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ON THE MECHANISM OF PHASE TRANSFER CATALYSIS

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A variety of organic reactions have recently been reported to be catalyzed by tetraalkylammonium salts. The generation of dichlorocarbene,[1,2] the alkylation of carbonyl and related compounds,[3,4] nucleophilic substitution,[5] and the benzoin condensation[6] are among the reactions which are facilitated by this approach. Two common features of these seem essential: the system has two phases consisting of a water layer and an organic layer and involves an anion as a base or nucleophile.

The synthetic utility of this approach has become increasingly apparent, but the mechanism of the catalysis has not been established. An encompassing scheme has been proposed by Starks in which the function of the tetraalkylammonium ion is to conduct anions into the organic phase where the reaction occurs.[5] But other recent reports suggest that the reaction may occur in (1) the aqueous phase,[6] (2) at an interface,[7] or (3) in a micellar phase.[2] We report here some results which provide strong evidence for the original phase transfer mechanism of Starks.

Our approach was to examine a system where product distribution would be a sensitive function of the site of the reaction. The reaction of secondary alkyl bromides with hydroxide ion is such a system. The classic work of Ingold provides a clear prediction that elimination products should predominate in typical organic media while substitution should match or exceed elimination in a highly aqueous environment.[8]

The two-phase reaction of 2-bromooctane with aqueous sodium hydroxide at 80° is accelerated at least 15-fold by addition of dodecyltriethylammonium bromide or tetrabutylammonium bromide, In a typical experiment, 100 ml of 2 N sodium hydroxide, 5 g of 2-bromooctane, 1 g of tetradecane as internal standard, and 0.5 g of a tetraalkylammonium bromide were stirred at 80° for 48 hours. The yields of octenes (ca. 28% 1-octene; 72% cis and trans 2-octene) and 2-octanol were determined by gas chromatography.

The result was 86% elimination: 14% substitution. The predominance of olefin products was not affected by changes in concentration, added organic solvents, or use of different ammonium ion catalysts; the range of 12 experiments was 81 to 94% elimination. Application of the Ingold criterion to this result conclusively excludes the bulk aqueous phase as the major reaction site.[9]

An independent argument against the aqueous phase was provided by an unsuccessful attempt to extend the Ingold criterion to primary alkyl bromides. Reaction of 1-bromooctane with sodium hydroxide under conditions as above was also accelerated by quaternary ammonium salts. The unexpected major product was di-n-octyl ether (75%) along with 1-octanol (20%) and 1-octene (5%). The alcohol was confirmed as intermediate in the formation of the ether; addition of 1-octanol to the reaction mixture increased the yield and rate of formation of dioctyl ether. Other alcohols produced unsymmetrical ethers; for example, addition of one equivalent of 1-butanol gave n-butyl n-octyl ether in 44% isolated yield along with 20% di-n-octyl ether.[10]

Since alkoxide and hydroxide ions are normally very similar in nucleophilicity toward alkyl bromides,[11] the high percentage of ether formation in the reaction of 1-bromooctane requires that the two anions are present in comparable concentrations in the reactive phase. This could not occur in the aqueous phase; the concentration of 1-octanol during the reaction never exceeds 0.1 M and water is more acidic than primary alcohols in water.[12] This preference for älkoxide is consistent with reaction in an organic phase where the concentration and acidity of 1-octanol could exceed those of water. A similar selectivity for larger anions has been observed in other phase transfer reactions.[3,5]

Having excluded the water phase from consideration, we can also quickly dispose of interface effects. Neither the product distribution nor the rate for either 2- or 1-bromooctane was significantly changed when a small magnetic stirring bar at ca. 400 rpm was substituted for a large mechanically driven stirrer paddle at ca. 2000 rpm. Since surface area is dependent on stirring speed, the lack of dependence on stirring rate indicates that reaction does not occur at the water-organic interface.[13]

Finally, the involvement of micelles is shown to be unnecessary by some qualitative observations on the effectiveness of various tetraalkylammonium salts in the reaction of 1-bromooctane. The data given in Table 1 can be summarized as follows:

(1) smaller ions like tetraethylammonium are not effective catalysts.

(2) larger cations are effective <u>regardless of shape</u>.

The greater efficiency of large cations than smaller ones is consistent with their increased distribution into the organic phase.[14] Particularly significant is the effectiveness of the tetrabutylammonium ion, since it does not have the rod-like shape of molecules which form conventional micelles.[15] Micelles could be involved with other catalysts, but the virtually identical product distributions as well as rates with dodecyltriethyl and tetrabutyl ammonium ions suggest a common mechanism in which micelles are not important.[16] The effect of catalyst concentration on rate will be examined in other systems to elucidate this point, but one report of first order dependence of a phase transfer reaction of catalyst concentration suggests the absence of any involvement of micelles.[5]

<u>Table 1</u>. Reaction of 1-bromooctane with 2 N NaOH and ammonium bromides (48 hr; 80°)

Catalyst	% reacted	Catalyst	% reacted
Me_4N	< 3	C_8-NEt_3	85
Et_4N	< 3	C_{12}-NEt_3	80
Pr_4N	12	C_{16}-NEt_3	96
Bu_4N	100	$(C_8)_3$-NEt	94

In sum, this work has shown that the phase transfer reaction does not occur in a bulk aqueous phase or at an interface and that micelles are unnecessary. All observations are consonant with the original phase transfer mechanism of Starks in which the function of the ammonium ion is to solubilize the anionic reagent in the organic phase. While these conclusions are strictly applicable only to the reaction of hydroxide ion with alkyl halides, it seems highly likely that the same factors are operative in a wide variety of systems.

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9. The applicability of the Ingold criterion, originally determined on isopropyl bromide, was confirmed for 2-bromooctane by examining the elimination-substitution competition in homogenous aqueous ethanol; the percentage elimination (E2) was 79 and 69 in 100% and 80% ethanol, respectively. In a homogenous solution of tetrabutylammonium hydroxide in the non-polar solvent benzene, elimination was 97%.
10. This procedure offers an alternative to the conventional Williamson ether synthesis. Yields for primary alcohols with primary bromides are about 60% if 2 moles of alcohol are used.
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14. Catalysis mechanisms involving tertiary amines can be ruled out, since tetraethylammonium ion, which should be the most prone to a Hoffman elimination, is ineffective.
15. Although tetraalkylammonium salts can show aggregation behavior (H. E. Wirth, J. Phys. Chem., 71, 2922 [1967]; S. Lindenbaum and G. E. Boyd, ibid., 68, 911 [1964]), they apparently do not solubilize organic substrates in the manner that micelles do; cf. J. E. Gordon, J. C. Robertson, and R. L. Thorne, ibid., 74, 957 (1970).
16. The anionic surfactant sodium dodecyl sulfate and the neutral surfactant Triton 100 were not effective as catalysts under conditions in Table 1. This observation is suggestive, but has no direct bearing on the possible involvement of micellar catalysis with the cations.