

# The Effect of the Solvent on the Reactivity of Potassium and Quaternary Ammonium Phenoxides in Nucleophilic Substitution Reactions

## Part III

JOHN UGELSTAD, TURID ELLINGSEN and ARVID BERGE

*Institute of Industrial Chemistry, Norges Tekniske Högskole, Trondheim, Norway*

The rate of alkylation of potassium and tetra-butylammonium phenoxide with butyl halides has been investigated in dioxane, tetrahydrofuran, acetonitrile, dimethylformamide and mixtures of dioxane and acetonitrile. Quaternary ammonium phenoxide was prepared *in situ*, allowing potassium phenoxide to react with tetra-butyl ammonium halides in the respective solvents. In dioxane solution replacement of the potassium ion by the quaternary ammonium ion leads to an increase in the rate of reaction by a factor of  $3 \times 10^4$ . It is found that the rate of alkylation of the quaternary phenoxide changes very little by change in solvent. This is in great contrast to the alkylation of potassium phenoxide where the rate increases by a factor of  $\sim 10^6$  from dioxane to dimethylformamide. It is suggested that quaternary ammonium phenoxide reacts as an ion-pair in ethereal solvents with low dielectric constants.

In previous papers<sup>1,2</sup> we have been concerned with the relative reactivity of potassium and sodium phenoxide in alkylation reactions in various aprotic solvents. Especially in solvents with relatively low dielectric constants it was found that the rate of reaction was dependent upon the cation, being about 40 times faster with potassium than with sodium phenoxide at a phenoxide concentration of about 0.025 M. We now have investigated the same alkylation reactions with tetra-butylammonium as cation.

Qualitative aspects are apparent from the literature on the effect of quaternary ammonium salts in nucleophilic substitution reactions. Curtin *et al.*<sup>3</sup> observed that the addition of quaternary ammonium bromide strongly accelerated the reaction of sodium 2,6-dimethylphenoxide with allyl bromide in ethereal solution. Zook and Gumby<sup>4</sup> found that addition of catalytic amounts of tetra-butylammonium iodide or perchlorate to a sodium enolate in ether

increased the rate of ethylation by a factor of three. In the reaction between benzyl thioalkoxide and 4-fluoronitrobenzene in dioxane-methanol solution, Kingsbury<sup>5</sup> found an accelerating effect of tetra-ethylammonium bromide. In the present paper the alkylation of potassium phenoxide and tetra-butylammonium phenoxide are compared in aprotic solvents like dioxane, tetrahydrofuran, acetonitrile, dimethylformamide and mixtures of dioxane and acetonitrile.

Quaternary ammonium phenoxide was most conveniently prepared *in situ* in the actual solvent. Addition of quaternary ammonium halide to a solution of potassium phenoxide gave a high yield of the quaternary phenoxide when the alkali halide formed in the exchange reaction precipitated from the solution. The ideal case for our purpose would be one with a highly soluble quaternary salt added, and an almost insoluble alkali halide formed. Tetra-butylammonium bromide and chloride were chosen because they are relatively soluble in most aprotic solvents. Potassium bromide and chloride are comparatively much less soluble in the same solvents.

## EXPERIMENTAL

### Procedure

The kinetic experiments were carried out as described in part I.<sup>1</sup> The tetra-butylammonium halides were dissolved in the various solvents to give the desired concentrations (rate of dissolution increased by a little warming of the flask if necessary), and then added to the solutions of potassium phenoxide. In all cases the potassium halide began to precipitate immediately according to the reaction:



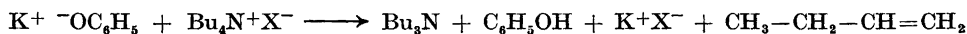
The degree of exchange,  $\text{K}^+ \longrightarrow \text{Bu}_4\text{N}^+$ , was measured when equilibrium was established, by analysing the reaction mixture for halide still being in solution by potentiometric titration with silver nitrate solution. When equimolar concentrations of the reactants were mixed and kept at 25°C for 1 h, the degree of exchange was found to be 70–95 %. The solubilities of the potassium halides are very small in the solvents used, and can generally be neglected. However, the solubilities of potassium chloride in dimethylformamide and of potassium bromide in acetonitrile are exceptional in that they both are of order 0.001–0.002 mole/l. No attempt was made to separate the quaternary ammonium and potassium phenoxides.

When the exchange reaction had reached equilibrium and the potassium halide had settled to the bottom of the flask, 50 ml of the clear solution were pipetted into the reaction flask. This operation, like all others that included transportation of salt or solution, was carried out in an atmosphere of nitrogen. The reaction was started by adding a calculated amount of butyl halide from a 1 ml measuring pipette, (time zero).

In all cases the alkylation reaction goes almost to completion, *i.e.* 90–95 % conversion of the phenoxide. Since tetra-butylammonium halide is re-formed as a product of the alkylation, it will in turn exchange with the rest of potassium phenoxide in solution.

Elimination and formation of olefin is theoretically possible during both the exchange reaction and the alkylation reaction.

I) In the exchange reaction:



II) In the alkylation reaction:

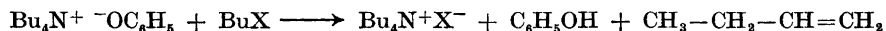
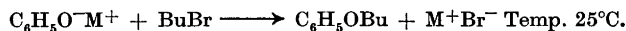


Table 1. Effect of potassium ion and tetra-butylammonium ion in the reaction between phenoxide and butyl bromide.



$\text{M}^+ = \text{K}^+ \text{ or } \text{Bu}_4\text{N}^+$ ,  $(\text{BuBr})_0 = 0.05 \text{ or } 0.10 \text{ mole l}^{-1}$

$r_1 = \text{initial consumption of phenoxide in mole l}^{-1} \text{ sec}^{-1}$ .

Run No.	Solvent	Initial phenoxide conc. mole l <sup>-1</sup>	Added Bu <sub>4</sub> N <sup>+</sup> Br <sup>-</sup> mole l <sup>-1</sup>	% exch. K <sup>+</sup> → Bu <sub>4</sub> N <sup>+</sup>	r <sub>1</sub> /(BuBr) <sub>0</sub> 10 <sup>5</sup> sec <sup>-1</sup>
1	Dioxane	0.0241	none	—	0.01 <sup>a</sup>
2		0.0237	0.0250	77	330 <sup>b</sup>
3		0.0191 <sup>c</sup>		77	250 <sup>b</sup>
4		0.0118 <sup>c</sup>		77	160 <sup>b</sup>
5		0.0244	0.0200	67	200 <sup>b</sup>
6		0.0244	0.0125	44	82
7		0.0241	0.0067	26	28
8		0.0246	0.0055	20	14
9		0.0245	0.0033	13	5.8
10		0.0247	0.0022	8	3.0
11		0.0245	0.0013	5	1.6
12	10 % Acetonitrile-90 % Dioxane	0.0242	none	—	0.22
13		0.0241	0.0247	76	400 <sup>b</sup>
14	50 % Acetonitrile-50 % Dioxane	0.0250	none	—	12
15		0.0250	0.0250	72	600 <sup>b</sup>
16	Acetonitrile	0.0245	none	—	40
17		0.0241	0.0247	70	300 <sup>b</sup>
18	Tetrahydrofuran	0.0241	none	—	0.16 <sup>a</sup>
19		0.0238	0.0250	82	750 <sup>b</sup>

<sup>a</sup> Values taken from Part II.<sup>2</sup>

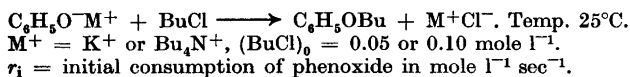
<sup>b</sup> Approximate initial rate determined as described in the experimental section.

<sup>c</sup> Dilutions from the original stock solution in run 2.

However, since phenol is a reaction product, the possibilities above may be investigated by analysing the reaction mixture for phenol. The reaction mixture obtained when the reaction between quaternary ammonium phenoxide (77 % K<sup>+</sup> → Bu<sub>4</sub>N<sup>+</sup> exchange) and butyl bromide in dioxane or acetonitrile had proceeded to a degree of conversion of 97 and 93 %, respectively, were treated in the manner described in Part I. Gas chromatographic analysis showed no higher phenol content than would be expected from the amount of unconverted phenoxide. That butyl phenyl ether was the product of alkylation, was confirmed by the same chromatograms.

Tetra-butylammonium chloride is so sparingly soluble in dioxane, that it was necessary to add a little acetonitrile in order to get the desired concentrations. For comparative purposes alkylations with both butyl bromide and butyl chloride were investigated in mixtures of acetonitrile-dioxane.

Tables 1 and 2 give the initial rates of alkylation obtained from the slope of the curve of phenoxide conversion versus time at zero conversion. In some cases the rate of alkylation is so high that only approximate values can be obtained. Nevertheless the highest rate values are considered to be correct within 20 %.

**Table 2.** Effect of potassium ion and tetra-butylammonium ion in the reaction between phenoxide and butyl chloride.

Run No.	Solvent	Initial phenoxide conc. mole l <sup>-1</sup>	Added Bu <sub>4</sub> N <sup>+</sup> Cl <sup>-</sup> mole l <sup>-1</sup>	% exch. K <sup>+</sup> → Bu <sub>4</sub> N <sup>+</sup>	r <sub>i</sub> /(BuCl) <sub>0</sub> 10 <sup>3</sup> sec <sup>-1</sup>
20	10 % Acetonitrile-90 % Dioxane	0.0244	none	—	0.0025
21		0.0241	0.0250	90	2.8
22	50 % Acetonitrile-50 % Dioxane	0.0251	none	—	0.084
23		0.0242	0.0250	90	4.0
24	Acetonitrile	0.0247	none	—	0.33
25		0.0233	0.0250	90	2.2
26	Tetrahydrofuran	0.0236	none	—	0.0023
27		0.0232	0.0250	92	4.9
28	Dimethylformamide	0.0246	none	—	12 <sup>a</sup>
29		0.0229	0.0250	88	17

<sup>a</sup>Values taken from Part II.<sup>3</sup>

## Reagents

*Potassium phenoxide* was prepared by the method of Kornblum and Lurie as described in Part I.

*Tetra-butylammonium bromide.* The quality "purum" from Fluka A.G., was ground in a mortar and dried in a vacuum before use.

*Tetra-butylammonium chloride.* The quality "pract" from Fluka A. G. was repeatedly crystallized from benzene-petroleum ether, then melted and kept at 100°C in a vacuum (1 mm Hg) for several hours.<sup>6</sup>

*Acetonitrile.* The quality "purum" from Fluka A. G., was dried with Union Carbide's Molecular Sieve 4A, then distilled from calcium hydride in an atmosphere of nitrogen.<sup>7</sup>

Quality and purification of other reagents used have been described in Parts I and II.<sup>1,2</sup>

## RESULTS AND DISCUSSION

Tables 1 and 2 give the results of phenoxide alkylations with butyl bromide and chloride in various aprotic solvents and solvent mixtures. For each run is given the initial phenoxide concentration, the concentration of quaternary ammonium halide initially added, the percentage of potassium ion exchanged by quaternary ammonium ion before butyl halide addition, and finally the initial rate of reaction divided by the initial butyl halide concentration.

In dioxane, runs 1–11, it is found that replacement of the potassium ion by tetra-butylammonium ion leads to a remarkable increase in the rate of reaction. Thus the reaction rate increases by a factor of  $3 \times 10^4$  when 77 % of the original  $K^+$  ions are exchanged by  $Bu_4N^+$  ions, runs 1 and 2. It is further evident that the rate of alkylation of the quaternary phenoxide changes but very little by a change in solvent. The rate in acetonitrile, run 17, is about the same as that in dioxane, run 2. As is evident from runs 2, 13, 15, 17 in Table 1 and runs 21, 23, 25 in Table 2, an increasing amount of acetonitrile in the acetonitrile-dioxane mixture does not noticeably influence the rate of alkylation of the quaternary phenoxide. Also, in pure dimethylformamide, run 29, the rate of alkylation is only 6 times higher than that in 90 % dioxane–10 % acetonitrile mixture, run 21. This is in great contrast to the rate of alkylation of potassium phenoxide which increases by a factor of  $\sim 10^5$  from dioxane to dimethylformamide.<sup>2</sup>

It is not possible to ascribe the invariable reaction rate in dioxane-acetonitrile mixtures and other solvents to an equality in the degree of dissociation of the quaternary phenoxide in the respective solvents. As might be expected, solutions of quaternary ammonium phenoxide in dioxane show very low electrolytic conductivity, whereas the conductivity in acetonitrile indicates a relatively high degree of dissociation.<sup>11</sup> Neither is it likely that the great difference in reactivity of quaternary phenoxide and potassium phenoxide in dioxane and tetrahydrofuran is due to a difference in the degree of dissociation of the two salts. Literature values on the dissociation constants of quaternary ammonium salts and alkali salts in ethereal solvents indicate that the quaternary phenoxide may be no more dissociated than the potassium phenoxide. It is for example shown by Bhattacharyya *et al.*<sup>8</sup> that in tetrahydrofuran the quaternary ammonium salts of tetraphenyl boride have about the same ion-pair dissociation constant as the alkali salts of the same compound. In acetonitrile and dimethylformamide which have dielectric constants about 36–37, the degree of dissociation of both potassium and quaternary ammonium phenoxides are no doubt relatively high. In these solvents free phenoxide ions are likely to be the overwhelming reacting species. From conductivity measurements potassium phenoxide ion-pairs in dimethylformamide are estimated to be 40–50 % dissociated at concentrations about 0.025 M.<sup>11</sup> An increase in the dielectric constant of the reaction medium may be responsible for some deactivation of the anion, as discussed in Part II,<sup>2</sup> but it is nevertheless quite remarkable to find almost the same reactivity of quaternary phenoxide in dioxane and tetrahydrofuran as in acetonitrile and dimethylformamide. Runs 2, 3, and 4 in Table 1 with variable concentrations of phenoxide in dioxane and with the same degree of  $K^+ \rightarrow Bu_4N^+$  exchange indicate that the reaction is first order with respect to the quaternary phenoxide. This may be taken to mean that the quaternary phenoxide exists solely as single ion-pairs in dioxane, and that the reacting entity is the ion-pair. (The reaction rates are, however, too fast to be determined with the desired precision and the reaction order cannot yet be adequately discussed.) The results therefore, may suggest that the tetra-butylammonium phenoxide ion-pair has a remarkable high reactivity which is moreover almost uninfluenced by the solvent. Possibly this may be

due to the large size of the cation giving a relatively low cation-anion interaction energy in the ion-pair.

The behaviour of the quaternary phenoxide shows some resemblance to the "self-solvating" catalysts, *i.e.* potassium polyethylene glycol monomethyl ethers used in conjugation isomerization.<sup>9,10</sup> These alkoxides have been found to be remarkably reactive compared to normal alkoxides. Their reactivity in contrast to normal alkoxides are relatively independent of the solvent. Also in the case of the self-solvating catalysts the results suggest that the reacting entity is the ion-pair, and the abnormal activity is explained by a reduced cation-anion interaction energy.

The tetra-butylammonium salt added initially to exchange with potassium phenoxide before the start of the reaction is, as mentioned, re-formed as a reaction product during the alkylation reaction. This is of great advantage for the following reasons: It is possible to keep a high rate of reaction through the whole alkylation process with relatively small amounts of quaternary salt added, since the quaternary halide which is formed in the alkylation reaction in turn will exchange with remaining phenoxide in solution. Finally, the quaternary halide may be recovered almost completely from the reaction mixture when the reaction is ended.

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