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Direct Evidence for the Hydroxide Extraction Mechanism in the Phase Transfer Catalyzed Cyclopropanation of 4-Halobutyronitrile in a Solid-Liquid System

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Abstract : The Hoffman degradation reaction is proposed as an unequivocal proof for the validity of the extraction mechanism in Phase Transfer Catalysis (PTC) in the presence of solid NaOH. 4-Chlorobutyronitrile is found to yield cyclopropyl cyanide *via* an extraction route while 4-bromobutyronitrile reacts to form the same product by the prevalent interfacial mechanism.

The mechanism of quaternary ammonium salt catalyzed nucleophilic substitution in phase transfer systems is well proven and is based on biphasic liquid/liquid or liquid/solid anion exchange followed by a replacement reaction in the bulk of the organic phase.[1] This simple concept was found to be inappropriate for the widespread family of PTC processes - alkylation of weak carbon and nitrogen acids and related reactions taking place in the presence of a hydroxide base.[2] For this class of reactions Makosza[3] proposed the "Interfacial Mechanism" where instead of direct extraction of the hydroxide anion its role is limited to an interfacial deprotonation of the substrate followed by extraction of the organic anion into the bulk of the organic phase where it further reacts with an alkylating agent such as alkyl halide or sulphate.[4] Although the "Extraction" and the "Interfacial" mechanisms were shown to differ in various parameters such as dependence on stirring rate, nature of the most effective catalyst and the rate determining step,[5] no experimental technique was advocated to distinguish between the two mechanisms. This paper proposes for the first time that the extraction mechanism is conceivable in PTC- hydroxide systems and provides direct evidence for the role of quaternary ammonium hydroxide intermediates in certain alkylation reactions.

We introduce the well known Hoffman degradation reaction, typical to quaternary ammonium hydroxides or fluorides,[6] but uncommon with ammonium salts of soft acids, as a direct probe and evidence of the existence of the extraction mechanism. The presence of tri-*n*-alkylamine, which can be quantitatively monitored in a reaction mixture, using gas chromatography, is claimed as a positive proof

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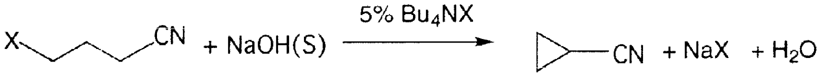
for the actual extraction of hydroxide anions paired with quaternary ammonium cations, into the organic phase.[7] On the other hand, the absence of Hoffman degradation products in a phase transfer reaction system is a positive evidence of the presence of an interfacial mechanism.

We have studied various synthetic and mechanistic aspects of the cyclization of 4-halobutyronitrile[8] by intramolecular alkylation (or gamma elimination) reaction under basic phase transfer conditions.[9] A unique phenomenon which immediately attracted our attention was the remarkable distinction in activity between 4-bromo- (**1**) and 4-chlorobutyronitrile (**2**) when reacted in a homogeneous solution (equation 1) or a heterogeneous solid/liquid phase transfer system (equation 2).[10]

(1)

1 X= Br **2** X= Cl



(2)

1 X= Br **2** X= Cl

When stoichiometric amounts of tetra-*n*-butylammonium hydroxide were reacted[11] with **1** and with **2** in xylene solution at 40°C, the initial reaction rate ratio was found to be rate **1**/ rate **2** = 5.7. The same reaction under heterogeneous conditions, using solid NaOH and 5 mol% of tetrabutylammonium halide catalyst [12] resulted in ratio rate **1**/ rate **2** = 0.10. Two other remarkable observations were:

[A] Cyclopropanation of **1** according to reaction 2 was effectively catalyzed by the "accessible"[13] quaternary ammonium catalyst trimethylbenzylammonium bromide. No reaction at all was observed with **2** in the presence of trimethylbenzylammonium chloride.

[B] The rate of the catalytic reaction of **2** was dependent on stirring rate only up to 400 rpm, while the reaction of **1** was sensitive to stirring rate up to 1100 rpm. At high stirring rate **1** reacted also in the absence of a catalyst. Consequently, the ratio rate **1**/rate **2** is also dependant on stirring rate. At 400 rpm this ratio increased to 0.45 and at 800 rpm to 1.0.

These observations clearly suggest different mechanisms for the two substrates **1** and **2**. We suggest that evidently the reaction of **1** proceeds *via* the interfacial mechanism while **2** reacts through an extraction mechanism. It is apparent that the reactivity of **2** with chloride as a leaving group is not sufficient to take place under the less potent interfacial mechanism. It should be noted, however that in both reactions relatively low activation energy was measured: 7.2 kcal/mol for **1** and 9.1 kcal/mol for **2**. This implies a partial role for mass transfer in the observed reaction rate of these two substrates.

Hoffman elimination is a typical decomposition reaction of quaternary ammonium hydroxide[14] or fluoride salts.[15] It is very slow for ammonium ion pairs with other anions, particularly with lipophilic soft anions. Thus, we confirmed that both Bu_4NCl and Bu_4NBr were found to be stable in xylene solution at 70°C for 96 hours. Bu_4NOH, on the other hand, decomposed completely after 30 minutes under these conditions but was stable in the presence of **2**.

In an attempt to measure the stability of the quaternary catalysts in reaction[16] (2) we have monitored the presence of tri-*n*-butylamine in the mixtures at certain time intervals. The assay of tri-*n*-butylamine in reaction samples could be accomplished by gas chromatography provided that the injector port temperature is maintained below 160°C to avoid on-column decomposition of the ammonium salt. We have studied the buildup of tributylamine with time in four experiments (identical initial concentration of the ammonium salts in all cases) : (A) Bu_4NCl in xylene was reacted with solid sodium hydroxide at 70°C. (B) Bu_4NBr was reacted under identical conditions as (A). (C) **1** was reacted according to equation (2) at stirring of 400 rpm. (D) **2** was reacted similarly. Results are shown in Figure 1.

Evidently, tributylamine is immediately formed in the absence of the substrate (experiment A) and is generated in experiment D at a similar rate but only after the substrate is completely consumed. In experiment B and C no decomposition was encountered in the presence or in the absence of the substrate. Bu_4NBr shows no tendency to exchange anions with the hydroxide base under these conditions and consequently remains stable. The fact that ammonium bromide salts are by far more stable than ammonium chloride salts was recognized earlier by Landini.[17]

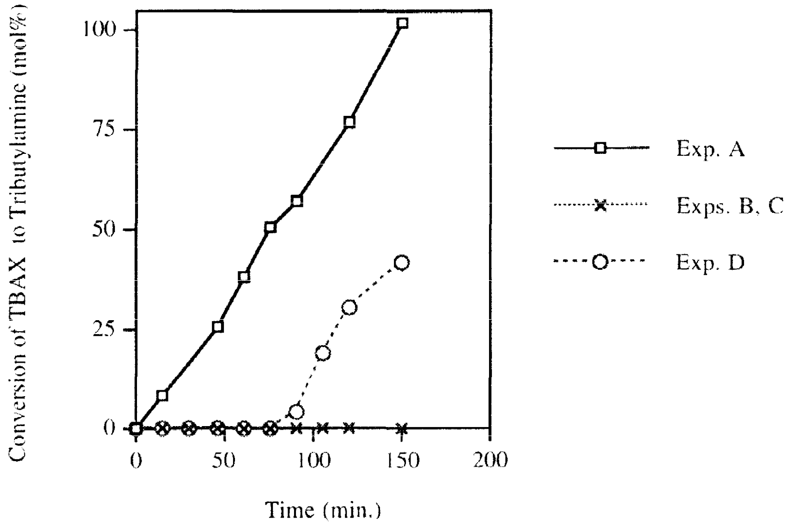


Figure 1. Decomposition of Bu4NX catalysts under various conditions.

These observations, linked with the above data lead to the conclusion that **1** and **2** follow different pathways in reaction (2). It is apparent that in the chloride system Bu_4NOH is a proven intermediate and that **2** reacts according to the extraction mechanism. In the course of the reaction the hydroxide anion instantly attacks the substrate to form a carbanion which couples with the quaternary cation to create an ion pair which eventually led to the product *via* intramolecular alkylation. This ion pair Q$^+$R$^-$ is stable under the reaction conditions and decomposition is observed only after the substrate is consumed. Following the same rationale, the bromo substrate **1** reacts through the interfacial mechanism in which the carbanion is formed at the interface followed by direct formation of the same Q$^+$R$^-$ without the Q$^+$OH$^-$ operating as a mediator. In the latter system Hoffman degradation is not observed during the course of the reaction nor after it comes to an end.

Executing these reactions (equation 2) with 50% aqueous NaOH solution instead of the solid base led to similar observations but with 70% lower reaction rates for both substrates. Interestingly we noted that the relative stability of Bu$_4$NBr under basic conditions in comparison with Bu$_4$NCl decreases when the solid NaOH is substituted with a 50% solution. This trend continues with more dilute solutions.

We believe that the arguments and conclusions presented here are a clear confirmation for the pertinence of the extraction mechanism in the described reaction and, most likely, in many other related PTC- hydroxide systems.

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10. It should be noted that synthetic procedures resulting with high yield and purity were developed in this study, both from **1** and from **2**. These will be published elsewhere.
11. Pure TBAOH was obtained by solvent evaporation (40 °C, 20 mmHg) of the commercial (Aldrich) 1M solution in MeOH. TBAOH (1.3 g, 5 mmol), 4-Br or Cl- butyronitrile (0.74 g . 5 mmol or 0.52 g, 5 mmol respectively) and 5 ml xylenes (b.p. 140°) as solvent were stirred at 40 °C. Reaction composition monitored by G.C. (30m, 5% diphenyl, 95% dimethylpolysiloxane Column and FID, Acenaphtene as internal standard). At least 8 samples were taken per run.
12. 4-Br or Cl- Butyronitrile (0.88 g, 6 mmol or 0.62 g, 6 mmol respectively), TBABr or Cl (95 mg,0.6 mmol or 85 mg, 0.6 mmol respectively), freshly powdered solid NaOH (480 mg, 12 mmol), and 10 ml xylenes were stirred at 70 °C. Analysis were performed as above.
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