JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 8, 810–824 (1995)

KINETIC AND SPECTROSCOPIC STUDIES OF THE HYDROLYSIS OF BIS(2,4-DINITROPHENYL ETHER)S OF POLY(ETHYLENE GLYCOL)

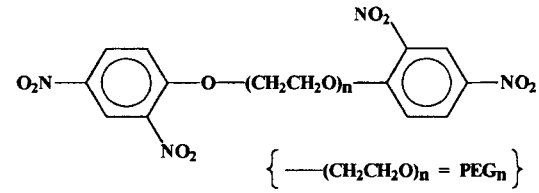
JULIAN M. DUST* AND MARY D. SECORD
Department of Chemistry, Sir Wilfred Grenfell College, Corner Brook, Newfoundland, A2H 6P9, Canada

Bis(2,4-dinitrophenyl ether)s of the water-soluble polymer poly(ethylene glycol) (PEG) are low-loading models for time-release herbicide systems and may potentially hydrolyse in basic aqueous media according to a mechanistic menu that includes elimination, aliphatic and/or aromatic displacement, as well as anchimerically assisted displacement involving O-6 of the polyether backbone. This paper study reports kinetic (second-order rate constants, k_2, and activation parameters) and ^{1}H (400 MHz) NMR results (monitoring of the reaction in DMSO-d_6 and D_2O) for the alkaline hydrolysis of a series of these ethers (DNPEGs). DNPEGs with varying average molecular weights (MW) of the polymer backbone (DNPEG-59, -1900 and -3200, where the numbers refer to the PEG MW) were studied, as were DNPEGs that differed only in the degree of end-group substitution, namely DNPEG-1900-59 and -81 (where the final numbers refer to the percentage substitution). The ^{1}H NMR studies show significant aryl ring hydrogen–deuterium exchange in the hydroxide–DMSO-d_6 and hydroxide–D_2O systems examined, as well as a poly(ethylene glycol) alkoxide (PEG-O$^-$) C-1 adduct in DMSO-d_6; the PEG-O$^-$ is displaced in an S_NAr fashion from DNPEG as a result of initial hydroxide attack at C-1 of DNPEG. The kinetic and spectroscopic results are discussed in the context of previous kinetic studies of alkaline hydrolysis of alkyl 2,4-dinitrophenyl ethers, recent ^{1}H NMR spectroscopic studies of electron-deficient aryl ethers and the mechanism of hydrolysis in the DNPEG systems. The possible significance of these results for the development of time-release herbicide systems is considered briefly.

INTRODUCTION

Polymers form the backbone of time-release delivery systems for a variety of bioactive agents including pesticides,[1] drugs,[2] herbicides[3] and perfumes.[3,4] In general, two approaches have been taken to the incorporation of these agents into polymers: covalent attachment, usually via hydrolytically labile bonds,[3–5] and entrapment in the polymer matrix either during copolymerization or cross-linking,[6,7] or in post-polymerization processing.[8] Entrapment can be further divided into those systems in which the bioactive agent is temporarily immobilized in a stable matrix, but can diffuse out,[6,8] and those that release the agent as the polymer decomposes, as from bioerosion.[9,10]

In the present study, a model polymeric herbicide was prepared and the kinetics of release were studied, under aqueous alkaline conditions, namely the bis(2,4-dinitrophenyl ether) of poly(ethylene glycol) (hereafter DNPEG,**1**). In a naive sense one could dissect this model compound into its component herbicide, 2,4-dinitrophenol, and the carrier polymer, poly(ethylene glycol), i.e. PEG.



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2,4-Dinitrophenol is a well known herbicide that acts by uncoupling the oxidative chain and so interferes with the formation of adenosine triphosphate (ATP), although the exact mechanism of the uncoupling has not been completely elucidated.[11] As a model bioactive agent, 2,4-dinitrophenol should be viewed as a herbicide that belongs to the broader class of nitroaromatics and nitroheteroaromatics. Compounds that contain the electron-withdrawing nitro group constitute a large class of drugs and bioactive agents as reviewed by Strauss.[12]

* Author for correspondence.

CCC 0894–3230/95/120810–15

Received 19 May 1995
Revised 14 August 1995

In examining the other part of the model polymeric herbicide, it should be noted that PEGs are poly(oxyethylenes) that have average molecular weights of less than 20 000 and also relatively narrow molecular weight distributions (i.e. the polymer approaches monodispersity and $MW \approx M_n \approx M_w$). PEGs are linear, water-soluble polymers that are biocompatible and nontoxic.[13,14] These properties, as well as their solubility in solvents ranging from dichloromethane and benzene to water and ethanol, account for the wide use of PEGs in chemical and biotechnical applications. A partial list of uses of PEGs and their derivatives includes their use: (1) as affinity ligands in aqueous two-phase partitioning,[15,16] (2) in the preparation of surfaces that reject proteins (e.g. for use in capillary electrophoresis),[17] (3) in peptide syntheses, as soluble supports,[18] (4) as recoverable phase-transfer agents,[19] (5) in drug modification, to improve water-solubility, for example,[2,20,21] and (6) for protein (e.g. enzyme) immobilization.[22] Preparation of many of these PEG derivatives has been reviewed by Harris and co-workers[23] and the literature on the use of these and other derivatives as phase-transfer catalysts and solvents for organic reactions is the subject of a review by Totten and Clinton.[24]

In the present case, we recognize the limitations of our model. First, even with full derivatization of the PEG, the degree of 'loading' of the bioactive agent is low. As a water-soluble polymer, any study of hydrolysis is facilitated. However, it could be argued that a biodegradable solid would be a preferable method of delivery, since problems associated with application of the herbicide, such as spray-drift, would be minimized. Nonetheless, the current study extends our work in the area of reactions of electron-deficient aromatic derivatives of polymers.[25,26] Moreover, the insights gleaned from the body of work will permit the design, preparation and study of more complex and realistic polymeric herbicide systems.

To probe the effect of the molecular weight of the polymer backbone, the current mechanistic study includes a range of DNPEGs (MW = 59, 1900 and 3200, namely, DNPEG-59, -1900 and -3200). Two different degrees of substitution were also examined for DNPEG-1900 (81% and 59%, hereafter, DNPEG-1900-81 and DNPEG-1900-59, respectively). The kinetic and 400 MHz ^{1}H NMR studies of the alkaline hydrolysis of these derivatives will be presented and discussed on the basis of comparison to suitable nonpolymeric systems and to the 2,4,6-trinitrophenyl (picryl) derivatives of PEG[25] and cellulose[26] that we have examined previously.

RESULTS

Kinetics

Aqueous alkaline solutions of substrates ([DNPEG] *ca* 5×10^{-5} mol l^{-1} in end groups) were prepared with excess standardized hydroxide in deionized, distilled water. These solutions were monitored spectrophotometrically at 420 nm, where 2,4-dinitrophenoxide ion ($DNPO^-$) absorbs free from overlap with the absorbance due to the substrates. Plots of $\ln(A_\infty - A_t)$ against time showed good linearity ($r \geq 0{\cdot}995$) under these conditions at 60 °C (e.g. Figure 1, where

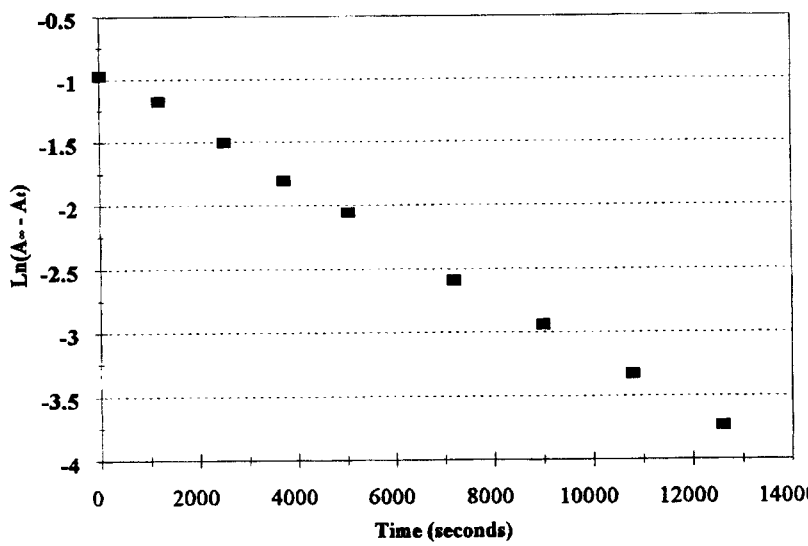


Figure 1. Sample pseudo-first order plot of natural logarithm of absorbance versus time is shown for the reaction of DNPEG-1900-81 with sodium hydroxide at 60 °C. Concentration of DNPEG, *ca* $4{\cdot}7 \times 10^{-5}$ mol l^{-1} in end-groups; concentration of NaOH, $2{\cdot}7 \times 10^{-2}$ mol l^{-1}. In this example, $k_{obs} = 2{\cdot}2 \times 10^{-4}$ s^{-1} and the linear regression line has a correlation coefficient r of 0·9998

Table 1. Variation of pseudo-first-order rate constant (k_{obs}) with hydroxide concentration for DNPEG-1900-81 at 60 °C

$[OH^-]$ (mol l^{-1})[a]	k_{obs} (s^{-1})[b]
$8{\cdot}157 \times 10^{-2}$	$6{\cdot}77\ (\pm 0{\cdot}48) \times 10^{-4}$
$6{\cdot}327 \times 10^{-2}$	$5{\cdot}00\ (\pm 0{\cdot}07) \times 10^{-4}$
$4{\cdot}577 \times 10^{-2}$	$3{\cdot}75\ (\pm 0{\cdot}20) \times 10^{-4}$
$2{\cdot}708 \times 10^{-2}$	$2{\cdot}16\ (\pm 0{\cdot}03) \times 10^{-4}$
$9{\cdot}324 \times 10^{-3}$	$7{\cdot}13\ (\pm 0{\cdot}14) \times 10^{-5}$

[a] 1800–200-fold excess of $[OH^-]$ over [DNPEG-1900-81].
[b] The standard deviation in k_{obs} is given in parentheses after each value; this was obtained from at least three separate runs.

$[NaOH] \approx 600 \times [DNPEG]$). The pseudo-first order rate constants, k_{obs} (Table 1), obtained over a range of OH^- concentrations (200–1800-fold excess of OH^-), for DNPEG-1900-81 were plotted against the OH^- concentrations to yield a straight line ($r = 0{\cdot}999$) that passed through the origin within the error of the line. The significance of this final observation will be discussed below.

Therefore, the results indicate that the rate law for release of 2,4-dinitrophenoxide ion, $DNPO^-$ is first order with respect to both the polymer and hydroxide concentration; thus,

$$d[DNPO^-]/dt = k_2[DNPEG\text{-}1900\text{-}81][OH^-] \quad (1)$$

The slope of the k_{obs} versus $[OH^-]$ line (Figure 2) is equal to the value of the second order rate constant, k_2. Based on the rate law found for DNPEG-1900-81 all other values for the second order rate constants herein presented were calculated from the pseudo-first-order rate constants, i.e. $k_2 = k_{obs}/[OH^-]$ (Table 2).

The form of the rate law [equation (1)] is consistent with a number of mechanisms that include a bimolecular rate-determining step. The mechanistic menu includes S_NAr displacement[27] (Path A, Scheme 1) and S_N2 displacement[28] (Path B) as well as elimination routes that have been omitted from Scheme 1 for sake of clarity. Path C involves anchimerically assisted formation of a cyclic oxonium ion concurrent with release of $DNPO^-$ in a unimolecular step that may be rate determining. Subsequently, if Path C1 is followed, 1,4-dioxane is formed as a co-product of the hydrolysis. It is therefore germane to the discussion to consider the results of a control experiment in which a sample of DNPEG-1900-81 was brought to reflux in pH 12·0 buffer. After 1 week the solution was extracted thoroughly but parsimoniously with diethyl ether. An aliquot of the ethereal extract was analyzed by gas chromatography. Neither the ether insoluble PEG derivative nor the equally insoluble $DNPO^-$ would be expected to chromatograph and neither did but, more importantly, the only peak found in the GC trace corresponded to diethyl ether; no peak was seen that could represent 1,4-dioxane.

An Arrhenius treatment of the temperature dependence of the observed rate constants, k_{obs}, for DNPEG-1900-81 (over the temperature range 25·0–81.0 °C,

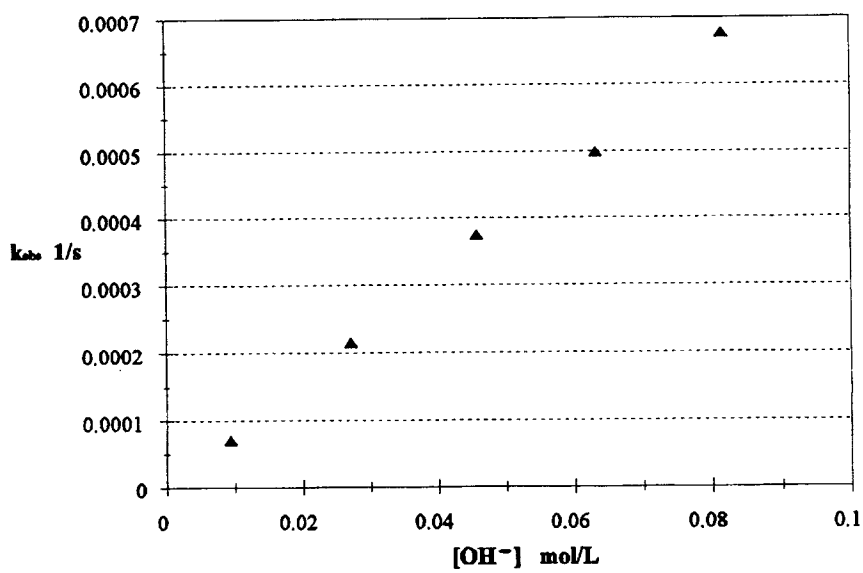
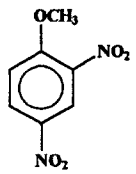
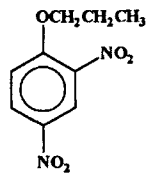
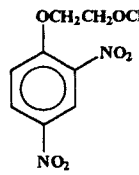


Figure 2. A typical plot of the pseudo-first order rate constant, k_{obs} versus hydroxide concentrations at 60 °C. (data taken from Table 1). The slope of the line represents the second order rate constant, k_2 (i.e. $8{\cdot}28 \times 10^{-3}$ l mol^{-1} s^{-1}), and the intercept ($-8{\cdot}0 \times 10^{-6}$ s^{-1}) falls within the statistical error in the intercept ($\pm 1{\cdot}1 \times 10^{-5}$ s^{-1}). The linear regression line has a correlation coefficient $r = 0{\cdot}992$

Table 2. Summary of second order rate constants (k_2) for aqueous alkaline hydrolysis at 60 °C

Substrate	k_2 (l mol^{-1} s^{-1})
	$1{\cdot}31 \times 10^{-2}$ [a]
	$7{\cdot}95 \times 10^{-3}$ [a]
	$7{\cdot}25(\pm 0{\cdot}23) \times 10^{-3}$ [b]
DNPEG-1900-81	$8{\cdot}05\ (\pm 0{\cdot}47) \times 10^{-3}$ [b]
DNPEG-1900-59	$7{\cdot}67\ (\pm 0{\cdot}22) \times 10^{-3}$ [b]
DNPEG-3200-100	$6{\cdot}49\ (\pm 0{\cdot}26) \times 10^{-3}$ [b]

[a] Extrapolated from the activation data of Murto and Murto.[29]
[b] Errors are given in parentheses for the present work and represent the standard deviation of at least three runs.

Table 3) yielded activation parameters ($E_a = 86{\cdot}1$ kJ mol^{-}, ln $A = 26{\cdot}1$) that are comparable to those reported by Murto and Murto[29] for aqueous alkaline hydrolysis of a series of 2,4-dinitrophenyl alkyl ethers (Table 4) that were shown to react via the S_NAr mechanism.[30]

The second-order rate constants obtained from the study of two DNPEGs that differ only in degree of substitution (DNPEG-1900-59 and DNPEG-1900-81), as well as the data for the hydrolysis of a range of 2,4-dinitrophenyl ethers that have PEG backbones of different lengths (including DNPEG-59, DNPEG-1900 and DNPEG-3200), are listed in Table 2.

^{1}H NMR studies

The reactions of DNPEG-1900-81 with hydroxide [$(CH_3)_4NOH$ (aq.)] and methoxide ($KOCH_3$ in MeOH) were examined by 400 MHz ^{1}H NMR spectroscopy with a view to detection of the anionic σ-bonded (Meisenheimer) complexes.[31] Such complexes are intermediates (or models for the rate-determining transition state) in the S_NAr mechanism for reaction of 2,4-dinitrophenyl ethers.[27,32] Since it is well-recognized that dimethyl sulfoxide (DMSO) is a solvent that enhances the magnitudes of the equilibrium constants for Meisenheimer complex formation,[32,33] these studies were undertaken primarily using DMSO-d_6 as solvent.

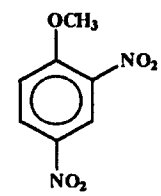
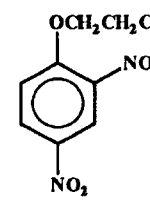
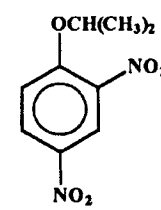
All chemical shifts are reported in parts per million (ppm relative to TMS or CHD_2SOCD_3 found in the DMSO-d_6 solvent or in a lock capillary where D_2O was

Table 3. Temperature dependence[a] of the second order rate constant (k_2) for DNPEG–1900–81 ([OH$^-$] = $6{\cdot}33 \times 10^{-2}$ mol l^{-1}; *ca* $800 \times$ [DNPEG-1900-81])

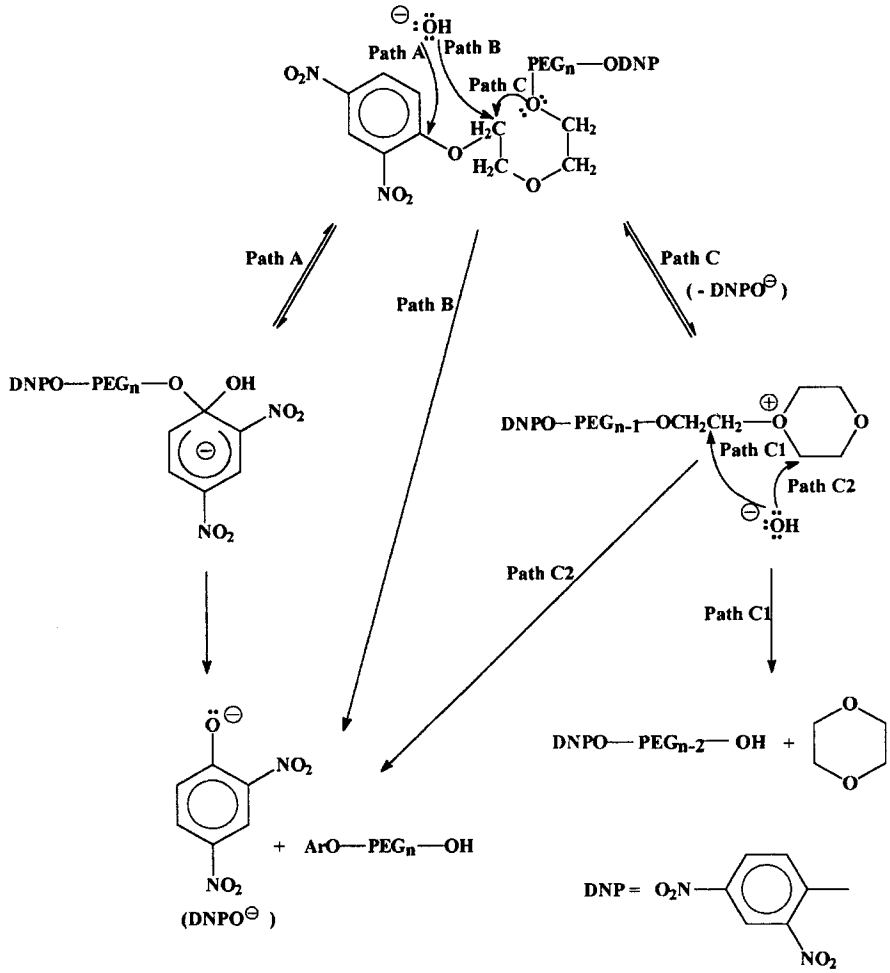
Temperature (°C)	k_2 (l mol^{-1} s^{-1})[b]
81·0	$3{\cdot}96\ (\pm 0{\cdot}11) \times 10^{-2}$
70·5	$1{\cdot}74\ (\pm 0{\cdot}03) \times 10^{-2}$
60·0	$7{\cdot}91\ (\pm 0{\cdot}11) \times 10^{-3}$
51·0	$3{\cdot}65\ (\pm 0{\cdot}15) \times 10^{-3}$
40·5	$1{\cdot}30\ (\pm 0{\cdot}54) \times 10^{-3}$
25·0	$1{\cdot}79\ (\pm 0{\cdot}74) \times 10^{-4}$

[a] Regression equation: $y = -1{\cdot}035 \times 10^4 x + 26{\cdot}11$ ($r = 0{\cdot}9946$).
[b] Calculated from: $k_{obs}/[OH^-]$ [equation (1)].

Table 4. Summary of activation parameters for alkaline hydrolysis of 2,4-dinitrophenyl ethers

Substrate	E_a (kJ mol^{-1})	Ln A
DNPEG-1900-81 (**1**)	86·1	26·1
	85·7	26·6[a]
	85·7	25·9[a]
	84·9	24·9[a]

[a] From Ref. 29.



Scheme 1

used as reaction solvent); coupling constants (J) are given in hertz.

Prior to injection of the nucleophile, the spectra of the substrates were scanned to assure purity. Thus, the spectrum of DNPEG-1900-81 in DMSO-d_6 displayed the following features, in common with DNPEG-1900-59 and DNPEG-3200-100: 3·50 (s, —CH_2—CH_2—O—, backbone), 3·80 (t, J = 4·4, DNP—O—CH_2—CH_2—O—PEG, β-methylene, where DNP = 2,4-dinitrophenyl), 4·47 (t, J = 4·4 Hz, DNP—O—CH_2—CH_2—O—PEG, α-methylene), 7·62 (d, J = 9·4 Hz, H_6 of dinitrophenyl ring), 8·49, 8·51 (d,d, J = 9·4, 2·8, H_5 of DNP) and 8·76 (d, J = 2·8, H_3 of DNP). Small extraneous peaks were found in some of the systems, notably a triplet at *ca.* 4·56, attributable to the terminal OH groups of unmodified PEG. This peak has been used previously in NMR end-group analysis to assign the degree of substitution for PEG derivatives.[25,34,35] Thus, comparison of the integral ratio for the 4·56 ppm triplet to the H_6 doublet of the dinitrophenyl ring of the attached end-group provides a check on the degree of substitution; in common with other systems in which this method was used, the degree of substitution values determined by NMR were lower than those obtained by complete hydrolysis of the derivatives (and subsequent analysis by UV–visible spectroscopy).

More importantly, some samples (of DNPEG-1900 or -3200) contained peaks at 3·96 (centre of a d,d, J = 13·5, 1·8 Hz), 4·18 (centre of a d,d, J = 14·3, 1·8) and 6·50 (centre of a d,d, J = 14·3, 13·5 Hz), which form an AMX system typical of vinyl groups.[36] These peaks can be assigned to a small amount of PEG bis(vinyl ether), presumably formed during the

preparation of the DNPEG samples. Pertinent to the assignment is the fact that the vinylic protons of commercial triethylene glycol bis(vinyl ether) appear at virtually the same chemical shifts as those assigned to the PEG bis(vinyl ethers) found in these systems. The integrals for these protons show that the bis(vinyl ether) makes up less than 3% of the original DNPEG samples.

Reaction of DNPEG-1900-81 with OH^- in DMSO-d_6

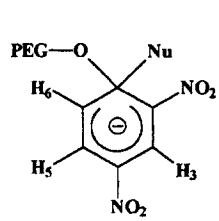
Injection of one equivalent of OH^- into a sample of DNPEG-1900-81 in DMSO-d_6 results in immediate loss of the signals for DNPEG. Resonances ascribed to the bis(vinyl ether) remain unchanged in the spectrum. These peaks are joined by two sets of new and somewhat broad signals in the downfield region (4·50–9·00 ppm) at 5·09 (d, J = 10·0 Hz) and 7·10 (d, J = 10·0 Hz) and 6·32 (d, J = 9·8 Hz), 7·78 (d, J = 9·8 Hz, with further unresolved coupling) and 8·58 ppm (ill-resolved doublet, $J \approx 3$ Hz).

The larger of the new sets of signals has chemical shifts that correspond to the 2,4-dinitrophenoxide ion, based on comparison with authentic 2,4-dinitrophenoxide, with two significant differences. The signal at 8.58 ppm, which corresponds to H_3 of $DNPO^-$, should be more intense and the resonance at 7·78, which represents H_5 of $DNPO^-$, should appear as a doublet of doublets in which the observed *ortho* coupling (9·8 Hz) is joined by *meta* coupling (typically 1–3 Hz). These observations can be understood in the context of hydrogen–deuterium exchange involving the added hydroxide, the DNPEG substrate and DMSO-d_6 solvent (see Discussion, Section 2).

Further support for the observation of H–D exchange in this system comes from analysis of the other smaller set of peaks, the 5·09, 7·10 set of doubets. These peaks could be assigned to a Meisenheimer adduct, but only if one signal is either obscured or otherwise missing from the spectrum. Simply put, whether the adduct is formed from attack at C-1, C-3 or C-5 (**2**, **3** and **4**, respectively, where Nu = OH, OPEG or nucleophile, generally), three distinct signals for the adduct should be seen in the downfield region (i.e. for H_3, H_5 and H_6) but in the present system only two sets of signals attributable to an adduct are seen. Again, if H_3 had completely exchanged then its signals would not appear in the spectrum. It is noteworthy that while only partial exchange is evident in the spectrum of the 2,4-dinitrophenoxide ion, the ultimate product of base hydrolysis of DNPEG, complete H–D exchange is apparent in the Meisenheimer adduct.

Assignment of the Meisenheimer adduct is not straightforward. As alluded to above, adducts formed from attack at C-1, C-3 and C-5 have been postulated in various 1-X-2,4-dinitrobenzene systems.[29,30,37–39] Further, if the C-3 position has undergone almost complete exchange with deuterium, then C-1 and C-3 adducts will appear similar. Only the H_5 and H_6 signals will be present in the spectrum and whether the adduct is a C-1 adduct or a C-3 adduct these signals will be expected to appear as doublets in similar positions in the spectrum. Therefore, the assignment of these signals to the C-1 adduct formed by attack of poly(ethylene glycol) alkoxide ($PEG\text{-}O^-$) at C-1 of DNPEG rests on careful comparison of the chemical shifts of this adduct with suitable model systems, as well a control experiment involving reaction of DNPEG with methoxide ion. It is generally accepted that all alkoxides display similar regioselectivity in Meisenheimer complex formation.[27b,31,32]

On the other hand, several possibilities for the identity of the Meisenheimer adduct may be ruled out. First, the chemical shifts of the corresponding protons of related C-5 adducts are significantly different from the positions found for the adduct in this study. For example, it has been reported[39] that the C-5 hydroxide adduct of 2,4-dinitrochlorobenzene has peaks at 5·64 (J = 6 Hz; H_5) and 5·32 (J = 6 Hz; H_6); the H_3 signal was absent in a DMSO-d_6-D_2O medium, also as a consequence of H–D exchange, but was observed in DMSO-d_6-H_2O (with solvent suppression) at 8·52 ppm. This assignment is consistent with NMR data reported in a study anent sulfite complexes of 1-chloro-2,4-dinitrobenzene.[40] On these grounds, it is unlikely that the Meisenheimer complex detected in the present study arises from attack at the C-5 position. While a C-3 adduct is another candidate for the identity of the signals found in the DNPEG–OH^- reaction system, evidence has been accumulating that C-3 O-centred adducts are less stable than their C-5 (or C-1) counterparts.[39,40] Since, in our system, the first definitive spectrum was acquired only within 20 min of mixing, it



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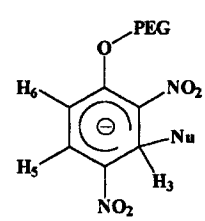

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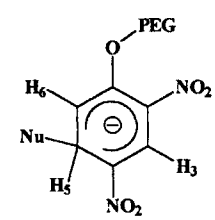

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would seem reasonable to assume that if a C-3 adduct had formed it would have decayed prior to our first observation. Note, again, that in the reaction of 2,4-dinitrochlorobenzene with hydroxide under similar conditions only the C-5 adduct was observed.[39]

Furthermore, Gold *et al.*[41] reported the ring chemical shifts of the C-3 hydride adduct of 2,4-dinitroanisole as 3·74 (H_3s), 7·42 (H_5) and 5·01 (H_6). The chemical shift of the H_3 signal would be expected to be sensitive to the electronic nature of the group attached at the C-3 position.[31] Therefore, any comparison should concentrate on the signals that correspond to H_6 and H_5. Thus, it should be noted that the C-3 acetonate adduct of methyl 2,4-dinitrobenzoate has peaks at 5·06 (H_6), 5·08 (H_3) and 7·43 ppm (H_5).[42a] The C-3 acetonate adduct of 2,2',4,4'-tetranitrodiphenyl sulfide has been reported to have resonances at 4·78 (H_6), 5·24 (H_3) and 7·25 (H_5).[42b] Clearly, the NMR signal for H_5 of C-3 adducts of 1-X-2,4-dinitrobenzenes appears between 7·2 and 7·5 ppm. No such signal appears in this region of the NMR spectra recorded in the DNPEG–OH^- reaction system in DMSO-d_6. For these reasons, the signals of the Meisenheimer adduct found in the DNPEG–OH^- system cannot represent a C-3 adduct.

Finally, if a C-1 adduct is the only likely candidate for the adduct observed in the DNPEG–OH^- system, it should be pointed out that a C-1 hydroxide adduct is unlikely. Even in systems in which the electrophile is more highly substituted with electron-withdrawing groups that stabilize a resultant Meisenheimer complex, C-1 hydroxide adducts are not observed so long as the C-1 position is also substituted by a reasonable leaving group. Thus, in the reaction of 2,4,6-trinitroanisole (TNA) with methoxide or phenoxide ions, hydroxide is generated as a result of equilibration of adventitious water in the DMSO-d_6 solvent with the nucleophiles/bases, and this OH^- reacts with TNA to yield an observable well-characterized C-3 adduct. No C-1 adduct was observed, although the displacement product that could arise from a C-1 adduct, picrate anion ($PicO^-$) was seen. Even when TNA was allowed to react with OH^- and monitored at lower temperature [0 °C, acetonitrile d_3–glyme-d_{10} (1:1)] only a C-3 adduct was observed.[43] The inability to observe a C-1 OH^- adduct of TNA, in which the negative charge in the adduct is dispersed over three stabilizing electron-withdrawing groups, appears to lie in the ease of decomposition of the adduct to other products, to MeOH and $PicO^-$ in the case of the C-1 TNA·OH^- adduct.[44] In any case, if a C-1 OH^- adduct of a trinitroaromatic cannot be observed by NMR, it seems unlikely that the C-1 DNPEG·OH^- adduct would be observable under the present conditions which are even less favourable than the lower temperature regime cited.

At long times (1 day), the spectrum was found to contain signals for $DNPO^-$, 2,4-dinitrophenol and PEG. All signals assignable to a Meisenheimer adduct were absent. Moreover, the peaks assigned to the PEG bis(vinyl ether) had not changed in position or intensity over the course of the reaction and remained unchanged in the final spectrum.

In a separate experiment, trifluoroacetic acid was injected into the NMR tube shortly after the first spectrum was recorded. The spectrum of the acidified sample included peaks for 2,4- dinitrophenol and for PEG; there were no signals attributable to a Meisenheimer adduct. This behaviour is typical of O-centred Meisenheimer adducts.[31,43]

Definitive assignment of the Meisenheimer adduct formed in the DNPEG–OH^- system required the following control experiment.

Reaction of DNPEG-1900-81 with MeO^- in DMSO-d_6

Reaction of 1 equiv. of MeO^- (as $KOCH_3$ in MeOH) with DNPEG-1900-81 in DMSO-d_6 led to the observation of the diminishment of the signals for the substrate and the appearance of new resonances attributable to a C-1 methoxide adduct of DNPEG (C-1 DNPEG·OMe^-). The spectrum acquired 5 min after mixing contains sharp, well resolved peaks for DNPEG-1900-81, in addition to the following intense signals ascribable to the C-1 DNPEG·OMe^- adduct: 5·05 (d, $J = 10·1$ Hz; H_6), 7·15 (centre of a d,d, $J = 10·1$, 2·7 Hz; H_5) and 8·63 ppm (d, $J = 2·7$ Hz; H_3). Significantly, in this initial spectrum the H_3 signal is clearly visible and has its appropriate intensity. Unlike the DNPEG–OH^- reaction system, this spectrum lacks signals for $DNPO^-$, but in common with that reaction system small signals for the bis(vinyl ether) are visible; these do not change over the course of the reaction.

Comparison can be made with literature values for the NMR chemical shifts assigned to the protons of the C-1 methoxide adduct of 2,4-dinitroanisole (i.e. C-1 DNA·OMe^-). These appear at 5·05 (d, $J = 10·1$ Hz; H_6), 7·15 (centre of d,d, $J = 10·1$, 2·4 Hz; H_5) and 8·62 ppm (d, $J = 2·4$ Hz; H_3).[45,46] Note the similarity to the signals found in the DNPEG–MeO^- reaction system (above). Further, consider the similarity between the chemical shifts and coupling constants for the signals of these two C-1 adducts of 2,4-dinitrophenyl alkyl ethers and the signals found in the DNPEG–OH^- system, that is: 5·09 (d, $J = 10·0$ Hz) and 7·10 ppm (d, $J = 10·0$ Hz). Hence the signals found in the DNPEG–OH^- system are assigned to H_6 and H_5, respectively, of a C-1 DNPEG·$OPEG^-$ adduct. The H_3 signal of the C-1 DNPEG·$OPEG^-$ adduct expected to appear at about 8·62 ppm is not observed and not apparently obscured by other signals, but is absent because of efficient H–D exchange with the solvent that occurs in the DMSO-d_6–OH^- medium but does not apparently occur in the methoxide reaction system.

Again, the C-1 complex proved to be acid labile. Addition of TFA to the NMR tube resulted in the

disappearance of the signals ascribed to the C-1 DNPEG·OMe$^-$ adduct.

In the initial spectrum, the comparative integrals permit an estimate of the extent of conversion of the DNPEG into the C-1 DNPEG·OMeO$^-$ adduct, viz 66%.

As the system is monitored small peaks that can be identified as DNPO$^-$, again with the H_3 signal clearly visible, appear (8 min after mixing), and grow with time until they rival the intensity of the peaks assigned to residual DNPEG (2 h) and, finally, (at 3·5 days) the spectrum consists only of unmodified DNPEG, DNPO$^-$ and the small resonances of unchanged PEG bis(vinyl ether).

Reaction of DNPEG-1900-81 with OH$^-$ in D_2O

In order to draw direct comparisons between the kinetic studies that had been done in aqueous NaOH and the NMR studies, the reaction of DNPEG-1900-81 with KOH in D_2O was also followed by 400 MHz ^{1}H NMR spectroscopy.

The preliminary spectrum taken of the water-soluble DNPEG in D_2O (DMSO-d_6 capillary as a lock and chemical shift standard) included the following resonances: 3·18 (centre of a broad band from 3·29 to 3·11 ppm, CH_2—CH_2O— backbone), 3·47 (ill-resolved triplet, DNP—O—CH_2—CH_2—O—PEG, β-methylene), 3·99 (ill-resolved triplet, DNP—O—CH_2—CH_2—O—PEG, α-methylene), 6·99 (d, J = 9·2 Hz, H_6 of DNP ring), 8·02 (d,d, J = 9·2, 2·4, H_5 of DNP ring) and 8·35 ppm (d, J = 2·4 Hz, H_3 of DNP). The spectrum also contained signals attributable to the PEG bis(vinyl ether); the peaks were shifted upfield in this solvent system to 3·69 (centre of a d,d, J = 13·2, 1·7), 3·88 (centre of a d,d, J = 14·1,1·7) and 5·98 ppm (centre of a d,d, J = 14·1, 13·2 Hz). Other peaks of the bis(vinyl ether) are obscured or overlap with those of the PEG backbone, as found previously in DMSO-d_6.

There is no detectable change upon mixing of 1 equiv. of KOH (in H_2O) with the D_2O sample of DNPEG-1900-81 or in spectra acquired within the first 13 min of mixing. However, in the spectrum recorded at 64 min small peaks can be detected at *ca* 6·17 (d, J = 9.2 Hz), *ca* 7·53 (ill-resolved, broad doublet) and at about 8·32 ppm (ill-resolved d) that are assignable to DNPO$^-$ in this medium. Over the course of 3 weeks (during which spectra were recorded at intervals of 1 day) the signals for the aryloxide grew and those of the starting material decreased until at 3 weeks only DNPO$^-$ remained in the system along with PEG and PEG bis(vinyl ether).

Although no signals for any Meisenheimer complex were detected during this NMR experiment, the final spectrum of the 2,4-dinitrophenoxide shows that exchange has occurred at the 3-position. The signal for H_3 in the final spectrum (a sharp doublet at 8·34 ppm, J = 2·2 Hz) has an integral that is about half the value of that found for the signals corresponding to H_5 (d,d, 7·54 ppm, J = 9·6, 2·2 Hz) or to H_6 (d, 6·20 ppm, J = 9·6 Hz). In this system the degree of H–D exchange is about 50%.

DISCUSSION

Reaction pathways

Scheme 1 details some of the potential pathways whereby the bis(2,4-dinitrophenyl ether) of poly(ethylene glycol) (DNPEG, **1**) could hydrolyse under aqueous alkaline conditions. Assuming hydroxide acts as the nucleophile, reaction could occur by S_NAr displacement,[27] where OH$^-$ attacks C-1 of the 2,4-dinitrophenyl ring (Path A). A C-1 DNPEG·OH$^-$ adduct or a transition state modelled on this putative adduct would then collapse to product by expulsion of the DNPO$^-$ leaving group. Alternatively, hydroxide could attack the α-methylene and displace DNPO$^-$ in a concerted S_N2-type reaction (Path B).[28] In fact, this direct displacement involving attack of a nucleophile on an alkyl carbon can compete with S_NAr displacement.[28b,47] The proposal has also been made that alkyl 2,4-dinitrophenyl ethers, wherein the sp^3-hybridized C of the ether is also tertiary, could be useful substrates for S_N1-type solvolyses, particularly acetolyses.[48]

Finally, Scheme 1 shows two possible anchimerically assisted pathways involving initial internal attack of the oxygen at the 6 position (O-6) to give a cyclic oxonium ion intermediate (Path C) with concomitant displacement of the 2,4-dinitrophenoxide ion. Subsequent attack of OH$^-$ on the ring methylene α to the oxonium ion centre (Path C2) leads to formation of the same product as those formed by Path A or B. However, OH$^-$ attack at the PEG α-methylene would result in displacement of 1,4-dioxane (Path C1) and formation of a new lower molecular weight PEG. A control experiment outlined above (see Results) eliminates Path C1 from further consideration; 1,4- dioxane was not detected in a separate larger scale alkaline hydrolysis of DNPEG.

Although, on the face of it, Path C2 would appear to be uncompetitive relative to Paths A or B in a basic medium where the relatively high concentration of nucleophilic OH$^-$ would favour bimolecular reaction routes, Path C2 could still make a contribution to the overall rate of hydrolysis, perhaps as an auxilliary term in a two-term rate law. In neutral or slightly acidic solution Path C could become the dominant pathway. In this context, it should be noted that participation from O-3 has been shown to be unlikely. Thus, sulfonates of 2-methoxyethanol, models for PEG derivatives that do not hydrolyse by the S_NAr route (Path A, Scheme 1), have been investigated by McManus and co-workers, who demonstrated that O-3 anchimeric assistance was not significant for hydrolysis of the tosylate and mesylate in aqueous ethanol, but rather that the reaction

proceeded with nucleophilic assistance from solvent.[49a] However, with 2-(2-methoxyethoxy)ethyl tosylate neutral hydrolysis was shown to proceed by competing pathways corresponding to S_N2 with solvent assistance and neighbouring group participation of the oxygen at the 6 position (O-6).[49b] PEG tosylate also undergoes neutral hydrolysis by competitive direct displacement and anchimerically assisted O-6 routes.[50] Hence, anchimerically-assisted pathways (Path C2) involving participation by O-6 could play a role in the present systems.

Scheme 1 omits possible elimination pathways from consideration, consistent with the NMR results which show that the PEG bis(vinyl ether) product initially found in all systems does not increase in concentration with time. Elimination pathways will not be discussed further.

We shall now consider the evidence, kinetic and spectroscopic, for the preferred mechanism of alkaline hydrolysis in these polymeric systems.

Kinetic evidence

The form of the rate law [equation (1)] determined for the alkaline hydrolysis of DNPEG-1900-81 is consistent with a mechanism involving a bimolecular rate-determining step as found in S_N2 or S_NAr displacements. Significantly, the k_{obs} versus $[OH^-]$ line that defines equation (1) (Figure 2) passes within experimental uncertainty through the origin. Clearly, no other process competes with the second-order displacement term, such as hydrolysis involving water as nucleophile[30,51] or anchimerically assisted displacement involving O-6.

With regard to hydrolysis where water acts as the nucleophile, an estimate can be made of the pseudo-first-order rate coefficient, $k(H_2O)$, if the following assumptions hold. First, attack of OH^- or H_2O is assumed to follow the same (S_NAr) mechanism. Secondly, rate coefficient ratios must remain approximately constant between 2,4-dinitrophenyl ethers and picryl ethers that have the same attached alkoxyl groups. From the data of Murto and Murto[29,30] the values of k_2 for aqueous alkaline hydrolysis of alkyl 2,4-dinitrophenyl ethers (25 °C) are 26 000–14 000 times smaller than those for their picryl analogues.[52] Comparison of the second-order rate constants (60 °C) for base hydrolysis of the picryl ether of methoxypoly(ethylene glycol) (M-PEG-OPic, where average MW of the M-PEG is 1900)[25] with that for DNPEG-1900-81 yields a similar reactivity ratio [i.e. k_2(DNPEG-1900-81)/k_2(M-PEG-OPic) = $3{\cdot}2 \times 10^{-4}$). Therefore, multiplication of an average $k(H_2O)$ value ($1{\cdot}6 \times 10^{-6}$ s^{-1})[30] by the average reactivity factor ($2{\cdot}3 \times 10^{-4}$) provides an estimated $k(H_2O)$ value for DNPEG-1900-81 (and, by extension, other DNPEGs) of $3{\cdot}6 \times 10^{-10}$ s^{-1}. This value is smaller than the uncertainty in the intercept of the k_{obs} versus $[OH^-]$ plot (Figure 2) determined at 60 °C. Note also that the estimated half-life for neutral aqueous hydrolysis of DNPEG is about 61 years.

Although anchimeric assistance of neutral hydrolysis via O-6 is a competitive process for PEG tosylate,[50] it appears unimportant in the hydrolysis of the DNPEG derivatives. It is apparent from Table 2 that the values of k_2 (and from Table 4 that the activation parameters) are similar for all of the alkyl 2,4-dinitrophenyl ether systems. Thus, 2,4-dinitroanisole, which cannot hydrolyse with participation of oxygen, has a rate constant, k_2, almost identical[29] with that found for 1-(2′-methoxyethoxy)-2,4-dinitrobenzene (DNPEG-59-100), which may hydrolyse with O-3 assistance, as well as by S_NAr and S_N2 routes. In turn, k_2 for DNPEG-1900-81 is also the same as the k_2 values reported for the other dinitrophenyl ethers, even though DNPEG-1900-81 may hydrolyse by all of the available pathways illustrated in Scheme 1 plus elimination pathways. These results suggest that hydrolysis proceeds (1) without a contribution from anchimeric assistance and (2) via either the S_NAr route or the S_N2 route, but not by some combination of competitive reactions.

In a previous comparison of the alkaline hydrolysis of methoxy[poly(ethylene glycol)] picryl ether (M-PEG-OPic) with the hydrolysis of the picryl ether of cellulose,[25,26] we argued that the significantly faster rate of hydrolysis of picryl cellulose (initially in neutral aqueous solution) could be accounted for by invoking differential polymer effects[24,53] or a self-catalytic process in the unbuffered picryl cellulose system.[26] In this context it is notable that the k_2 values for alkaline hydrolysis of two DNPEGs that differ only in degree of substitution (DNPEG- 1900-59 and -81) are identical within experimental error. Increasing the polymer chain results in a slight decrease in the value of k_2 for DNPEG-3200-100 as compared with DNPEG-1900-81 or DNPEG-59-100 (Table 2). Thus, the results suggest only a small polymer effect for these PEG systems. It follows that the rate enhancement for the picryl cellulose system relative to the picryl PEG system must arise from a large polymer effect for the cellulose system, perhaps indicative of efficient anchimeric assistance in this case, although self-catalysis cannot be ignored.

^{1}H NMR studies in DMSO and water

The tentative conclusions concerning the mechanism of alkaline hydrolysis are further refined by consideration of the results of the NMR studies. Thus, reaction of hydroxide with DNPEG-1900 in DMSO-d_6 led to formation of a C-1 DNPEG·OPEG$^-$ adduct, along with 2,4-dinitrophenoxide ion, $DNPO^-$. These results are consistent with the following reaction sequence in DMSO: attack of hydroxide at C-1 (perhaps following attack at C-3/C-5 positions and rearrangement to the more stable C-1 adduct)[38–40] leading to displacement of $PEG\text{-}O^-$, formation of $DNPO^-$ and, in turn, attack of

PEG-alkoxide on the C-1 position of unmodified DNPEG to give the C-1 DNPEG·OPEG$^-$ adduct that is observed.

It is not surprising that the putative C-1 hydroxide adduct (C-1 DNPEG·OH$^-$) is unobserved. Such hydroxide adducts that are substituted at the C-1 position by acceptable leaving groups are generally transient[31,32] and may decompose via a process of internal proton transfer to give the electron-deficient phenoxide and corresponding alkanol as has been suggested for C-1 OH$^-$ adducts of picryl ethers.[44] However, C-1 dialkoxy adducts are generally the thermodynamically preferred adducts relative to regioisomeric C-3 (or C-5) adducts, at least partly as a result of stereoelectronic stabilization,[54,55] and these C-1 adducts lack this facile proton transfer decomposition pathway.

Nonetheless, the results indicate that Meisenheimer complex formation that arises from attack on the electron-deficient aromatic ring is feasible in the DNPEG-OH$^-$ systems. Detection of the C-1 DNPEG·OH$^-$ adduct that is the central intermediate along the reaction pathway (Scheme 1, Path A) was not possible but the C-1 DNPEG·OPEG$^-$ adduct that was observed plausibly arises from initial S_NAr displacement of PEG-O$^-$ by OH$^-$ (DMSO-d_6), followed by attack of PEG-O$^-$ on DNPEG at C-1. In D_2O no adducts were detected; DNPEG reacted slowly over time to give DNPO$^-$ and PEG. This is in accord with the well-known ability of DMSO to enhance the equilibrium constant for formation of Meisenheimer complexes relative to water or other hydroxylic solvents.[33]

Observation of the displacement product DNPO$^-$ in the DNPEG–MeO$^-$ DMSO-d_6 control experiment, where S_NAr displacement is not possible, suggests that an S_N2 mechanism is competitive in this system[28,47] although DNPO$^-$ could arise from S_NAr displacement involving very low equilibrium concentrations of OH$^-$ formed by equilibration between adventitious water (generally found in commercial DMSO-d_6) and MeO$^-$ The latter alternative is consistent with behaviour documented in NMR spectroscopic studies of related systems.[43]

Hydrogen-deuterium exchange

In the reaction of DNPEG-1900-81 with OH$^-$, as monitored by ^{1}H NMR spectroscopy in either DMSO-d_6 or D_2O, extensive aryl ring hydrogen–deuterium exchange occurred. In fact, assignment of the C-1 DNPEG·OPEG$^-$ adduct was hampered by the lack of a signal for H_3 in the DMSO-d_6 system. The absence of this signal is indicative of efficient H–D exchange in this case. However, the assignment could be made by comparison of the spectroscopic characteristics of the C-1 DNPEG·OPEG$^-$ adduct to those of the C-1 DNPEG·OMe$^-$ adduct identified in DMSO-d_6–MeO$^-$ MeOH, as well as to analogous C-1 adducts.[31,39,40] Interestingly, in the DMSO-d_6–MeO$^-$ MeOH system no H–D exchange was detected.

It is well known that exchange of ring H for D can be competitive with Meisenheimer complex formation.[56,57] In general, such exchange occurs preferentially at a position *ortho* to two nitro groups, i.e. at C-3 in a 1-X-2,4-dinitrobenzene.[39,56,57] Meisenheimer complexes do not undergo exchange themselves,[58] and nor do polynitroaryloxides (e.g. DNPO$^-$).[59] Exchange occurs in solutions that are relatively dilute in base, but exchange is greatly enhanced in solvents that contain appeciable amounts of aprotic dipolar solvents, including DMSO and acetonitrile. Thus, our observation of aryl H–D exchange in the current DNPEG systems agrees with the general understanding of related reaction systems.

More recently, Bunton and co-workers[39,59,60] have proposed a unified scheme of reaction in which initial single electron transfer (SET) from OH$^-$ to the polynitroaromatic substrate gives rise to a hydroxyl radical–nitroaromatic anion radical pair. This central intermediate may undergo aryl H–D exchange or may collapse to give a productive (i.e., C-1) Meisenheimer complex, that leads to displacement products, or to give unproductive (C-3 and/or, depending on structure, C-5) Meisenheimer complexes. The proposal has been a controversial one, although consistent with the reinterpretation of many formal two-electron (spin-paired) reaction mechanisms in terms of SET,[61] or transition states involving varying degrees of radical character.[62] For example, Crampton *et al.*[38c] were unable to detect the radical–anion radical pair, and other studies aimed at trapping the intermediate aryl anion radical via intermolecular cyclization have failed to do so.[63]

Clearly, the current study was not designed to probe this controversy, but it is significant to re-emphasize that while aryl H–D exchange occurs with OH$^-$ in DMSO-d_6-D_2O solvent as well as in D_2O, no such H–D exchange was observed with methoxide in the DMSO-d_6-MeOH medium. This is puzzling since alkoxides are effective bases and exchange between an aryl anion, formed from free DNPEG, and solvent should be favourable. On the other hand, if the reaction proceeded by the SET pathway, it could be argued that the methoxyl radical–DNPEG anion radical pair collapses to a Meisenheimer complex product so much more rapidly than the corresponding hydroxyl radical–DNPEG anion radical pair that H–D exchange does not occur. A definitive answer to the mechanism of H–D exchange in this and related systems will require further study.

Conclusions and implications for time-release herbicide systems

In this work, we have shown that a range of bis(2,4-dinitrophenyl ether)s of poly(ethylene glycol) (DNPEGs)

undergo alkaline hydrolysis by a second-order overall rate law consistent with the S_NAr displacement mechanism. No evidence was found for competitive anchimerically assisted displacement or for elimination pathways in the release of 2,4-dinitrophenoxide from the DNPEGs. The kinetic and activation data are similar to those found for other low molecular weight alkyl 2,4-dinitrophenyl ethers and indicate that any polymer effect for DNPEGs, if present, is small. NMR studies show that while Meisenheimer complexes could be detected, these were either non-productive complexes or complexes formed after the initial displacement occurred, e.g. the C-1 DNPEG·OPEG$^-$ adduct formed by attack of the PEG-O$^-$ alkoxide on residual DNPEG; the PEG-alkoxide itself arises from an initial S_NAr displacement involving OH$^-$ and the starting DNPEG. Efficent aryl H–D exchange was observed in the DNPEG–OH$^-$–DMSO-d_6 reaction system and in D_2O solvent, but not in the control DNPEG–MeO$^-$–DMSO-d_6 system. This result may indicate very rapid collapse of an intermediate methoxyl radical–DNPEG anion radical pair relative to the corresponding hydroxyl radical case.

Finally, our results show that DNPEG can act as a model of a time-release herbicide, albeit one that carries and could deliver only a low dose of model herbicide. The relatively clean kinetics and the similarity in behavior found between the DNPEG systems and lower molecular weight compounds suggest that rate constants for release of herbicide from lower molecular weight systems can be extrapolated to the polymeric systems. However, an estimate of the first order rate constant for release of 2,4-dinitrophenol from DNPEG in neutral water [$k(H_2O)$] is $3{\cdot}6 \times 10^{-10}$ s^{-1}, which yields a pseudo-first-order half-life for DNPEG of about 61 years at 60 °C. Clearly, at more typical temperatures of application and release (15–20 °C) in the presence of natural water that would be expected to have a pH value of 5·6 (but ranging to as low as 3·9),[64] the rate of release would be impractically slow. Obviously, our model system is a preliminary one, differentiated from more realistic systems by the low loading of herbicide available for release and by the impractically slow rate of release under natural conditions. Further research will proceed to systems that are more realistic, using low molecular weight models as guides.

EXPERIMENTAL

Poly(ethylene glycols). Poly(ethylene glycols) (PEGs) of nominal molecular weights 3400, 2000, 1450 and 1000 were either purchased from Aldrich or were provided as a gift from Union Carbide Canada. These samples were analyszd by size exclusion high-performance liquid chromatography (SEHPLC) using a Bio-Rad LC system fitted with either a TSK 2000 (Toya Soda) or SOTAPhase (Rainen) SE column (0·5% aqueous NaN_3 eluent, flow rate 1·0 ml min^{-1}, refractive index detector). The SE columns were calibrated with molecular weight (MW) standards (Polyscience or Polymer Laboratories) that covered the MW range 586–23 000; column efficiencies were found to be 58 000–70 000 theoretical plates based on ethylene glycol. From this analysis (performed by Dr M. R. Sedaghat-Herati, Southwest Missouri State University), the polymers of nominal MW 3400 and 2000, used in the present study, were assigned MW of 3200 and 1900, respectively. These average MW values were used in all mole calculations.

Preparation of the bis(2,4-dinitrophenyl ether) of poly(ethylene glycol) (DNPEGs). 2,4-Dinitrofluorobenzene, triphenylmethane and n-butyllithium (nominally 1.6 M in hexanes) were obtained from Aldrich and were used without further purification. Solvents (benzene, dichloromethane and diethyl ether) were purchased from BDH or Caledon. Benzene was stored over 4A molecular sieves for a minimum of 24 h prior to use. All PEG samples used in the preparation of DNPEGs were dried by azeotropic distillation with benzene before reaction. The DNPEGs were prepared by the method of Cooke et al.,[65] in which the dry PEG (in benzene) was first titrated with n-butyllithium to a triphenylmethane end-point; the resultant lithium PEG alkoxide was then added to an excess of 2,4-dinitrofluorobenzene in benzene. Purification of the polymer involved initial filtration followed by repetitive dissolution in dichloromethane and precipitation from copious amounts of cold diethyl ether. To produce DNPEGs with varying degrees of substitution the preparation was carried out with 2·2 or 6 equiv. of 2,4-dinitrofluorobenzene; the former conditions produced the material labelled DNPEG-1900-59 (59% substituted) and the latter the material labelled DNPEG-1900-81 (81% substituted). Similarly, DNPEG-3200-100 was prepared using 10 equiv. of 2,4-dinitrofluorobenzene.

Preparation of 1-(2'-ethoxyethoxy)-2,4-dinitrobenzene (DNPEG-59-100). 1-(-2',-Methoxyethoxy)-2,4-dinitrobenzene was prepared according to the method of Whalley[66] by reaction of 1-fluoro-2,4-dinitrobenzene with excess 2-ethoxyethanol and five drops of triethylamine. The initial product was a yelllow oil that was then dissolved in warm methanol and water was added until the solution turned cloudy. The product oiled out several times and each time the supernatant was decanted and the residue was dissolved in methanol-water. A pale yellow solid was isolated the third time; yield 33%. m.p. 37–38 °C (lit.[66] 38 °C). ^{1}H NMR (δ, ppm, DMSO-d_6): 3·45 (s, CH_3O—), 3·86 (t, J = 4·48 Hz) and 4·44 (t, J = 4·48 Hz, O—CH_2—CH_2—O), 7·38 (d, J = 9·25 Hz, H_6 of DNP ring), 8·45, 8·43 (d,d, J = 9·25, 2·78 Hz, H_5 of DNP ring) and 8·72 (d, J = 2·78 Hz, H_3 of DNP ring).

^1H NMR experiments. ^1H NMR data were obtained using a Bruker AM-400 NMR spectrometer operating at 400·1 MHz (Queen's University at Kingston). Deuterated dimethyl sulfoxde (DMSO-d_6; Merck) was treated sequentially three times with 4A molecular sieves prior to use. Wilmad PP-507 NMR tubes were typically used for all NMR experiments; chemical shifts are reported relative to the DMSO-d_5H signal at 2·500 ppm in the solvent or, in the case of the experiments in D_2O, the DMSO-d_5H signal from a capillary of DMSO-d_6 used as the lock standard; coupling constants are given in Hertz as obtained from computer printouts.

(a) Characterization of PEG derivatives. Generally, ^1H NMR spectra (DMSO-d_6) of all of the DNPEGs, regardless of the molecular weight of the PEG backbone, were the same: 3·50 [broad s, $-(CH_2-CH_2-O)_n$, polymer backbone], 3·80 (t, $J = 4·38$ Hz, DNP—O—CH_2—CH_2—O—, β-ethylene), 4·47 (t, $J = 4·38$ Hz, DNP—O—CH_2—CH_2—O—, α- methylene, 7·62 (d, $J = 9·38$ Hz, H_6 of the DNP ring), 8·49, 8·51 (d,d, $J = 9·38$, 2·84 Hz, H_5 of the DNP ring) and 8·76 (d, $J = 2·84$ Hz, H_3 of the DNP ring). All samples were free of 2,4-dinitrophenol peaks. The degree of substitution, based on the integral for any residual OH signal (t, 4.56),[25,34] for each DNPEG was 28% for DNPEG-1900-59, 97% for -1900-81 and 100% for -3200-100.

(b) A representative NMR experiment. A solution of DNPEG-1900-81 (0·020 mol l^{-1}) was prepared from a weighed quantity of the DNPEG (23 mg; $1·6 \times 10^{-5}$ moles of end-groups; $1·0 \times 10^{-5}$ mol) dissolved in 0·500 ml of dry DMSO-d_6 in a septum-capped vial that had been swept with N_2 just prior to preparation of the solution. This solution was transferred into a septum-capped NMR tube with a syringe. An initial NMR spectrum was obtained to ascertain the purity of the sample. To initiate the reaction, 1 equiv. of tetramethylammonium hydroxide (2·7 mol l^{-1} in H_2O; 6 ml; $1·6 \times 10^{-5}$ mol of OH^-) was injected into the sample tube. The first spectrum, consisting of 16 scans per FID, was acquired within 4 min of mixing, but contained broad signals that could not be completely analyzed. The first clean spectrum was recorded within 13 min of mixing. Spectra were then recorded at various intervals up to 1 day from the time of mixing.

In a separate experiment, trifluoroacetic acid (5 µl) was injected into the tube shortly after the first clean spectrum was recorded. After mixing, a new spectrum was acquired; it showed the disappearance of signals attributed to the C-1 DNPEG·OPEG$^-$ adduct and the re-appearance of well resolved signals for starting DNPEG.

Kinetic experiments. Ultraviolet–visible spectra were recorded on a Beckman DU-65 spectrophotometer, thermostated with a circulating water bath. The temperature of the bath was adjusted so that a thermocouple placed in a blank UV cell registered the desired temperature with a fluctuation of ±0·5 °C.

(a) Characterization of PEG derivatives. All of the DNPEGs had similar spectroscopic characteristics. For example, the spectrum (H_2O) of DNPEG-3200-100 (ca 5×10^{-5} mol l^{-1} in end-groups), scanned from 280 to 550 nm, displayed UV–visible peaks at 300 nm (log $\varepsilon = 4·23$) and 438 nm (log $\varepsilon = 3·02$). The region between 400 and 426 nm defines a minimum in the DNPEG spectrum. 2,4-Dinitrophenoxide (2,4-dinitrophenol dissolved in pH 12·0 buffer) has absorption maxima at 358 (log $\varepsilon = 4·14$) and 395 nm (log $\varepsilon = 4·04$). Therefore, 420 nm was chosen at the wavelength for monitoring the reaction, a wavelength close to one of the maxima for 2,4-dinitrophenoxide ion but falling within the region of a DNPEG minimum.

The degree of substitution of the DNPEGs was determined in the following way. A weighed sample of the DNPEG (28·8 mg in the case of DNPEG-1900-81) was dissolved in 25·0 ml of pH 12·0 buffer in a 50 ml round bottomed flask, fitted with reflux condenser. The solution was boiled (one week). At the end of the week an aliquot was removed and the absorbance at 358 and 395 nm measured. The percentage substitution was determined from the ratio of the intensity found to the intensity calculated for total release of 2,4-dinitrophenoxide from a 100% substituted sample, using the absorption maxima previously found for 2,4-dinitrophenoxide ion in pH 12·0 buffer. The same procedure yielded degrees of substitution for DNPEG-1900 of 59% and 81% and for DNPEG-3200 of 100%.

(b) Kinetics. In a typical experiment, a DNPEG-1900-81 (or other DNPEG) stock solution was prepared by dissolution of *ca* 0·10 g of the DNPEG in 100·0 ml of distilled, deionized water. This solution was stored in the refrigerator at *ca* 10 °C. Stock solutions of NaOH of approximate concentrations of 0·090, 0·070, 0·050, 0·030 and 0·010 mol l^{-1} were similarly prepared. The exact NaOH concentrations were determined by titration with standard acid, which, in turn, had been standardized by titration using potassium hydrogen phthalate as the primary standard.

Reaction samples of DNPEG were prepared by pipetting 1·0 ml of the substrate stock solution into a 10·0 ml volumetric flask; the solution was then made up to the mark with the NaOH solution of interest. The final concentration of DNPEG was *ca* $5·0 \times 10^{-5}$ mol l^{-1} in DNPEG (*ca* $1·0 \times 10^{-4}$ mol l^{-1} in end-groups) and the hydroxide concentration varied from 200- to 1800-fold excess relative to DNPEG. At least three reaction samples were prepared at the same time. An initial (time = zero) measurement (A_t, $t = 0$)

was recorded at 420 nm and then the stoppered volumetrics were immersed in the thermostated bath (60 ± 0·5 °C). Readings were taken at 20 min intervals for the first 2 h and thereafter at 1 h and then 5 h intervals. All reactions were monitored for at least five half-lives, at which point the final absorbance (A_∞) was constant.

The data yielded good linear pseudo-first-order and k_{obs} vs [OH^-] plots (cf. Figs 1 and 2). Once the form of the rate law was established for DNPEG-1900-81, values of k_{obs} for the other DNPEG systems were determined as outlined and second-order rate constants, k_2, were calculated from k_{obs}. Arrhenius parameters were obtained by measurement of k_{obs} at various temperatures for DNPEG-1900-81 and the data treated as usual.

Gas chromatographic control experiment: the search for 1,4-dioxane. A control experiment was undertaken to determine whether 1,4-dioxane was produced as a co-product in the hydrolysis of DNPEG. A Hewlett-Packard Model 5280 gas chromatograph with thermal conductivity detector was used in the analysis. The GC was fitted with a 10 m × 0·53 mm i.d. glass capillary column (5% phenylmethylsilicone, 2·65 μm film thickness). Under the following conditions dioxane was readily detectable (to a lower limit of 200 ppm in a sample of diethyl ether and dioxane; retention time 0·368 min) and well separated from the intense peak representing diethyl ether: oven temperature, 70 °C (isothermal); inlet temperature, 115 °C; detector temperature, 200 °C; detector attenuation, 0; chart speed, 6 cm min^{-1}, carrier gas, UHP helium; injection volume, 3·0 μl).

A sample of DNPEG-1900-81 (0·979 g) was dissolved in 20·0 ml of pH 12·0 buffer. The sample was boiled for 1 week and after it had cooled to room temperature it was extracted thoroughly but with a minimum volume of diethyl ether. Repetitive 3·0 μl injections of the ether extract on the column failed to show any signal for 1,4-dioxane.

ACKNOWLEDGEMENTS

The authors acknowledge continuing financial assistance from Sir Wilfred Grenfell College, in the form of a Principal's Research Award (J.M.D.) Dr M. Reza Sedaghat-Herati (Southwestern Missouri State University) is thanked for PEG molecular weight analyses and Professor Erwin Buncel (Queen's University at Kingston) is warmly thanked for the hospitality shown during a recent visit.

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