

The Effect of the Solvent on the Reactivity of Sodium and Potassium Phenoxides in Nucleophilic Substitution Reactions

Part I. Polyethylene Glycol Dimethyl Ethers as Solvents*

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The alkylation of potassium and sodium phenoxides with butyl halides has been investigated kinetically using tetrahydrofuran and the dimethyl ethers of ethylene glycol as solvents. The rates of the reactions increase markedly with increasing chain length of the glycol ethers. In tetraethylene glycol dimethyl ether the reaction rate is about 150 times higher than that in monoethylene glycol dimethyl ether, using equimolar concentrations (0.1 M) of potassium phenoxide and butyl chloride at 25°C. With sodium phenoxide a rate increase of comparable magnitude is found by changing the solvent from mono- to tetraethylene glycol dimethyl ether. Hexaethylene glycol dimethyl ether as solvent at 60°C gave reaction rates about 3 times higher than those with the tetraethylene glycol dimethyl ether as solvent. In tetrahydrofuran the rate is only 1/8 of that in monoethylene glycol dimethyl ether at 25°C.

The reaction rate depends chiefly upon the capacity of the solvent to solvate the alkali ions specifically. In the polyethylene glycol dimethyl ethers, several oxygen atoms in the same molecule cooperate in the solvation of the alkali ion.

For the displacement reaction between a neutral molecule and an ion, $Y^- + RX \rightarrow YR + X^-$, the classical theory predicts that the rate of reaction should be only slightly dependent upon the reaction medium. This is so because the reaction goes through a transition state of the type $Y^{\delta-} \cdots R \cdots X^{\delta-}$, where the total amount of ionic charge is the same as in the initial state. A change in the solvent medium could be expected to have approximately the same influence on the activity of both the anion and the transition state.

For short distance interactions, however, a specific solvation of the different species involved in the reaction may be expected, leading to a difference in the solvation of the Y^- ion and of the transition state. In recent years

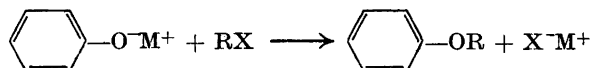
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there have been many reports in the literature¹⁻⁶ which show that this type of reaction may be strongly affected by the solvent medium. The reaction usually proceeds much faster in dipolar aprotic solvents such as dimethyl formamide than in protic solvents such as alcohols, because the deactivation by hydrogen bonding with protic substances is greater for the smaller anion with its concentrated charge than for the transition state where the charge is dispersed. The hydrogen bonding effect is greatest for the smallest anions, and this may cause the reactive order of the anions, often referred to as its nucleophilicity, to change as the reaction medium is changed from a protic to a dipolar aprotic solvent system.¹⁻³

Another effect which in many respects may be similar to that of hydrogen bonding in protic media, is the combination of the reacting anion with a cation. This may happen in solvents where the dissociation of the reacting salt is incomplete, that is, where ion pairs and greater aggregates are present. For this type of interaction it might be expected that the interaction energy of the cation and the reacting anion would be considerably greater than that of the cation and the transition state, the final effect being dependent upon the difference in size and charge distribution of the anion and the transition state. It may therefore be expected that the free anions are more reactive than the ion pairs. Attempts have been made to treat this problem quantitatively. Acree postulated his "dual law of catalysis" as early as 1912.^{7a-d} More recently other authors⁸⁻¹⁵ have assumed that both the free ions and the ion pairs are able to react, and in some cases they have calculated the specific rate constants for the free ions and for the ion pairs. The contribution of the ion pairs to the overall rate of reaction is, however, often very dubious and difficult to assess. In all cases reported it has been found that the reactivity of the free anion is greater, and usually much greater than that of the ion pair.

We have for some time been studying the use of polyethylene glycol dimethyl ethers as solvents or additives in certain organic reactions. In previous papers^{16,17} it was shown that the rate of isomerization of olefinic hydrocarbons in a reaction system catalyzed by potassium *t*-butylate increased as the chain length of the polyether used as solvent or additive increased. This was believed to be due to a specific alkali ion solvation by the polyether solvent. The increase in chain length of the polyether of course results in a greater number of oxygen atoms in the same molecule. It was assumed that several oxygen atoms in the same molecule of polyether cooperated to bring about the solvation of the alkali ion. This leads to a more effective solvation of the alkali ion as the chain length of the ether increases and thereby to a greater degree of dissociation of the potassium *t*-butylate.

From the above discussion of the nucleophilic substitution reaction with alkali salts it was hypothesized that the same effect of increasing chain length of the polyether would be observed when polyethylene glycol dimethyl ethers were used as solvents for the reaction. The alkylation of sodium and potassium phenoxides with butyl halides in polyethylene glycol dimethyl ethers of variable chain length have been investigated:



The reactions lead to the formation of alkali halide salts. The solubility and the degree of dissociation of these compounds in the solvent under investigation may in some cases be expected to influence the degree of dissociation of the reactant, the alkali phenoxide, considerably.

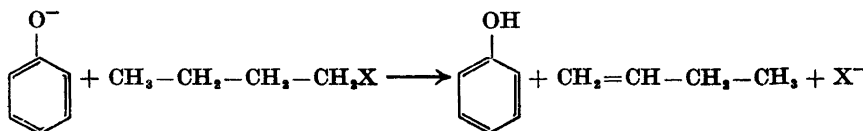
The experimental second order rate constant may then change as the reaction proceeds, and therefore, it was preferable to use initial rates only when comparing different reaction systems. For this reason the reaction was only followed up to about 10 % conversion of the alkali phenoxide, and the rate constant was evaluated from the measurements below 5 % conversion. If the product salt is much better dissociated than the alkali phenoxide, it is possible that even an experimental rate constant, determined at such low degrees of reaction, does not represent absolutely the actual initial rate constant. Therefore, we do not exclude the possibility that some of the rate constants given in this paper are somewhat lower than the real initial rate constants. However, this difficulty should not seriously influence the general conclusions drawn as to the effect of the solvents on the reactivity of the alkali phenoxides.

EXPERIMENTAL

Procedure

Dried alkali phenoxides were dissolved in the various solvents to give the desired concentrations, transferred to 50 or 100 ml round flasks with glass stoppers, and placed in a constant temperature bath held at the desired reaction temperature. The reaction was started by adding a calculated amount of butyl halide to the thermostated phenoxide solution with a 1 ml measuring pipette, and the reaction flask was immediately vigorously shaken (zero time). Aliquots of 5 or 10 ml were withdrawn at regular intervals and added to a known excess of 0.02 N hydrochloric acid. The course of reaction was followed by a determination of unreacted phenoxide, back-titrating the excess hydrochloric acid with 0.02 N sodium hydroxide (methyl red as indicator). Usually nine analysis were taken from the reaction mixture, during the first 10 % of the conversion of phenoxide. The whole procedure, including the preparation of the solutions and the kinetic experiments, was carried out in an atmosphere of nitrogen. In addition to the kinetic measurements at low conversion, a few experiments were followed almost to completion, and it was established that the conversion of phenoxide was very high, more than 95 %. This is in agreement with the results of Kornblum *et al.*¹⁸ who carried out alkylation of phenoxides in concentrated solutions. They showed that despite the fact that the phenoxide ion is an ambident anion, the alkylation product was almost exclusively the phenyl ether (*i.e.* that O-alkylation had occurred), except in those cases where extremely strong hydrogen bonding solvents like water or fluorinated alcohols were used.

In the present investigation butyl halides have been used as the alkylating agents, and there was therefore a theoretical possibility of olefin formation through an elimination reaction.



Because the elimination reaction leads to the formation of phenol, it should be possible to determine the degree of elimination by making an analysis of the phenol content of the reaction mixture. For this purpose the following procedure was used:

The reaction mixture (50 ml) was analysed for unreacted alkali phenoxide, then poured into 200 ml of distilled water, acidified with hydrochloric acid, and extracted with six 50 ml

portions of benzene. The combined benzene solutions were then washed with a little cold ($<5^{\circ}\text{C}$) water, and dried over anhydrous magnesium sulphate. The solution was then evaporated in vacuum to a volume of about 25 ml. This was analysed on a Pye Argon gas chromatograph, using an Apiezon L prepared column at a temperature of 100°C . A second gas chromatogram was made with a known quantity of phenol added to the sample to confirm that the peaks obtained gave true values of the phenol content of the sample.

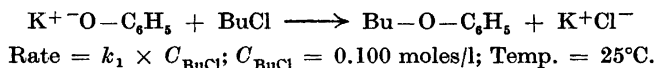
More than 95 % of the initial phenoxide content of the reaction mixture was allowed to react before the solution was analysed in the manner described.

Such analysis were carried out on the products of the reactions between potassium phenoxide and butyl chloride, and between potassium phenoxide and butyl bromide, using tetraethylene glycol dimethyl ether as solvent at 25°C . With butyl chloride there was no detectable phenol produced from an elimination reaction. With butyl bromide the phenol content equivalent to an elimination reaction was approximately 3 %. Although an extraction process like the one described may not give an absolutely quantitative measure of the degree of elimination, the results are satisfactory for our purpose, and we may conclude that the evaluated initial rates are almost entirely the rates of the substitution reactions.

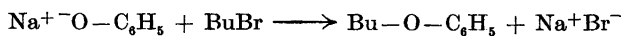
Reagents

Potassium and sodium phenoxides were prepared by the method described by Kornblum and Lurie.¹⁹ A mixture of phenol and alkali hydroxide in a methanol-water solu-

Table 1. Experimental first order rate constants k_1 calculated from measurements of initial rates.



Solvent	Potassium phenoxide moles/l	$k_1 \times 10^5 \text{ sec}^{-1}$
Mono-EGDME	0.1000	0.0071
	0.0474	0.0068
	0.0239	0.0050
	0.0251	0.0052
Di-EGDME	0.0972	0.085
	0.0497	0.076
	0.0489	0.074
	0.0238	0.050
Tri-EGDME	0.0269	0.054
	0.1009	0.83
	0.0960	0.80
	0.0600	0.69
Tetra-EGDME	0.0524	0.62
	0.0262	0.45
	0.0255	0.45
	0.0270	0.47
Tetra-EGDME	0.1010	1.1
	0.0976	1.1
	0.0495	0.75
	0.0542	0.75
	0.0235	0.56
	0.0243	0.55

Table 2. Experimental first order rate constants k_1 calculated as in Table 1.

$$C_{\text{BuBr}} = 0.100 \text{ moles/l; Temp.} = 25^\circ\text{C.}$$

Solvent	Sodium phenoxide moles/l	$k_1 \times 10^5 \text{ sec}^{-1}$
Mono-EGDME	0.0981	0.03
	0.0981	0.03
	0.0495	0.03
	0.0474	0.03
	0.0244	0.03
Di-EGDME	0.0979	0.58
	0.0975	0.57
	0.0485	0.49
	0.0485	0.50
	0.0240	0.43
Tri-EGDME	0.01	1.1
	0.05 insoluble	
	0.0217	
Tetra-EGDME	0.0976	5.6
	0.0973	5.6
	0.0487	4.6
	0.0491	4.5
	0.0243	3.7
	0.0245	3.8

tion was evaporated to dryness, then recrystallized from a little water and twice recrystallized from acetone-ether. The crystalline salts were carefully washed with ethyl ether, and stored under a layer of petrol ether (b.p. 40–60°C). Before use, the salt was dried in vacuum (1 mm Hg) over a boiling water bath for at least 3 h. Molecular weights of the salts were determined by dissolving a known quantity of salt in a known quantity of hydrochloric acid, and titrating the excess acid with sodium hydroxide. The molecular weights of the phenoxides used were within 0.5 % of the theoretical values.

Ethylene glycol dimethyl ether (Mono-EGDME) The "purum" quality from Fluka AG.

Diethylene glycol dimethyl ether (Di-EGDME) The "pract." quality from Fluka AG.

Triethylene glycol dimethyl ether (Tri-EGDME) The "pract." quality from Fluka AG.

Tetraethylene glycol dimethyl ether (Tetra-EGDME) The "purum" quality from Fluka AG.

Hexaethylene glycol dimethyl ether (Hexa-EGDME) "Für die Gaschromatographie" from Theodor Schuchardt GMBH & Co.

Tetrahydrofuran (THF) "Für Chromatographie" from E. Merck AG.

The purification of the polyethylene glycol dimethyl ethers, performed by repeated treatments with fresh sodium wire followed by distillation under reduced pressure in an atmosphere of nitrogen, has already been described.^{17,18} The tetrahydrofuran was boiled with sodium under reflux for 48 h, and distilled in an atmosphere of nitrogen.

The purified solvents were analysed before use by gas chromatography, and in all cases a purity of >99 % was obtained.

Butylbromide (BuBr). The "purum" quality and *butylchloride* (BuCl), the "puriss" quality, both from Fluka AG., were purified by fractional distillation in the presence

of calcium hydride in an atmosphere of nitrogen. Gas chromatograms of the fractions used showed one single peak. No acid was present in the butyl halides.

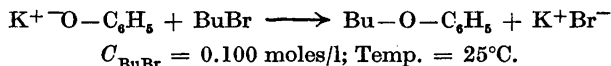
Nitrogen. Fractionated and purified by Norsk Hydro. Nitrogen with argon more than 99.99 % pure, water content less than 0.001 %.

RESULTS AND DISCUSSION

The experimental first order rate constants for the reactions occurring between potassium or sodium phenoxides and butyl halides in polyethylene glycol dimethyl ethers of variable chain lengths are given in Tables 1–4. These data have been used in calculating the relative rates which are given in Table 5.

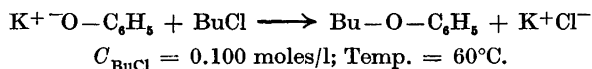
The relative rates clearly establish that increase in chain length of the polyethylene glycol dimethyl ethers results in increase in the rate of reaction. This confirms our earlier work^{16,17} using only potassium compounds. The results given in Table 5 demonstrate that the effect of the chain length is of comparable magnitude for sodium and for potassium salts, although the absolute rates with the same alkyl halide are considerably lower with sodium than with potassium phenoxide. The rate intervals between the different polyglycol

Table 3. Experimental first order rate constants k_1 calculated as in Table 1.



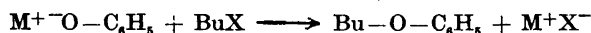
Solvent	Potassium phenoxide moles/l	$k_1 \times 10^5 \text{ sec}^{-1}$
Mono-EGDME	0.0982	1.6
Di-EGDME	0.0968	19
Tri-EGDME	0.0994	~190
Tetra-EGDME	0.0994	~300

Table 4. Experimental first order rate constants k_1 calculated as in Table 1.



Solvent	Potassium phenoxide moles/l	$k_1 \times 10^5 \text{ sec}^{-1}$
Mono-EGDME	0.0947	0.12
Di-EGDME	0.0946	1.0
Tri-EGDME	0.0945	6.1
Tetra-EGDME	0.0934	8.7
Hexa-EGDME	0.0963	~25

Table 5. Relative rates in the polyethylene glycol dimethyl ethers calculated from the values given in Tables 1, 2, 3, and 4. The comparisons are made at equimolar concentrations = 0.1 moles/l.



M ⁺	X	Temp.°C	Relative rates				
			Mono-EGDME	Di-EGDME	Tri-EGDME	Tetra-EGDME	Hexa-EGDME
K ⁺	Cl	25	1	12	117	154	
K ⁺	Br	25	1	12	~120	~185	
Na ⁺	Br	25	1	18	—	180	
K ⁺	Cl	60	1	8	51	72	~200

ethers are similar for the reactions with butyl chloride and butyl bromide when the same alkali phenoxide is used (Table 5). The small differences in the relative rates are most likely due to the difficulties in measuring the fastest reactions with the techniques employed. The experiments with hexaethylene glycol dimethyl ether as solvent (Table 5) were carried out at 60°C, because the potassium phenoxide is only sparingly soluble in this solvent at 25°C while it is sufficiently soluble at 60°C. The reaction rate was found to be three times higher than the corresponding rate in tetraethylene glycol dimethyl ether at 60°C. Investigations with polyethers of still higher chain lengths are in progress, as it seems possible that the effect of increasing chain length has not yet reached a maximum by the hexaethylene compound.^{17,21}

Tables 1 and 2 show that the reaction orders with respect to the phenoxides are far from unity. With sodium phenoxide in monoethylene glycol dimethyl ether, the reaction rate seems even to be practically independent of the phenoxide concentration, giving zero order with respect to phenoxide. The highest order with respect to phenoxide is found when the polyethylene glycol dimethyl ethers of highest chain length are used as solvents. According to the results

Table 6. Dielectric constants of the polyethylene glycol dimethyl ethers. (Measured on a dipole meter: DMOI from Wissenschaftlich Technische Werkstätten, GmbH, (measuring frequency: 2 megacycles).)

	25°C	60°C
Mono-EGDME	6.99	6.00
Di-EGDME	7.27	6.40
Tri-EGDME	7.51	6.69
Tetra-EGDME	7.68	6.87

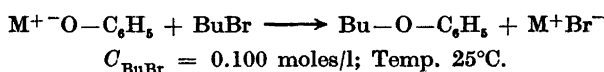
given in Table 1, the rate of the reaction with potassium phenoxide in tetraethylene glycol dimethyl ether is approximately proportional to the square root of the concentration of potassium phenoxide. The low orders with respect to the phenoxide found in some of the polyethers suggest the formation of ionic associations higher than pairwise.

The dielectric constants of the various polyethylene glycol dimethyl ethers at either 25° or 60°C are all very similar, as shown in Table 6, and the great variation in the rate of reaction observed in the different ethers can obviously not be explained from the small change in dielectric constant. This supports the earlier hypotheses, that short range interactions between the ether oxygen atoms and alkali ions play an important role in the solvation process, and that the effect of increasing chain length is due to a cooperation of several oxygen atoms in the same molecule in the solvation of an alkali ion.

The relationship between the structure of a compound and its ability to solvate alkali ions is a field which is still only partially explored. The Born equation for the charging of a monovalent ion in a continuous dielectric is: $\Delta G_{el} = e^2/2\epsilon r$, where e is the electron charge and r is the radius of the ion, and ϵ is the dielectric constant of the medium. Denison and Ramsey,²² by application of the Born cycle, derived, for the dissociation constant of an ion pair in media of not too high dielectric constant, the expression: $-\ln K = e^2/a\epsilon kT$, where a is the centre to centre distance of the ions in the ion pair and k is Boltzmann's constant. An increasing amount of evidence is accumulating, however, which indicates that specific ion-solvent interaction may play a predominant role in the solvation of ions. This view has led to expressions for the dissociation constants of ion pairs, where energy terms calculated from ion-dipolar interactions with solvent molecules immediately surrounding the ions are added to the Born energy.^{23,24}

Several attempts have been made to estimate the solvation energy of alkali ions.^{25,26} One approach to the problem has been to calculate the ion-dipole interaction energy between the ions and the solvent molecules in the primary and eventually in the secondary solvation shell. This energy is then added to a Born energy term with an adjusted value of r . Zaugg, however, from measurements of the effect of different additives on the reactivity of sodio-malonic ester in benzene, concluded that there is no direct relationship between the dipole moment of a compound and its ability to solvate alkali ions. Zaugg lists a number of substances which show an extraordinary capacity to solvate the sodium ion, and attributes this effect to the fact that these substances have a high electron density in the π orbital at the oxygen atom. The Born energy must, however, be involved in the solvation process of the ions (and may probably, in aprotic solvents, give a better approximation for the solvation of the anions than for the solvation of the cations). Investigations in solvent mixtures containing a polyether and a substance of high dielectric constant

Table 7. Experimental first order rate constants k_1 calculated as in Table 1.



Solvent	$\text{M}^+ = \text{K}^+$ moles/l	$k_1 \times 10^6 \text{ sec}^{-1}$	rel.rate	$\text{M}^+ = \text{Na}^+$ moles/l	$k_1 \times 10^5 \text{ sec}^{-1}$	rel.rate
THF	0.0241	0.16	1	0.0238	0.0043	1
Mono-EGDME	0.0243	1.3	8	0.0244	0.033	8

may possible give a better insight into the importance of the dielectric factor. Such investigations are in progress.

Tetrahydrofuran, with only one ether oxygen in the molecule, has a dielectric constant of 7.39 at 25°C,²⁰ almost the same as the constants for the polyethers. It was therefore investigated as a solvent in the substitution reaction in order to make a comparison with the polyethers. Results from the alkali phenoxide-butyl bromide reaction in tetrahydrofuran are given in Table 7. For comparison, the results from the same reaction carried out in monoethylene glycol dimethyl ether are included.

Tetrahydrofuran is inferior to monoethylene glycol dimethyl ether in the solvation of both potassium and sodium ions. These results are in agreement with the observations made by Zaugg⁶ concerning the alkylation of sodio-malonic esters, namely that ethylene glycol dimethyl ether is superior to tetrahydrofuran in the solvations of sodium ions.

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