Reactions of Cerium(IV) Ammonium Nitrate with Aromatic Compounds in Acetonitrile. Part 1. The Mechanism of Side-chain Substitution

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Benzene, alkylbenzenes, and phenolic ethers react with cerium(IV) ammonium nitrate in acetonitrile to give nitro-compounds and (if α-hydrogen atoms are present) also the products of side-chain substitution. With many substrates, the major products of side-chain substitution are benzyl nitrates but compounds which can give rise to particularly stable benzyl cations give mainly products from reaction with the solvent. Relative rates of side-chain substitution have been determined by the competition method: the results indicate reaction *via* a radical cation and the isotope effect $k_H/k_D = 2.3$ observed in reactions with $[^2H_{10}]$-*p*-xylene suggests that proton loss from this radical cation is, at least partly, rate-determining.

THE reactions of aromatic compounds with cerium(IV) salts have been studied under a number of conditions [1-3] with particular attention to reactions with cerium(IV) ammonium nitrate in acetic acid.[4] Under these conditions, the main products normally involve substitution in the side-chain sometimes with ring acetoxylation. These reactions have been considered to involve the preliminary formation of an aromatic radical cation, followed by loss of an α-proton from the side-chain and oxidation of the resulting benzyl radical to a benzyl cation.[5] Either the formation of the radical cation or the subsequent proton loss can apparently be rate-determining.[4] However, more recently, the direct transfer of an α-hydrogen atom from the side-chain to the oxidising agent has been suggested as the preferred reaction path,[6] for subsequent oxidation of the radical would give rise to the same products. Electrochemical studies suggest that the $NO_3^{\bullet}$ radical formed by oxidation of a nitrate ion could be effective in removing the α-hydrogen atom.[6] The absence of a hydrogen-isotope effect in some side-chain substitutions points against this as a general explanation of these reactions [4] but it may apply in examples where the oxidation to the radical cation is difficult.

Very little work has been done on analogous reactions of cerium(IV) ammonium nitrate in acetonitrile as solvent but the literature suggests that these reactions are unusual in that, at least for toluene, the expected side-chain substitution is replaced by nitration of the aromatic ring.[7] Nitration by cerium ammonium nitrate has been reported also for benzene,[7] anthracene,[7] and aromatic amines.[8,†] Nothing is known concerning the mechanism of these reactions but the substitution in aromatic hydrocarbons has been considered to involve radical cations partly because of the analogy with the side-chain substitutions and partly because of the unusual isomer ratio reported for the nitration of toluene.[7]

Our interest lies essentially in nitration by cerium(IV) ammonium nitrate in acetonitrile but, since side-chain substitution also occurs [9] under these conditions, we have investigated these reactions to determine whether or not radical cations are involved as intermediates.

The extent and nature of the side-chain substitution in the reactions of a number of aromatic compounds with cerium ammonium nitrate in acetonitrile is shown in Table 1.[‡] For many of the substrates (but not for toluene) the times chosen refer to the product composition when reaction is almost over but a considerable amount of starting material is then left since the stoicheiometry of the side-chain substitution involves two cerium ions per aromatic molecule. This is shown in the equation below in which, for simplicity, the additional nitrate ions of the $Ce(NO_3)_6^{2-}$ complex are omitted.

$$ArCH_3 + 2Ce(NO_3)_4 \longrightarrow ArCH_2ONO_2 + 2Ce(NO_3)_3 + HNO_3 \quad (1)$$

The significance of the percentage product compositions in Table 1 is reduced by the fact that the product compositions depend on the conditions of reaction and particularly on the time. This is illustrated in Table 1 by the two results for mesitylene and is shown in more detail by the result for *m*-xylene in the Figure (A). A number of substrates were studied and all showed an increase in the ratio of ring substitution to side-chain towards the end of reaction. The reaction of *m*-xylene with cerium(IV) ammonium nitrate was studied in the presence of added 3,5-dimethylbenzyl nitrate and a standard (n-decane). Analysis of the product composition by g.l.c. as a function of time showed no nitromesitylene and no significant change in the 3,5-dimethylbenzyl nitrate : n-decane ratio: the change in the product ratio does not therefore arise from the decomposition or rearrangement of the nitrates formed. The most likely explanation involves the nitration of the aromatic substrate by the nitric acid set free in the side-chain substitution [equation (1)]. The work in Part 2 shows that nitration by nitric acid appears to be strongly catalysed by the cerium(IV) salt.

For several reasons, these reactions are unsuitable for a conventional kinetic analysis. One difficulty comes from the complexity of the system of reactions, for the ring and

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[†] Nitration of aromatic amines by cerium(IV) ammonium nitrate will also occur in acetic acid as solvent [8] but this is not true for aromatic hydrocarbons.[4]

[‡] The composition of the mixture of aromatic nitro-compounds formed is given in Part 2.

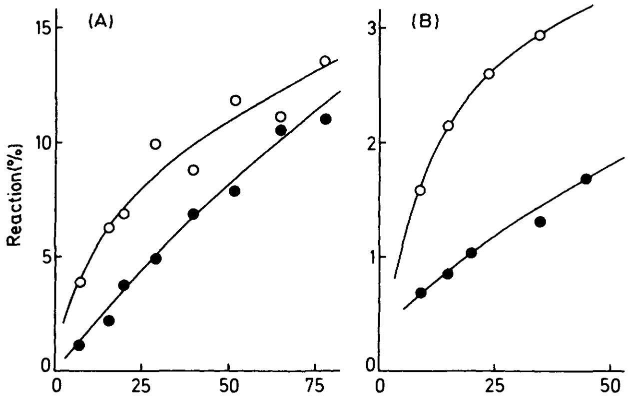
side-chain substitutions have different stoicheiometries and different kinetic forms during an individual kinetic run [*cf.* Figure (A)]. Another difficulty comes from the fact that the reaction mixture, although initially homogeneous, becomes heterogeneous during reaction because of the precipitation of a polymeric cerium salt. We attempted to overcome this difficulty by the use of very low concentrations of the cerium salt accompanied by spectrometric analysis (in the u.v.–visible region) of the reaction mixture. This work was abandoned because of evidence of some photochemical catalysis of changes in the reaction mixture.

TABLE 1

The nature and extent of side-chain substitution in the products from the reactions of aromatic compounds (0.5 mol dm^{-3}) with ceric ammonium nitrate (0.5 mol dm^{-3}) in acetonitrile at 84 °C

Substrate	*t*/min	Major product (%) [a]	Other products (%) [a]
Toluene	172	$PhCH_2ONO_2$ (34)	
Ethylbenzene	172	PhCHMeNHAc (27)	Two unidentified (4)
Isopropylbenzene	172	(23%) [b]	
t-Butylbenzene	120	(only aromatic nitration)	
m-Xylene	30	*m*-$MeC_6H_4CH_2ONO_2$ (64)	*m*-MeC_6H_4CHO (3)
p-Xylene	120	*p*-$MeC_6H_4CH_2ONO_2$ (74)	Three unidentified (15)
Mesitylene	15	3,5-$Me_2C_6H_3CH_2ONO_2$ (66)	
Mesitylene	120	3,5-$Me_2C_6H_3CH_2ONO_2$ (50)	
Anisole	2	(only aromatic nitration)	
p-Methylanisole	5	polymeric material	*p*-$(OMe)C_6H_4CH_2NHAc$

[a] The percentage of aromatic nitration corresponds to the difference between the sum of these percentages and 100%. [b] Partly the amide ($PhCMe_2NHAc$) but with other unidentified products.



Percentage of product in the reaction of aromatic compounds with cerium(IV) ammonium nitrate in acetonitrile. Conditions: (A) *m*-xylene, 0.4 mol dm^{-3}; cerium(IV) ammonium nitrate, 0.4 mol dm^{-3}, 84 °C; (B) mesitylene, 0.092 mol dm^{-3}; cerium(IV) ammonium nitrate, 0.23 mol dm^{-3}, 60 °C. Open circles, $ArCH_2ONO_2$; filled circles, $ArNO_2$

Studies of the first few percent of reaction have been carried out by g.l.c. analysis of samples taken from the reaction mixture. The determination of the true initial rate is difficult because the composition–time plots show unexpected curvature over this region [Figure (B)]. Results for the formation of 3,5-dimethylbenzyl nitrate from mesitylene are given in Table 2 in terms of the yield of product after reaction for 3.5 min. The relative rates of reaction calculated from these yields give an apparent order of 0.7 with respect to mesitylene and of 1.3 with respect to the cerium(IV) salt; however, the unconventional kinetic form of the reaction reduces the significance of these figures. Orders >1 with respect to cerium(IV) ammonium nitrate have been observed in reactions of aromatic compounds with cerium(IV) ammonium nitrate in acetic acid and have been attributed to a salt effect.[10] The comparison of the yields in the presence and absence of light shows no evidence of catalysis by laboratory lighting (Table 2).

The relative reaction rates of different substrates have been determined by competition since this appeared to be more reliable than the determination of relative initial rates. A mixture of two substrates was allowed to react with cerium(IV) ammonium nitrate in acetonitrile and a series of samples was extracted over the first 10% of reaction and analysed by g.l.c. The results are given in Table 3 and refer to the relative rates of formation of the major products listed in Table 1. With the exception of ethylbenzene, the results refer therefore to the relative rates of formation of substituted benzyl nitrates. These are a reasonable measure of the relative reactivities towards side-chain substitution as a whole since the other side-chain products do not amount to more than 17% of side-chain substitution (Table 1). A direct comparison of competition between the most reactive (*p*-xylene) and least reactive (toluene) compounds in Table 3 gave the overall relative reactivity as 208. This is probably less accurate than the value obtained by stepwise comparison (150) (Table 3) but confirms the large spread in the observed reactivities.

TABLE 2

The yield of 3,5-dimethylbenzyl nitrate after 3.5 min reaction of mesitylene and cerium(IV) ammonium nitrate in acetonitrile at 84 °C

$[Ce^{IV}]$ mol dm^{-3}	[ArH] mol dm^{-3}	$10^3[ArCH_2ONO_2]$ mol dm^{-3}
0.2	0.045	2.64
0.2	0.090	3.68
0.2	0.092	3.88 [a]
0.2	0.43	12.8
0.2	0.81	19.1
0.2	0.96	21.5 [a]
0.2	0.96	25.3
0.093	0.43	6.87
0.4	0.43	45.9

[a] In the absence of light.

TABLE 3

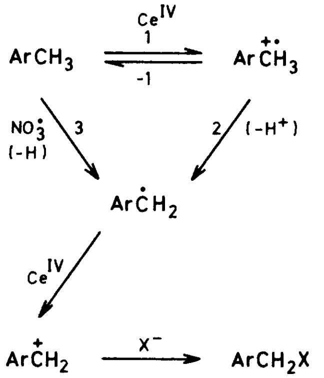
Relative reactivities (by competition) in the side-chain substitution reactions of aromatic compounds with ceric ammonium nitrate in acetonitrile at 84 °C

Substrate	Other component	Relative reactivity Obs.[a]	W.r.t. PhMe	Corr.[b]
(A) Toluene			(1)	(1)
(B) Ethylbenzene	(A)	1.5	1.5	2.2
(C) *m*-Xylene	(A)	13	13	6.6
(D) Mesitylene	(C)	5.0	65	22
(E) 3,5-Dimethyl-t-butylbenzene	(D)	1.2	76	38
(F) [$^2H_{10}$]-*p*-Xylene	(D)	0.96	62	31
(G) *p*-Xylene	(D)	2.3	150	75

[a] Direct comparison with other component. [b] With respect to the reactivity of toluene as unity but corrected to allow for the different numbers of α-hydrogen atoms.

DISCUSSION

The main purpose of this part of the work was to determine whether radical cations are intermediates in these side-chain substitution reactions since this has implications for the mechanism of nitration (see Part 2). Two possible mechanisms of side-chain substitution are set out in the Scheme. We are concerned with the distinction between the two-stage formation of the radical by the separate loss of an electron and a proton (steps 1 and 2) and the single-stage loss of a hydrogen atom to $NO_3^{\bullet}$ (step 3). Both mechanisms appear to operate simultaneously in the anodic oxidation of such compounds as mesitylene using acetic acid–nitrate electrolytes.[6]



SCHEME

On this matter, the substituent effects in Table 3 point unequivocally to the radical cation interpretation. Hydrogen atom transfer from a methyl group to electronegative radicals ($CCl_3^{\bullet}$, $Cl^{\bullet}$, $Br^{\bullet}$, $RO_2^{\bullet}$) gives ρ values[11] of *ca.* −0.5 to −2 at 60 °C. The range of substituents studied here is insufficient for us to demonstrate clearly that our reactions follow a conventional Hammett plot but the scale of substituent effects can be seen from the fact that a plot* of log (relative rate) against Σσ for the compounds toluene, *m*-xylene, *p*-xylene, mesitylene, and 3,5-dimethyl-t-butylbenzene gives a ρ value of −11.6 (*r* 0.98). The value of ρ is reduced to −9.85 (*r* 0.99) when a statistical correction is applied to the relative rates to allow for the different number of α-hydrogen atoms (Table 3, last column). This correction appears appropriate since the result for [$^2H_{10}$]xylene in Table 3 suggests that proton loss from the radical cation is at least partly rate-determining. A reversible oxidation to the radical cation would explain the curvature observed in the composition–time plots over the first few percent of reaction [Figure (B)] since the concentration of the radical cation and hence the overall reaction rate should depend on the $Ce^{IV}:Ce^{III}$ ratio (*cf.* ref. 4). The rate coefficients for proton loss from such radical cations are not very sensitive to alkyl substitution in the ring[13] but the large substituent effects can be understood in terms of the relative concentrations of the radical cations.

The effect of replacing a methyl group by an ethyl group is also inconsistent with the hydrogen atom transfer reaction. In such transfer reactions, an ethyl group is more reactive than a methyl group (per α-hydrogen) by a factor which depends on the attacking radical and varies from 2.5 (for $Cl^{\bullet}$) to 50 (with $CCl_3^{\bullet}$).[14] In all examples, the effect of an α-methyl substituent is much greater than that of a *p*-methyl substituent. In the present reaction, the effect of replacing a methyl by an ethyl substituent (a factor of 2.2 per α-hydrogen) is outside the previous range and very much less than that of a *p*-methyl substituent [a factor of 75 (Table 3)].

As far as the product-determining step is concerned, it is interesting that those substrates that would form the more stable carbonium ions (ethylbenzene, *p*-methylanisole) give products resulting from reaction with the solvent while the products from the others involve reaction with a nitrate ion (Table 1). Presumably, the more stable carbonium ions live long enough to escape from the complex after the final oxidation stage (Scheme) while the others react with one of the nitrate ligands. The formation of the nitrates in this way is consistent with earlier studies.[5]

EXPERIMENTAL

Materials.—Cerium(IV) ammonium nitrate was the AnalaR reagent and was dried at 100 °C before use. The organic substrates were laboratory reagents: almost all were found to be >99.5% pure by g.l.c. and were used without further purification. Mesitylene was dried over phosphorus pentaoxide and fractionally distilled under vacuum (b.p. 32 °C at 0.3 mmHg). Acetonitrile was heated

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* Using σ_m^{Me} −0.07, $\sigma_m^{Bu^t}$ −0.10, σ_p^{Me} −0.17.[12]

under reflux with phosphorus pentaoxide followed by distillation. The purity was checked by g.l.c.

Reactions.—A solution of cerium(IV) ammonium nitrate in acetonitrile (usually 45 cm^3) was heated to the required temperature or under reflux. After *ca.* 5 min, a solution in acetonitrile (usually 5 cm^3) of other reactants (+ a g.l.c. standard) at the same temperature was added. During reaction the colour of the solution changed from red to yellow and a precipitate formed. After the required time, the usual method of analysis involved quenching the reaction with about an equal volume of water followed by extraction with ether or chloroform, partial removal of the solvent, and analysis by ^{1}H n.m.r. and g.l.c. To check for water-soluble products, some mixtures were analysed by allowing the solution to cool, filtering off the precipitate, removing part of the solvent, and then treating as above. In the determination of relative reactivities or initial rates, a number of samples were extracted from the same mixtures. Some experiments were carried out under nitrogen and in the dark but these changes did not have a significant effect on the product composition, initial rate, or relative reactivity.

Product Analysis.—The identification of the products was based initially on a combination of the ^{1}H n.m.r. spectrum and g.l.c.–m.s. using a Pye 204 gas chromatograph with a 5 ft × 0.25 in O.D. column packed with OV 17 on Chromosorb W-HP and temperature programming (70—170 °C, 4 °C min^{-1}) coupled to a VG 7070 spectrometer. Where necessary, the identification was confirmed by the isolation of individual products by preparative g.l.c. using a Varian 712 f.i.d. instrument with a 10 ft × 3/8 in O.D. column packed with 20% silicone oil MS 200/200 on Supasorb. One product (3,5-dimethylbenzyl nitrate) was separated by h.p.l.c. using three 25 cm × 0.25 in O.D. columns in series packed with Partisil 10 silica gel with dichloromethane as the eluant. The quantitative analysis of the products was carried out on a Perkin-Elmer F11 f.i.d. instrument in conjunction with a Perkin-Elmer model 2 integrator and a Kienzle printer calculator. Temperature programming was normally necessary (80—170 °C, 5 °C min^{-1}). At least two different columns were used for each analysis but the compositions quoted are based on the following: 4 m × 1/8 in O.D. column packed with silicone oil MS 200/200 on Chromosorb, WAW DMCS (80—100) (isopropylbenzene, xylene, 3,5-dimethyl-t-butylbenzene, and mesitylene); 4 m × 1/8 in O.D. column packed with 10% Carbowax M20 on Phase Sep. WAW DMCS (80—100) (*p*-xylene, anisole, *p*-methylanisole); 6 ft × 1/8 in O.D. column packed with 5% SE 30 on Supasorb (ethylbenzene, t-butylbenzene). The products from toluene presented some difficulty since, on the silicone oil column, the benzyl nitrate overlapped with the peak for the *o*-nitro-isomer and, on the Carbowax column, the benzyl nitrate overlapped with the peak for the *m*-nitro-isomer. The ratio of side-chain substitution to aromatic substitution was then based on the results for both columns and confirmed from a study of the ^{1}H n.m.r. spectrum.

Reactivity Measurements.—Reaction rates were determined by extracting 4—5 samples of a reaction mixture containing also an inert standard (normally benzyltrichloromethane) over the first 10% of reaction. After quenching, these were analysed by g.l.c. and the concentrations were calculated from the areas relative to the standard after corrections for the relative response of the species. Studies of relative reaction rates were carried out in the same way using two aromatic compounds with concentrations adjusted to give approximately equal amounts of nitro-products. Measurements were restricted to $<10\%$ reaction of the more reactive compound and the relative reactivity was then calculated from the ratios of the initial concentrations and product concentrations.

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