Mechanism of Solid/Liquid Phase-transfer Catalysis in the Presence of Potassium Carbonate: Alkylation of Pyrrolidin-2-one

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Solid potassium carbonate is the base chosen for the solid/liquid phase-transfer catalysed benzylation of pyrrolidin-2-one. A kinetic and mechanistic study has been carried out in which the effects of various parameters on the behaviour of the system have been evaluated. It was concluded that this reaction proceeds *via* the 'interfacial mechanism' and no extraction of the carbonate anion is taking place. In addition, the essential role of water in this process was found to be similar to its function in the 'extraction mechanism.'

Aqueous sodium hydroxide (usually 50% w/w) is a commonly used reagent in phase-transfer catalysed (PTC) reactions. Typical examples are *C*-, *N*-, or *O*-alkylations, carbene addition and various condensations.[1] Several clear differences in mechanism were observed between reactions using hydroxide ion (PTC/OH) and other anions (PTC/X).[2] The highly hydrophilic and hard hydroxide anion is usually not extracted into the organic phase and its function is at the interface *via* the interfacial mechanism, compared with the extraction mechanism operating in most PTC/X systems. Solid potassium carbonate has recently become a popular basic reagent in phase-transfer systems, both in solid/liquid[3] and in solid/liquid/gas[4] systems. In addition to being milder and less corrosive and promoting fewer side reactions it also has the advantage of being applicable as a dry material, in the absence of water. The use of anhydrous systems is an advantage when water-sensitive substrates are involved.

Solid/liquid phase-transfer catalysed exchange reactions (PTC/X) are sensitive to the presence of trace amounts of water.[5] It was shown by using the optimal amount of water that not only were very hydrophilic anions extracted and reacted, but also that reaction rates were maximized.[6-8] While the critical role of water in heterogeneous substitution reactions is well established,[5] only a little information is available for the function of water in the synthetically more useful base-initiated reactions (PTC/OH).[2] In the alkylation of phenylacetonitrile, for example, the reaction order with respect to the hydroxide ion concentration was found to be 5.3.[9] A similar exceptionally high reaction order was observed in the hydroxide-ion-initiated isomerization of allylbenzene.[10] The reactivity of the hydroxide ion in the Hofmann degradation of quaternary ammonium salts was found to vary over four orders of magnitude by changing the concentration of sodium hydroxide from 10 to 50 weight% in water.[11] It was suggested that both the nucleophilicity as well as the basicity of the hydroxide anion are both enhanced with lower hydration.[2] Despite the obvious conclusions only few studies have been made using solid sodium or potassium hydroxide as a base. Thus, Dehmlow has concluded that powdered potassium hydroxide is the most effective base for the alkylation of benzamide.[12] We found that the preparation of lipophilic quaternary ammonium hydroxides by direct exchange with caustic soda can be achieved only with solid hydroxide.[13]

Many examples are known, on the other hand, in which solid potassium carbonate has been applied to phase-transfer systems. Typical examples are the following: Michael reaction,[14] alkylation of highly acidic compounds,[15] preparation of amino acids,[16] Wittig synthesis,[17] Darzen's condensation,[18] and aldol-type condensation as well as some polymerization processes.[19]

Despite numerous examples of the synthetic application of potassium carbonate in phase-transfer systems, no attempt has been made until now to study the mechanism of these reactions. We have examined the role of water and the general mechanism of the solid/liquid phase-transfer catalysed *N*-alkylation of pyrrolidin-2-one in the presence of solid potassium carbonate using benzyl chloride as an alkylating agent, equation (1). Although we observed that this reaction is up to ten times faster when sodium hydroxide is the base, there is still a disadvantage in using caustic bases which cause side reactions, particularly hydrolysis of both the substrate and the alkylating agent as well as decomposition of the quaternary ammonium catalyst.

We came to the conclusion that this reaction proceeds *via* the interfacial mechanism and that water has an important role in the process.

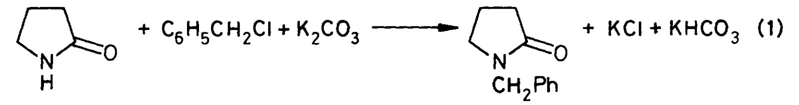
Results

In a typical procedure, pyrrolidin-2-one (25 mmol) and benzyl chloride (25 mmol) were mixed (constant stirring speed of 600 rpm) with solid potassium carbonate (50 mmol) and tetrabutylammonium bromide (TBAB) (2.5 mmol) in toluene (25 cm^3) at 80 °C. The only organic product identified in the reaction mixture was *N*-benzylpyrrolidin-2-one. The progress of the reaction was monitored by g.c. analysis of samples taken from the organic phase. A typical reaction profile is shown in Figure 1. This kinetic profile indicates a typical catalytic mechanism with shifting order. The reaction starts with zero-order kinetics and shift to first order after *ca.* 40% conversion.

The initial zero-order kinetics simplified the rate measurements. We have examined the role of various parameters on the behaviour of the system, as described in the following sections.

Effect of Temperature.—Reaction (1) was carried out at temperatures of 60, 80, 90, and 102 °C under the conditions shown in Figure 1. From the measured rate constants we have calculated the activation energy of this reaction to be 12.4 kcal mol^{-1}. This figure suggests that a physical step of mass transfer has some role in the overall process but it is definitely not the sole rate-determining step.

Effect of Catalyst Amount.—The variation of the initial rate of reaction (1) with the concentration of the TBAB catalyst is shown in Figure 2. The behaviour shown in Figure 2 is typical in phase-transfer systems.[20] The rate increases linearly with the amount of the catalyst up to 15 mol% where the rate levels off. This phenomenon can be attributed to the limited interfacial



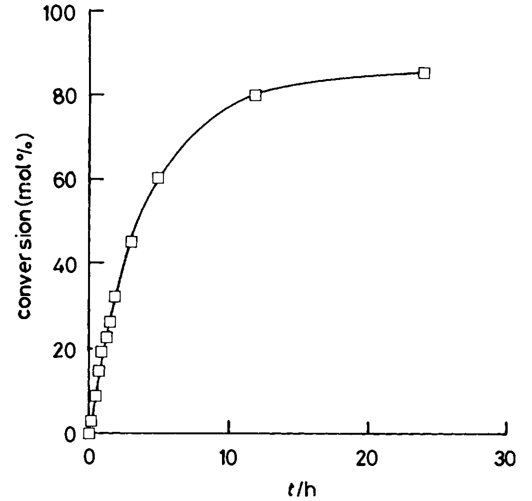


Figure 1. Profile of reaction (1). *Reaction conditions:* 2-pyrrolidinone (25 mmol) and benzyl chloride (25 mmol) were mixed (const. stirring speed 600 rpm) with solid K_2CO_3 (50 mmol) and TBAB (2.5 mmol) in toluene (25 cm^3) at 80 °C.

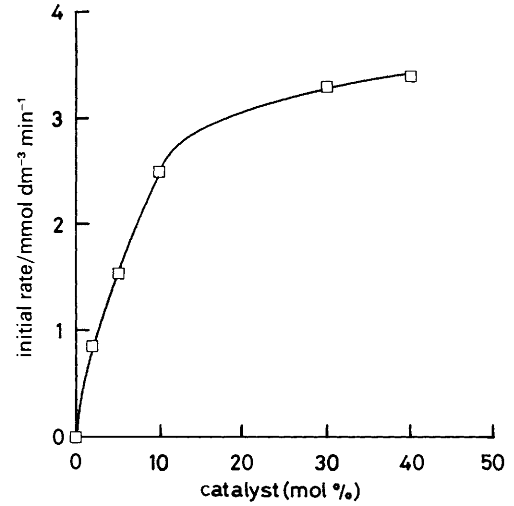


Figure 2. Effect of catalyst concentration. *Reaction conditions:* see Figure 1.

area in the system which becomes saturated with catalyst molecules so further addition has only a minor effect on the observed rate.

Effect of Catalyst Structure.—Several quaternary ammonium salts were applied as catalysts in reaction (**1**) under identical conditions. The initial rates are presented in Table 1. It is quite clear from the results presented in Table 1 that smaller, more accessible,[2] quaternary catalysts are more active in this reaction. This observation is typical of phase-transfer reactions which take place *via* the interfacial mechanism.[2]

In addition, the anion also has a significant effect on the rate. A given quaternary cation is more efficient when associated with small hydrophilic anions than when paired with large hydrophobic anions. It should be kept in mind, however, that this effect is limited to the very initial stages of the reaction since while the reaction proceeds, chloride anion is released and exchanged, to a certain degree, with the original anion.

Table 1. Initial rates with different catalysts.[a]

Run	Catalyst	Initial rate/ mmol dm^{-3} min^{-1}
1	Tetrabutylammonium iodide	1.69
2	Tetrabutylammonium bromide	2.49
3	Tetrabutylammonium fluoride	3.95
4	Tetrahexylammonium chloride	1.45
5	Didecyldimethylammonium bromide	1.73
6	Triethylbenzylammonium chloride	5.00

[a] Reaction conditions: as in Figure 1.

Effect of Mixing.—While reactions that proceed *via* the extraction mechanism are effected by mixing only to a limited degree (usually mechanical stirring at 400 rpm is sufficient to achieve maximum rate) in the interfacial mechanism, where mass transfer has a stronger role, the impact of stirring is more significant and the rate increases, even above 1 000 rpm.[2] The dependence of the initial rate of reaction (1), on the speed of stirring is shown in Figure 3.

Figure 3 clearly indicates that stirring affects the reaction rate even above 1 000 rpm. This phenomenon is typical of the interfacial mechanism. It should be mentioned, however, that the measurements made above 600 rpm reflect the rate only at the very initial stage of the reaction. We found it very difficult to handle the mixing of solid/liquid systems at high speed for long periods of time. The solids tend to accumulate on the glass walls and to lose contact with the process. Consequently the following runs were carried out with mixing at 600 rpm although it was clear that in this mixing the system is not completely free from mass-transfer effects.

Effect of the Amount of Base.—Since the carbonate base is added as solid its concentration could not be varied. We have thus examined the effect of the quantity of potassium carbonate used on the initial rate. The results are presented in Figure 4. The linear dependence clearly suggests that the potassium carbonate participates in the rate-limiting step of reaction (1).

When other bases were applied in reaction (1) the only active base except potassium carbonate was sodium hydroxide (solid) which was found to be 10 times faster (initial rate 26 mmol dm^{-3} min^{-1} under conditions identical with those of Figure 1). Calcium carbonate, sodium and potassium hydrogencarbonate as well as sodium carbonate (all as solids containing 16 wt% water for reasons which will be clarified later) showed no activity. The stoicheiometry of the process as shown in equation (1) is therefore confirmed; the potassium hydrogencarbonate released does not react any further and no water is formed in the process.

Effect of Water.—Small amounts of water have a critical effect on phase-transfer reactions, particularly in solid/liquid systems.[5] In a series of experiments we examined the role of water in reaction (1). The results are presented in Figure 5.

It should be noted that we were unable to dry the potassium carbonate completely so that the point at zero water could not be examined and is an assumption based on our previous experience with similar systems. As a rule of thumb, quaternary ammonium catalysts are not active in solid/liquid extractions

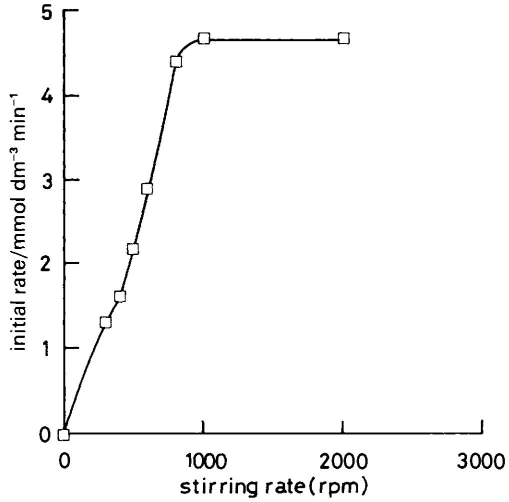


Figure 3. Effect of stirring on reaction rate. *Reaction conditions:* see Figure 1.

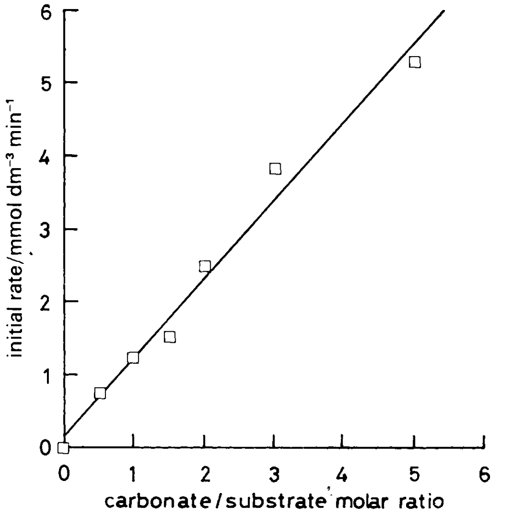


Figure 4. Effect of the amount of base. *Reaction conditions:* see Figure 1.

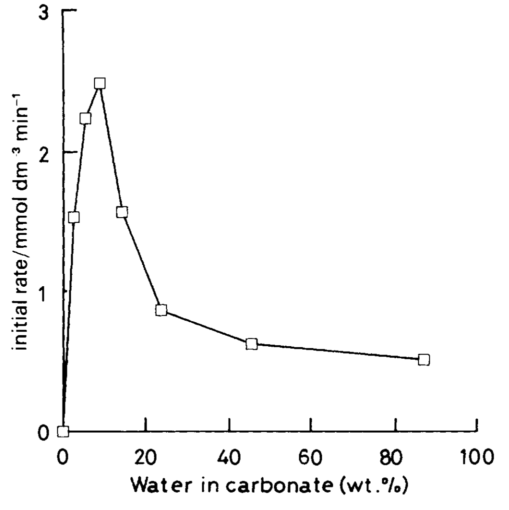


Figure 5. Effect of water on the initial rate. *Reaction conditions:* see Figure 1.

unless traces of water or other highly polar solvents are present. The general behaviour shown in Figure 5 is also typical of phase-transfer systems.[5] We have recently argued that the rate initially increases in these experiments since the water film on the solid reagent allows the transport of anions to the organic phase. Beyond a certain point, however, the rate decreases due to hydration of the anions in the organic phase which reduces their nucleophilicity.[21] Karl–Fischer analysis of the organic phase in the experiments of Figure 5 indicated that < 16% water in the carbonate the organic phase remained practically dry through the reaction. Above this point more water is transported to the toluene phase until saturation is reached at *ca.* 35% initial water in the carbonate. It should be noted that potassium carbonate is very hygroscopic when it contains < 16% water but completely loses this property when a larger amount of water is present. It should also be noted that water is neither formed nor consumed in reaction (1). To our surprise, dry and partially wet (16%) sodium carbonate which was totally inactive in reaction (1) showed some activity when applied as a 30% aqueous solution (initial rate 0.1 mmol dm^{-3} min^{-1}).

Discussion

Three possible mechanisms for reaction (1) are as follows.

(a) *Extraction Mechanism.*—This route is based on Starks' classical PTC mechanism in which reactive anions are extracted to the organic phase *via* an anion exchange process.[22] Carbonate anion is thus extracted to the organic phase where it deprotonates the substrate to form a pyrrolidinone anion which attacks the benzyl chloride in a substitution reaction to yield the product and reform the catalyst for another extraction cycle. This mechanism can be rejected mainly because it has been shown in several instances that carbonate anion cannot be extracted by quaternary ammonium salts into organic solvents.[1] This is quite different from the hydroxide anion which was found to be extractable under certain circumstances.[2]

(b) *Nucleophilic Catalysis.*—We have shown in several instances that quaternary ammonium ion pairs can activate various substrates *via* hydrogen bonding.[23] Even aniline was shown to be partially deprotonated in presence of quaternary ammonium reagents.[24]

In a similar manner we can assume direct interaction between the catalyst and the substrate through hydrogen bonding which creates a partial negative charge on the nitrogen atom of the substrate:

$$\mathrm{PyH} + \mathrm{Q^+Cl^-} \longrightarrow \mathrm{Py\cdots H\cdots Cl^-Q^+} \qquad (2)$$

The adduct formed reacts in a nucleophilic substitution of benzyl chloride:

$$\mathrm{Py\cdots H\cdots Cl^-Q^+} + \mathrm{PhCH_2Cl} \longrightarrow \mathrm{PhCH_2Py} + \mathrm{Q^+Cl^-\cdots HCl} \qquad (3)$$

The adduct of the catalyst with the released hydrochloric acid is transported to the solid carbonate where it is neutralized:

$$\mathrm{Q^+Cl^-\cdots HCl\,(org)} + \mathrm{K_2CO_3\,(aq)} \longrightarrow \mathrm{Q^+Cl^-\,(org)} + \mathrm{KCl\,(aq)} + \mathrm{KHCO_3\,(aq)} \qquad (4)$$

In this mechanism we can expect that the catalyst anion will play a major role in the process. The order of decreasing reactivity should be $F^- > Cl^- > Br^- > I^-$. This order was evidently observed. On the other hand, if this was the actual mechanism then some conversion should be observed even in the absence of a carbonate base. We did observe a slow reaction taking place in the absence of carbonate (7% conversion after 24 h) but only when a stoicheiometric amount of tetrabutylammonium fluoride was applied. None of the other catalysts

Table 2. Solubility of salts (g per 100 cm^3 water) at 80 °C.

Salt	Solubility
K_2CO_3	147.2
$KHCO_3$	33
KCl	50.1
KBr	92.3
Na_2CO_3	37.8
$NaHCO_3$	12.0
NaCl	38.4
NaBr	12.0

showed even minor activity under such conditions. We conclude that this mechanism has only a minimal role, if any, in this process. It should also be noted, however, that we were unable to detect any change in the N–H absorption frequency in the i.r. spectrum of pyrrolidin-2-one upon addition of a stoicheiometric amount of tetrabutylammonium fluoride.

(c) *The Interfacial Mechanism.*—This mechanism, introduced by Makosza, is typical of most PTC reactions in which sodium hydroxide is the aqueous phase reagent. This mechanism which was reviewed recently[2] is characterized by the following.

(i) Hydroxide ion is not extracted into the organic phase. Deprotonation of the substrate is taking place at the interphase and consequently the organic anion is extracted and reacts in the bulk of the organic phase.

(ii) Small, more 'accessible'[25] catalysts are more active than large lipophilic quaternary salts which usually function better in the extraction mechanism.

(iii) The rate-determining step in the process is the anion exchange at the interphase while in the extraction mechanism it is usually the chemical reaction in the organic phase.

Based on our results we can safely argue that reaction (1) proceeds *via* the interfacial mechanism according to the following steps:

(i) Interfacial deprotonation of the substrate:

$$\text{PyH (org)} + K_2CO_3\text{ (s)} \rightleftharpoons Py^-K^+\text{ (interphase)} + KHCO_3\text{ (s)} \quad (5)$$

(ii) Extraction of the pyrrolidinone anion by the catalyst:

$$Py^-K^+\text{ (interphase)} + Q^+Cl^-\text{ (org)} \rightleftharpoons Q^+Py^-\text{ (org)} + KCl\text{ (s)} \quad (6)$$

(iii) Substitution reaction in the bulk of the organic phase:

$$Q^+Py^- + PhCH_2Cl \longrightarrow PhCH_2Py + Q^+Cl^- \quad (7)$$

Our results are all consistent with this sequence of steps and indicate that the rate-determining step is the second stage equation (6). At a given amount of water in the system the rate will be linearly dependent on the concentrations of the substrate and the catalyst and the surface area of the carbonate. The rate is independent on the concentration of benzyl chloride.

The effect of water has not been studied in the past in systems reacting *via* the interfacial mechanism. This is mainly due to the difficulties in handling dry—or almost dry—sodium and potassium hydroxide. Our findings in this work indicate that the role of water in this system is very similar to its role in the extraction mechanism, *i.e.* no reaction in the absence of water, increased rate with gradual addition of water until a maximum is achieved and decreased rate when a larger amount of water is present. In the extraction mechanism the decrease in rate was attributed to the reduced nucleophilicity due to hydration of the anions.[5,21] In our case, reaction (7) is evidently not rate determining so the nucleophilicity of the anion has no role in the overall rate. The lower rate with higher amount of water can therefore be attributed to the lower basicity of the hydrated carbonate or to slower interfacial anion exchange at the water saturated interphase.

The inactivity of solid sodium carbonate deserves some elaboration. Since the basicity of sodium and potassium carbonate is essentially the same in aqueous solution we tend to believe that the difference in activity stems from another property. Comparing the solubilities of the salts involved in the system we found (see Table 2) that the solubility of potassium carbonate is significantly higher than that of its halides and hydrogencarbonate. For sodium carbonate, however, the difference is smaller. We evidently can conclude that when the amount of water in the system is limited the sodium halides will be hydrated preferentially to the carbonate. The opposite behaviour is expected for potassium; here the carbonate will be hydrated and dissolved prior to the halides or the hydrogencarbonate. On the other hand, when sodium carbonate was applied in aqueous solution there is no competition for hydration and some activity in the alkylation process is observed. A similar phenomenon of competitive hydration was reported for the extraction mechanism when very hydrophilic anions were involved.[6] We cannot state at this point whether hydration is required for the deprotonation step, equation (5), or for the extraction step, equation (6). We tend to assume that both steps require the presence of hydration water although inhibition of the first step is sufficient to stall the whole process.

Experimental

Materials.—Chemicals were purchased from Aldrich Chemical Co. and were used without further purification.

Typical Synthetic Procedure.—Pyrrolidin-2-one (2.125 g, 25 mmol), benzyl chloride (3.163 g, 25 mmol), potassium carbonate (6.9 g) containing 16 wt% water (50 mmol) and tetrabutylammonium bromide (0.805 g, 2.5 mmol) were mixed in toluene (200 cm^3) at 80 °C. After 24 h the mixture was cooled and filtered and the toluene was evaporated. G.c. analysis of the crude product indicated 86% conversion, with >99% selectivity, to 1-benzylpyrrolidin-2-one. The product was purified by fractional distillation under vacuum (overall yield 76%) and its structure was confirmed by m.s. and n.m.r. analysis as well as by comparison with an authentic sample.

Typical Kinetic Run.—This was conducted by the above procedure with tetradecane (0.15 g) as an internal standard. Samples were taken every 15 min and analysed by gas chromatography.

Analysis.—Water was determined by Karl–Fischer analysis using a Mettler DL-40 titrator. G.c. analyses were conducted using a Varian 3700 gas chromatograph with FID detector and HP 3390A integrator. Column: 0.25″ × 1.80 m, 10% OV-17 on chromosorb W. Carrier gas: He, flow rate 30 cm^3 min^{-1}. Temperature program: 170 °C (1 min); 25 °C min^{-1} to 220 °C (5 min). Retention times: benzyl chloride (1.58 min), pyrrolidin-2-one (1.75 min), tetradecane (standard 3.01 min), and 1-benzylpyrrolidin-2-one (4.17 min).

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