiments. (The n.m.r. runs relate to higher concentrations.)

Reaction Mechanism.—The detection of hydride Meisenheimer adducts in our solutions is not by itself evidence that such species are intermediates in the nucleophilic aromatic substitution reaction. Thus, it could be argued that the addition reaction leading to a reversible formation of 3M (1) might be entirely distinct from the supposedly slower direct formation of an adduct 2M (5), an unstable species not detected in the n.m.r. spectrum, which might rapidly eject a nitrite group with formation of the product of nucleophilic aromatic substitution.

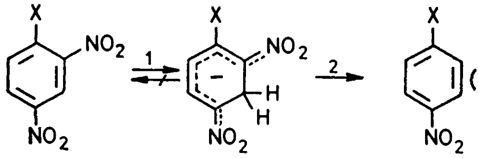


(5)(2M)



(6)

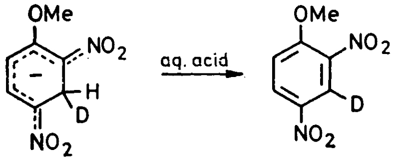
[Such a mechanism would be roughly analogous to the aromatic hydrogen exchange of 1,3-dinitrobenzene in solutions of sodium methoxide, where the observed reversible formation of the Meisenheimer adduct (6) is irrelevant to the mechanism of the exchange.[24]] This hypothesis is not attractive in view of the apparent lack of interconversion of 3M and 5M. This observation suggests that these Meisenheimer adducts do not easily revert to the parent compound. Such reversion would be essential to the formation in fair yield of the substitution product by a mechanism that does not involve one of these adducts as an intermediate on the reaction path. The alternative hypothesis is to assume that 3M or 5M is a precursor of 1-X-4-nitrobenzene in the reaction of 1-X-2,4-dinitrobenzene with sodium borohydride, *i.e.* in the general case of the 3-adduct the reaction proceeds according to equation (1). The second step of the sequence (1) implies the occurrence of a hitherto unrecognised type of molecular rearrangement, involving the intramolecular migration of hydrogen from the 3-position to the 2-position. The additional possibility of an intramolecular migration across the ring (rather than to an adjoining carbon atom) does not seem to be as important to the interpretation of our results, in view of the exclusive formation of 1-X-4-nitrobenzenes from



(1)

those substrates for which the Meisenheimer adduct at the 3-position predominates (see Table 4).

Since no close precedent for the mechanism of reaction (1) is known to us, we have sought further evidence from a labelling experiment, using 2,4-dinitroanisole as substrate. On labelling the 3-position with deuterium, reaction of the substrate with ordinary sodium borohydride should, according to this mechanism, result in the production of 4-nitroanisole containing some deuterium in the 2-position. The requisite labelling of the starting material was effected by careful mixing of 2,4-dinitroanisole with sodium [$^2H_4$]borohydride, followed by decomposition of the Meisenheimer adduct and excess of borohydride species with dilute aqueous acid. The recovered dinitroanisole was purified so as to be quite free of 4-nitroanisole. The adduct formed in the first step would be (8), and its decomposition would lead

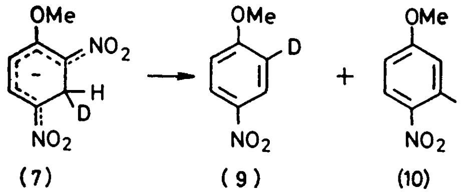


(7) (8)

mainly to the labelled product (8) since a kinetic isotope effect should appreciably favour loss of protium rather than deuterium in this step. Whilst formation of a 5-hydride adduct has not been observed with 2,4-dinitroanisole under similar conditions (see Table 4), we cannot altogether rule out the possibility that this labelling procedure may have led to a minor amount of deuterium incorporation at the 5-position. However, this would not affect the interpretation of the outcome of the following experiment with this labelled material. It is more important to note that formation of a Meisenheimer adduct involving the 6-position would be totally at variance not only with the experiments reported in this paper but also with the entire body of experience concerning the structural features conducive to the formation of Meisenheimer adducts.[25] We therefore consider deuterium labelling at the 6-position not to occur during the above procedure.

The labelled material was then subjected to reaction with ordinary sodium borohydride in DMSO solution. This reaction should again produce the adduct (7) as a first step and, if the subsequent formation of 4-nitroanisole involves intramolecular migration of hydrogen from the 3- to the 2-position, that product should then have some incorporation of deuterium at the 2-position. In this reaction a kinetic isotope effect should favour migration of protium. Accordingly, the 4-nitroanisole formed is expected to contain some deuterium at both 2- and 3-positions, the latter predominating. From the relative intensities in the deuteron magnetic resonance spectrum of the isolated product we conclude that some 4-nitro[2-^{2}H]anisole (9) was indeed formed, and that the amount of the simultaneously produced 4-nitro[3-^{2}H]-anisole (10) (the generation of which involves migration of protium) was *ca.* 2.5 times greater [see equation (2)].

This experiment therefore supports the reaction



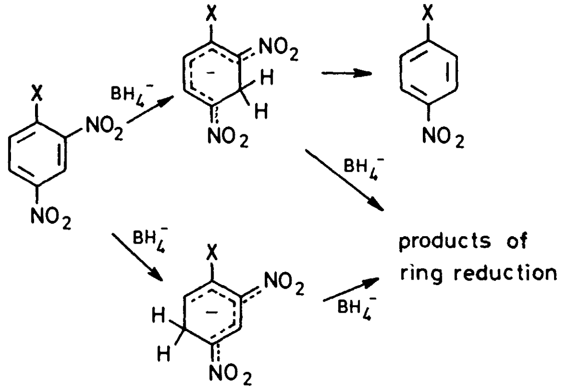
(2)

(7) (9) ca. 30% (10) ca. 70%

sequence (1) as the course of the nucleophilic replacement of the nitro-group by hydrogen in the reaction of 2,4-dinitrobenzene derivatives with sodium borohydride in DMSO solution.

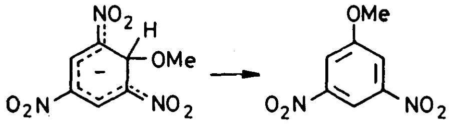
The second step of reaction sequence (1), or reaction (2), can, accordingly, be looked upon as an internal displacement of nitrite by hydride in an anionic species, and hence as a novel type of neighbouring-group participation.

The connection between intermediates and final products then appears to be as follows:



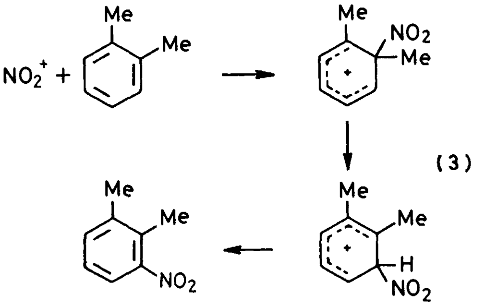
The further intervention of reducing agent (favoured at higher concentrations) would account for the variable yield of products of ring reduction. The result that the hydride adduct at the 3-position leads exclusively to substitution at the 2-position (and not to any at the 4-position) may be the consequence of the steric requirements of the group X. When X is large, the 2-nitro-group is expected to be twisted out of coplanarity with the aromatic ring, with interruption of conjugation. On the other hand, the 4-nitro-group is unencumbered so that the bond through which that group is attached to the aromatic ring retains some double-bond character and is, therefore, less easily broken. These indirect steric effects on the geometry of the 2-nitro-group may also be the cause of the relative importance of the formation of the two alternative Meisenheimer adducts. However, ordinary electronic effects of the group X and its hydrogen-bonding capacity are also expected to play some role.

There is at present no evidence to answer the question whether the mechanism of equation (1) is also applicable to other nucleophilic displacements of nitro-groups or even more generally to nucleophilic aromatic substitution reactions. It has previously been noted that the second-order rate law for the formation of 3,5-dinitroanisole from 1,3,5-trinitrobenzene in methanolic sodium methoxide [26] is not inconsistent with the idea that the product results directly from the observed Meisenheimer adduct (11). In the absence of the type of evidence adduced here, Gold and Rochester [26] regarded this mechanism, involving intramolecular migration of methoxy, as improbable compared with the simpler direct substitution reaction involving free trinitrobenzene and methoxide ion. The validity of this judgement now appears less certain. Analogous hydrogen shifts have also previously been considered, but rejected on the basis of further experiments, for certain *cine*-substitutions by NH_2 groups.[27]



(11)

General Terminology.—Whilst mechanisms of this type do not appear to have previously been found in the context of nucleophilic aromatic substitution, there are some analogies in electrophilic aromatic substitution. As Myhre [28] first suggested, it is thought that an entering nitro-group may migrate to a position adjoining that which it occupied in the cyclohexadienyl cation (the so-called Wheland intermediate, the analogue of the Meisenheimer adduct intermediate in nucleophilic aromatic substitution). An example of this mechanism (in this context described as migration of an '*ipso*-substituent ')[29] is the formation of 1,2-dimethyl-3-nitrobenzene from *o*-xylene *via* the route (3).



(3)

The analogy between reactions (1) and (3) will be obvious, and it seems appropriate to have a common name for what now appears to be a more general mechanism in aromatic chemistry. Because the term '*ipso*' was introduced to denote attack by a reagent at a substituted nuclear position,[30] its use is inappropriate in connection with our example of nucleophilic aromatic substitution by a hydride donor. Accordingly we propose that mechanisms such as (1) or (3) should be referred to as cases of ' vicinal attack ', implying that the entering group first attacks and attaches itself to a ring position vicinal to the position that it occupies in the reaction product and from which the leaving group is displaced.

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