

Review

Interfacial Processes—The Key Steps of Phase Transfer Catalyzed Reactions

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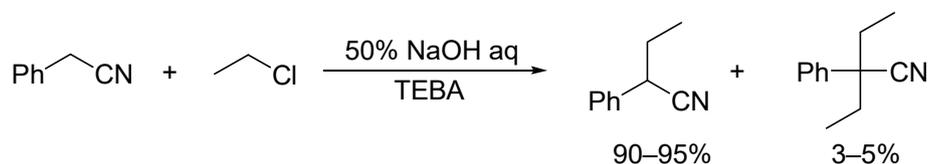
Abstract: After short historical introduction, interfacial mechanism of phase transfer catalyzed (PTC) reactions of organic anions, induced by aqueous NaOH or KOH in two-phase systems is formulated. Subsequently experimental evidence that supports the interfacial deprotonation as the key initial step of these reactions is presented.

Keywords: carbanions; dichlorocarbene; sodium hydroxide; interfacial processes; quaternary ammonium salts; phase transfer catalysis; alkylation

1. Introduction

Phase-Transfer Catalysis (PTC) is presently widely applied in chemical industry based on organic synthesis, such as pharmaceutical, agrochemical, cosmetic etc. The importance of this catalysis is illustrated by value of sales of the PT catalysts that, according to the report of Market & Market Company in 2019, was exceeding 1 billion USD [1]. A particularly valuable variant of PTC are reactions of organic anions, mostly carbanions, but also *O*- and *N*-anions, generated and carried out in the presence of concentrated aqueous NaOH or KOH, catalyzed by tetraalkylammonium (TAA) salts. In this review we would like to discuss mechanistic features of these reactions, particularly interfacial processes that are key steps of generation of the reacting anions.

The first example of industrial application of such catalytic processes was manufacturing of 2-phenylbutyronitrile via reaction of phenylacetonitrile with ethyl chloride carried out in the presence of 50% aqueous NaOH and benzyltriethylammonium chloride (TEBA), 1 mol %, without solvent, by small Polish company, Isopharm, started in 1960 [2] (Scheme 1).



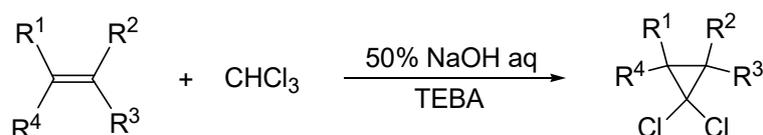
Scheme 1. Production of 2-phenylbutyronitrile according to Polish Patent 46,030 (1962).

It should be stressed that carbanions associated with TAA cations in lipophilic ion pairs entering the organic phase exhibit much higher nucleophilic activity than those associated with potassium, sodium or lithium cations in organic solvents, thus the reactions proceed rapidly in spite of their low concentrations that cannot exceed concentrations of the TAA salts (usually 1% molar).

This process was elaborated on the basis of short note by a French chemist Jarrouse [3]. At that time this nitrile was usually manufactured via reaction of phenylacetonitrile with ethyl bromide in the

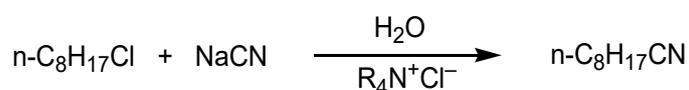
presence of sodium amide in anhydrous toluene. Taking into account cost of the starting materials, solvents and investment assuring safe operation with sodium amide and regeneration of the solvent, cost of the catalytic process was below 30% of the cost of the known procedure.

Thus we can presently celebrate 60 year anniversary of introduction of PTC into chemical industry. This patent and subsequent patents and publications presenting alkylation of carbanions in the presence of aqueous NaOH and TEBA catalyst [4–7] have not raised wider interest to these catalytic processes. Only the 1969 report that dichlorocarbene can be generated and react efficiently with alkenes via treatment of chloroform and alkenes by concentrated aqueous NaOH in the presence of TEBA [8], was widely recognized and convinced chemical community that concentrated aqueous alkali and TAA catalysts in two immiscible phase system is a general and efficient way for generation and reactions of carbanions (Scheme 2).



Scheme 2. Synthesis of *gem*-dichlorocyclopropanes via addition of dichlorocarbene, generated in the presence of aqueous NaOH and TAA catalyst, to alkenes.

Subsequently in 1971 Charles M. Starks reported that reactions of inorganic anions with nonpolar organic compounds proceed efficiently in two phase systems: organic phase and inorganic salt in aqueous solution, when catalyzed by TAA salts and coined the term Phase Transfer Catalysis [9] (Scheme 3).

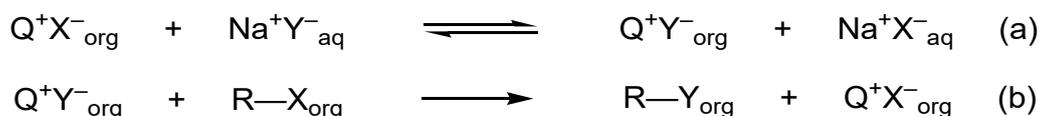


Scheme 3. Nucleophilic substitution in alkyl halides by inorganic anions, catalyzed by TAA salts in two-phase systems.

The value of the catalytic liquid-liquid two-phase systems for reactions of inorganic and organic anions, catalyzed by TAA salts, was immediately recognized as indicated by reviews published in 1973 [10] and 1974 [11] and plenary lecture at First IUPAC Conference on Organic Synthesis in 1974 [12].

The main question was therefore how the catalytic system operates. There were no doubts that reacting anions, organic or inorganic, are continuously introduced into organic phase in form of lipophilic ion pairs with TAA cations supplied by the catalyst, thus the key question that should be answered is how these ion pairs are formed.

The PT catalyzed reactions of inorganic anions Y^- with e.g., alkyl halides RX proceed between sodium or potassium salts of Y^- in form of aqueous solution and RX neat or dissolved in a nonpolar solvent. The reactions proceed thanks to continuous transfer of Y^- from aqueous into the organic phase in form of ion pairs with lipophilic TAA cations, Q^+Y^- . These lipophilic ion pairs are formed via continuous ion exchange between inorganic salts dissolved in the aqueous phase and lipophilic TAA salts (Q^+X^-) in the organic phase. The overall substitution process is shown on Scheme 4.



Scheme 4. Equilibrium of ion exchange between aqueous and organic phases decides about PT catalyzed nucleophilic substitution by inorganic anions. (a) Ion exchange between the aqueous and organic phases; (b) nucleophilic substitution in the organic phase

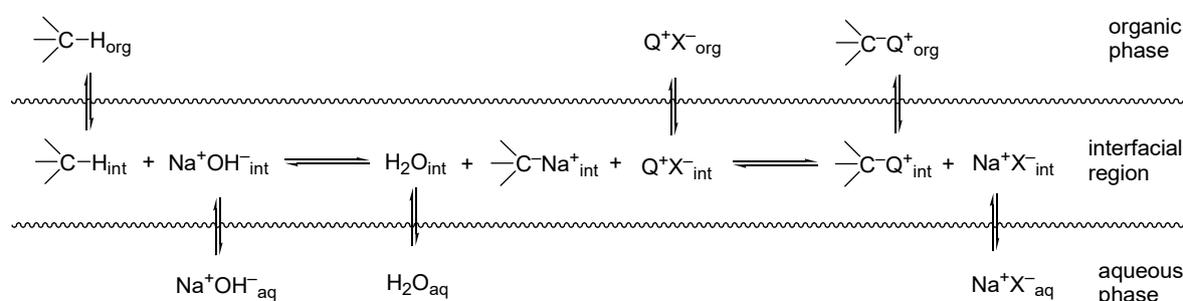
This extraction mechanism was formulated by Starks [9]. Depending on the lipophilicity of Q^+X^- , the ion exchange can proceed via its partial migration into the aqueous phase or at the interface between the phases. From this scheme it is evident that success of the PTC nucleophilic substitution with inorganic anions depends on the equilibrium (Scheme 4a) governed by relation of the hydration energy of ions X^- and Y^- . Iodide anions have low hydration energy therefore alkyl iodides cannot be used as alkylating agents.

The reactions of carbanions (and other organic anions) carried out in the presence of concentrated aqueous NaOH are more complicated because they embrace initial deprotonation of the carbanion precursors. Simple extraction mechanism—ion exchange of TAA salt with NaOH and transfer of TAA hydroxide into organic phase, where the deprotonation takes place—is unacceptable due to high hydration energy of hydroxide anions, thus unfavorable extraction equilibrium (Scheme 5).



Scheme 5. Unfavorable anion exchange equilibrium for formation of TAA hydroxides in two-phase systems.

Moreover, the extraction mechanism is unacceptable because attempts of generation and reactions of dichlorocarbene by treatment of a mixture of chloroform and alkene with separately prepared anhydrous TAA hydroxide failed [8]. Generated carbene rapidly reacted with water produced via deprotonation of chloroform in the organic phase. Therefore, interfacial mechanism was proposed: deprotonation of CH acids takes place at the interface between the immiscible phases, organic and concentrated aqueous NaOH solution. The produced carbanions are associated with sodium or potassium cations hence cannot enter organic nor aqueous phases. Ion exchange with TAA salt dissolved in the organic phase proceeds at the interface. The produced lipophilic ion pairs enter the organic phase where the reactions proceed [12] (Scheme 6).



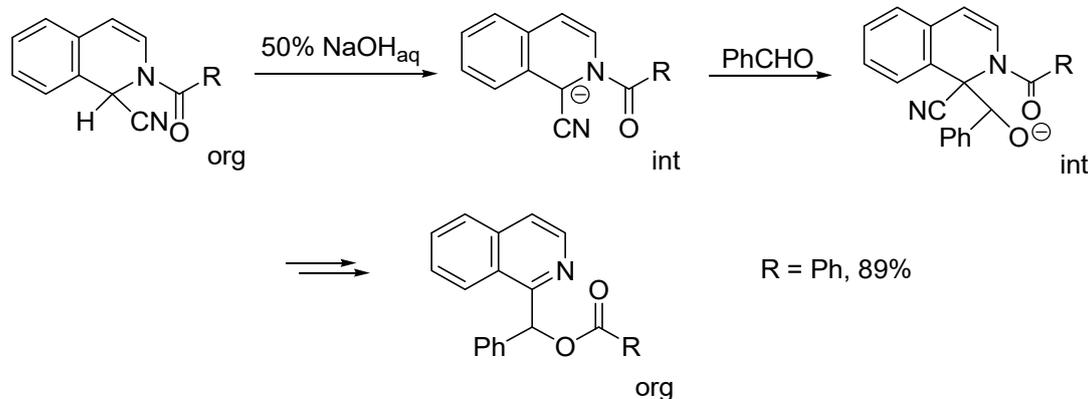
Scheme 6. Interfacial mechanism of generation and transfer of carbanions in two-phase systems.

This initially speculative mechanism was subsequently supported experimentally and, on its basis, specific features of reactions of carbanions and carbenes were rationalized. The experimental confirmation of the interfacial mechanism and its consequence are discussed in this review.

2. Reactions of Carbanions at the Interface

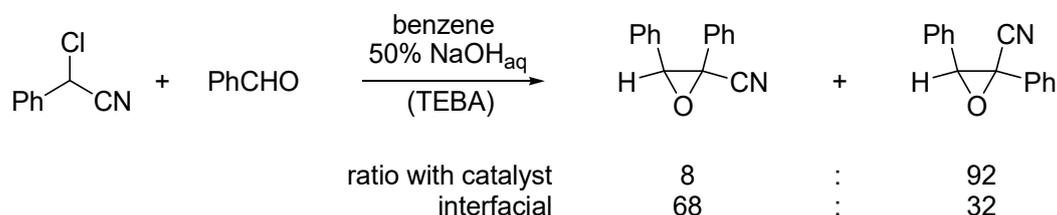
Interfacially generated carbanions cannot migrate into organic phase because they are associated with sodium cations, nor into the aqueous phase because of strong salt out effect. Their concentration is small, and they are accessible with difficulty, so are unable to react with moderately active electrophiles such as alkyl halides. Nevertheless, butyl iodide under somewhat elevated temperature reacts with phenylacetonitrile at the interface with 50% aqueous sodium hydroxide [13]. Aromatic aldehydes are very active electrophiles, thus the addition of carbanions to the carbonyl group proceeds rapidly. However, the addition is a reversible process. Because of that reaction of aldehydes with carbanions generated and located at the interface proceeds efficiently only when a fast subsequent reaction converts

the initially formed aldol type anions into stable product. For example, addition of benzaldehyde to carbanion of the Reissert compound generated at the interface is followed by rapid intramolecular rearrangement connected with rearomatization to form benzoate [14] (Scheme 7).



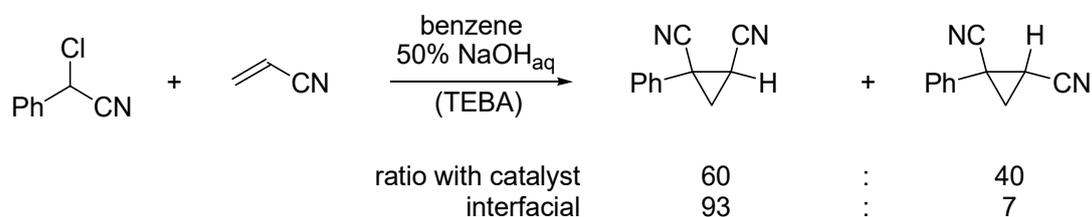
Scheme 7. Interfacial reaction of the Reissert compound with aldehydes in the presence of aqueous NaOH.

Highly convincing are results of the Darzens reaction of interfacially generated α -chlorocarbanions with aldehydes. The reaction of α -chlorophenylacetonitrile with benzaldehyde proceeds efficiently without TAA catalyst at the interface between benzene solution and 50% aqueous NaOH. Moreover, stereochemical results of the interfacial reaction and the reaction catalyzed by TAA salt that proceeds in bulk solution are different [15] (Scheme 8).



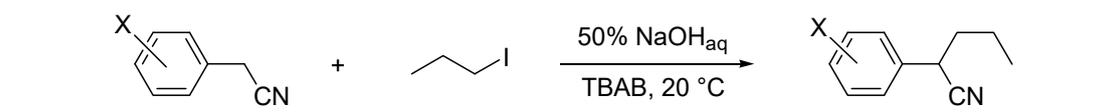
Scheme 8. Interfacial and TAA catalyzed reactions of α -chloronitrile with aldehyde.

Similarly, synthesis of cyclopropanes can proceed via Michael addition of acrylonitrile to interfacially generated carbanion of α -chlorophenylacetonitrile. Additionally in this case stereochemical outcome of the interfacial reaction and the reaction catalyzed by TAA salt that proceeds in solution is different [16] (Scheme 9).



Scheme 9. Interfacial and TAA catalyzed reactions of α -chloronitrile with acrylonitrile.

Interesting results that support interfacial mechanism of hydroxide anion induced PTC reactions of carbanions were obtained in reactions with charged electrophiles. *N*-alkylpyridinium salts that are source of lipophilic cations are also active electrophiles, nevertheless they were used as catalysts in some PTC reactions ([17], pp. 142–145). Exposition of chloroform solution of *N*-benzhydryl- and



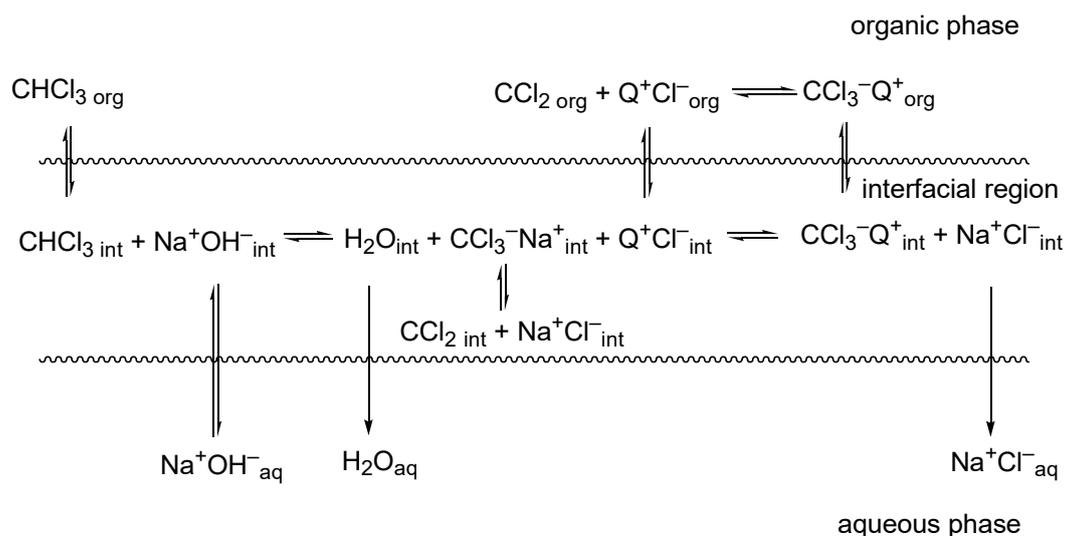
| | | | | | | |
|-----------------|-------|------|------|------|---------------------|---------------------|
| X | 4-MeO | 4-Me | H | 4-Cl | 3,4-Cl ₂ | 2,4-Cl ₂ |
| pK _a | 23.8 | 22.9 | 21.9 | 20.5 | 18.7 | 17.5 |
| conversion, % | 4 | 10 | 17 | 45 | 55 | 90 |

Scheme 11. Effect of CH acidity of the carbanion precursors on inhibition of their deprotonation by iodide anions.

It appears therefore that inhibitory effect of iodide anions in PTC alkylation of carbanions is not due to competitive transfer of these anions into organic phase, but due to accumulation of iodide anions on the surface of the aqueous phase, hence its basicity is diminished. In this situation deprotonation of weak CH acids does not proceed, therefore alkylation of carbanions is inhibited, whereas more acidic carbanion precursors are deprotonated and the produced carbanions are efficiently alkylated by active alkylating agents—alkyl iodides. It can be therefore concluded that basicity of the interface between organic phase and 50% aqueous sodium hydroxide is affected by the presence of halogen anions that are accumulated at the surface of the aqueous phase due to low hydration energy.

4. Specific Features of Generation and Reactions of Dichlorocarbene under PTC Conditions

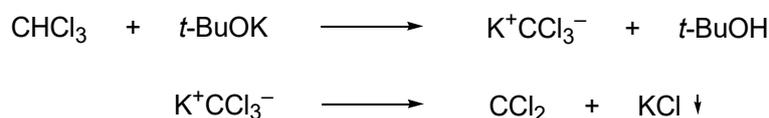
Successful generation and reactions of dichlorocarbene (DCC) under action of aqueous NaOH on chloroform [8] was really surprising because all preceding reports stressed the necessity of strictly anhydrous conditions and even use of sublimed potassium *t*-butoxide as a base [24]. Efficiency of the PTC system is due to a few reasons: a) 50% (saturated) aqueous NaOH, in which approximately there is one molecule of water for one ion, is in fact a strong desiccation agent, hence there are no traces of water in the organic phase; b) upon deprotonation of chloroform on the interface generated trichloromethyl anions are introduced into organic phase as lipophilic ion pairs with TAA cation. Further processes: reversible dissociation of trichloromethyl anions into DCC and its addition to alkenes proceeds in the organic phase without contact with water and hydroxide anions [25] (Scheme 12).



Scheme 12. Mechanism of interfacially initiated generation of dichlorocarbene.

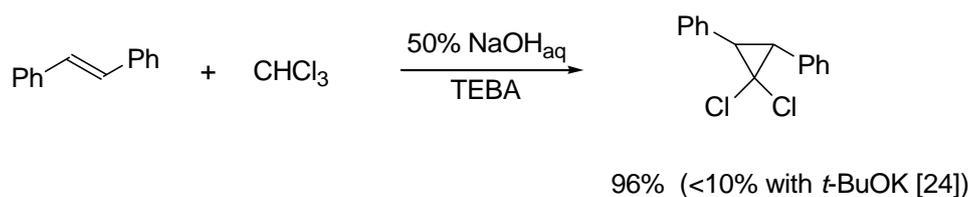
All components of this equilibrium are soluble in the organic phase, hence in the case of moderately nucleophilic alkenes the carbene can react back with chloride anion to form TAA⁺ CCl₃[−] ion pair, so it can be kept "ready for use". This was confirmed experimentally because it was shown that under

PTC conditions overall rate of the consumption of chloroform correlates with rate of the addition of DCC, therefore is a function of nucleophilicity of alkenes [26]. On the other hand, under classical conditions: treatment of chloroform with *t*-BuOK in strictly anhydrous solvent, DCC is generated irreversibly, because dissociation of trichloromethyl carbanion results in formation of insoluble KCl [24,25] (Scheme 13).

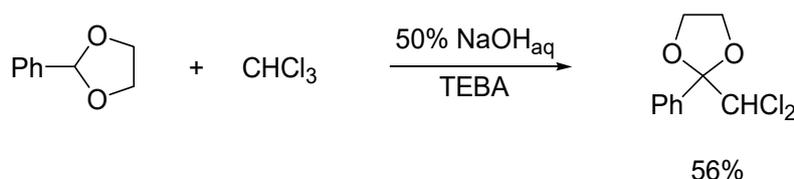


Scheme 13. Irreversible generation of dichlorocarbene under action of *t*-BuOK in anhydrous solvents.

The strongly promoted extraction mechanism, namely ion exchange between TAA chloride and sodium hydroxide producing TAA hydroxide that enter the organic phase where deprotonation of chloroform and further reactions take place, is excluded for two reasons: equilibrium of this ion exchange is unfavorable for TAA hydroxide, and particularly due to observation that attempts to use separately prepared TAA hydroxide for generation and reactions of DCC gave negative results—the carbene is mostly hydrolyzed. Reversibility of formation of DCC under PTC conditions is of particular value in the case of slow final reaction, e.g., addition of DCC to alkenes of moderate nucleophilicity [27] (Scheme 14) or insertion into CH bond [28] (Scheme 15), that thanks to PTC become synthetically useful reactions.



Scheme 14. Reversibility of PTC generation of dichlorocarbene assures high yields of its addition to alkenes of low nucleophilicity.

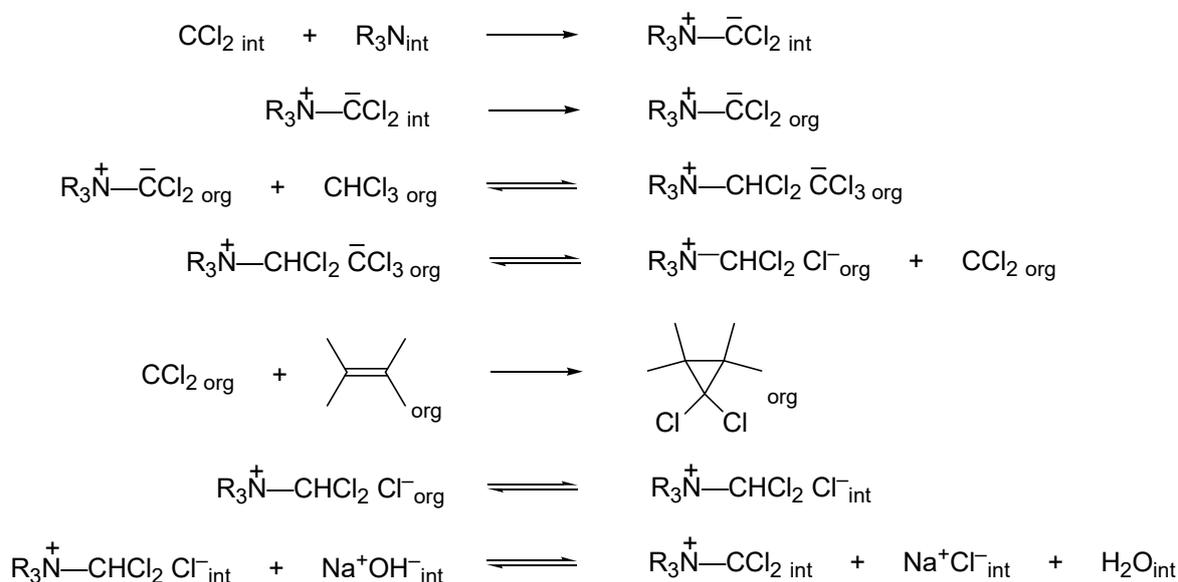


Scheme 15. Reversibility of PTC generation of dichlorocarbene assures good yields of its insertion into C-H bonds.

The PTC conditions are applicable also for generation and reactions of other dihalocarbenes: dibromocarbene, chlorofluorocarbene, bromofluorocarbene etc., from bromoform, dichlorofluoromethane and dibromofluoromethane respectively. However, the reactions of dibromochloromethane with alkenes, carried out in the presence of typical TAA salts, such as TEBA, results in the formation of a mixture of bromochloro-, dibromo- and dichlorocyclopropanes. This undesired lack of selectivity is due to reversibility of the dissociation of initially generated dibromochloromethyl anions to bromochlorocarbene and its reactions with halogen anions [26]. On the other hand, irreversible dissociation of dibromochloromethyl anions generated in the presence of potassium *t*-butoxide assures selective formation of bromochlorocyclopropanes [24].

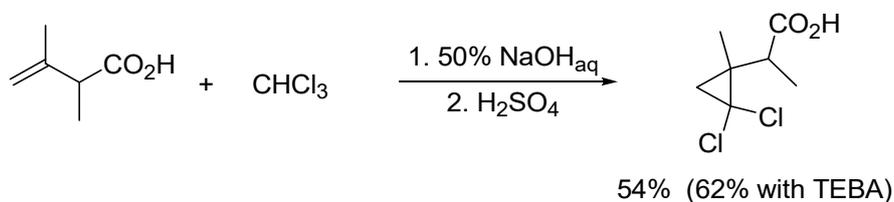
Trichloromethyl anions are generated at the interface, where they enter fast ion exchange with TAA salt to form lipophilic ion pairs that are entering the organic phase. Nevertheless, the trichloromethyl anions can also dissociate at the interface to form DCC. Interfacially located DCC has no possibility to

react with alkenes that are insufficiently active nucleophiles, however trialkylamines, much stronger nucleophiles, can react with interfacially located DCC to form the ammonium ylide. This ylide can migrate into the organic phase where it acts as a base to deprotonate chloroform. The generated trichloromethyl anion dissociates to form DCC that adds to alkenes to give dichlorocyclopropane. Trialkylamines can therefore act as catalysts in PTC dichlorocyclopropanation [29,30] (Scheme 16).



Scheme 16. Interfacially generated dichlorocarbene reacts with trialkyl amines. They can act as PT catalysts.

Interfacially generated DCC undergo also hydrolysis via reaction with hydroxide anions to produce chloride and formate anions. It should be therefore clarified why in the PTC dichlorocyclopropanation the hydrolysis is practically negligible. In the experiment: chloroform (1 mol), styrene (1 mol), TAA chloride (0.01 mol) and aqueous NaOH (excess), the first 3–5% of chloroform was hydrolyzed, subsequent dichlorocyclopropanation proceeded practically without hydrolysis [31]. It was therefore concluded that produced chloride anions of lower hydration energy than hydroxide anions accumulate at the interface and protect DCC against hydrolysis. Formation of DCC at the interface, in the absence of TAA catalysts is also confirmed by the reactions of β,γ -unsaturated acids. These acids exposed to 50% aqueous NaOH are obviously deprotonated but the sodium carboxylates cannot enter the aqueous nor organic phases. Thus, interfacially generated DCC being in close vicinity to these carboxylates adds to the double bond even in the absence of the PT catalysts. Addition of TAA salts only slightly improves the yields [32,33] (Scheme 17).



Scheme 17. Interfacially generated dichlorocarbene adds to β,γ -unsaturated acids.

5. Direct Observation of Interfacially Generated Carbanions

The presented and discussed earlier in this paper experimental verification of the interfacial mechanism of PTC reactions of carbanions generated in the presence of aqueous NaOH unambiguously confirm that the deprotonation of the carbanion precursors occurs at the phase boundary (in the

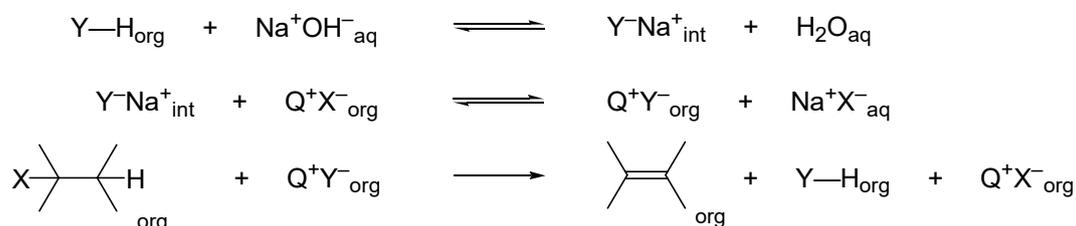
interfacial region). Such generated carbanions cannot enter the organic nor aqueous phases and remain at the interface unless the catalyst—source of lipophilic cations—is introduced. Fast ion exchange with TAA salt in the interfacial region produces lipophilic ion pairs <carbanion-TAA cation> that enter the organic phase. Interfacial mechanism of generation of carbanions under PTC conditions is confirmed by observations of the interfacial reactions.

For final confirmation of this mechanism it is necessary to perform direct observation of interfacially located carbanions. In order to achieve that, the proper surface-specific experimental method is needed. We have recently found that surface-specific spectral technique—surface second harmonic generation (SHG)—can be used after proper modification for this purpose [34]. In this technique the surface between two immiscible liquids is illuminated with focused high intensity fs-laser pulses. Then second harmonic light can be generated only from molecules situated at the interface, not in bulk (due to symmetry reasons). It allows to record the second harmonic spectra of only these species that are located at the interface. In order to use this technique for observation of interfacially generated carbanions *p*-nitrobenzylphenyl sulfide was selected as the model carbanion precursor—because of its appropriate CH acidity and because its carbanion exhibits strong light absorption in the visual region, resulting in feasibility of SHG experiments. Exposition of a solution of this CH acid in chlorobenzene to 50% aqueous NaOH does not result in coloration of the organic nor aqueous phase (proven by high spectral studies of the bulk). After illumination of the surface between two solvents by a laser beam (1030 nm) a second harmonic signal at a range 510–520 nm of substantial intensity was detected. No second harmonic signal is detected when two phase system: chlorobenzene/50% NaOH aqueous is illuminated, indicating that SH signal comes from an interfacially generated species from the sulfide. Introduction of small amount of a TAA bromide into the organic phase results in progressing of its strong coloration due to transfer of the ion pair of the produced carbanion with the TAA cation. Absorption spectra of the separated organic phase indicated maximum at 525 nm, matching to second harmonic spectra recorded earlier. It was therefore shown that the species detected by SHG at the interface is identical with the carbanion transferred into the organic phase in the form of ion pair with a TAA cation. Since the intensity of the SHG signal is proportional to the interfacial concentration of the carbanion, it was also possible to show that the interfacial basicity of aqueous KOH of the same molarity as 50% NaOH (ca 12.5 M) is much stronger (results in higher surface concentration of carbanion). Indeed, there are many observations of higher efficiency of aqueous KOH than NaOH of equal molarity for generation of carbanions under PTC conditions [35]. Similar experiments with two phase system toluene/40% aqueous tetramethylammonium hydroxide (ca 3.6 M) has shown that basicity of the interfacial region is even somewhat stronger than 50% NaOH although concentration of hydroxide anions is much lower. It was therefore shown that hydration energy of the cations associated with hydroxide anion is determining basicity of the interfacial region. This observation suggests possibility of enhancement of basicity of commonly used, inexpensive 50% aqueous NaOH. Addition of small quantities of cesium hydroxide or tetramethylammonium hydroxide should result in cocatalytic effect, leading to the enhanced phase transfer catalysis and further boost of reaction yield.

6. Phase Transfer Catalyzed Base Induced β -Elimination

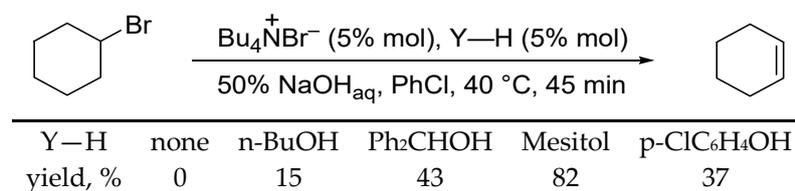
In the preceding sections the interfacial mechanism of PTC reactions in the presence of aqueous NaOH was unambiguously evidenced. Formulation of interfacial mechanism of reactions of carbanions and carbenes was based on two major circumstances, the most important of them is highly unfavorable ion exchange equilibria between hydroxide and halogen anions, hence negligible transfer of hydroxide anions into the organic phase. It was therefore well documented that transfer of hydroxide anions from the aqueous NaOH into organic phase proceeds in negligible degree. In this situation it appears that PTC cannot be an efficient tool for base induced β -elimination of hydrogen halides from haloalkanes to form alkenes. Nevertheless, there are many reports of successful PTC β -elimination of HCl and HBr in laboratory and industry ([17], pp. 420–423). It appears that these processes proceed at the interface, or by minute quantities of TAA hydroxide.

We have supposed that the problem can be solved (at least partially) by use of cocatalysts—compounds Y-H that upon deprotonation at the interface with aqueous NaOH produce lipophilic anions Y⁻ of high basicity but low nucleophilicity. These anions upon transfer into organic phase in form of ion pairs with TAA cations shall react with haloalkanes via β-elimination, not substitution pathway (Scheme 18).



Scheme 18. Concept of cocatalysis in PTC β-elimination reactions.

Using as a model reaction β-elimination of hydrogen bromide from bromocyclohexane we have tested this hypothesis taking a few alcohols and phenols as the potential cocatalysts [36]. Under standard conditions shown on Scheme 19 following degree of the β-elimination was observed.



Scheme 19. Search for efficient cocatalyst in PTC β-elimination.

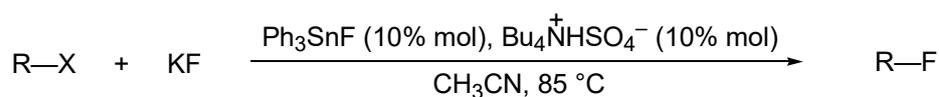
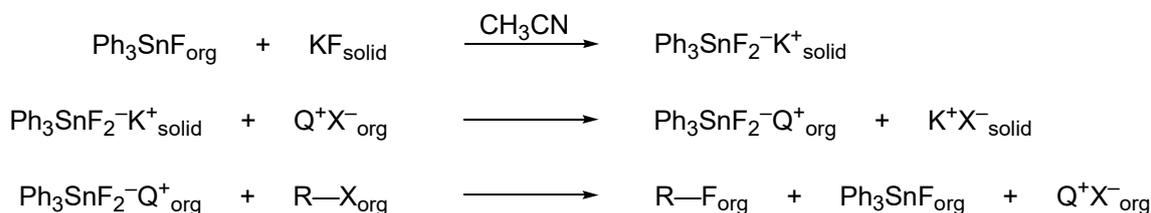
Effectiveness of the cocatalyst depends on its OH acidity and basicity of the O-anions. Thus *t*-BuOH and *n*-BuOH of low acidity are converted into anions to negligible or low degree thus are inefficient cocatalysts. On the other hand *p*-chlorophenol, a strong OH acid, is fully converted into anion but of low basicity thus is also inefficient as cocatalyst. Alcohols of higher acidity, containing aryl and perfluoroalkyl substituents are active cocatalysts. The most efficient is mesitol of reasonable OH acidity and basicity of its anion. It should be stressed that in this case ratio of competing substitution to β-elimination is 1:164. It appears therefore that mesitol, readily available product, is the most recommended cocatalyst for β-elimination. Surprisingly this simple and efficient cocatalytic variant of PTC β-elimination process has not found wider application in organic synthesis.

7. PTC Fluorination

Although this review is devoted to interfacial processes in PTC reactions induced by concentrated aqueous sodium hydroxide, it appears appropriate, following the preceding section, to present another type of cocatalytic PTC process. We would like to present this variant of PTC because it offers perhaps the most efficient solution of a difficult and important question—PT catalyzed nucleophilic fluorination. Due to high charge density and high energy of hydration, liquid-liquid PTC is not applicable for nucleophilic substitution with fluoride anions. There are a few variants of solid-liquid PTC reactions of fluoride anions used as potassium fluoride, but of limited application. The frequent disadvantage of these methods is undesired β-elimination by highly basic fluoride anions [37,38].

We have elaborated a simple and efficient way of PT catalyzed fluorination of alkyl halides or sulfonates with solid potassium fluoride using a cocatalyst—a compound Y able to associate reversibly with fluoride anion so salt of TAA with lipophilic YF⁻ can be readily transferred into the organic solution to deliver a source of fluoride anion. In the organic solution YF⁻ can dissociate to liberate highly active fluoride anions or react directly with alkyl halides or sulfonates as a source of nucleophilic fluoride.

We have found that Ph_3SnF is an efficient cocatalyst that reacts with a TAA salt and solid KF to form TAA salt of $\text{Ph}_3\text{SnF}_2^-$ anion. This salt in acetonitrile reacts with alkyl halides or sulfonates to afford nucleophilic fluorination [39,40] (Scheme 20).

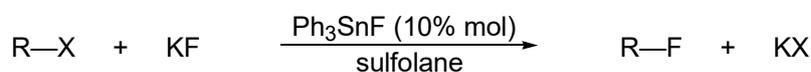
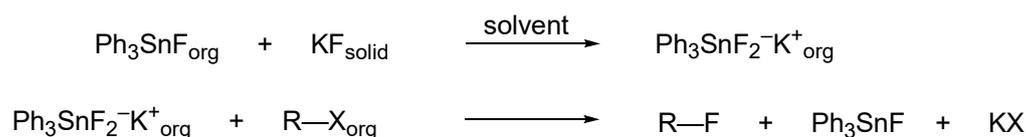


RX (yield, %): PhCH_2Br (~100), $n\text{-C}_8\text{H}_{17}\text{OMs}$ (90),
 $n\text{-C}_6\text{H}_{13}\text{CH}(\text{CH}_3)\text{OMs}$ (82), $\text{CH}_3\text{CH}(\text{OMs})\text{CO}_2\text{Et}$ (89)

Scheme 20. Cocatalytic system for PTC nucleophilic fluorination of alkyl halides and sulfonates.

It should be stressed that under these catalytic conditions the substitution proceeds efficiently also in the case of alkyl halides and sulfonates that in the reaction with free fluoride anions enter side reaction—base induced β -elimination. It appears therefore that the catalytic process does not proceed via dissociation of $\text{Ph}_3\text{SnF}_2^-$ anion to generate fluoride anions in the organic phase, but via direct reaction of the alkyl halides and sulfonates with this complex anion that does not exhibit basicity.

It should be mentioned that potassium salt of $\text{Ph}_3\text{SnF}_2^-$ anion is soluble in dipolar aprotic solvents—DMF, sulfolane etc., thus an alternative variant of PTC can be realized, in which Ph_3SnF acts as a catalyst that continuously transfers KF in form of $\text{K}^+\text{Ph}_3\text{SnF}_2^-$ into the organic solution, thus catalyze nucleophilic fluorination [41] (Scheme 21).



RX (yield, %): PhCOCH_2Br (92), $n\text{-C}_8\text{H}_{17}\text{OMs}$ (90),
 $n\text{-C}_6\text{H}_{13}\text{CH}(\text{CH}_3)\text{OTs}$ (80)

Scheme 21. New type of solid-liquid PTC for nucleophilic fluorination.

These results suggest that the system Ph_3SnX ($\text{X}=\text{F}, \text{Cl}$) and solid potassium fluoride with or without TAA halide is an efficient source of soluble, nucleophilic but not strongly basic fluoride anion.

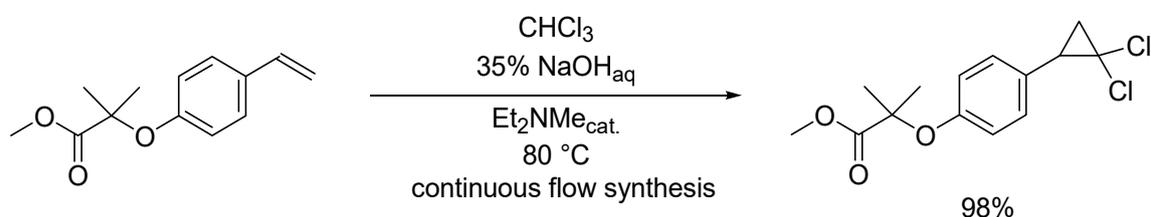
8. Effect of the Size of Interface

The key steps of PTC reactions carried out in the presence of concentrated aqueous NaOH are interfacial processes of deprotonation, therefore of crucial importance is size of the interface. In the

PTC reactions carried out under the common batch conditions size of the interfacial area depends mostly on the speed of stirring. There are a few papers in which relation of the speed of stirring with the rate of the chemical reactions was studied in order to establish mechanism of the process. Since the first step of the PTC reactions of carbanions and other anions derived from weak organic acids is interfacial deprotonation followed by ion exchange and transfer of the anions into the organic phase where they enter further reactions it appears that the observed rates of the reaction should depend on the size of the interface, hence speed of the agitation. Situation is however more complicated, because rate constant of the reaction in the organic phase can be the deciding factor. In the case of very fast reactions in the organic phase, speed of agitation can decide to some extent on overall rate of the reaction. On the other hand when the rate constant of the reaction in the organic phase is not high, overall rate can mimic zero order kinetics because concentration of the reacting anions in the organic phase is constant, whereas electrophilic reagent is in great excess. Thus, in general, kinetic of PTC reaction in two immiscible phase systems in correlation with speed of stirring, when phases are of various viscosity is in our opinion not a reliable tool for differentiation of the extraction and interfacial mechanism.

An important factor that affects efficiency of the PTC reactions of carbanions in the liquid-liquid two-phase systems is effect of the structure of the TAA cations on rate of the interfacial ion exchange and transfer of the formed lipophilic ion pairs from the interface into the bulk of the organic phase. This very complicated problem was studied and thoroughly discussed by Denmark [42].

Recently alternative approaches to assure large size of interfacial region between two immiscible liquid phases are under investigation—reactions carried out in microreactors or continuous microflow systems. Passing two immiscible liquids through narrow tubing can result in laminar or turbulent flow depending on density and viscosity of the liquids and speed of flow. Turbulent flow assures particularly large interfacial surface. This technique was successfully applied for a few reactions that proceed without a PT catalyst, and also PT catalyzed reactions, particularly for generation and reactions of dibromo- [43,44] and dichlorocarbenes [45] (Scheme 22).



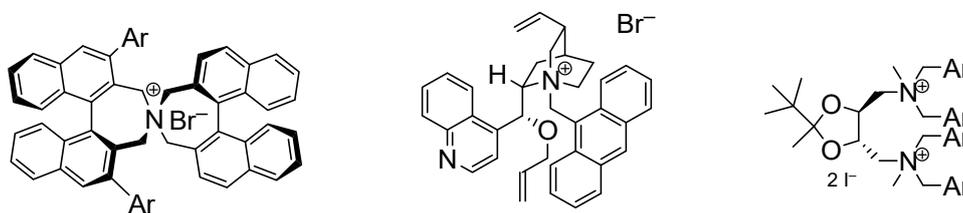
Scheme 22. Addition of PTC generated dichlorocarbene to alkenes in continuous flow system.

In these papers specific features of two phase reactions in flow systems are thoroughly discussed.

9. Asymmetric Synthesis via PT Catalyzed Reactions of Carbanions

Particularly attractive application of PTC in chemistry of carbanions is asymmetric synthesis induced by chiral TAA cations. Carbanions generated at the interface with concentrated aqueous NaOH are transferred into organic phase in form of lipophilic ion pairs with TAA cations. Chiral TAA cations can affect stereochemical outcome of the reactions of prochiral carbanions with electrophilic partners thus induce enantioselectivity. In the ion pairs carbanions are associated with TAA cations due to electrostatic forces. In the transition states of the alkylation of prochiral carbanions the negative charge is distributed on the alkylating agents, hence the differences of free energies of the diastereoisomeric transition states with chiral TAA cations become negligible and no induction is observed. The problem was successfully solved when chiral TAA cations able to enter additional association with carbanions were used. The key question is selection of the chiral TAA salts that induce high enantioselectivity of the reactions of the prochiral carbanions. The most common TAA salts that assure high enantioselectivity are quaternized cinchona alkaloids containing a variety substituents able to additionally interact with

the carbanions. Efficient PT catalysts that assure high enantioselectivity of reactions of carbanions are also spiro-bis-binaphthyl TAA salts, chiral analogues of crown ethers, bis-TAA salts synthesized from tartaric acid etc. (Scheme 23).



Scheme 23. Examples of efficient chiral PT catalysts.

Reviews of enantioselective PTC reactions catalyzed by various types of chiral catalysts are published [46–49]. A systematic search for TAA salts as efficient asymmetric PT catalysts based on quantitative structure activity-selectivity relationship was recently published [50]. Discussion in all these studies of enantioselective PT catalyzed reactions of carbanions was based on interfacial mechanism of generation of carbanions.

10. Concluding Remarks

In this short review a variety of experimental results is presented that unambiguously confirm interfacial mechanism of PTC reactions of carbanions. Thus it was evidenced that the initial step of these reactions is deprotonation of the carbanion precursor on the phase boundary between organic phase and concentrated aqueous NaOH followed by ion exchange of interfacially located carbanions and TAA salts to form lipophilic ion pairs that enter organic phase. It was also shown that basicity of the surface of the NaOH aqueous solution can be modified by presence of inorganic anions and cations. This possibility can extend applicability of the PTC reactions of organic anions.

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