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THE EXTRACTION OF ALKOXIDE ANIONS BY QUATERNARY AMMONIUM PHASE TRANSFER CATALYSIS

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Abstract Only trace amounts of hydroxide ion can be extracted from aqueous solution into non-polar organic media by quaternary ammonium salts. Addition of small amounts of primary alcohols, particularly certain diols, dramatically changes the behaviour of systems, and surprising amounts of base can be found in the organic apolar phase. The competitive extraction halide/alkoxide was investigated for various ammonium salts. Quantitative measurements were carried out for the evaluation of selectivity constants for extraction of simple primary alkoxides by tetra-n-hexylammonium chloride in benzene.

The first[1] and one of the most useful synthetic applications of phase transfer catalysis (PTC) is the preparation of ethers *via* the biphasic Williamson reaction according to the general equation[2] (1):

$$R'X + ROH + OH^{\ominus} \xrightarrow{PTC} ROR' + H_2O + X^{\ominus} \quad (1)$$

where R and R′ are primary or secondary alkyl or aryl residues, X is a halide and the caustic base is usually sodium or potassium hydroxide in aqueous solution. The phase transfer catalysts of choice are lipophilic quaternary ammonium or phosphonium salts but crown ethers[3] and polyethylene glycols[4] were also successfully applied. The introduction of PTC modifications of the traditional procedure allowed simpler work-up, cheaper raw materials, and higher selectivities. As a result the new method was applied to numerous syntheses [survey: Ref. 2], including symmetrical and non-symmetrical aliphatic and aromatic ethers, crown ethers, sugar ethers, ethers of hydroxyl amines, and various poly ethers.[5] Etherification under PTC condition has also found some analytical applications. The mechanism of reaction (1) was proposed by several authors and includes the following steps:[2]

(a) Alcohol alkoxide equilibrium which takes place at the interphase or in the aqueous phase (Eq. 2).

$$ROH + OH^{\ominus} \rightleftarrows RO^{\ominus} + H_2O \quad (2)$$

This is actually an acid-base equilibrium and its equilibrium constant is the acidity constant K_{HA} of the alcohol.[6,7]

(b) Extraction of the alkoxide ion from the aqueous phase or from the interphase into the bulk of the organic phase by anion exchange and ion pair extraction with the quaternary ammonium cation (Eq. 3).

$$QX_{(org)} + RO^{\ominus}_{(aq\ or\ interphase)} \rightleftarrows QOR_{(org)} + X^{\ominus}_{(aq)} \quad (3)$$

where Q is the quaternary cation and $X^{\ominus}$ is the anion originally introduced with the catalyst or anion substituted according to Eq. (1). The equilibrium constant for this type of anion exchange across the interphase was termed by Gordon and Kutina[8] and by Starks[9] as selective constant K^{sel}. It is usually expressed in reference to the extraction of chloride.

(c) The final step in the overall process (1) is the nucleophilic substitution in the organic phase which yields the ether product and releases the catalyst for another catalytic cycle (Eq. 4).

$$R'X + QOR \rightarrow R'OR + QX \quad (4)$$

While steps (a) and (c) of the above mechanism were studied in some detail by several authors, step (b) is known only from inference. No measurements were made to determine the nature of this equilibrium and no data are available for quantitative evaluation of K^{sel} inspite of the fact that it is an important factor in the kinetics of the Williamson reaction.

A mechanism which is similar in nature was proposed for the PTC alkylation of weak acids and for the dihalocarbene formation from chloroform and bromoform:[2] Interfacial equilibrium formation of the anion of a weak acid by interaction with aqueous base and subsequent ion pair extraction.[10] The higher lipophilicity and thus selective extractability of carbon, nitrogen, or alkoxide anions allows the activation and reaction of acids which are 10^8 or even 10^{10} times weaker[11,12] than water by simple hydroxide bases. This is obviously one of the major achievements of phase transfer catalysis.

There is another, very important preparative aspect that must be considered: The alkoxide ion extracted according to Eq. (3) is not only a reactive nucleophile but also a strong base. It was shown, for example, that 10^{-3} M benzyltrimethylammonium t-butoxide is 1000 times more basic than potassium t-butoxide (both in t-butanol[13]). Extracted alkoxide bases can be applied in principle to numerous base-catalyzed reactions, e.g. oxidations, eliminations and isomerizations. Better quantitative understanding of the mechanism of the alkoxide ion pair formation and extraction is thus highly desirable.

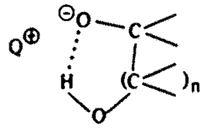
RESULTS AND DISCUSSION

Although in early PTC literature the direct extraction of the hydroxide ion into the organic phase by onium salts was proposed[14] it is now generally accepted that this extraction is virtually negligible if other, more lipophilic anions competing for extraction are present in the system and a non-polar solvent is used.[2,9]

We have verified this fact again by attempting the extraction of aqueous sodium hydroxide solutions with organic solvent containing various quaternary ammonium salts. Aqueous solutions of 1 M to 18 M sodium hydroxide were contacted in vigorous shaking for 20 min with 0.1 M chlorobenzene and dichloromethane solutions of onium salts NR_4X where $R = n\text{-}C_4H_9$ (Bu), $n\text{-}C_5H_{11}$ (Pen), $n\text{-}C_6H_{13}$ (Hex), $n\text{-}C_7H_{15}$ (Hep), and $n\text{-}C_8H_{17}$ (Oct), and $X^\ominus = Cl^\ominus, Br^\ominus, I^\ominus$.

After phase separation, titration of the organic phase showed traces of base presence only if concentrated sodium hydroxide solutions were employed and if chloride was the counter ion. The Cl → OH exchange was found for NBu_4Cl to $NOct_4Cl$ for chlorobenzene as solvent to be in the order of 1-2%; i.e. 98% of the salts remained in the NR_4Cl form. However, upon addition of trace amounts of various alcohols, a dramatic change in the behaviour of the systems was observed and significant amounts of base could be detected in the organic phase.[15] Results of experiments where 50% aqueous caustic solutions were extracted by equal volumes of 0.1 M $NOct_4Br$ in chlorobenzene containing 0.1 M of various alcohols are summarized in Table 1. Data are presented as per cent of the maximum amount possible. (Assuming one molecule of $^\ominus OR$ can be extracted by one molecule of onium salt.)

It is apparent that the order of decreasing alkoxide extraction with monohydric alcohols is primary > secondary > tertiary. The better extractivity of diol anions can be attributed to the relatively high acidity of these alcohols in part, but it seems that the main factors are the distance between the two hydroxyl groups and the skeletal structure: e.g. pinacol which contains two tertiary hydroxyl groups shows high activity, while 1,5-pentanediol with two primary hydroxyls is useless, and the difference in performance between 2,5-hexanediol and 2,5-dimethylhexanediol is remarkable. It is reasonable to assume that a stable ion pair is formed by intramolecular H-bonding with a typical structure of this general type:



A similar partial self-solvation has been inferred recently for KOH/polyethylene glycol complexes.[16] Stability of such complexes will be strongly dependent on the skeletal structure and the interaction of side groups.

It is important to note that in the absence of the onium salt even the best diols transfer only very little basicity to the non-polar phase. This contrasts sharply to the behaviour of polyethyleneglycols: under our conditions, 0.1 M solutions of PEG 600 and 1000 carry 17.1 or 17.8% basicity, respectively, and this value is **not** increased by $NOct_4Br$!

In a second series of experiments, the competitive extraction of the pinacol anion (2,3-dimethyl-2,3-butanediol) was probed in the presence of various halides and ammonium ions of different size (Table 2). The expected order of decreasing ability for base

Table 1. Extraction of base by chlorobenzene solution of tetra-n-octylammonium bromide and alcohols (0.1 M each) from an equal volume of 50% NaOH (per cent of the maximum possible basicity)

	%		%
Primary alcohols		**Diols**	
Ethanol	4.5	1,5-Pentanediol	<0.2
1-Propanol	5.0	1,6-Hexanediol	(emulgation)
2-Methyl-1-propanol	4.4	2,5-Hexanediol	5.2
1-Pentanol	4.3	2,2-Dimethyl-1,3-propanediol	18.4
1-Hexanol	4.3	2-Methyl-2,4-pentanediol	28.0†
1-Heptanol	4.8	2,3-Dimethyl-2,3-butanediol	25.8
1-Octanol	2.0	2,5-Dimethyl-2,5-hexanediol	32.0
1-Dodecanol	0.8		
Secondary alcohols		**Diol monoethers**	
2-Propanol	1.9	Ethyleneglycol monoethylether	8.9
2-Pentanol	1.2	Diethyleneglycol monobutylether	8.7
2-Hexanol	1.1	Glycerol isopropylideneacetal	13.0
2-Octanol	0.7		
Cyclohexanol	0.5		
4-tert-Butylcyclohexanol	1.5		
2-tert-Butylcyclohexanol	2.0		
4-Methylcyclohexanol	2.0		
tert-Alcohols			
tert-Butanol	0.3		
2-Methyl-2-butanol	0.2		

† In the absence of $NOct_4Br$, this diol transfers 4% base.

Table 2. Base extraction by chlorobenzene solutions of onium salts and pinacol (0.1 M each) from an equal volume 50% NaOH (per cent of the maximum possible basicity)

	$Bu_4N^\oplus$	$Pen_4N^\oplus$	$Hex_4N^\oplus$	$Hep_4N^\oplus$	$Oct_4N^\oplus$	$Oct_4P^\oplus$
$Cl^\ominus$	7	31	35	34	40	26
$Br^\ominus$	8	20	23	22	26	
$J^\ominus$	6	5†	8	7	9	

† Saturated solution only because solubility < 0.1 M.

Table 3. Extraction of the pinacol anion by tetraoctylammonium halides in chlorobenzene/50% aqueous sodium hydroxide

Catalyst anion	Molar ratio NR_4X/pinacol	Extracted base (% of maximum possible) referred to NR_4X	referred to pinacol
Br	1:1	26	26
	1:2	50	25
	1:10	60	6
	1:100	50	0.5
Cl	1:1	40	40
	1:2	78	39
	1:10	88	8.8
	1:100	90	0.9

extraction Cl > Br > I is found. Interestingly, the most lipophilic cation exhibits the highest selectivity. This indicates that the extracted species is lipophilic in nature and that it is more compatible with cations with longer alkyl chains. We have observed the opposite phenomenon in extraction of the hydrophilic formate ion.[17] It is therefore unlikely that a hydroxide ion pair is playing an important role in the extraction process.

After separation of the organic phase containing the base, excess of benzyl chloride was added to the solution followed by heating the mixtures to 80° for 3 hr. The major product obtained from the benzyl chloride was the benzyl ether derived from the corresponding alcohol which was identified by gas chromatographic analysis. In the case of diols selective formation of monobenzyl ethers was found.[18]

The concentration of extracted base is dependent on the amount of alcohol added. This is shown in Fig. 1 where the effect of varying concentrations of n-butanol and benzyl alcohol on extraction of base by $NHex_4Cl$ and $NHex_4Br$, respectively, is presented. As could be expected, this dependence is not linear and approaches a maximum value at higher alcohol concentrations. Table 3 gives the results of similar experiments with pinacol and $NOct_4Cl$ and $NOct_4Br$.

The aqueous sodium hydroxide concentration is also an important factor in the extraction process. Figure 2 presents the concentration of base in the organic phase as a function of the aqueous phase hydroxide

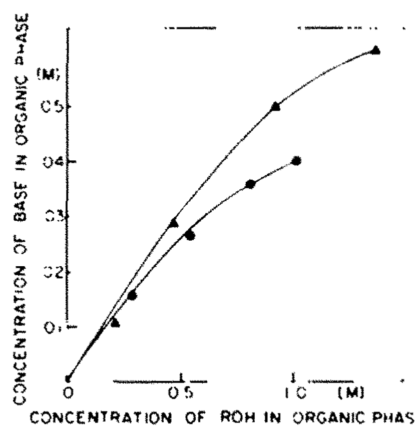


Fig. 1. Extraction of base by n-butanol and benzyl alcohol in the NaOH/tetra-n-hexylammonium system as function of the alcohol concentration. ▲ benzyl alcohol–NaOH–tetra-n-hexylammonium bromide. ● n-butanol–NaOH–tetra-n-hexylammonium chloride. (Experimental conditions: equal volumes of 2 M aqueous NaOH solution and 0.0688 M tetra-n-hexylammonium salt benzene solution contacted in presence of the alcohol for 20 min.)

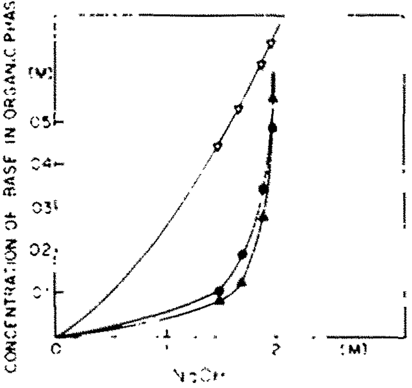


Fig. 2. Extraction of base by NaOH/tetra-n-hexylammonium chloride/alcohol system as function of the aqueous hydroxide concentration at constant ionic strength 2. ▽ 1.85 M benzyl alcohol. ● 3.3 M n-propanol. ▲ 4.3 M ethanol. (Experimental conditions: as in Fig. 1 with addition of NaCl to the aqueous phase to total salt concentration of 2 M.)

concentration in presence of n-propanol, n-butanol, and benzyl alcohol. The ionic strength of the aqueous phase in these runs was maintained constant by adding sodium chloride.

The observations support the proposed mechanism of the PTC Williamson synthesis.[2] We think that the mechanism for base extraction presented by Agarwal and Diamond[15] in which a hydroxide ion pair is extracted along with three alcohol molecules is not completely correct. It might very well be that an alkoxide ion pair is similarly extracted complexed with three alcohol molecules, a claim which was also raised by Starks.[9] The behaviour of onium salts is thus different from the behaviour of crown ethers where hydroxide ion can be coextracted with alkoxide ion.[3]

It should be noted that no direct relation could be found between the water solubility of the alcohol added and the amount of extracted base. The extraction process can work very effectively even when the alcohol does not dissolve at all in the aqueous phase (50% sodium hydroxide solution forms a separate phase even with ethanol). This indicates that the alkoxide formation according to Eq. (2) is not necessarily a homogeneous process in the aqueous phase but can take place at the interphase where the base in the aqueous phase absorbs a proton from the alcohol residing in the organic phase and the so formed sodium alkoxide is adsorbed on the interphase. This mechanism of anion formation is quite common in PTC with bases and was originally proposed by Makosza.[19]

The amount of free alkoxide in basic alcohol solutions can be evaluated if the K_{HA} of the alcohol in the particular system is known.

Murto has defined the stoichiometric equilibrium constant for hydroxide alkoxide equilibrium K'_{HA},[6,7]

$$K'_{HA} = \frac{[H_2O][RO^\ominus]}{[ROH][OH^\ominus]} = \frac{X_{H_2O}[RO^\ominus]}{X_{ROH}[OH^\ominus]} \qquad (5)$$

where X_{H_2O} and X_{ROH} are the molar fraction of the water and the alcohol, respectively. Equation (5) is valid in dilute solutions where concentration can be used rather than activities. K'_{HA} is changing very little with the nature of the solvent but it is strongly dependent on the structure of the alcohol.

If we assume that Eq. (5) can be applied in biphasic systems we can calculate the concentration of free alkoxide ion directly according to

$$[RO^\ominus] = \frac{K'_{HA} X_{ROH}[OH^\ominus]}{X_{H_2O}}. \qquad (6)$$

Since equal volumes of the two phases are used then the concentration of $OR^\ominus$ and $OH^\ominus$ can be expressed as volumetric, aqueous phase concentration even if the alkoxide ion is actually located at the interphase. When tetrahexylammonium chloride solution is contacted with aqueous sodium hydroxide in presence of alcohol, alkoxide ion is formed according to Eq. (2), followed by anion exchange process (Eq. 3).

For the exchange process of the type presented in Eq. (3) a selectivity constant can be defined[8]

$$K^{sel}_{Cl/OR} = \frac{[QOR]_{org}[Cl^\ominus]_{aq}}{[QCl]_{org}[OR^\ominus]_{aq}}. \qquad (7)$$

Table 4. Acidity and selectivity constants for alcohols based on Figs. 3–6

Alcohol	K'_{HA}	K^{sel}
Ethanol	0.65	0.74
Propanol	0.4	2.50
Butanol	0.4	4.87
Benzyl alcohol	2.0	10.15

Chloride anion in the aqueous phase can be determined directly by titration, [QOR] can be assumed to be the total amount of base titrated in the organic phase. [QCl] can be calculated by mass balance of the initial amount of quaternary salt introduced and $[OR^\ominus]_{aq}$ can be calculated by Eq. (6) provided that K'_{HA} is known.

We contacted dilute sodium hydroxide solutions (1.5–2 M) at constant ionic strength with benzene solutions of $NHex_4Cl$ in presence of ethanol, n-propanol, n-butanol, and benzyl alcohol. For each experiment the magnitude of [QOR], [QCl], $[OR^\ominus]$, and $[Cl^\ominus]$ was measured or calculated as described. For each alcohol the product $[QOR] \times [Cl^\ominus]$ was plotted *vs* $[QCl] \times [OR^\ominus]$ at various initial hydroxide concentrations. From the slope of each graph K^{sel} for the above alkoxides was estimated using linear regression analysis. The data are shown in Figs 3–6 and summarized in Table 4. Although the intercept, which should theoretically be zero, turns up in some cases to be positive or negative the linear correlation is very good. Based on the data presented in Table 4 we can conclude that primary alkoxides are effectively extracted under the above conditions with selectivity constants, relative to chloride, larger than one (except for ethoxide and probably methoxide). The alkoxide would not be effectively extracted if the competing counter ion was bromide. We showed in the case of formate[20] that high selectivities can be enforced in oversaturated solutions, where halide anions precipitate. Tables 1 and 2 show the limits of such practices in the present case.

The extracted anion is a nucleophile in the Williamson synthesis but it can also be utilized as a strong base. Initial experiments that we performed

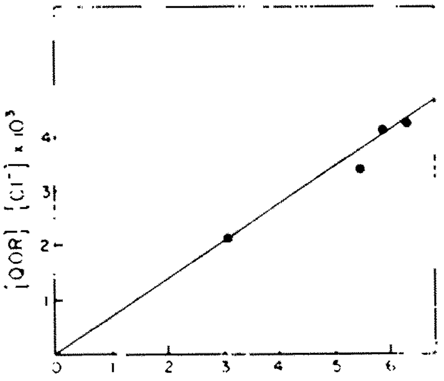


Fig. 3. $K^{sel}_{Cl/OR}$ for ethyl alcohol.

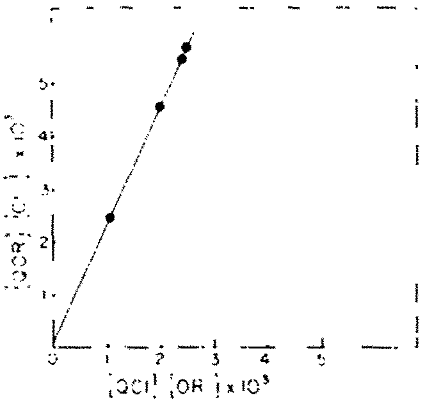


Fig. 4. $K^{sel}_{Cl,OR}$ for n-propanol.

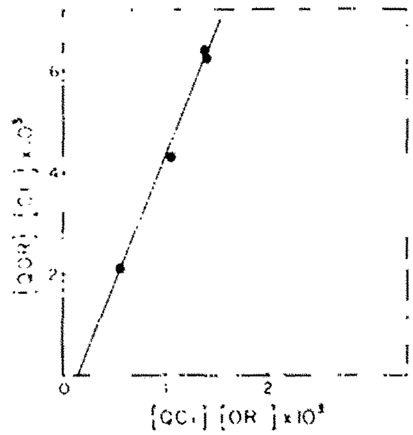


Fig. 5. $K^{sel}_{Cl,OR}$ for n-butanol.

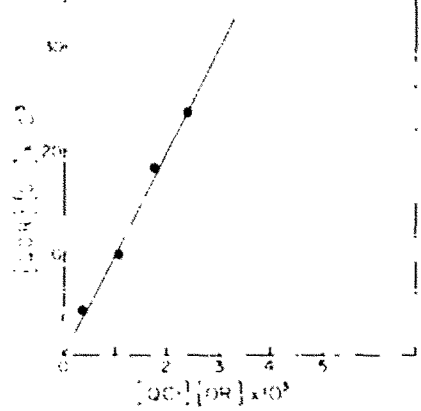


Fig. 6. $K^{sel}_{Cl,OR}$ for benzyl alcohol.

(Experimental conditions for Figs 3–6: 0.0688 M tetra-n-hexylammonium chloride in benzene (100 ml), 20 g alcohol, contacted with 100 ml 1.5–2 M NaOH with make-up of NaCl to total ionic strength 2.

indicate that addition of the trace amount of primary alcohols increases the rates of the base-catalyzed isomerization of allyl benzene,[21] the base-catalyzed autoxidation of fluorene,[22] and the formation of alkynes from vic. dibromides,[23] all under PTC conditions. Further research on the application of alcohols in base extraction is now in progress.

EXPERIMENTAL

Materials: Analytical grade solvents and reagents were all obtained from Fluka. The quaternary ammonium salts were freeze-dried immediately before weighing.

Extraction procedure: Extraction of 50% NaOH aq solutions: 200 ml of chlorobenzene containing 0.1 M of the quaternary ammonium salt and 0.1 M of the alcohol were concentrated with 200 ml of 50% (w/w) NaOH aq with vigorous shaking for 20 min. After phase separation a 100 ml sample from the upper part of the organic phase was equilibrated similarly with 100 ml of 15% (w/w) NaBr aq soln. After phase separation an aliquot of the aqueous phase was titrated with 0.1 M HCl soln.

Extraction of 1–2 M *sodium hydroxide solutions*: 100 ml benzene containing 20 g of an alcohol and 0.03–0.1 M of tetra-n-hexylammonium chloride was vigorously contacted for 20 min with 100 ml 1.5–2 M NaOH aq soln containing NaCl to make up a total ionic strength of 2. After phase separation a 100 ml sample from the upper part of the organic phase was contacted with 100 ml 0.1 M HCl soln which was back titrated with 0.1 M NaOH.

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