

Role of a Third Liquid Phase in Phase-Transfer Catalysis

Doron Mason, Shlomo Magdassi, and Yoel Sasson*

Casali Institute of Applied Chemistry, School of Applied Science and Technology, The Hebrew University of Jerusalem, Israel

Received June 4, 1991

The elimination of phenethyl bromide to styrene under phase-transfer catalytic conditions is shown to be sharply accelerated if a three-liquid-phase system can be engineered. Tetrabutylammonium bromide can promote such a system under certain conditions of temperature and concentration, the third phase being rich in catalyst. Excessively concentrated alkali causes a drop in the rate of elimination by nearly 1 order of magnitude, as does a small change in temperature. Such effects are due to destabilization of the third phase and precipitation of the catalyst. None of the observations described apply to either the tetrapropyl or the tetrapentyl salts. The data are explained by reference to anomalous physical and surface chemical properties of the tetrabutyl salt.

Introduction

Since Makosza's classic work^{1,2} it was generally held that hydroxide-mediated phase-transfer catalysis (PTC) is best catalyzed by nonsymmetrical quaternary ammonium cations possessing several ethyl substituents at the nitrogen.³⁻⁵ Recently, we have shown an unconsidered, solvent-dependent correlation between surface and catalytic activities, such that the tetrabutyl salt was especially efficient in some cases. Almost all work to date has used 1-5 mol % of catalyst, above which only a slight increase in activity is expected and cost effectiveness is reduced. In this paper, we discuss the use of high concentrations of catalyst and highlight once more how unusual insights can be achieved through a study of the physical chemistry of the catalyst.

When a large quantity of electrolyte is added to an aqueous solution of a surfactant "coascervation" may occur, in which an additional surfactant-rich liquid phase is formed.^{7,8} Since we had already reported surfactant behavior of phase-transfer catalysts,⁶ it seemed of interest to look for coascervation phenomena and to evaluate any effect this might have on catalysis. Additional support for this line of thinking is provided by the documented formation of an additional liquid phase ("omega phase") in solid-liquid PTC systems involving crown ethers⁹ and the formation of a catalytically active third phase in polyethylene glycol-potassium hydroxide systems.¹⁰ More direct evidence comes from the work of Wang and Weng¹¹ on the conversion of benzyl chloride to benzyl bromide using tetrabutylammonium bromide, in which a third liquid phase could be obtained which led to faster reaction rates.

We have studied the effect of high concentrations of a range of symmetrical quaternary ammonium bromides on the rate of hydroxide-mediated elimination. Tetrabutylammonium bromide uniquely forms a third liquid phase, and this leads to clear and significant effects on the reaction rate for phenethyl bromide. This phase-transfer

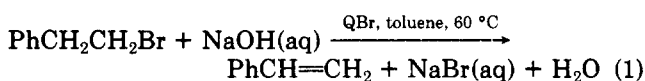
Table I. Composition of the Third Phase

	wt. %	molar ratio
toluene	44.4 (±2)	3.95
water	2.2 (±0.1)	1.00
TBuAB	52.6 (±1)	1.34
OH ⁻	50 ppm	
tributylamine	not detected	

catalyzed reaction has been reported to involve direct elimination by the catalyst and subsequent neutralization at the interface.¹²

Formation and Properties of the Third Liquid Phase. Upon successive additions of tetrabutylammonium bromide (TBuAB) to a mixture of toluene and 40% NaOH the two-phase system gives way to a three-phase system. The third liquid, intermediate in density, builds up at the interface, growing in thickness as more TBuAB is added. Table I shows an analysis of such a third phase prepared in the absence of organic reactants, showing it to be extremely rich in catalyst. Water is present to a small extent, about 3 mol for every 4 mol of salt. Although this phase is in contact with 40% NaOH, it contains very little hydroxide ion and is practically neutral. This contrasts with the work of Wang and Weng¹¹ in which inorganic reagent was incorporated into the third phase. Tributylamine was not detectable; this latter being tested to preclude any involvement of Hoffman degradation product in formation of the phase. The phase is fluid, though more viscous than water, and is formed above 38 °C and up to at least 90 °C. At lower temperature the TBuAB remains largely insoluble in the system. The use of similar quantities of either the tetrapropyl- or the tetrapentyl salt simply leads to precipitation of excess catalyst. In the case of the tetrapentyl salt the excess can be dissolved on heating, but only a two-phase system results. The more lipophilic tetrahexylammonium bromide can be incorporated at high concentration, but again only a two-phase system results. Thus, among symmetrical quaternary ammonium bromides, third-phase formation is a unique property of the tetrabutyl salt.

Catalytic Effect of the Third Phase on Reaction Rate. Figure 1 shows the rate of the phase-transfer-catalyzed conversion of phenethyl bromide to styrene at 60 °C in the presence of increasing concentrations of several catalysts (eq 1). The media are toluene and 40% aqueous



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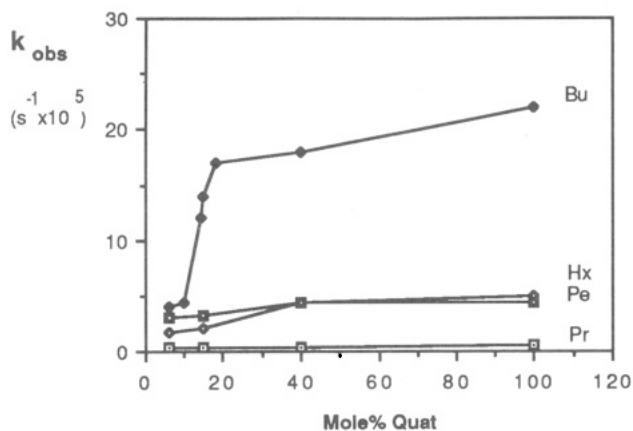


Figure 1. Rate of phenethyl bromide elimination versus concentration of tetrapropyl-, -butyl-, -pentyl-, and -hexylammonium bromide catalysts.

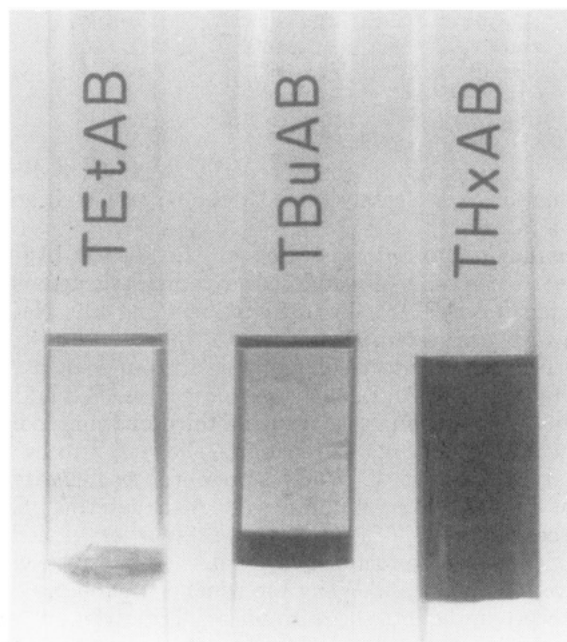


Figure 2. Phenethyl bromide in toluene contacted with 40% NaOH in the presence of various quaternary ammonium bromides.

sodium hydroxide. Tetrapropylammonium bromide is largely ineffective in this medium. The tetrapentyl and tetrahexyl salts show regular catalytic behavior, their effectiveness levelling off at high concentration. The tetrabutyl salt shows two sharp discontinuities, with its activity jumping by a factor of 4 or 5 at high concentration. This behavior is correlated with the formation of the third liquid phase, identifiable by the formation of droplets at the interface, which begins at 11 mol % TBuAB, while at higher concentration a continuous liquid phase with clear boundaries is observed. Figure 2 compares the reaction system in the presence of tetraethyl-, -butyl-, and -hexyl salts. A colored species has been added to sharpen the visual effects.

Additional support for the correlation between the third phase and the accelerated reaction rate is shown in Table II. Here, a reaction mixture forming a three-liquid system was separated into its component layers and then reconstructed from the toluene layer and fresh alkali, without the middle phase. The rate of reaction dropped by over half, compared with that obtainable by the original mixture. When the toluene layer was centrifuged at 10 000 rpm to remove any entrained droplets of the third phase,

Table II. Effect of Removal of the Third Phase

	rate constant (s ⁻¹) at 65 °C
three-phase system (20% catalyst)	17×10^{-5}
upper phase + fresh alkali	6.3×10^{-5}
centrifuged upper phase + fresh alkali	3.7×10^{-5}
two-phase system (6% catalyst)	3.2×10^{-5}

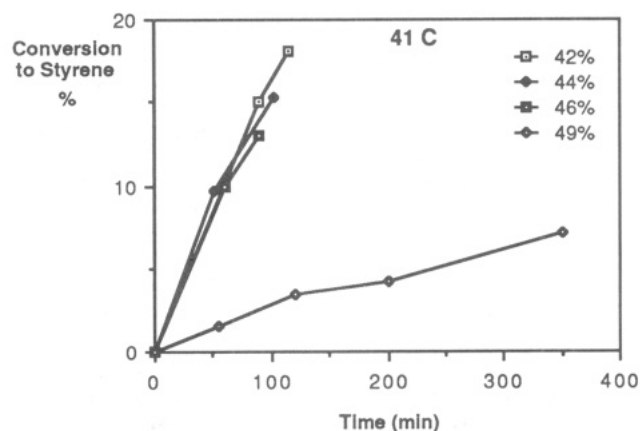


Figure 3. Reaction profiles for elimination by increasing concentrations of alkali.

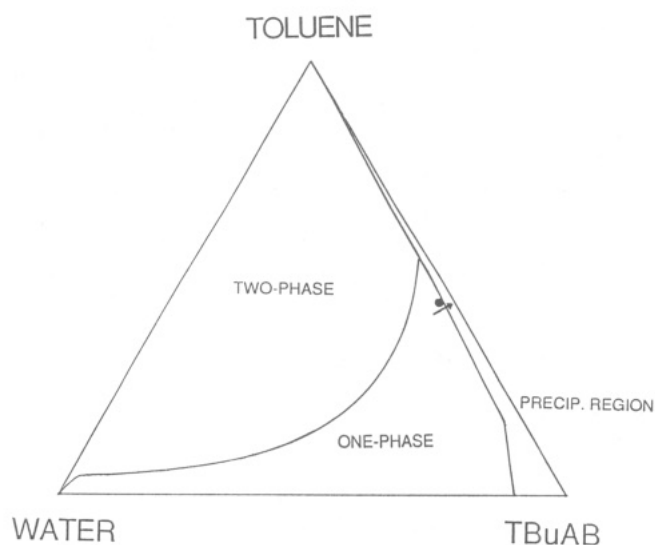


Figure 4. Phase diagram showing third-phase composition and the nature of its instability.

the rate dropped by a total factor of 4, bringing it close to that obtained in the two-phase, low-concentration region.

Inhibition of Elimination by Excess Base. The existence and stability properties of the TBuAB-rich third phase can yield some strange effects. Figure 3 shows the phenethyl bromide elimination reaction at 41 °C in the presence of 42, 44, 46, and 49% aqueous sodium hydroxide. On passing from 46 to 49% the rate of reaction drops by nearly 1 order of magnitude. We appear to be observing the inhibition of base-catalyzed elimination by an excess concentration of base! The answer to this puzzle lies in the stability of the third liquid phase. As the base becomes very concentrated it dehydrates the catalyst phase, causing its destabilization and the precipitation of catalyst. Indeed, in the presence of 49% NaOH two liquids and a solid are present instead of the three liquid phases observed at lower alkali concentration. This solid was later shown by single-crystal X-ray analysis to be anhydrous, solvent-free tetrabutylammonium bromide.

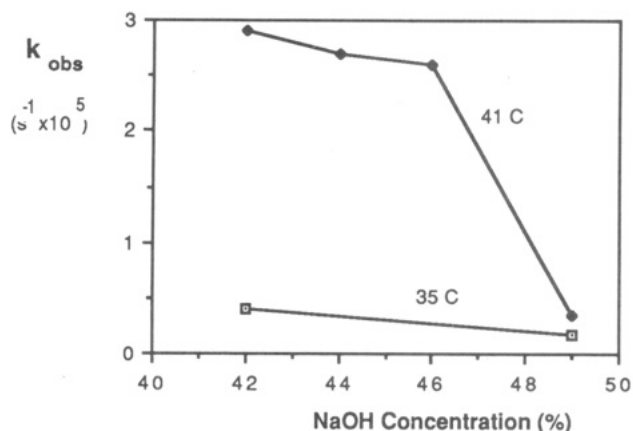


Figure 5. Phenethyl bromide elimination rate versus alkali concentration at two different temperatures.

In order to better understand the phase behavior of the system, a phase diagram (Figure 4) was constructed at 44 °C for toluene, water, and tetrabutylammonium bromide—the three components of the third phase (Table I above). Figure 4 shows that these species form a common phase over a wide range of compositions (“one phase” region). The filled circle represents the composition recorded in Table I. As we move from this position in the direction of the arrow to lower water content the phase becomes unstable and we move into a region of precipitation. This is consistent with the kinetic observations, assuming implicitly that increased concentration of NaOH is equivalent to reduced free-water content. Thus, the inhibition of elimination by excess base is in fact caused by the destruction of the efficient alternative “third phase pathway”.

Unusual Temperature Sensitivity of Elimination.

Figure 5 shows the relationship between elimination rate and concentration of the alkali at two different temperatures. The upper curve at 41 °C is a transposition of Figure 3, while the lower curve at 35 °C is considerably different. In fact, if we focus on the case of 42% NaOH we see that the rate drops by almost 1 order of magnitude on cooling by only 6 °C! This result also is explicable in terms of the formation and stability of the third phase. The phase behavior is extremely sensitive to temperature, such that at 35 °C even 42% NaOH is sufficient to prevent third phase formation. Thus, precipitation of the catalyst was observed for the three low points in the diagram.

A Physical Model of the Three-Liquid Catalysis. In a static system the three phases separate according to their relative densities, with the catalyst-rich phase at the interface. This cannot serve as a physical model for a stirred system, and a true picture of the relative locations of the phases in the dispersion is required. In fact, mild agitation is sufficient to obtain a dispersion which could be evaluated by microscopic observation. Part of the field contained a concentric arrangement in which dispersed droplets of one phase were coated by a thick layer of a second liquid, this being suspended in the continuous third phase (Figure 6a). Upon cooling, the catalyst-rich phase destabilized and revealed itself to be the coating phase, and a halo of bright crystals could be observed through crossed polars (Figure 6b). Through selective staining of the catalyst and organic phases we were able to show that the inner droplets were in fact the aqueous phase, this was coated by catalyst-rich phase, and the whole was dispersed in the toluene. These observations allow us a tentative interpretation of the variation of reaction rate with catalyst concentration (Figure 1). Following the onset of third-phase formation,

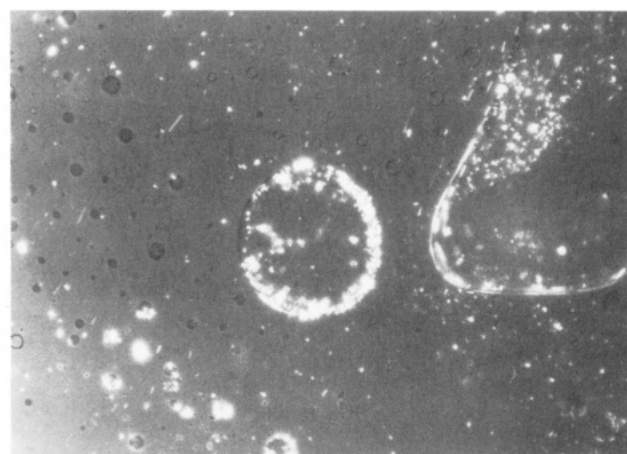
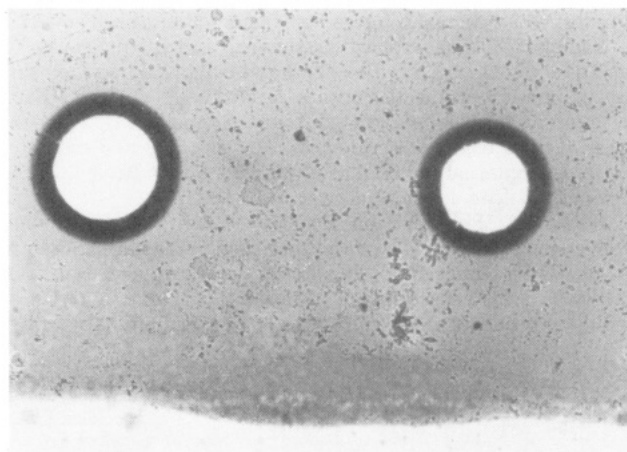


Figure 6. (a, top) Two droplets of alkali dispersed in toluene and coated by a layer of third phase. Staining by Sudan III. (b, bottom) Cooled droplet through crossed polars showing halo of precipitated TBuAB.

we can envisage a rapid increase in reaction rate as more and more of the alkali droplets become coated, followed by a levelling off as excess catalyst simply thickens the existing coating.

Summary

We have shown the anomalous ability of the phase-transfer catalyst tetrabutylammonium bromide to form a third liquid phase when used at concentrations beyond those normally employed in PTC systems. This phase is rich in catalyst and may induce a strong enhancement of reaction kinetics. The stability conditions for this phase need to be carefully matched to the media used. Failure to observe this leads to sudden loss of activity due to precipitation of the catalyst. Whilst a detailed mechanism of the third-phase pathway is still under study, a microscopic observation has been recorded in which the catalyst-rich phase is seen to coat dispersed droplets of the aqueous phase. Finally, on a general note, the benefit of an interdisciplinary approach to phase-transfer catalysis has again been demonstrated.

Experimental Section

Quaternary salts and phenethyl bromide were commercial chemically pure grades (Fluka, Aldrich). Toluene was Baker analytical grade and sodium hydroxide was analytical grade (Merck).

Reactions were carried out in a 21-mm diameter glass tube, fitted with a screw cap and an elastomer-backed Teflon liner, and containing two 10 × 3 mm magnets. Stirring was achieved using a Cole-Parmer Magne-4 in which four stirrers are driven by a common belt. Catalyst concentrations are mol % with respect

to substrate. Reaction volumes were 5 mL organic, 1 mL aqueous.

Samples of 0.1 mL were withdrawn at appropriate time intervals and added to 0.1 mL of dilute HCl and 0.5 mL of toluene. The upper phase was injected onto a capillary GC column. Each reaction profile was constructed from 5-8 samples. Conversions were derived from the ratio of starting material to *o*-dichlorobenzene as internal standard. Results were reproducible to $\pm 5\%$. Phenethyl alcohol formation was negligible.

Kinetics. This reaction deviates from first order at high conversion due to catalyst decomposition.¹² We have chosen to fit first-order curves up to the point of significant deviation. For reactions at high catalyst concentration this is up to about 80% while for others it may be as low as 30%. Evaluation by initial

rate procedures yields essentially the same results and conclusions.

The phase diagram was constructed by equilibrating about 90 compositions for 5 days at 44 °C (± 0.2) in a thermostated water bath. Each composition was placed in a tube identical to those used for reactions, sealed additionally with Parafilm, checked against loss in weight, and the number of phases recorded.

Photomicrographs were obtained on a Nikon microscope system equipped with crossed polars at 100 or 400 \times magnification.

Registry No. NaOH, 1310-73-2; phenethyl bromide, 103-63-9; tetrapropylammonium bromide, 1941-30-6; tetrabutylammonium bromide, 1643-19-2; tetrapentylammonium bromide, 866-97-7; hexylammonium bromide, 4328-13-6; styrene, 100-42-5.

Synthesis of All Stereoisomers of Eudesm-11-en-4-ol. 1. Stereospecific Synthesis of the Trans- and Cis-Fused Octahydro-8-hydroxy-4a,8-dimethyl-2(1H)-naphthalenones. Conformational Analysis of the Cis-Fused Compounds

Ronald P. W. Kesselmans, Joannes B. P. A. Wijnberg,* and Aede de Groot*

Laboratory of Organic Chemistry, Agricultural University, Dreyenplein 8,
6703 HB Wageningen, The Netherlands

Nanne K. de Vries

DSM Research, P.O. Box 18, 6160 MD Geleen, The Netherlands

Received May 29, 1991

An efficient method has been developed for the synthesis of the octahydro-8-hydroxy-4a,8-dimethyl-2-(1H)-naphthalenones **9a-d**, which are suitable intermediates in the total synthesis of trans- and cis-fused 1-hydroxyeudesmane sesquiterpenes. Starting from the trans-fused dione **7** the corresponding hydroxy ketones **9a** and **b** could be easily prepared. The cis-fused hydroxy ketones **9c** and **d** were synthesized starting from the dione **8**. Protection of the C(7) carbonyl function of **8** as its dimethyl acetal followed by treatment with CH_3Li gave the hydroxy ketone **9c**. On the other hand, protection of the C(7) carbonyl function of **8** as its ethylene acetal and subsequent treatment with CH_3MgI afforded the hydroxy ketone **9d** as the main product. NMR studies revealed that **9c** exists predominantly in the steroid conformation and that **9d** exists exclusively in the nonsteroid conformation.

Examinations of the defensive secretion of termite soldiers of a number of genera have revealed the presence of several eudesmane alcohols. The cis-fused amiteol (**1**) is the major compound of the secretion of *Amitermes excellens*.¹ The trans-fused eudesmane sesquiterpenes, intermedeol (**2**) and neointermedeol (**3**), have been isolated from the secretion of *Velocitermes velox*² and *Subulitermes bailey*,³ respectively. The latter compounds have also been found in several plant species,⁴ just as another trans-fused stereoisomer, selin-11-en-4 α -ol (**4**).⁵ The existing confusion around the structure elucidation of these eudesmanes,⁶⁻¹¹ the poor availability of physical and

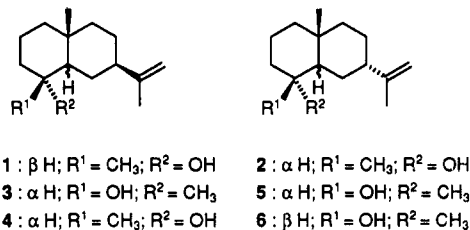


Figure 1.

spectral data, and their interesting biological activities^{1,2,4b} have initiated a synthetic program at our laboratory leading to all possible stereoisomers of these eudesmane alcohols (Figure 1).

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