COCATALYSIS IN PHASE-TRANSFER CATALYZED β-ELIMINATION REACTIONS [1]

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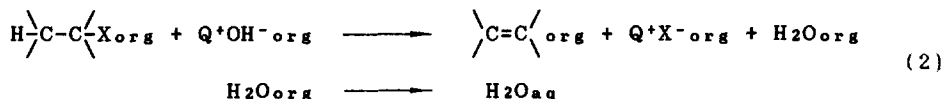PL-01-224 Warszawa, Kasprzaka 44/52

Abstract: The phase-transfer catalyzed β-elimination of HBr from alkyl bromides with aqueous NaOH in two-phase systems proceeds efficiently when tetraalkylammonium salts and weak HO- or HN-acids are used as the catalysts. The latter continuously produce basic, moderately nucleophilic, lipophilic anions, which in the form of tetraalkylammonium salts afford the elimination in the organic phase.

Phase - transfer catalysis (PTC) is presently a well established methodology in organic synthesis, applicable to a wide variety of reactions, mostly those, in which inorganic and organic anions, particularly carbanions, and carbenes are involved.[2] From the very beginning this technique has attracted great interest as a powerful tool in organic synthesis and has found immediate applications,[3] also in industrial processes.[4] This methodology is particularly advantageous in reactions of carbanions and carbenes, because strictly anhydrous organic solvents and expensive, dangerous bases, typically applied for such reactions, can be replaced with aqueous solution of sodium hydroxide.[5] Amongst numerous processes effected by sodium (or potassium) hydroxide and PTC, the β-elimination reactions have not found satisfactory solution and still remain a challenge.[2] The main obstacle in successful application of the PTC for the β-elimination of HX from an organic molecule lays in the very nature of the catalytic process, namely ion-exchange equilibrium. Highly efficient generation and reactions of carbanions in the presence of aqueous NaOH and the PT catalyst (usually tetraalkylammonium salt Q⁺X⁻) stems from the mechanism of the catalysis. The crucial step in those catalytic processes - abstraction of proton - occurs at the phase boundary between the organic phase and aqueous NaOH. The interfacially generated and located carbanions enter ion-exchange process with the catalyst to form lipophilic ion pairs, which migrate into the organic phase, where further reactions take place. Thus formation of Q⁺OH⁻ and its extraction (eq. 1) into the

organic phase is not a step in the catalytic generation and reactions of carbanions, hence those reactions are not affected by very unfavourable exchange equilibrium:[5,6]

$$Q^+X^-_{org} + NaOH_{aq} \rightleftharpoons Q^+OH^-_{org} + NaX_{aq} \tag{1}$$
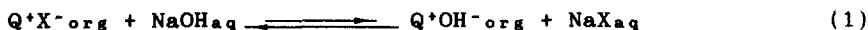
On the other hand, the PT catalyzed elimination (eq.2) requires that OH^- anions are extracted into the organic phase as Q^+OH^- ion pairs, therefore this process is strongly related to the ion-exchange equilibrium (eq. 1), which determines concentration of OH^- in the organic phase:
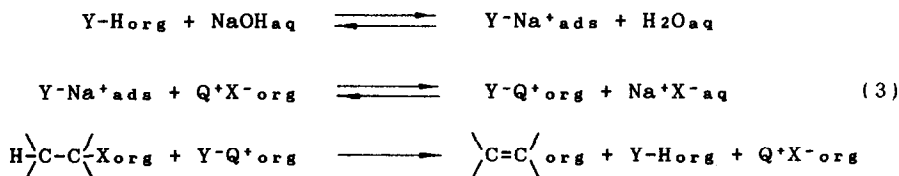
$$H{-}C{-}C{-}X_{org} + Q^+OH^-_{org} \longrightarrow C{=}C_{org} + Q^+X^-_{org} + H_2O_{org}$$

$$H_2O_{org} \longrightarrow H_2O_{aq} \tag{2}$$

As the elimination proceeds, concentration of X^- anions increases and according to eq. 1 concentration of OH^- in the organic phase becomes negligible, hence the elimination is arrested.

For this reason possibility of direct application of PTC methodology for the β-elimination appears doubtful, although there are some examples reported, particularly when a highly lipophilic catalyst was applied.[7]

On the other hand elimination reactions have been successfully realized under ion-pair extraction conditions, since they provide equimolar quantities of Q^+OH^-, produced via ion-exchange between aqueous NaOH and tetrabutylammonium hydrogen sulfate.[8] However, because equimolar quantities of expensive $Bu_4N^+HSO_4^-$ are used instead of catalytic amounts of quaternary onium salts, the main advantage of PTC process has been lost in this case.

Yet another possibility of the application of this catalytic principle for the elimination reactions can be envisaged. It consists in the use of a third partner - a weak organic acid Y-H, which in the two-phase system would form a lipophilic anion Y^- being a weak nucleophile, but a strong base. Such anion would enter the organic phase as the ion pair Q^+Y^-, where it could effect elimination to form an alkene, Y-H and Q^+X^-. Subsequent deprotonation of Y-H at the phase boundary would regenerate Y^- and the cycle would be repeated continuously (eq. 3):

$$Y{-}H_{org} + NaOH_{aq} \rightleftharpoons Y^-Na^+_{ads} + H_2O_{aq}$$

$$Y^-Na^+_{ads} + Q^+X^-_{org} \rightleftharpoons Y^-Q^+_{org} + Na^+X^-_{aq} \tag{3}$$

$$H{-}C{-}C{-}X_{org} + Y^-Q^+_{org} \longrightarrow C{=}C_{org} + Y{-}H_{org} + Q^+X^-_{org}$$

Such a process was already observed and reported by one of us as early as in 1966, when alkylation of phenylacetonitrile with 1,2-dibromoethane and 1,2-dichloroethane was attempted in the catalytic two phase system (50% aq.NaOH, $Et_3N^+CH_2Ph$ Cl^-). The expected product, 1-cyano-1-phenylcyclopropane, was formed in negligible quantities, the main process being elimination of hydrogen halide to form the vinyl halide.[9] Since the nitrile was not consumed, it could be used in amounts below 10% of the dihalide to achieve full conversion of the latter, therefore it acted as a second catalyst. This early example represents therefore the above formulated concept (eq. 3) for Y-H = $PhCH_2CN$. Phenylacetonitrile carbanion is, however, a powerful nucleophile, entering preferentially the substitution reaction and cannot be used as a second catalyst in a general case of elimination. On the other hand RO^- and R_2N^- anions are, as a rule, less nucleophilic than carbanions of similar basicity, thus HO- and HN- acids seem to be more appropriate as Y-H (eq. 3).

As model compounds for studying the elimination reaction bromocyclohexane $\underline{1}$; 2-bromo-5-methylhexane $\underline{2}$, α-bromostyrene $\underline{3}$ and 1-bromooctane $\underline{4}$ were used, in preliminary experiments 2,2,2-trifluoroethanol $\underline{5}$, 2-methylindole $\underline{6}$ and trityl alcohol $\underline{7}$ were selected as relatively efficient precursors of lipophilic, strongly basic anions Y^- in the PTC elimination reactions.

Experimental

Reactions were carried out in a small, 3-necked flask, fitted with thermometer, reflux condenser, magnetic stirrer and a sampling capillary pipette.

Mixtures of appropriate haloalkane, solvent and catalysts were added in one portion to a stirred saturated aqueous NaOH (15 mL, 290 mmol) and the reactions were conducted at temp. given below for time indicated in Table 1. The mixtures were cooled and organic layers analyzed by GLC, the solvents were serving as internal standards. Molar ratios of the catalysts and haloalkanes, specified in Table 1, were based on initial amounts.

Entries 1-13: $\underline{1}$ (4.3 mL, 34.9 mmol) or $\underline{2}$ (4.0 mL, 25 mmol), o-dichlorobenzene (1 mL), tetrabutylammonium bromide and $\underline{5}$ or $\underline{6}$ as indicated in Table 1. The reactions were started at 64°C, and carried out at 73-75°C (exothermic effect and heating). Entries 14-17: $\underline{3}$ (2 mL, 16.9 mmol) o-dichlorobenzene (2 mL) or benzonitrile (2 mL), tetrabutylammonium bromide and $\underline{5}$ as indicated in Table 1. The reactions were started at 40°C and carried out at 45°C. Entries 18-22: $\underline{4}$ (4.0 mL, 23.2 mmol), o-dichlorobenzene (2 mL)

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Table 1. Selected experiments of the phase-transfer cocatalytic dehydrobrominations

Entry	R-Br	Molar percent of QX	Kind and molar percent of YH		Reaction time (minutes)	Yield of elimination product
1	1	2.7	5	2.7	10	60
2	1	2.7	5	5.5	10	75
3	1	2.7	5	5.5	30	98
4	1	2.7	6	5.5	10	45
5	1	2.7	no		90	7
6	1	no	5	5.5	90	0
7	1	no	6	5.5	60	0
8	2	2.7	5	5.5	10	45
9	2	2.7	5	13.2	60	95
10	2	2.7	6	5.4	60	46
11	2	2.7	no		120	16
12	2	no	5	13.1	120	0
13	2	no	6	8.0	120	0
14	3	4.9	5	19.5	60	64
15 a	3	4.9	5	19.5	60	76
16 a	3	4.9	no		60	10
17 a	3	no	5	19.5	120	0
18	4	4.4	5	18.3	90	24 b
19	4	4.4	7	15.0	90	45 c
20	4	4.4	no		90	16 d
21	4	no	5	18.3	90	0
22	4	no	7	15.0	90	0

a: Benzonitrile as a solvent has been used instead of o-dichlorobenzene, applied in all other experiments

b: 28% of RBr consumed to form ROR, total conversion of RBr: 68%

c: 38% of RBr consumed to form ROR, total conversion of RBr: 91%

d: 22% of RBr consumed to form ROR, total conversion of RBr: 38%

and tetrabutylammonium bromide as specified in Table 1, were added to hot (105°C) aqueous NaOH, whereas 5, dissolved in minute amount of tetrahydrofuran, was added in three equal portions after 20, 40 and 60 min. at 105°C.

Results and discussion

Results of the elimination experiments shown in Table 1 indicate, that indeed compounds: 5, 6 and 7 are efficient cocatalysts.

The appearance of lipophilic, strongly basic anions in organic phase, even in minute amounts, results in a strong effect on the elimination process. For example in the case of 1 when both catalysts: Q⁺Br⁻ and 5 or 6 are present, high conversion has been attained after 10 min. (entries 1 and 4), whereas when only one: either Q⁺Br⁻ or 5 (or 6) are present, there is negligible conversion even after 90 min. This time is sufficient for total conversion of 1 into alkene under conditions of entries 1-4. Similar results were obtained in the case of 2 (entries 8 - 13) although this bromide undergoes elimination somewhat slower (compare entries 2 and 8 or 4 and 10). One can expect, that some shortage of cocatalysts 5 or 6 may occur due to the alkylation of their anions. Indeed, some amounts of the corresponding trifluoroethyl ether as well as N-and C-alkylated indoles were detected by GLC in experiment entries 8 and 10. Interestingly in the case of 2 the elimination without the cocatalyst (entry 11) occurs to a significant extent, particularly when the bromide was not meticulously purified and apparently contained the alcohol. It appears that hydrolysis of the bromide may provide small amounts of the alcohol, which can serve as a source of lipophilic anion instead of 5. Indeed, the alcohol was detected in the reaction mixture and when added in bigger amounts exhibited desired effect, although substantially weaker than 5 or 6. This observation can be instrumental in explaining some examples of unexpectedly efficient PTC eliminations reported earlier.[7] When a proper cocatalyst was applied, in which anionic center was shielded by bulky substituents, it was even possible to effect elimination from primary alkyl halides, although in this case formation of the corresponding ethers occurred to a significant extent (entries 18-20).

In the current literature there is a few reports, that PTC elimination can be promoted by addition of some alcohols to the reaction systems.[10-13] Although in some of those papers term "cocatalyst" has been employed, they do not contain clear cut formulation of the concept, that lipophilic, strongly basic, but moderately nucleophilic alkoxide anions, which are continuously generated at the interface with aqueous alkali, act as the base

in those processes. In addition, peculiar speculations concerning existence of complicated associates in such processes are presented,[12] or no reasonable correlation between the alcohol structure and its activity has been observed.[10,11]

In analyzing anticipated cocatalytic effect of a chosen alcohol on the PTC elimination reaction it appears that three main factors should be taken into consideration: a) acidity of the alcohol, which determines acid-base equilibrium at the interface, b) lipophilicity of the alkoxide anion, which determines solubility of the ion pair RO^-Q^+ in a nonpolar organic phase and therefore crucial ion exchange equilibrium (3) and c) relation: basicity vs nucleophilicity of RO^-, which is strongly affected by the steric effects.

We may suppose that some peculiar results of the PTC elimination processes promoted by alcohols can be rationalized just taking into account interplay of those three factors instead of sophisticated and speculative hypotheses.[10-12] Results of this experimental work enable us to put forward the general layout of the phase transfer cocatalytic cycle (Fig.1), which may serve as a summary of the concept formulated in our paper.
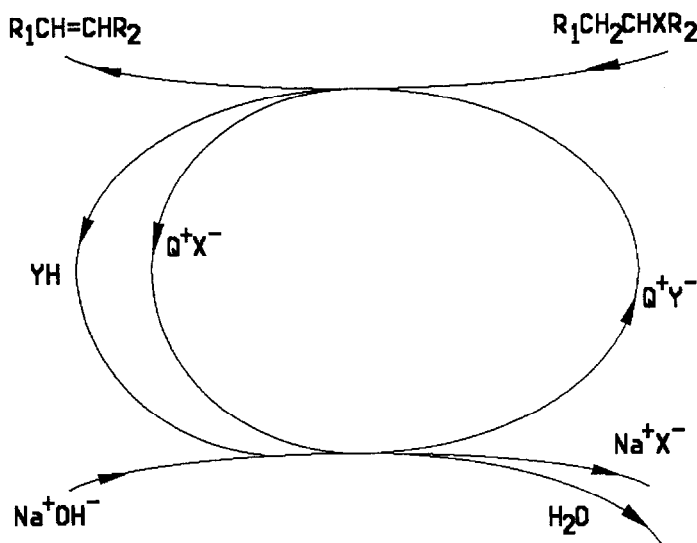

Fig.1. General layout of the phase-transfer cocatalytic
dehydrohalogenation

Acknowledgement

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