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Phase transfer catalysis in dichlorocarbene chemistry: basic principles and specific features*

M. Mąkosza[a]* and M. Fedoryński[b]

[a] Institute of Organic Chemistry, Polish Academy of Sciences,
44 ul. Kasprzaka, 01-224 Warsaw, Poland.
Fax: +48 (22) 632 6681. E-mail: icho-s@icho.edu.pl
[b] Faculty of Chemistry, Warsaw University of Technology,
3 ul. Noakowskiego, 00-664 Warsaw, Poland.
Fax: +48 (22) 628 2714. E-mail: mifed@ch.pw.edu.pl

The discovery, basic mechanistic concepts, and specific features of generation and reactions of dichlorocarbene under phase transfer catalysis conditions are discussed in a concise way.

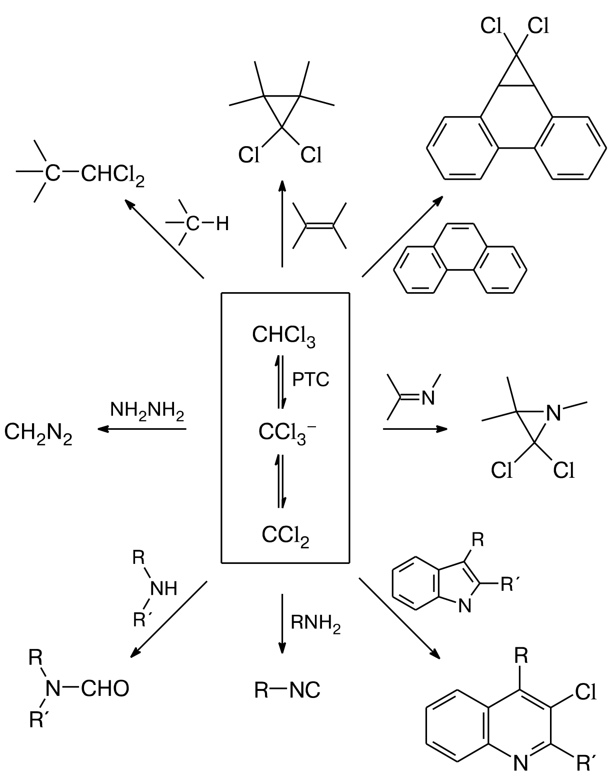
Key words: dichlorocarbene, phase transfer catalysis, *gem*-dichlorocyclopropanes, phase transfer reactions.

Phase transfer catalysis (PTC) provides a simple and efficient methodology for reactions of anionic species with lipophilic partners. PTC is particularly efficient for generation and reactions of carbanions *via* deprotonation of appropriate precursors with concentrated aqueous sodium hydroxide solutions in the presence of tetraalkylammonium (TAA) salts (see monographs and reviews[1a—i]). A large and important field of application this technology has found for generation of carbenes *via* α-elimination process, namely, generation of some α-halocarbanions which can further lose a halogen anion to form carbenes, particularly, generation of dichlorocarbene (DCC) from chloroform.[2,3]

Observation that DCC can efficiently be generated and enters a variety of reactions *via* treatment of chloroform with aqueous sodium hydroxide in the presence of TAA salts as catalysts was a major development in chemistry of carbenes[2] (Scheme 1).

It was particularly interesting that in spite of high electrophilic activity of DCC and, as a consequence, high rates of its reactions with hydroxide anions and water, reactions of DCC generated in the presence of aqueous sodium hydroxide proceed usually with organic reactants in high yields, whereas its hydrolysis is negligible. It shall be stressed that traditional methods for generation of DCC recommend use of freshly sublimed potassium *tert*-butoxide, flame-dried glassware, and strictly anhydrous solvents.[4]

Scheme 1



PTC conditions: 50% aqueous NaOH, $R_4N^+X^-$ (cat.).

The mechanism of catalytic action of TAA salts and specific features of generation and reactions of DCC under PTC conditions are reasonably well clarified (see review papers[1,3a,c,5]). However, even in recent publications and textbooks one can encounter incorrect mechanistic pictures.[6] It is therefore appropriate to pub-

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lish a short essay that presents up to date the mechanism and specific features of PTC generation and reactions of DCC.

All processes between components of two mutually immiscible liquid phases proceed initially in the interfacial region. The boundary between two immiscible phases is not a geometric surface, but a region (volume) where, due to thermal motion, components of phases A and B are in contact[1h] (Fig. 1).

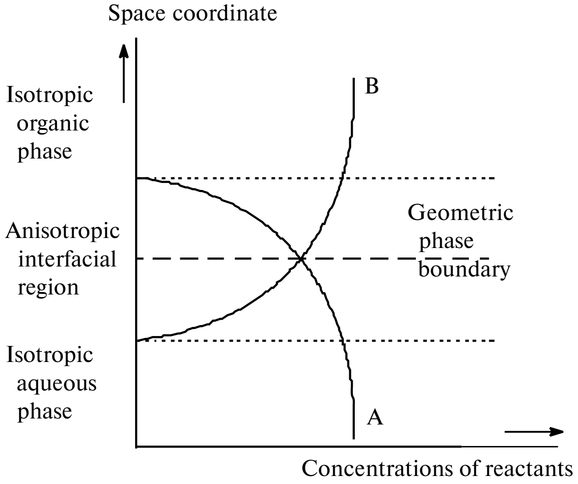


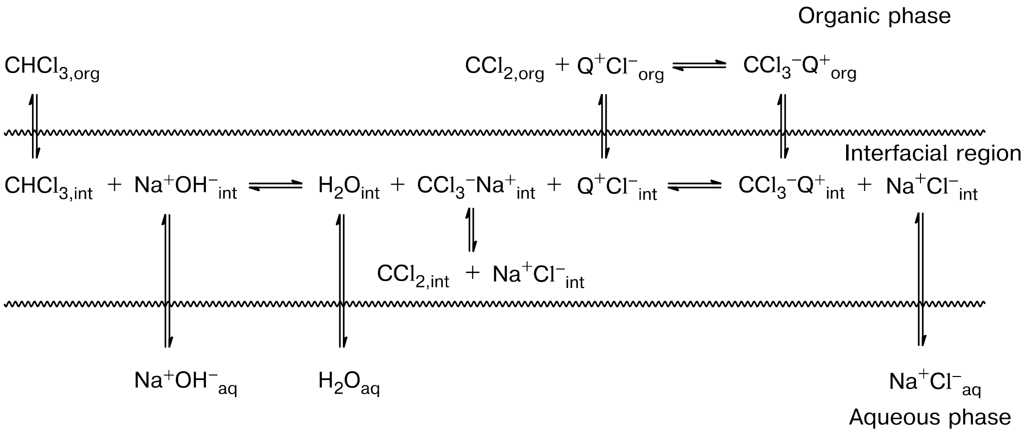
Fig. 1. Representation of the interfacial region between two immiscible phases in which there is a gradient of concentrations. Curves A and B represent concentrations of components of organic and aqueous phases, respectively.

In the anisotropic interfacial region, contrary to the isotropic bulk phases, there is a gradient of concentration. In this interfacial region, components of the immiscible phases can encounter each other and react; however, due to extremely small volume of this region and short residence time, only reactions that proceed with high rate constants can be observed.

Analyzing a particular two-phase system chloroform—50% aqueous NaOH, total mutual immiscibility of the organic and aqueous phases should be first of all mentioned due to strong salt out effect and strong binding of water by sodium cations and hydroxide anions. In fact, this "aqueous" phase is a strong desiccator and can be considered as a "liquid" NaOH. Taking into account molecular weight of water (18 Da) and NaOH (40 Da), which produces two ions, in such solutions there is roughly one molecule of water per each ion.

Since abstraction of proton from such a strong CH acid as chloroform proceeds with high rate constant, in the interfacial region trichloromethyl carbanions are generated; however, sodium salts of these carbanions cannot migrate neither to the organic nor to the aqueous phase. They can dissociate in the interfacial region to chloride anions and DCC. The latter in the interfacial region can rapidly react with water or hydroxide anions to produce chloride and formate anions. Taking into account high energy of hydration of sodium and hydroxide ions, the produced chloride anions are pushed out of the bulk of the aqueous phase and accumulate in the interfacial region. As a consequence, DCC is surrounded by these anions and is protected against further hydrolysis. Also addition of DCC to alkenes leading to *gem*-dichlorocyclopropane derivatives being a relatively slow reaction does not occur in the interfacial region. Due to this phenomenon and reversibility of the dissociation of trichloromethyl carbanions to DCC, hydrolysis of chloroform in such a two-phase system is very limited. When in such a two-phase system a TAA salt (Q^+X^-) or other sources of lipophilic cations such as alkali metal cations complexed with crown ethers are present, ion exchange, a fast diffusion-controlled reaction, proceeds in the interfacial region, so lipophilic ion pairs $CCl_3^-Q^+$ are formed. Such lipophilic ion pairs migrate into the organic phase where they dissociate to form DCC and Q^+Cl^- (Scheme 2).

Scheme 2



Since all components of the equilibrium

$$CCl_3^-Q^+ \rightleftharpoons CCl_2 + Q^+Cl^-$$

are soluble in the organic phase and in the organic phase there is no base (hydroxide anions), neither its conjugated acid (water), DCC can be kept "ready for use" for a reasonably long time, thus even its reactions with moderately active partners proceed satisfactorily.

It should be stressed that when chloroform is deprotonated with potassium *tert*-butoxide in a nonpolar solvent, according to the traditional procedures, potassium chloride formed in the reaction

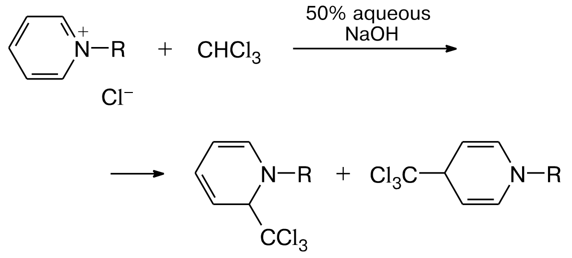
$$CCl_3^-K^+ \longrightarrow CCl_2 + K^+Cl^-,$$

is insoluble in the reaction medium, so dissociation of trichloromethyl anion to DCC and chloride anion is practically irreversible. DCC once formed under these conditions must react. Thus, when the acceptor (alkene) is of moderate activity, competing reactions between DCC and presenting *tert*-butanol or potassium *tert*-butoxide do proceed, dropping the yield of the desired product.

This general picture of generation and reactions of DCC in the presence of 50% aqueous NaOH and phase transfer catalyst is supported by a few observations.

(1) Treatment of mixtures of alkenes and chloroform with freshly generated TAA hydroxide (produced *via* ion exchange between a solution of TAA hydrogensulfate and 50% aqueous NaOH) resulted mostly in hydrolysis of chloroform, and the addition of DCC to alkenes was a minor process. This observation excluded extraction of hydroxide anions into the organic phase as the reaction pathway.

Scheme 3



(2) *N*-Alkylpyridinium salts dissolved in chloroform and treated with concentrated aqueous NaOH react with trichloromethyl anions to produce adducts in positions 2 and 4 of the pyridinium ring[7,8] (Scheme 3).

These salts treated with concentrated aqueous NaOH in toluene or chlorobenzene undergo rapid decomposition *via* the formation of unstable adducts of hydroxide anions.[8] This result strongly supports the interfacial generation of trichloromethyl anions as the pathway operating in the PTC system; therefore, the formation of TAA hydroxide ion pairs as a path for generating trichloromethyl anions can be excluded.

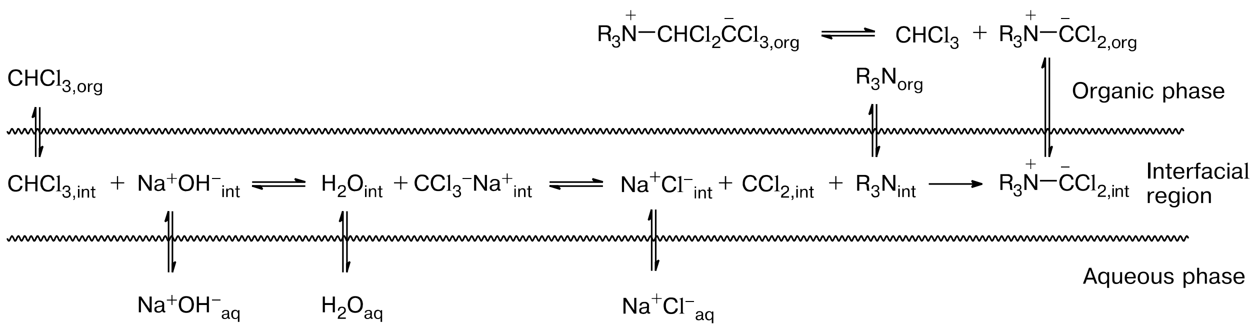
(3) Addition of DCC to alkenes of low nucleophilicity, *e.g.*, to *trans*-stilbene, proceeds much more efficiently when carried out under the PTC conditions than when freshly sublimed potassium *tert*-butoxide used under strictly anhydrous conditions. This indicates that under PTC conditions DCC is in real equilibrium with trichloromethyl carbanion thus is kept "ready for use" for a long time.

(4) When styrene and chloroform are treated with 50% aqueous NaOH in the presence of 1% benzyltriethylammonium chloride (TEBA), the hydrolysis of chloroform takes place essentially only at the beginning of the reaction, and the subsequent addition of DCC takes place with a negligible degree of hydrolysis.[9] As a consequence, addition of 3—5% sodium chloride to aqueous NaOH prevents hydrolysis of DCC.[9]

(5) Some trialkylamines catalyze efficiently the generation of DCC in the PTC system.[10] Being highly active nucleophiles, they are able to react with DCC formed in a low concentration in the interfacial region with the formation of ammonium ylides. The lipophilic ylides enter the organic phase, where they act as bases deprotonating chloroform[11] (Scheme 4).

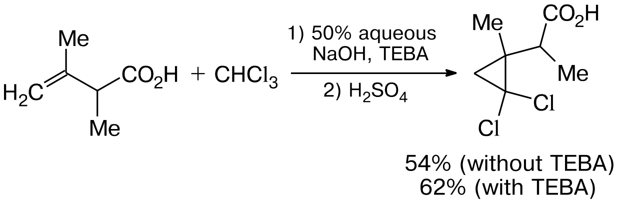
(6) Alkenoic acids bearing a double bond in the β,γ- or γ,δ-positions (not in the α,β- or δ,ε-positions) add DCC in the two-phase system chloroform—50% aqueous NaOH also without a catalyst[12] (Scheme 5). Addition of TAA

Scheme 4



salts to such systems does not affect significantly the reaction course. One can suppose that sodium salts of these acids are located in the interfacial region in such a way that the double bond is in a position enabling the addition of DCC. No doubts that such an addition can occur only in the interfacial region.

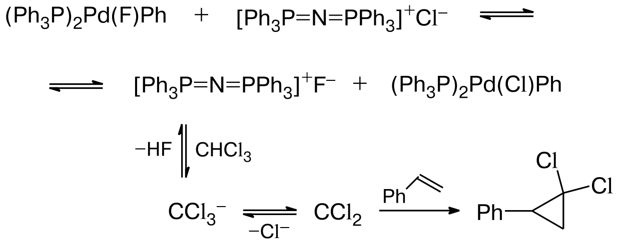
Scheme 5



TEBA is $Et_3N^+BnCl^-$

(7) Solutions of nucleophilic and highly basic "naked" fluoride anions, generated in chloroform in a ligand exchange reaction between the palladium fluoride complex $(Ph_3P)_2Pd(F)Ph$ and $[Ph_3P{=}N{=}PPh_3]^+Cl^-$, are stable at room temperature for several days (Scheme 6). After addition of an alkene, the fluoride disappeared rapidly and appropriate *gem*-dichlorocyclopropane was formed in good yields.[13] This is a good proof that equilibria between chloroform, trichloromethyl anion, and DCC in a homogeneous solution are shifted to the right only when the carbene is irreversibly trapped by an alkene.

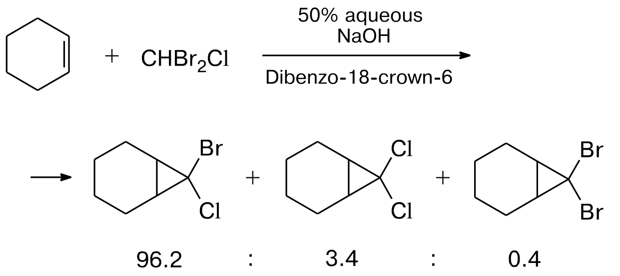
Scheme 6



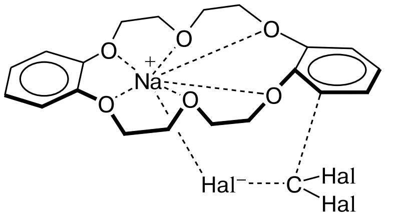
(8) The measured rate of consumption of chloroform in the two-phase system chloroform—alkene—TAA salt—50% aqueous sodium hydroxide is a function of nucleophilicity of alkenes.[14]

The presented specific features of the behavior of DCC generated in the PTC system disclose general interfacial mechanism of the catalytic process. This mechanistic picture considers the catalyst as a source of lipophilic cation regardless of more subtle effects of the catalyst nature on the fine features of the reaction course.[15] For example, PTC α-elimination from dibromochloromethane in the presence of alkenes and common lipophilic TAA salts, such as TEBA, leads to a mixture of all three possible dichloro-, dibromo-, and bromochlorocyclopropanes.[14] This is a direct consequence of the above mentioned equilibria between trihalomethyl carbanions, carbenes, and halogen anions, thus equilibrium between these species in the organic phase results in equilibration of the halogen substituents. It was found, however, that, when dibenzo-18-crown-6 was used as the phase transfer catalyst in the case of relatively active alkenes, practically pure *gem*-bromochlorocyclopropanes can be obtained in a yield of 63%[16,17] (Scheme 7).

Scheme 7



One can suppose that the presence of this crown decelerates the equilibria described earlier by the way of formation of a complex of the electrophilic carbene with electron-rich aromatic ring of the crown ether.[18] The size of the hole in dibenzo-18-crown-6 is large enough for the sodium cation to be complexed asymmetrically, which makes one of the rings richer in electrons.

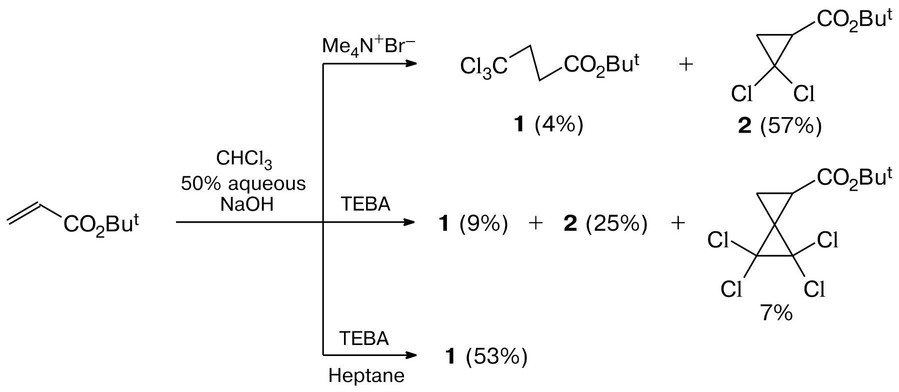


In the case of electrophilic alkenes, *e.g.*, acrylic esters, able to react with both trichloromethyl anion and DCC, it is possible to control to some extent the reaction course choosing appropriate catalyst and solvent as it is exemplified below[19—21] (Scheme 8).

Since tetramethylammonium (TMA) cations are small, $CCl_3^-Me_4N^+$ ion pairs are rather tight and inactive and, as a result, the trichloromethyl anion does not react with the Michael acceptor. However, the $CCl_3^-Me_4N^+$ ion pair may reside much further from the boundaries of the interfacial region than does the $CCl_3^-Na^+$ ion pair, and can dissociate there to dichlorocarbene, which slowly adds to the electrophilic alkene. It is also possible that the $CCl_3^-Me_4N^+$ ion pair is less stable than other $CCl_3^-TAA^+$ species and decomposes to Me_4NCl and DCC before a Michael reaction can occur.

Similar reactions of chloroform with acrylic esters carried out in the presence of TEBA and heptane as a solvent

Scheme 8



(equal of chloroform volume) led exclusively to the Michael addition products with good yields.[22] The presence of heptane solvent shifts the equilibrium

$$^{-}CCl_3Q^+ \rightleftharpoons CCl_2 + Q^+Cl^- \ (Q = BnN^+Et_3)$$

to the left. One can expect that in such a system the nonpolar solvent decreases the solubility of $Q^+CCl_3^-$ ion pair in the organic phase but its solubility is still better compared to TEBA. On the other hand, the presence of a nonpolar solvent should not exert a strong effect on the tightness of this ion pair. As ion pairs with TEBA cation are less tight than these with TMA, the trichloromethyl anion is reactive enough to add to the Michael acceptor.

In more than sixty years of history of DCC chemistry one can point out a few cornerstones of its development.

(1) Hine established the intermediacy of DCC in hydrolysis of chloroform with aqueous sodium hydroxide.[23]

(2) Doering and Hoffmann demonstrated that DCC generated by treatment of chloroform with bulky base Bu^tOK can add efficiently to alkenes giving *gem*-dichlorocyclopropane derivatives.[24] This was a starting point of application of DCC in synthetic organic chemistry.

(3) One of us introduced the two-phase method of generation of DCC by treatment of chloroform with concentrated aqueous sodium hydroxide and TAA catalyst.[2] This PTC method exerted the major impact on studies of reactions of DCC and promoted application of these reactions in organic synthesis.

(4) Nefedov developed the method of spectroscopic investigation of unstable molecules, among them is DCC trapped in low-temperature inert matrices.[25]

(5) Moss solved fundamental problems of the behavior and reactivity of DCC by preparation of 3,3-dichlorodiazirine from which DCC can be generated in the absence of any additional reagents and, hence, philicity, solvation, complexation, absolute rate constants, and activation parameters of reactions of DCC can be studied.[26,27]

We hope that this short outline of the basic principles, mechanism, and specific features of phase transfer generation of dichlorocarbene will help researchers to select proper conditions for efficient use of this technique and proper interpretation of the results and refresh interest in this fascinating field. We also hope that some incorrect schemes that are still present in textbooks will be eliminated.

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