

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

Part II. The Relative Reactivity of Sodium and Potassium Phenoxides in Different Aprotic Solvents*

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The rate of alkylation of potassium and sodium phenoxide with butyl halides has been investigated kinetically in dimethylformamide, acetone, dimethyl sulfoxide, and *p*-dioxane. Results of previous investigations on the same reaction in tetrahydrofuran and polyethylene glycol dimethyl ethers of variable chain lengths are also included in the discussion in order to give more extensive comparison of the solvent effect on the rates of reaction. Initial rates evaluated from measurements at a low degree of reaction have been used in the comparison of the rates of alkylation in the different solvents.

The rate of the alkylation reaction increases in the sequence of solvents: *p*-dioxane < tetrahydrofuran < acetone < dimethylformamide \sim dimethyl sulfoxide. In the two latter solvents the rate is extremely high, being about 300 times higher than in acetone. Such a high ratio cannot be explained solely by the difference in the dielectric constant of the solvents. The rate will depend, to a large extent, upon the ability of the solvent to solvate the alkali ion specifically. This is also evident from the fact that the rate of the potassium phenoxide alkylation in, for example, tetraethylene glycol dimethyl ether ($\epsilon = 7.7$) is about 31 times higher than that in acetone ($\epsilon = 20.7$).

In the solvents where the alkali solvating group is ether oxygen, and which have relatively low dielectric constants ($\epsilon \sim 7$), the ratio between the rates of alkylation of potassium and sodium phenoxide is about 30-40, using a phenoxide concentration of 0.025 M at 25°C. The corresponding ratio is only 2-5 in the solvents where the alkali solvating group is a carbonyl or a sulfoxide group, and which have a relatively high dielectric constant ($\epsilon \sim 20-45$).

Measurements at higher degrees of reaction emphasize the necessity of using initial rates when comparing the effect of the solvent on the rate of the reactions.

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In a previous paper (Part I)¹ it was shown that the rate of alkylation of potassium and sodium phenoxides in polyethylene glycol dimethyl ethers was very dependent upon the chain length of the polyether used as solvent. By increasing the chain length from mono- to hexaethylene glycol dimethyl ether it was possible to obtain a considerable increase in the rate of reaction.

In recent years many examples have been given in the literature²⁻¹⁰ which show that special types of dipolar aprotic solvents such as dimethylformamide and dimethyl sulfoxide are very suitable solvents for nucleophilic substitution reactions giving high rates of reaction and high yields of products. It was therefore desirable to make a comparison between the polyether solvents already investigated and one of these aprotic dipolar solvents. The kinetics of the alkylation of sodium and potassium phenoxide in dimethylformamide have been studied rather extensively. In order to get information about the effect of the nature of the solvent on the absolute reactivity of the alkali phenoxide, and especially on the relative reactivity of the sodium and the potassium phenoxide, investigations with a number of other solvents have also been carried out.

As mentioned in Part I, the reactant salt and the product salt may have a mutual influence on the solubility and degree of dissociation of each other. The comparison between the rates in the different solvents are therefore preferably done by evaluating initial rates. At the end of this paper the results of some experiments which were followed up to high conversions of the alkali phenoxide are given.

EXPERIMENTAL

Procedure. The kinetic experiments were carried out in the same manner as described in Part I. The rate of reaction was determined by estimating the consumption of alkali phenoxide. During the preparation of the solutions and the kinetic experiments, an atmosphere of purified nitrogen was maintained.

To confirm that the measured rates are representative for the substitution reaction solely, products of the reaction between potassium phenoxide and both butyl chloride and butyl bromide in dimethylformamide were analysed for phenol by the method described in Part I. The gas chromatographic analysis showed a phenol content corresponding to about 2 % of phenoxide converted, when the total conversion of phenoxide was 97 %.

Reagents. Potassium and sodium phenoxide were prepared by the method of Kornblum and Lurie as described in Part I.

1,4-Dioxane. The quality "Für Chromatographie", from E. Merck A.G., was refluxed with sodium for 48 h and distilled from sodium in an atmosphere of nitrogen. B.p. 100–102°C.

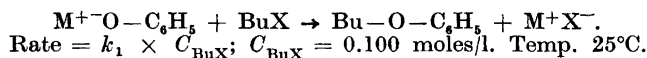
Acetone. The quality "pro analysi und für Chromatographie", from E. Merck A. G., was dried with Union Carbide's molecular sieve 4A, then fractionally distilled in an atmosphere of nitrogen. B.p. 56.5°C.

Dimethylformamide (DMF). The quality "Lösungsmittel für die Spektroskopie", from E. Merck A. G., was dried with a molecular sieve 4A, then distilled under reduced pressure in an atmosphere of nitrogen.

Dimethyl sulfoxide (DMSO). The quality "F:18.45° Kp. 189°," from Dr. Theodor Schuchardt GMBG & Co., was purified by crystallization and dried with a molecular sieve 4A.

4-Iodonitrobenzene. The quality "purum" from Fluka A.G., was crystallized from ethanol and dried in a vacuum. M.p. 171°C.

Table 1.



Solvent	X =	M ⁺ = K ⁺ moles/l	$k_1 \times 10^5 \text{sec}^{-1}$	M ⁺ = Na ⁺ moles/l	$k_1 \times 10^5 \text{sec}^{-1}$
DMF	Cl	0.0966	21	0.0975	2.7
	Cl	0.0488	16	0.0503	2.6
	Cl	0.0246	12	0.0244	2.3
DMSO	Cl	0.0247	9.0	0.0238	4.4
Tetra-EGDME	Cl	0.0243	0.55	—	—
1,4-Dioxane	Br	0.0244	0.01	—	—
THF	Br	0.0241	0.16	0.0238	0.0043
Acetone	Br	0.0249	4.9	0.0247	1.2
Tetra-EGDME	Br	0.025	150*	0.0243	3.7

* The rate constant was measured with 0.1 M potassium phenoxide. The value given in the table is calculated on the basis that the order of reaction with respect to potassium phenoxide is the same with butyl bromide and butyl chloride.

Sodium iodide. The quality "puriss sicc" from E. Merck A. G. was crystallized from ethanol and dried in a vacuum.

The purity of the solvents was confirmed by vapour phase chromatography, and a purity degree > 99 % was obtained in all cases. Quality and purification of other reagents used have been described in Part I. The following abbreviations are used: Mono-EDGME, Di-EGDME and Tetra-EGDME for mono-, di-, and tetraethylene glycol dimethyl ether respectively, BuBr and BuCl for butyl bromide and butyl chloride.

RESULTS AND DISCUSSION

In Table 1 is given the experimental first order rate constant for the reaction between potassium and sodium phenoxide with butyl chloride in dimethylformamide at different initial concentrations of alkali phenoxide. The results of alkylation with butyl chloride or butyl bromide in dimethyl sulfoxide, dioxane, tetrahydrofuran, acetone, and tetraethylene glycol dimethyl ether, at a single concentration of phenoxides are included in the table.

Table 2 compares the rates of alkylation of sodium and potassium phenoxide in the different solvents investigated. The values for tetrahydrofuran and for the polyethylene glycol dimethyl ethers are taken from Part I, and are included in Tables 1 and 2 for comparison. Table 2 confirms the statement given in Part I, *i.e.* that the rates of the alkylation in the polyethylene glycol dimethyl ethers of high chain length are "abnormally" high in view of the relatively low dielectric constants of these compounds. This is especially the case in the alkylation of potassium phenoxide. The rate of this reaction is 31 times faster in Tetra-EGDME than in acetone.

The rate of the alkylation reactions are much faster in DMF and DMSO than in acetone (Table 2). This is in agreement with previously obtained results

Table 2. $M^+O-C_6H_5 + BuX \rightarrow Bu-O-C_6H_5 + M^+X$. Rate = $k_1 \times C_{BuX} \cdot C_{M^+} = 0.025$ moles/l, $C_{BuX} = 0.100$ moles/l. Temp. 25°C.

Solvent	Dielectric constant	X =	$(M^+ = K^+)$ $k_1 \times 10^3 \text{sec}^{-1}$	$(M^+ = Na^+)$ $k_1 \times 10^3 \text{sec}^{-1}$	$\frac{k_1(M^+ = K^+)}{k_1(M^+ = Na^+)}$
1,4-Dioxane	2.2	Br	0.01	—	—
THF	7.4	Br	0.16	0.0043	37
Mono-EGDME	7.0	Br	1.3	0.033	39
Di-EGDME	7.3	Br	12	0.43	28
Tetra-EGDME	7.7	Br	150	3.7	40
Acetone	20.7	Br	4.9	1.2	4
DMF	36.7	Br	—	340 *	—
DMF	36.7	Cl	12	2.3	5
DMSO	45	Cl	9.0	4.4	2

* Because of the higher rate of the reaction only an approximative value can be given.

and confirm the assumption of Zaugg⁶⁻⁸ that these compounds have a specific action that cannot be ascribed solely to the high dielectric constants of these compounds. DMF and DMSO also give considerably higher rates of the alkylation reactions than even the higher polyethylene glycol dimethyl ethers investigated. This is especially so in the case of the sodium phenoxide. The tables indicate, however, that the dielectric constant, although not the only factor, may have a considerable influence on the rate of the present alkylation reaction. Thus, the rate in tetrahydrofuran is about 16 times higher than in dioxane. The rate in acetone is again 31 times higher than that in tetrahydrofuran.

Table 2 shows that there is a striking difference in the relative reaction rate of the potassium and the sodium phenoxide in the different solvents. In the media with ether oxygen and with low dielectric constant (~ 7) the ratio of the rate of reaction with potassium and sodium phenoxide is approximately 30–40. In the solvents where the alkali solvating group is $>CO$ or $>SO$ and which have high dielectric constants, a levelling effect is obtained, reducing the rate ratio between the potassium and the sodium phenoxide to 2–5. It should be noted that the degree of dissociation of both sodium and potassium phenoxide are low, even in dimethylformamide, as will be evident from Table 1. This levelling effect cannot therefore be due to an approach to total dissociation of the phenoxides. The results are still too few to allow any detailed discussion of the reason for this difference; whether it is due to the difference in dielectric constant or to the specific behaviour of the carbonyl oxygen or sulfoxide oxygen and the ether oxygen.

If the free anion is assumed to be the only reacting species from the reactant salt, the dielectric constant of the solvent may be responsible for two different effects.

i) An increasing dielectric constant of the solvent medium may be expected to lead to an increase in the degree of dissociation of the reactant salt. The effect of the dielectric constant on the dissociation constant K of an ion pair is given by the Denison-Ramsey equation:¹¹

$$-\ln K = e^2/a\epsilon kT \quad (\text{I})$$

where e is the electron charge, a is the "distance of closest approach" in the ion pair, ϵ is the dielectric constant of the solvent, k is Boltzmann's constant and T is the absolute temperature.

ii) According to classical theory¹² the reactivity of the free anion with a neutral molecule is expected to decrease, though very slightly, with increasing dielectric constant of the solvent. However, to what degree the reactivity of the free anion varies with the dielectric constant is as yet unknown. It may be expected to depend upon the difference in size and charge distribution between the anion and the transition state. The following equation has been proposed to account for the variation in the rate of reaction with the dielectric constant of the solvent in a reaction between a free anion and a neutral molecule:¹³

$$\ln k = \ln k_0 + \frac{e^2}{2\epsilon kT} \left(\frac{1}{r} - \frac{1}{r^\ddagger} \right) \quad (\text{II})$$

where k is the second order rate constant of the reaction in a medium with dielectric constant ϵ , and k_0 is the rate constant when $\epsilon = \infty$. r and r^\ddagger are the size of the reacting anion and the transition state respectively, k and T are defined in equation (I). An increase in the value of K with increasing dielectric constant may then be expected to be counteracted by a reduced reactivity of the free anion as the dielectric constant increases. However, it is not possible to predict the net effect of the dielectric constant on the overall rate of reaction from the equations above. For most reactions with an incompletely dissociated salt it is reasonable to expect that the increase in the value of K (eqn. I) with increasing value of ϵ is considerably greater than the simultaneous decrease in the value of k (eqn. II). An increase in the dielectric constant of the medium should then give an increase in the rate of the reaction.

In the reaction discussed in this paper it has been assumed that the ability of the solvent to solvate the alkali ions specifically by short range interactions has considerable importance in the dissociation of the reactant salt. Eqn. I has been corrected to account for specific solvation by Fuoss,¹⁴ who gives the following expression for the dissociation constant of an ion pair:

$$-\ln K = \frac{e^2}{a\epsilon kT} - \frac{E_s}{kT} \quad (\text{III})$$

where the term E_s/kT accounts for specific solvent solute interactions. Since our reaction is carried out in aprotic solvents we expect that the value of E_s is chiefly dependent upon specific solvation of the alkali ions *i.e.* the cations. It appears from the discussion above that an increase in the value of K , brought about by an increase in the value of E_s , is not accompanied by a simultaneous decrease in the value of k (equation II). Contrarily a decreasing value of k results if the increase in K is brought about an increase in the value of ϵ , as mentioned. Therefore, a comparison of the rates of reaction in various aprotic media with considerably different dielectric constants

may not give a correct picture of the relative degree of dissociation of the reactant salt in the various solvents.

In Part I the efficiency of the polyethers as solvents was thought mainly to be due to their ability to solvate the alkali ions specifically by short range interactions with the ether oxygens. The effect may be ascribed to the term E_s which increases as the chain length of the polyether increases. In a polyether the value of K is expected to become relatively high regarding its low dielectric constant. However, considerably higher values of K are likely to be found in the solvents with the highest dielectric constants investigated. The following effect may contribute to give the relatively high rates of reaction in the polyethers: Compared to solvents with higher dielectric constants, the low dielectric constants of the polyethers may be expected to give a comparatively high reactivity of the free anions in accordance with eqn. II.

Measurements at higher conversions

If the alkali phenoxide is completely dissociated in the solvent under investigation, the reaction will remain first order with respect to the phenoxide during a run. In the case, however, where the dissociation of the alkali phenoxide is incomplete, complications may occur from the influence of the salt formed on the degree of dissociation of the alkali phenoxides. If, for simplicity of discussion, it is assumed that only ion pairs and free ions are present, the dissociation constant of the ion pair is given by:

$$K = \frac{\alpha}{1-\alpha} C_{M^+} \gamma^{\pm 2}$$

where α is the dissociation degree of the alkali phenoxide, C_{M^+} is the concentration of alkali ion in solution and γ^{\pm} is the mean activity coefficient of the free alkali ion and the phenoxide ion. From the above equation it is seen that, for the dissociation degree α to remain constant during the reaction, the product $C_{M^+} \gamma^{\pm 2}$ has to keep constant. This is only to be expected if the dissociation degree of the alkali phenoxide and the salt formed is the same. Only in this case therefore it may be expected that the second order rate constant remains constant during a run.

A decrease in the concentration of M^+ ion during a run may occur if the salt formed in the reaction precipitates or if the product salt has a considerably smaller dissociation constant than the alkali phenoxide. In that case it may be expected that the dissociation degree of the phenoxide increases as the reaction proceeds. Consequentially the experimental second order rate constant will be expected to increase at the same time. An example of a run where the second order rate constant increases with increasing degree of reaction is the reaction between potassium phenoxide and butyl chloride in tetraethylene glycol dimethyl ether (Table 3). The potassium chloride formed by the reaction precipitates from the beginning of the reaction, and the degree of dissociation of the phenoxide will therefore increase as the reaction proceeds. This leads to a steady increase in the second order rate constant. It should be noted that the values given for the experimental second order rate constant in Table 3

Table 3. $\text{K}^+\text{O}-\text{C}_6\text{H}_5 + \text{BuCl} \rightarrow \text{Bu}-\text{O}-\text{C}_6\text{H}_5 + \text{K}^+\text{Cl}$. Solvent Tetra-EGDME. 0.100 moles/l equimolar concentrations. Temp. 25°C. Rate = $k_2 \times C_{\text{phenoxide}} \times C_{\text{halide}}$.

% conversion of phenoxide		$k_2 \times 10^4 \text{ l}\cdot\text{mole}^{-1}\text{sec}^{-1}$	
2.5		1.12	
	4.3		1.19
5.5		1.12	
8.7		1.16	
	19.5		1.28
25.1		1.25	
26.7		1.30	
	32.4		1.33
37.6		1.34	
48.2		1.37	
	55.8		1.42
	62.5		1.51
	66.6		1.52

The table gives results from two separate runs. The rate constants given in the table are calculated from the expression: $k_2 = (1/t) \times x/[a(a-x)]$ where t is the time, a is the initial amount of phenoxide in moles/l, and x is the amount of phenoxide reacted.

are at every degree of conversion calculated with zero time as reference, so that the real increase in the rate constant with increasing conversion is somewhat greater than is apparent from the table.

Alkali iodides are known to be very soluble and highly dissociated in DMF.¹⁵ The results of Table 1 indicate strongly that the alkali phenoxides investigated are only dissociated to a small degree in DMF at the concentrations used. It might therefore be predicted that the experimental second order rate constant for the alkylation of alkali phenoxides with an iodo compound will decrease markedly as the reaction proceeds. The decrease in the value of the rate constant should be most pronounced with sodium phenoxide.

A second order rate constant has been reported for the reaction between sodium phenoxide and 4-iodonitrobenzene in dimethylformamide.⁴ This is, however, not a constant second order reaction.* Following the reaction kinetically it has been found that the experimental second order rate constant decreases as the reaction proceeds to relatively high conversion. A few experiments with sodium phenoxide and 4-iodonitrobenzene were carried out, and the effect of added sodium iodide on the initial rate of reaction was investigated.

Fig. 1 shows how the reaction proceeds with 0.05 M equimolar initial concentrations of sodium phenoxide and 4-iodonitrobenzene in dimethylformamide at 25°C. Percent conversion of phenoxide is plotted against reaction time. The experimental second order rate constant was found to decrease steadily as the reaction proceeded. At a conversion of phenoxide of 6.2 %, 29.5 %, and 52.8 % the experimental values for the second order rate constant

* A. J. Parker: Private communications.

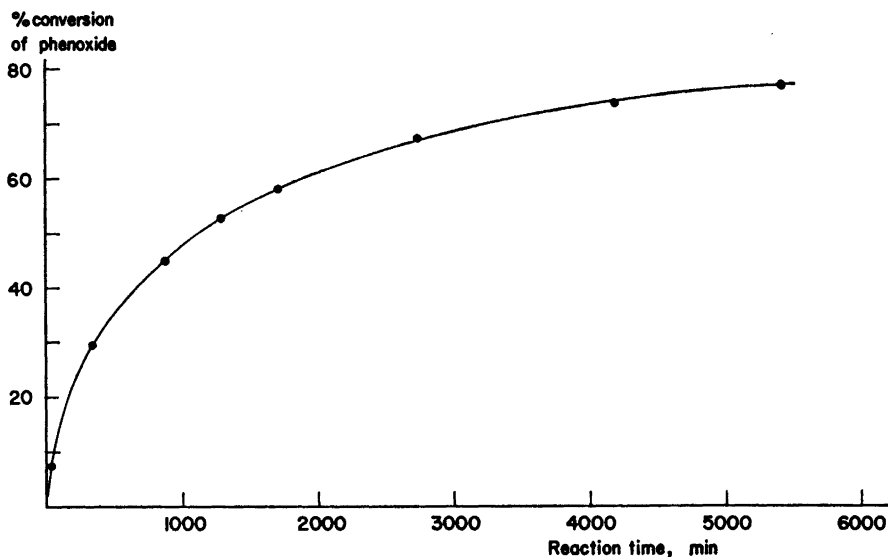


Fig. 1. The reaction: $\text{Na}^+\text{OC}_6\text{H}_5 + \text{NO}_2\text{-C}_6\text{H}_4\text{-I}$. 0.05 M equimolar concentration in DMF. 25°C.

were respectively 5.7×10^{-4} , 4.3×10^{-4} , and 3.0×10^{-4} (l-moles⁻¹ sec⁻¹). These values are all calculated with time zero as reference time, the real drop in the rate is, of course, even greater.

Table 4 gives the results of a few measurements of initial rates with different initial concentrations of the reactants and, in addition, the initial rate in the case where a given amount of sodium iodide was added from the start. Runs No. 1 and 2 in Table 4 show that the dissociation degree of sodium phenoxide in dimethylformamide is very low and confirm the results given in Table 1. Furthermore runs No. 1 and 3 in Table 4 show that the reaction is first order with respect to 4-iodonitrobenzene. The addition of 0.025 M sodium iodide to the reaction mixture (run No. 4, Table 4) causes the initial second order

Table 4. $\text{Na}^+\text{O-C}_6\text{H}_5 + \text{NO}_2\text{-C}_6\text{H}_4\text{-I} \rightarrow \text{NO}_2\text{-C}_6\text{H}_4\text{-O-C}_6\text{H}_5 + \text{Na}^+\text{I}^-$.
Rate = $k_2 \times C_{\text{phenoxide}} \times C_{\text{halide}}$. Solvent DMF. Temp. 25°C.

No.	Initial concentrations of reactants	Initial rate constants $k_2 \times 10^4 \text{ mole}^{-1} \text{ sec}^{-1}$
1	0.050 M phenoxide + 0.050 M iodo comp.	5.6
2	0.025 M phenoxide + 0.050 M iodo comp.	10
3	0.050 M phenoxide + 0.025 M iodo comp.	5.6
4	0.025 M phenoxide + 0.025 M iodo comp. + 0.025 M NaI	2.9

rate constant in the reaction between 0.025 M equimolar concentrations of sodium phenoxide and 4-iodonitrobenzene to decrease about 3.5 times.

When the reaction referred to in Fig. 1, with 0.050 M equimolar initial concentrations of the reactants, has reached 50 % conversion, the reaction mixture will contain 0.025 M sodium phenoxide, 0.025 M 4-iodonitrobenzene and 0.025 M sodium iodide. This composition is precisely the same as the one investigated in run No. 4 in Table 4 with added sodium iodide. From the curve in the figure the instantaneous second order rate constant at 50 % conversion is calculated to be about $2.8 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec}^{-1}$, that is approximately the same value as the initial second order rate constant in run No. 4. These results leave no doubt that the marked decrease in the experimental second order rate constant through a run is caused by the influence of the reaction product, sodium iodide, on the dissociation of the sodium phenoxide in dimethylformamide. The results emphasize the necessity of using initial rates when comparing the effect of solvents on the rates.

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