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Kinetic studies of the reactions of some phenols and alkyl aryl ethers with dinitrogen pentoxide in perfluorocarbon solvents

Michael R. Crampton,[a] **Linda M. Gibbons**[a] **and Ross Millar**[b]

[a] *Chemistry Department, Durham University, Durham, UK DH1 3LE*
[b] *DERA, Fort Halstead, Sevenoaks, Kent, UK TN14 7BP*

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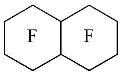
The reaction of dinitrogen pentoxide in perfluorocarbon solvents with phenols and alkyl aryl ethers carrying halogeno ring-substituents results in nitrodehydrogenation. Rate measurements show that the preferred orientation of nitration is *ortho* > *para* > *meta* to the hydroxy group; the kinetic isotope effect, k_H/k_D, has a value close to unity. Phenols show considerably higher reactivity than similarly substituted alkyl phenyl ethers, and a mechanism is suggested involving initial interaction of N_2O_5 with the hydroxy function followed by reaction *via* cyclic transition states.

Perfluorocarbons, such as perfluorodecalin **1** and perfluoroethers **2**, are now commercially available over a wide boiling-point range. They are chemically inert, non-toxic liquids and are almost completely immiscible with most organic solvents and with water. This inertness has led to their increasing use, with the possibility of recycling, as solvent systems, or as 'bulking agents' in which the reagents may not be soluble.[1–3]



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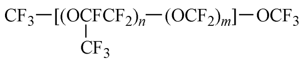
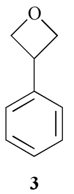


$CF_3{-}[(O\underset{CF_3}{C}FCF_2)_n{-}(OCF_2)_m]{-}OCF_3$

2

We find that dinitrogen pentoxide, N_2O_5, has appreciable solubility, *ca.* 1 mol dm^{-3}, in these solvents and report here some kinetic studies of its reactions with aromatic phenols and with aromatic alkyl ethers. N_2O_5 is known to be a versatile nitrating agent[4] and solutions in dichloromethane have been used in the syntheses of nitramines and of nitrate esters.[5] It has been reported that pyridine may be successfully nitrated at the *meta*-position using N_2O_5 in the presence of sulfur dioxide;[6,7] some aromatic nitrations by N_2O_5 are catalysed by zeolites.[8] The reaction of 3-phenyloxetane, **3**, with N_2O_5 in dichloromethane may result in aromatic ring-nitration together with oxetane ring-opening to give 2-arylpropane-1,3-diol nitrates. While the former process is likely to involve a normal nitronium ion mechanism the latter process has been shown to have a second-order dependence on N_2O_5 and the likely mechanism involves donation of a nitronium ion by the first N_2O_5 molecule and a nitrate ion by the second.[9]



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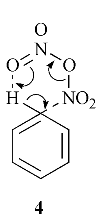

4

The only previous detailed kinetic study of aromatic nitration by N_2O_5 in a homogeneous solution dates from 1950. Ingold and co-workers[10] studied, using dilatometry, the nitrations of several halogeno- and alkoxycarbonylbenzenes in carbon tetrachloride or its mixtures with nitromethane. Working with concentrations of the aromatic compounds, *ca.* 1 mol dm^{-3}, which were in large excess of the N_2O_5 concentration, *ca.* 0.05 mol dm^{-3}, they identified two reaction pathways. The first involved direct attack of molecular N_2O_5 on the aromatic species and a cyclic transition state, **4**, was postulated. A second pathway, involving catalysis by nitric acid to the second or third power, was interpreted as a solvent effect in which the nitric acid facilitated the ionisation of N_2O_5 to give NO_2^+ as the nitrating agent.

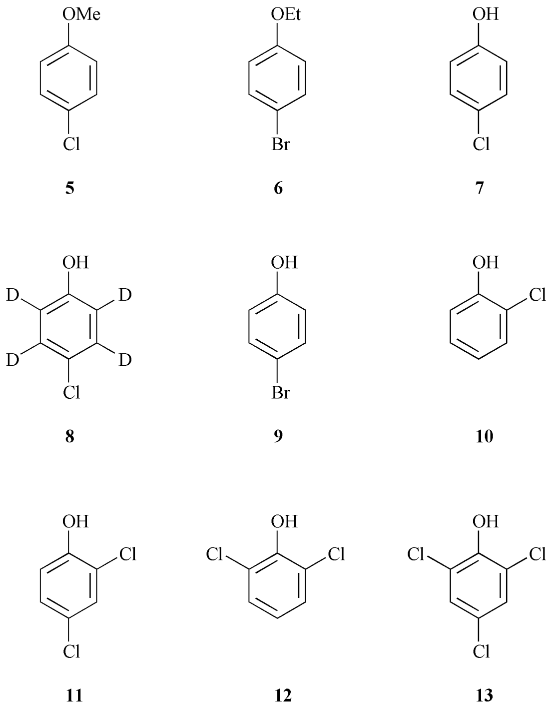

Fig. 1

Results and discussion

Studies were made of the reactions of N_2O_5 in solvent **1** with 4-chloromethoxybenzene, **5**, 4-bromoethoxybenzene, **6**, several monohalogenated phenols, **7**–**10**, two dichlorinated phenols, **11** and **12**, and with 2,4,6-trichlorophenol, **13**. Structures are given in Fig. 1. Rate measurements were made with concentrations of N_2O_5 in large excess of substrate concentrations, *ca.* 10^{-4} mol dm^{-3}, and first-order kinetics were observed. The choice of substrates was to some extent limited by the use of spectrophotometry to follow the reactions so that a significant change

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in UV absorbance during reaction was required. (The wavelengths used for measurement, corresponding to the absorption maxima of the products, are given in Table 5.)

Typical kinetic data for reactions of 4-bromoethoxybenzene, **6**, 2-chlorophenol, **10**, 4-chlorophenol, **7**, and 2,4,6-trichlorophenol, **13**, are reported in Tables 1–4. In each case the first-order rate constants increase linearly with N_2O_5 concentration indicating a first-order dependence on the nitrating agent as indicated in eqn. (1). The positions of nitration were, in most

$$k_{\text{obs}} = k_2[N_2O_5] \qquad (1)$$

cases, determined by isolating the products in small-scale synthetic reactions. It is of interest that only in the reaction of **10** were two kinetic processes observable; these correspond to initial reaction at the 6-position, followed by dinitration to give the 4,6-dinitro derivative. The synthetic experiments with **5** indicate that following initial reaction at the 2-position there is slow formation of the 2,6-dinitro derivative. However the UV spectra of the mononitro derivative, λ_{max} 316 nm, ε 2000 dm^3 mol^{-1} cm^{-1}, and dinitro derivative, λ_{max} 309 nm, ε 2200 dm^3 mol^{-1} cm^{-1}, are not sufficiently different to allow kinetic measurements.

It is significant that all these reactions involve replacement of hydrogen rather than any of the other ring-substituents. It is known[11,12] that nitration of *para*-substituted anisoles may result in formation of nitrophenols in a reaction which involves attack at the *para*-position, demethylation and re-arrangement of the dienone intermediate. There was no evidence for such processes in the present work.

The most straightforward inference from the experimental observation that the observed reactions have a first-order dependence on the N_2O_5 concentration is that reaction involves attack on the substrates by molecular N_2O_5. Water[13] has an extremely low solubility, <10 ppm, in **1**, and inorganic salts and nitric acid are virtually insoluble. Hence ionisation of N_2O_5 or reaction through the prior formation of nitric acid are unlikely. It should also be reported that rate constants showed good reproducibility. Thus the use of the same stock-solution of N_2O_5 on different occasions, or the use of different freshly-prepared stock solutions gave rate constants which were identical within experimental error.

Nitrous acid catalysed nitrations of aromatic molecules have been reported and may be particularly important for phenols.[14–16] Although there is no obvious source of nitrous acid in the present systems it was thought to be worthwhile to check this possibility. However the presence of low concentrations of urea or penicillamine, which are known to be nitrous acid traps,[17] was found to have no measurable effect on rate constants indicating that this pathway was unimportant.

There are several features of the results in Table 5 which must be taken into account when discussing the mechanism of nitration. The results indicate that the phenols **7** and **9** are *ca.* fifty times more reactive than the corresponding alkyl aryl ethers **5** and **6**. This is significant since the electronic effect of OH and OR groups is expected to be quite similar. Thus σ^+ values[18] at the *para*-position are −0.92 for OH and −0.78 for OMe, and in classical nitronium ion nitrations in sulfuric acid 4-chlorophenol is faster than 4-chloroanisole by only a factor of two.[12] The results in Table 5 show that the rate constants have similar values in solvents **1** and **2**, and in these non-polar media ionisation of the phenols to give phenolate anions is extremely unlikely.

A second feature of the results is that the orientation of nitration of phenols is dominated by the hydroxy group, the order being *ortho* > *para* > *meta*. Thus 2-chlorophenol, **10**, is nitrated most rapidly at the 6-position, and in the dichlorophenols **11** reacts more rapidly than **12**. Since the orienting effect of the hydroxy group is dominant, reaction usually occurs *meta* to the chlorine substituents. Comparison of the reactivities of **11** and **7** in Table 5 shows that allowing for the statistical factor the electronic effect of chlorine,[18] σ_{meta} 0.37, is surprisingly small. In **13** where positions *ortho* and *para* to OH are blocked, substitution occurs at the *meta*-position.

Comparison of the rate constants for reaction of **7** with its tetradeuterio equivalent **8** gives a value for k_H/k_D, the kinetic isotope effect, of 1.34. This value, close to unity, indicates that C–H bond breaking is unlikely to be rate-limiting in the substitution process,[19] at least for the phenol derivatives.

We do not have a completely satisfactory mechanistic explanation for these results. Although reaction *via* cyclic transition states analogous to **4** is an attractive possibility, it does not explain the much higher reactivity of phenols than of the corresponding alkyl aryl ethers. Also a value for k_H/k_D significantly greater than that observed might have been expected since C–H bond breaking is involved. A possible alternative pathway for reaction of the phenol derivatives is shown in Scheme 1.

This involves initial interaction of N_2O_5 with the hydroxy function to give a hydrogen bonded species **14**, followed by interaction with a ring position through a cyclic transition state **15**. This yields a cyclohexadienone intermediate **16** which rapidly rearranges to give the substitution product. This scheme avoids the formation of ionic intermediates and, since electro-

Table 1 Kinetic data for the reaction of **6** with N_2O_5 in **1** at 25 °C

$[N_2O_5]$/mol dm^{-3}	k_{obs}/s^{-1}	$k_2{}^a$/dm^3 mol^{-1} s^{-1}
0.0058	0.0067	1.2
0.0068	0.0083	1.2
0.0096	0.012	1.3
0.0103	0.013	1.3
0.0115	0.015	1.3
0.0134	0.018	1.3

[a] Defined by eqn. (1).

Table 3 Kinetic data for the reactions of **7** and **8** with N_2O_5 in **1** at 25 °C

	7		**8**	
$[N_2O_5]$/ mol dm^{-3}	k_{obs}/s^{-1}	$k_2{}^a$/ dm^3 mol^{-1} s^{-1}	k_{obs}/s^{-1}	$k_2{}^a$/ dm^3 mol^{-1} s^{-1}
0.00098	0.052	53	0.039	40
0.00196	0.105	54	0.080	41
0.00392	0.22	56	0.17	44
0.00588	0.34	58	0.24	41

[a] Defined by eqn. (1).

Table 2 Kinetic data for the reactions of **10** with N_2O_5 in **1** at 25 °C

$[N_2O_5]$/mol dm^{-3}	k_{fast}/s^{-1}	$k_{2,\text{fast}}{}^a$/dm^3 mol^{-1} s^{-1}	k_{slow}/s^{-1}	$k_{2,\text{slow}}{}^b$/dm^3 mol^{-1} s^{-1}
0.0031	0.048	15	0.0021	0.68
0.0062	0.084	14	0.0039	0.63
0.0091	0.105	12	0.0054	0.59

[a] Second-order rate constant for nitration at the 6-position. [b] Second-order rate constant for dinitration.

Table 4 Kinetic data for the reaction of **13** with N_2O_5 in **1** at 25 °C

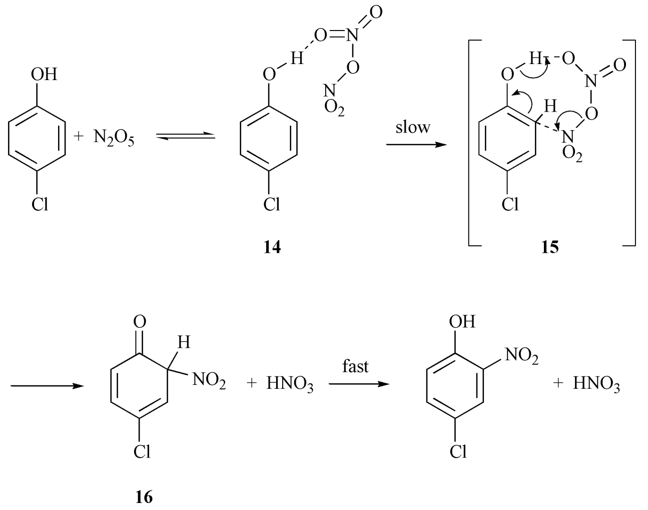
$[N_2O_5]$/mol dm^{-3}	k_{obs}/s^{-1}	$k_2{}^a$/dm^3 mol^{-1} s^{-1}
0.0019	0.0069	3.6
0.0037	0.013	3.5
0.0075	0.025	3.3
0.011	0.035	3.2
0.015	0.040	2.7

[a] Defined in eqn. (1).

Table 5 Summary of kinetic results for reaction with N_2O_5 at 25 °C

			k_2/dm^3 mol^{-1} s^{-1}	
Reactant	λ^a/nm	Position of nitration	Solvent **1**	Solvent **2**
5	316	2	0.5 ± 0.1	—
6	298	2	1.3 ± 0.2	—
7	354	2	55 ± 3	45 ± 2
8	354	2	41 ± 3	—
9	354	2	63 ± 3	—
10	342	6 (fast)	14 ± 2	17 ± 2
		6 + 4 (slow)	0.63 ± 0.05	
11	360	6	22 ± 4	20 ± 4
12	274	4	10 ± 2	8 ± 1
13	389	3	3.3 ± 0.3	—

[a] Wavelength of measurement for kinetic data.

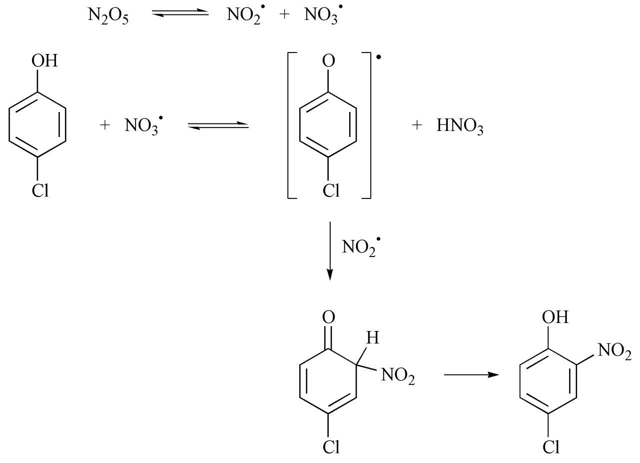


Scheme 1

philic attack will occur perpendicular to the plane of the aromatic ring, may allow rapid reaction at the *ortho*- and *para*-positions.

A further possibility is that radical species produced by homolysis of N_2O_5 may be involved in the nitration. Lower oxides of nitrogen show little nitrating ability, requiring strongly forcing conditions for reaction.[20] However it has been shown that nitrogen trioxide, an electron deficient radical, may initiate nitration of benzene.[21] The proposed mechanism[21] involves electron transfer from nitrogen trioxide to the benzene derivative to give a radical cation–anion pair; attack by NO_2 gives a cationic intermediate which can deprotonate to give the product. A directly analogous mechanism for the reactions we have studied is unlikely since ionic intermediates will be unstable in the solvents we have used.

A more likely possibility, outlined in Scheme 2, involves hydrogen abstraction from the phenol by nitrogen trioxide to yield a phenoxy radical, which may subsequently react with nitrogen dioxide It is not easy to discard this mechanism on experimental grounds since there are no simple radical traps[22] for NO_2. It was found that addition of 1,3-dinitrobenzene, a powerful electron acceptor, had no effect on the rate constant but this compound would not necessarily be expected to influence the pathway in Scheme 2. Further there is precedent for the reaction of phenoxy radicals with nitrogen dioxide to yield nitrophenols.[23] This mechanism can account for the higher reactivity of phenols than of alkyl aryl ethers but not for the enhanced *ortho*-substitution. Hence it is less likely than that outlined in Scheme 1.



Scheme 2

The results indicate the possibility of using N_2O_5 in perfluorocarbon solvents for synthetic work. The products of reaction can be readily isolated and the solvent is inert and can be re-cycled.

Experimental

Perfluorodecalin, **1**, was obtained from F2 Chemicals, and perfluoroether HT-135, **2**, was purchased from the Montefluos Company. Alkyl aryl ethers and phenols, including 2,3,4,5,6-pentadeuteriophenol were the purest available commercial specimens.

4-Chloro-2,3,5,6-tetradeuteriophenol

Pentadeuteriophenol was dissolved in acetic acid and the solution was cooled in an ice bath. Chlorine gas was bubbled through the solution until a weight increase corresponding to one molecular equivalent had occurred.[24,25] GCMS analysis of the residue left after solvent evaporation indicated that the major product (87%) was a monochlorinated phenol. This was identified as the 4-chloro derivative from the ^{13}C NMR spectrum in [$^2H_6$]DMSO which showed bands at δ 153.4, 116.8, 130.1 and 127.6. These positions are close to those calculated[26] using substituent effects for carbons at the 1, 2 and 6, 3 and 5, and 4 positions respectively of 4-chlorophenol. The bands at δ 116.8 and 130.1 were triplets, J 25 Hz, as expected for carbon atoms adjacent to deuterium atoms.[27]

N_2O_5 solutions

N_2O_5 was prepared by ozonation of N_2O_4 as described previously,[5] and was stored at −60 °C. Stock solutions in **1** and **2**, solubilities *ca.* 1 mol dm^{-3}, were prepared immediately before use. Concentrations were determined by extracting an aliquot, reacting with excess water, and titrating the liberated nitric acid with standard alkali.

Equipment and kinetic measurements

^1H NMR spectra were recorded in [$^2H_6$]DMSO with a Varian Mercury 200 MHz spectrometer. J-values are given in Hz. Mass spectra were recorded on a Micromass Autospec instrument and GCMS on a Fisons VG-Trio spectrometer. UV spectra and kinetic measurements were made with a Perkin-Elmer Lambda

2 spectrophotometer. Rate constants were obtained from absorbance measurements analysed for single and/or double exponential processes. The effects of additives were examined. Rate constants for reaction of **10** with N_2O_5 were measured in solvent **1** saturated with either urea, or with penicillamine as nitrous acid traps; values were found to be unaffected within experimental error by these additions. Similarly the rate constant for reaction of **11** with N_2O_5 was unaffected by the presence of added 1,3-dinitrobenzene.

Product analysis

General procedure. A mixture of the substrate, *ca.* 0.01 mol dm^{-3}, and N_2O_5, 0.04 mol dm^{-3}, in solvent **1** was stirred at 25 °C for a predetermined time. On addition of distilled water a solid separated which was filtered under vacuum and dried. Analysis was by ^1H NMR spectroscopy.

From substrate **5**. Reaction after 2 minutes indicated the formation of 2-nitro-4-chloroanisole (70%) δ 8.02 (1H, s, H3), 7.72 (1H, d, J 9, H5), 7.39 (1H, d, J 9, H6), 3.91 (3H, s, CH_3) and 2,6-dinitro-4-chloroanisole (30%) δ 8.51 (2H, s, H3, H5), 3.92 (3H, s, CH_3). After 1 hour the proportion of mono- and di-nitrated products was 50 : 50.

From substrate **7**. After 10 minutes reaction the only product observed in 89% yield was 2-nitro-4-chlorophenol δ 7.95 (1H, s, H3), 7.56 (1H, d, J 9, H5), 7.15 (1H, d, J 9, H6).

From substrate **10**. The sample quenched after 20 seconds showed the formation of 2-chloro-6-nitrophenol (30%) δ 7.35 (1H, m), 7.20 (1H, m), 6.90 (1H, m) and 2-chloro-4,6-dinitrophenol (70%) δ 8.54 (1H, d, J 3, H5), 8.05 (1H, d, J 3, H3). After 20 minutes complete conversion to 2-chloro-4,6-dinitrophenol was indicated.

From substrate **13**. A product was separated after reaction for 1 hour. In this case ^1H NMR analysis was not diagnostic. EIMS indicated formation of 3-nitro-2,4,6-trichlorophenol with *m*/*z* 241. The alternative possibility of formation of 2,4,6-trichloro-4-nitrocyclohexadienone is less likely since *ipso* attack in phenols requires the presence of fairly bulky groups.[28]

From substrate **9**. Here a different isolation procedure was used. After reaction for 1 minute the product was extracted with dichloromethane and neutralised with potassium hydrogen carbonate. After decanting the solution the solvent was removed under reduced pressure to yield 2-nitro-4-bromophenol in 65% yield. δ 8.04 (1H, s, H3), 7.76 (1H, d, J 9, H5), 7.10 (1H, d, J 9, H6).

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