Deactivation of Anion Phase Transfer Catalysis by Hydrogen Bonding Extraction of Acidic Compounds

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Normal phase transfer catalysis, particularly of esterification and etherification reactions, is inhibited if free acids (*e.g.* phenols or carboxylic acids) are present in the system; since free acids are generated by aqueous phase hydrolysis a controlled basic pH is recommended for these processes.

The common mechanism for phase transfer catalysed (PTC) reactions in the presence of lipophilic onium salts[1,2] is *via* a heterogeneous anion exchange according to the general equation (1) which is followed by a nucleophilic substitution or by another transformation in the organic phase. Q^+ is a quaternary cation, X^- is a leaving group, and Y^- is the attacking nucleophile which is either introduced as an anion or generated *in situ e.g.* by a strong base.[3]

$$QX_{(org.)} + Y^-_{(aq.\ or\ solid)} \rightleftarrows QY_{(org.)} + X^-_{(aq.\ or\ solid)} \qquad (1)$$

Another mechanism which is far less well known is the non-stoicheiometric extraction of the acidic compounds HZ from aqueous phase to organic phase *via* hydrogen bonding [equation (2)].

$$QX_{(org.)} + HZ_{(aq.)} \rightleftarrows OX \cdots (HZ)_{n(org.)} \text{ or } Q^+(HXZ]^- \cdots (HZ)_{n-1(org.)} \qquad (2)$$

This type of extraction is actually an acid–base equilibrium. The position of the equilibrium, which determines the distribution coefficient, depends on the nature of Q^+, X^-, HZ, and the type of solvent used. Various acids were found to distribute into the organic phase according to equation (2) and they are: hydrochloric and hydrobromic acid,[4] sulphuric acid, acetic acid, formic acid, phenols,[5] and even weak acids like hydrogen peroxide,[4] water,[6–9] and aliphatic alcohols.[10] We and others have recently reported the co-extraction of hypochlorous acid along with the hypochlorite anion.[11,12]

The extraction according to equation (2) was used for synthesis in two ways. (i) QX was used as a base; when X^- is fluoride the ion pair is a particularly strong base and this was used in eliminations, condensations, *etc.*[13] (ii) QX was used as an extractant; hydrochloric and hydrobromic acids were extracted into the organic phase and used for the transformation of alcohols to alkyl halides,[14] cleavage of ethers,[15] and Markovnikov addition to olefins.[16] Hydrogen peroxide was extracted and used for the oxidation of olefins[17] and ketones.[18]

We have now observed that the two PTC mechanisms (1) and (2) are competitive in nature; when extraction according to equation (2) is taking place the normal PTC process, with equation (1) as the first step, is significantly inhibited. Part of this phenomenon was observed earlier in an examination of the role of the water of hydration in PTC processes.[6–9] It is known that quaternary onium ion pairs are extracted into organic phases together with a certain amount of water. The hydration ratio was measured quantitatively and was found to depend on the organic solvent and the nature of the cation and particularly on the anion in the ion pair. The rates of the PTC reactions are significantly higher if the water of hydration can be lowered or eliminated *e.g.* by using water-free systems (solid–liquid PTC) or by introducing dehydrating caustic bases *e.g.* 50% sodium hydroxide or 60% potassium hydroxide.[19]

We report here that the problem can be far more serious if free acids, stronger than water, are present in the PTC systems. A typical example is the esterification of n-hexyl chloride with aqueous sodium formate in the presence of a quaternary ammonium catalyst (5 mol %) [equation (3)] at 95 °C. This reaction can be carried out in the presence or absence of an organic solvent. The reaction follows pseudo first-order kinetics if the concentration of the aqueous phase is above the saturation value (75% w/w).[20]

$$RCl_{(org.)} + HCO_2Na_{(aq.)} \xrightarrow{QX} ROCOH_{(org.)} + NaCl_{(aq.)} \quad (3)$$

When solid sodium formate (containing 2% water) (2 equiv.) was added to n-hexyl chloride (2.6 M in mesitylene, 1 equiv.) in the presence of tetra-n-butylammonium bromide (0.05 equiv.) at 95 °C a pseudo first-order rate constant of 5.1×10^{-3} min^{-1} was measured. Addition of either formic acid, acetic acid, or phenol (0.1 equiv.) reduced the rate constant by more than an order of magnitude to $0.3 \pm 0.1 \times 10^{-3}$ min^{-1}. On the other hand addition of sodium hydrogen carbonate (0.1 equiv.) increases the rate constant to 5.9×10^{-3} min^{-1}.

Aqueous solutions of sodium formate at 25 °C contain approximately 0.01% of free formic acid formed by hydrolysis. This fraction increases significantly at higher temperatures and in the presence of an organic phase containing an onium salt by a process of dissociation–extraction[21] according to the two equilibrium processes (4) and (5).

$$HCO_2, Na + H_2O \rightleftarrows HCO_2\,H + NaOH \quad (4)$$

$$HCO_2, H_{(aq.)} + QX_{(org.)} \rightleftarrows QX \cdots HCO_2, H_{(org)} \quad (5)$$

The formic acid extracted *via* this mechanism has a retarding effect on the normal esterification process. Addition of a base *e.g.* a carbonate or hydrogen carbonate stops the formate hydrolysis and formic acid extraction and thus has a positive effect on the rate constant.

The hydrolysis–extraction process is naturally more pronounced if larger amounts of water are present in the system. Thus with 75% w/w aqueous sodium formate in the above esterification process a rate constant of 8.7×10^{-4} min^{-1} was measured. Upon addition of potassium carbonate (0.1 equiv.) the rate constant doubles to 17.4×10^{-4} min^{-1}.

Formic acid can be generated in the system by a different mechanism, namely by using a hydrogen sulphate catalyst. The rate constants for reaction (3) as catalysed by tetra-n-butylammonium chloride, bromide, and iodide, and hydrogen sulphate were 8.7×10^{-3}, 5.1×10^{-3}, 1.3×10^{-3}, and 0.9×10^{-3} min^{-1}, respectively. The halide catalysts behaved as would be expected but the hydrogen sulphate catalyst, which is usually considered as the catalyst of choice, performed very poorly. The reason is apparently the *in situ* formation of formic acid according to equation (6). It can be concluded that hydrogen sulphate catalysts should be avoided in PTC esterification of carboxylic and other weak acids unless neutralized by a strong base.

$$HCO_2^- + HSO_4^- \rightarrow HCO_2H + SO_4^{2-} \quad (6)$$

The hydrolysis–extraction reaction becomes more of a problem when salts of even weaker acids are involved. For example, when an aqueous sodium phenolate solution (1.87 M) is treated with an equal volume of *o*-dichlorobenzene containing tetra-n-heptylammonium bromide (0.05 equiv.) approximately 3% of the phenol can be found as free non-dissociated acid in the organic phase, in addition to the phenolate anion normally extracted as an ion pair. Upon addition of n-butyl bromide (1.95 equiv.) to the above system an etherification process took place with an observed rate constant of 4.8×10^{-3} min^{-1}. If sodium hydroxide was added to the above system (NaOH : phenol 2.5 : 1) the rate constant increased more than three-fold to 15.6×10^{-3} min^{-1}. If however the NaOH : phenol ratio was reduced to 0.5 : 1 the rate constant was only 0.5×10^{-3} min^{-1}. A similar trend was observed for a series of experiments where the phenol : sodium hydroxide ratio was altered but with varying aqueous phase volumes to keep the ionic strength constant.

In simple halogen-exchange reactions the aqueous phase is usually at pH 7 and hydrolysis and hydrogen-bonding extraction do not take place. However if acid is added externally the rate of exchange is strongly affected. We examined the exchange of n-hexyl chloride with 84% w/w aqueous calcium bromide catalysed by tetra-n-hexylammonium bromide (5 mol %). The rate of this process[22] was slowed by a factor of four if hydrobromic acid (5 mol %) was added to the system.

It can be concluded that in PTC reactions catalysed by onium salts, the presence of acids which can be extracted by hydrogen bonding should be avoided. In reactions of carboxylates, phenolates, and other salts of weak acids which undergo extensive hydrolysis the pH of the aqueous phase should be kept high so as to avoid the presence of free acid in the organic phase.

The retarding effect of free acids on the normal PTC substitution process can be attributed to the masking and deactivation of the anion *via* hydrogen bonding.

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