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POLY(ETHYLENE GLYCOL)S AS PHASE TRANSFER CATALYSTS IN THE ALKOXYLATION OF HALOBENZENES OF ALKYL ARYL ETHERS

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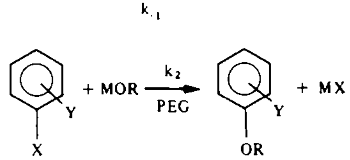
Abstract—Mono and di-halobenzenes and alkoxide ions gave monoalkoxybenzenes, but no phenols, when catalyzed by high molecular weight poly(ethylene glycol)s as phase transfer catalysts. Bromobenzenes were more reactive than chlorobenzenes but gave more side products, and for alcohols the reactivity was primary > secondary > tertiary.

Although a vast amount of reactions have been performed using the technique of phase transfer catalysis,[1,2] aromatic nucleophilic substitutions have rarely been performed by this method. There are several exceptions. Crown ethers have been used in solid–liquid phase transfer catalysis in the methoxylation of x-dichlorobenzene[3] and chromium tricarbonyl complexes of chlorobenzenes[4] both using potassium methoxide crown ether complexes as "naked" nucleophiles. Also, potassium superoxide has been used in crown ether catalyzed reactions.[5] Quaternary ammonium salts have been used in the conversion of m-dinitrobenzene into m-nitroanisole[6] and in the formation of ethers from p-nitrochlorobenzene.[7] The use of poly(ethylene glycol)s (PEG) or their ethers (PEGE) as phase transfer catalysts is also rare in comparison to the much better known crown ethers, cryptands, and quaternary onium salts. Their use has been limited to aliphatic nucleophilic substitutions,[8,9] Williamson reactions,[10] oxidations,[11] and reductions.[12] Poly(ethylene glycol)s have yet to be used for phase transfer catalyzed aromatic substitution reactions.

We wish to report on the reaction of mono- and di-halobenzenes with alkoxide ions formed *in situ* from the corresponding alcohol and hydroxide base catalyzed by polyethylene glycols by eqn 1. It is important to emphasize the economic advantage in the *in situ* formation of the alkoxide anion by the equilibrium reaction (eqn. 1a) as opposed to the use of alkoxide ions formed by alkali metals in alcohols (eqn. 2).

(1a) $\mathrm{ROH + MOH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MOH + H_2O}$

(1b)



R = alkyl, aryl
M = alkali metal
X = Br, Cl
Y = Br, Cl, H

$$2M + 2ROH \rightarrow 2MOR + H_2. \qquad (2)$$

Poly(ethylene glycol)s are especially attractive for this type of reaction for two major reasons. In comparison to quaternary onium salts they are stable to alkaline especially at higher temperatures where the quaternary salts undergo Hoffmann elimination[13] to tertiary amines; in comparison to crown ethers and cryptands in that they are much cheaper.

EXPERIMENTAL

General procedure for reactions performed in open systems

In a three necked 100 ml flask equipped with a water cooled reflux condenser, mechanical stirrer (Heidolph RZR-04) and a thermometer were placed 0.1 mol mono- or di-halobenzene, 0.2 mol alkali hydroxide and 0.2 mol n-pentanol. For reactions performed with a catalyst 4 g of poly(ethylene glycol) of various molecular weights was added. The reaction mixture was heated with an air bath with a temperature controller to reflux (140–150°) and stirred at 800 rpm for 6 hr and then cooled and analyzed.

General procedure for reactions performed in closed systems

In a 500 ml air heated, Teflon lined Berghof high pressure autoclave equipped a thermocouple, temperature and digital pressure readout, and an electromagnetically induced Teflon stirrer were placed 0.1 mol o-dichlorobenzene, 0.2 mol potassium hydroxide, 0.5 mol alcohol, and 4 g of PEG-6000. The autoclave was heated to 150° and the reaction mixture stirred at 600 rpm for 6 hr. The autoclave was then cooled and the reaction mixture analyzed. All chemicals were commercially available and used without further purfication.

Analysis

After the reaction mixture was cooled, 50–70 ml of distilled water was added and the mixture stirred to dissolve all salts. The organic phase was separated and extracted once with 50 ml of distilled water. The combined water phases were diluted to 500 ml and analyzed by volumetric titration for halide. An aliquot was taken, neutralized with acetic acid to pH 7 and titrated with 0.1 M $AgNO_3$ with $KCrO_4$–$K_2Cr_2O_7$ as indicator. Conversions were computed from the amount of halide found. Selectivity and product identification was carried out by GLC of the organic phase. The Gas Chromatograph used was a Packard 427 with an FID detector. The column used was 15% OV-17 on Chromosoro 120–140 mesh packed volumn with N_2 as carrier gas. Compounds not available for comparison such as o-pentoxychlorobenzene were synthesized by PTC catalyzed Williamson reactions using the corresponding phenols and alkyl halides.[14] For example o-pentoxychlorobenzene was synthesized by mixing o-chlorophenol and pentyl bromide with 50% NaOH and a PTC catalyst. After the reaction the samples were distilled and checked by GLC, and the following boiling points were obtained: Compound, experimental boiling point, literature boiling point. Pentoxybenzene, 198–200, 94–96 at 23 mm Hg;[15] o-chloropentoxybenzene, 248–250, 78–80 at 0.1 mm Hg; [15] p-chloropentoxybenzene, 255–258, 113–115 at 0.5 mm Hg;[15] p-bromopentoxybenzene, 236–265, 81–83 at 0.01 mm Hg;[15] o-chlorobutoxy-benzene, 240–242, 244–245 16; o-chloropropoxybenzene 222–223, not found; o-chloro-t-butoxybenzene, 218–220, not found; o-chloroisopropoxybenzene, 188–190, 192.[17] In addition to analyzing the products in the organic phase, samples of the water phase were taken and acidified and checked for the presence of phenols.

RESULTS AND DISCUSSION

When looking at the reaction scheme as presented previously (eqn 1) one can see that there are numerous factors which can affect the overall reaction. Among these are the polyethylene glycol catalysts. Apart from the obvious effect of the presence of the catalyst on the reaction, one must take into account the range of average molecular weights ($\bar{M}_w$ from 150 to 20,000,000) and the effect of this weight on the reaction catalysis. A second factor to be considered is the substrate type. One may expect differences between aryl bromides and aryl chlorides because of the different carbon-halogen bond strengths if the usual $SnAr_2$ reaction mechanism is taking place. In addition there is the effect of the various substituents and their position to be considered. A third factor which must be examined is the equilibrium reaction 1a where the alkoxide anion is formed. Specifically important is the effect of various alcohols (primary, secondary, tertiary) and bases on this equilibrium.

In Table 1 one can find the results of the effect of the average molecular weight, $\bar{M}_w$, on the reaction conversion. The number of oxyethylene groups, $CH_2{-}CH_2{-}O$ is constant whereas the molar concentration of the catalyst decreases with the rising $\bar{M}_w$. It is important to point out that at low molecular weights the reaction is almost noncatalytic, whereas at higher molecular weights the catalysis is accelerated until a plateau is reached at an average molecular weight of approx. 6000. Others have noted this effect[10,18–21] but have given no explanation for this phenomenon. Kitazume and Ishikawa[22] found an opposite effect where low molecular weight PEG were more effective catalysts. They explained this by stating that the high molecular weight catalysts were less soluble in the reaction solvent (acetontrile) and therefore less active. We wish to stipulate two conclusions which are interrelated. The first is that the addition of polyethylene glycol does not accelerate the reaction because of increased solubility of the alkoxide anion in the organic phase by changing the solvent composition. It is likely that if such were the case the chain length of polyethylene glycol would have little effect on the reaction catalysis, since polyethylene glycols have similar macro properties no matter what the chain length. The second stipulation is that the increased catalysis of the high molecular weight PEG, though the molar concentration decreases, is due to the increased degree of complexation with rising molecular weights[23,24] of the potassium pentoxide nucleophile. The increased degree of complexation causes the anion to become more "naked", thus a more potent nucleophile and thereby catalyzing the reaction more effectively. The existence of a plateau has two possible explanations. Either, though there is still an increase in complexation with rising molecular weight it is offset by decreased molar catalyst concentration or, there is no further complexation increase but due to the length of the catalyst chain there are several catalytic centers on one PEG molecule.

Table 1. The effect of the average molecular weight of the PEG catalyst on reaction conversion[a]

Average molecular weight M_w of PEG	Conversion of p-dichlorobenzene, % mol (b)	Conversion of o-dichlorobenzene, % mol (c)
none	7.1	29.5
150	8.2	31.3
200	10.7	32.0
400	20.5	40.0
600	21.7	42.5
1000	20.1	44.1
1500	22.3	43.6
3400	24.8	49.0
6000	33.0	61.4
8000	29.9	66.7
14000	27.5	63.2
20,000,000	28.1	65.5

[a] Reaction conditions: 0.1 mol dichlorobenzene, 0.2 mol KOH, 0.2 mol n-pentylalcohol, 4.0 g PEG, T = 140–150°, time—6 hr.

[b] They only product p-n-pentoxychlorobenzene.

[c] The only product was o-n-pentoxychlorobenzene.

Conversions and selectivity for the etherification of various halobenzenes with pentoxide ions are summarized in Table 2. One can examine these results at several levels. First the difference between mono- di- and tri-halobenzenes. Quite expectedly the order of reactivity was found to be tri > di > mono. It is interesting to note that although halogen anions are not generally considered strong activators for aromatic nucleophilic substitutions, we found strong activating effects for this reaction. Monosubstituted halobenzenes hardly underwent reaction and therefore it is not surprising that we found no disubstitutions whatsoever under these reaction conditions considering the deactivating effect of the alkoxide substituent. Second, when observing the results we can see the different behavior for bromobenzenes and chlorobenzenes. With chlorine as the halogen substituent we found no reductions. On the other hand with bromobenzenes we found a significant amount of reduction. This side reaction is well-known[25] and is more pronounced the higher the reaction temperature. Since the carbon-bromine bond is weaker than the carbon-chlorine bond, the effect is more pronounced for bromobenzenes. It is important to note that the addition of poly(ethylene glycol) greatly increases the selectivity in favor of the substitution reaction versus the reduction reaction. We believe that since reduction and substitution are competing reactions, the addition of PEG making the pentoxide anion a more potent nucleophile has the effect of increasing the selectivity for the substitution reaction by increasing its rate. Since no cine-substitutions were found in any reaction, we assume the reaction was of a $SnAr_2$ type mechanism and not a benzyne mechanism. A third observation that can be made concerns the position of the second substit-

Table 2. Conversion and selectivity in etherification of various halobenzenes with and without PEG-6000 as catalyst[a]

Substrate	Conversion, % mol without/with catalyst	Desired Product	Selectivity, % mol without/with catalyst	Additional products
o-dichlorobenzene	29.5/61.4	o-pentoxychlorobenzene	100/100	none
p-dichlorobenzene	7.1/33.0	p-pentoxychlorobenzene	100/100	none
m-dichlorobenzene	20.7/53.4	m-pentoxychlorobenzene	100/100	none
p-dibromobenzene	27.0/71.5	p-pentoxybromobenzene	39/85.5	bromobenzene pentoxybenzene
p-bromochlorobenzene	31.8/49.6	p-pentoxychlorobenzene p-pentoxybromobenzene (b)	82/94	chlorobenzene
bromobenzene	8.0/15.5	pentoxybenzene	85/98	benzene
chlorobenzene	0.5/2.1	pentoxybenzene	100/100	none
1,2,4 trichlorobenzene	60.1/93.8(c)	dichloropentoxybenzene	——(d)	———

[a] Reaction conditions: 0.1 mol halobenzene, 0.2 mol KOH, 0.2 mol n-pentanol and 4 g PEG-6000 at 150° for 6 hr.
[b] Product ratio was p-pentoxychlorobenzene/p-pentoxybromobenzene 10/1.
[c] Conversion after 3 hr.
[d] Not analyzed for lack of comparative chemicals.

Table 3. Conversion as a function of alcohol species in etherification of o-dichlorobenzene with PEG-8000 as catalyst[a]

Alcohol	Conversion, % mol	Product (b)
methanol	66.0	o-methoxychlorobenzene
ethanol	27.6	o-ethoxychlorobenzene
n-propanol	28.5	o-propoxychlorobenzene
n-butanol	24.3	o-n-butoxychlorobenzene
n-pentanol	25.3	o-n-pentoxychlorobenzene
i-propanol	13.5	o-i-propoxychlorobenzene
t-butanol	5.1	o-t-butoxychlorobenzene
water	1.5 (c)	o-chlorophenol

[a] Reaction conditions: 0.1 mol o-dichlorobenzene, 0.2 mol KOH, 0.5 mol ROH, and 4 g PEG in autoclave at 150° for 6 hr.
[b] These were the only products found.
[c] After 24 hr.

uents in dichlorobenzenes. The ortho and meta isomers are the most active whereas the para isomer is much less so. Others[3] found that meta isomers were much less active than the ortho isomer in a potassium methoxide crown ether catalyzed reaction, attributing the phenomenon to reduced stability of the reaction intermediate. Our results concur with the results found more than 65 yr ago[26] in a similar reaction. The activation of the ortho isomer is due to inductive effects whereas the meta isomer is activated by resonance effects, the para isomer being deactivated or non-activated. Therefore the established order of activating effect was o > m > p, results substantiated by our results.

Table 3 describes the effect of different alcohols on the etherification of o-dichlorobenzene. Since the reaction was carried out in a closed vessel the reaction conditions were different and conversions were lower. One can see that the order of activity is methanol > primary alcohols > secondary > alcohols > tertiary alcohols > water. In an attempt to explain these results one can use the equilibrium constants found by Murto,[27] for the formation of alhoxide anions (eqn (1a). He measured equilibrium constants for methanol, 3.4, for ethanol to pentanol, 0.65–0.4, for isopropanol, 0.043, and for t-butanol, 10^{-4}. This satisfactorily explains the general order of activity that was found for the reaction. However, the predicted concentrations of iso-propoxide and tert-butoxide are very low and it is surprising that any reaction occurred. We attribute the results to the fact that when measuring nucleophilicity of alkoxide onions the order is tert-butoxide > iso-propoxide > primary alhoxides > methoxide. The increased nucleophilicity of tertiary and secondary alkoxides partially offset their low concentrations. It is also possible that the affinity of tertiary and secondary alkoxides to the polyethylene glycol catalyst is greater than the affinity for primary alcohols therefore shifting the equilibrium. This theory is currently being tested in our laboratory. The lack of activity of the hydroxide ion is explained by solvation of the anion by water molecules rendering it an ineffective nucleophile. This also explains that in none of the reactions where alcohol was present were there any phenols as reaction products due again to the solvation of hydroxide ions by alcohol molecules, even though hydroxide ions were present in a significant amount.

CONCLUSION

Polyethylene glycols were used as phase transfer catalysts for nucleophilic substitution of halogens by alkoxides in various halobenzenes. The alkoxide ions were present *in situ* by the reaction between an alcohol and potassium hydroxide. The molecular weight of the polyethylene glycol was found to have a significant influence on the reaction catalysis, the higher the molecular weight the more effective the catalysis. Bromobenzenes were more reactive than chlorobenzenes but underwent reduction as a side reaction. The addition of PEG improved the selectivity towards substitution, reducing reduction products. Primary, secondary, and tertiary alcohols all undergo the reaction, even though the predicted concentration of secondary and tertiary alkoxides is low.

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