

Phase-transfer catalysis. A general green methodology in organic synthesis*

Mieczyslaw Makosza

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland

Abstract: Basic concept of phase-transfer catalysis (PTC), its field of applications and specific features as the most general, efficient, and environment-friendly green methodology of organic synthesis, particularly for industrial processes, is discussed.

Organic synthesis is the principal way to produce chemical products of practical applications such as pharmaceuticals, plant protection agents, dyes, photographic chemicals, monomers, etc. Transformations of starting materials into desired final products usually require a number of chemical operations in which additional reagents, catalysts, solvents, etc. are used. Thus, in the course of synthesis, besides the desired products, many waste materials are produced because transformations of educts into products are not quantitative and selective processes, particularly due to the use of these additional components. These wastes should be regenerated, destroyed, and disposed, consuming much energy and creating heavy burden on the environment. It is therefore of great importance to develop and use synthetic methodologies that minimize these problems. Perhaps one of the most general and efficient methodologies that fulfill this requirement is phase-transfer catalysis (PTC) [1].

This methodology is applicable to a great variety of reactions in which inorganic and organic anions and also carbenes react with organic substrates. It consists in use of heterogeneous two-phase systems—one phase being a reservoir of reacting anions or base for generation of organic anions, whereas organic reactants and catalysts (source of lipophilic cations) are located in the second, organic phase. The reacting anions are continuously introduced into the organic phase in the form of lipophilic ion-pairs with lipophilic cations supplied by the catalyst. Most often tetraalkylammonium cations serve this purpose.

Reactions to which PTC is applicable can be divided into two major categories:

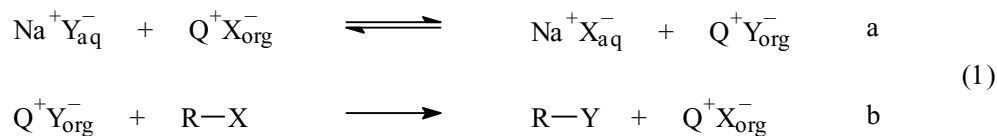
1. Reactions of anions that are available as salts, for example, sodium cyanide, sodium azide, sodium acetate, etc.
2. Reactions of anions that should be generated *in situ*, such as alkoxides, phenolates, N-anions of amides or heterocycles, etc. and particularly carbanions

In the former case the salts are used as aqueous solutions or in the form of powdered solids, whereas the organic phase contains organic reactants neat (when liquid) or in appropriate solvents. Since the phases are mutually immiscible the reaction does not proceed unless the catalyst, usually a tetraalkylammonium salt, Q^+X^- is present. The catalyst transfers continuously reacting anions into the organic phase in form of lipophilic ion-pairs produced according to the ion-exchange equilibrium (1a), where they react further, for example, with alkyl halides affording nucleophilic substitution (1b).

A variety of other reactions with participation of inorganic anions such as addition, reduction, oxidation, etc. is efficiently executed using this methodology.

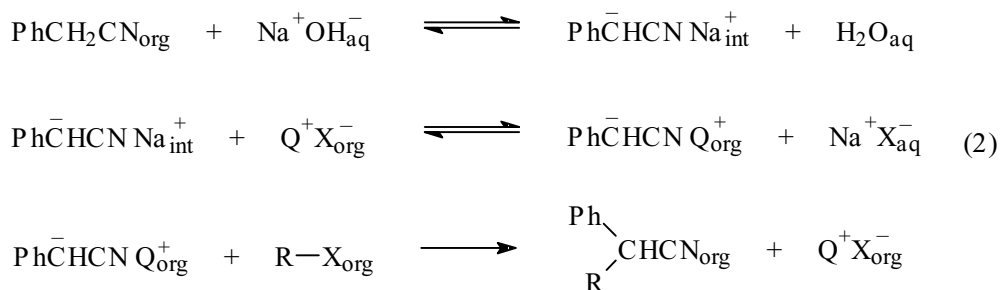
Phase-transfer catalyzed reactions of organic anions are mechanistically more complicated. In these cases the inorganic phase contains base such as conc. aqueous or solid NaOH or KOH or solid K_2CO_3 , whereas the organic phase contains the anion precursor, an electrophilic reactant and eventually

*Pure Appl. Chem. Vol. 72, No. 7, 2000. A special topic issue on green chemistry.

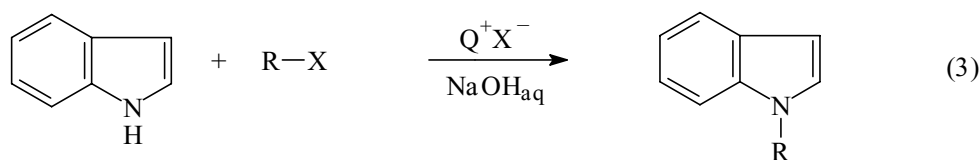


a solvent [1,2]. Alkylation of phenylacetonitrile via reaction of its carbanion with alkyl halide exemplifies application of this methodology and helps to describe how the system operates.

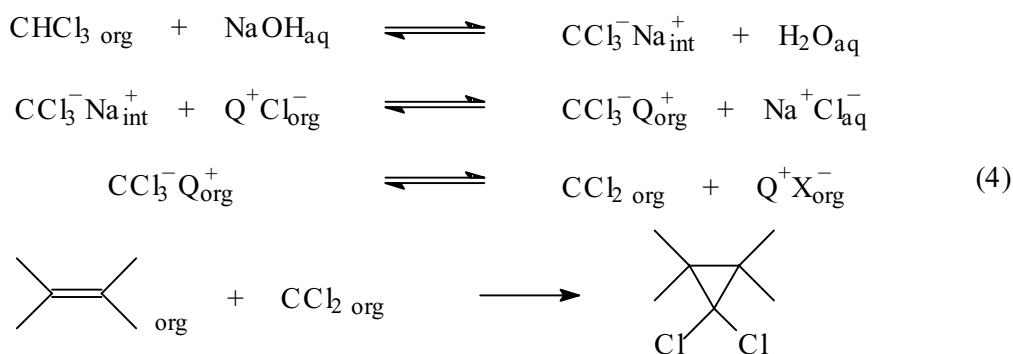
No reaction occurs when a mixture of phenylacetonitrile, an alkyl halide and 50% aq. NaOH is vigorously stirred. Upon introduction of a tetraalkylammonium halide in a catalytic amount, usually 1% molar, exothermic reaction produces phenylalkylacetonitrile [3]. The process follows eq. 2 where subscripts: org, aq, int, denote organic and aqueous phase and interfacial region.



In a similar way numerous other CH acids, alcohols and NH acids are efficiently alkylated as exemplified with N-alkylation of indole eq. 3 [4].



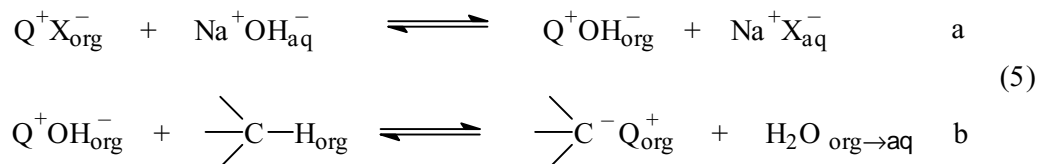
Under similar conditions dihalocarbenes and some other carbenes can be generated via α -elimination and introduced into a variety of reactions [2,3].



On the basis of numerous reports it is evident that phase-transfer catalysis is the most efficient way for generation and reactions of these and similar active intermediates [1].

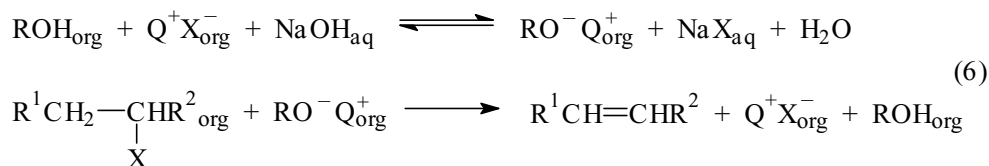
This methodology is efficiently applicable to a plethora of other base-induced reactions of organic anions, particularly carbanions, such as the Darzens, Wittig and Michael reactions, generation and reactions of sulfonium ylides etc [1,2].

It should be stressed that generation of carbanions or other organic anions does not proceed via ion exchange of type (5a) followed by deprotonation of the carbanion precursor in the organic phase (5b) because ion exchange equilibrium (5a) for $X^- = Cl^-$ and Br^- is strongly shifted to the left, hence concentration of Q^+OH^- in the organic phase is negligible. It was well documented that deprotonation of the corresponding precursors takes place at the phase boundary [6].



Since dihalocarbenes are known to react rapidly with OH^- and water it is evident that they are generated in the organic phase where OH^- and water is absent, as shown in eq. 4.

Although OH^- anions can not be continuously transferred into the organic phase as Q^+OH^- when halide anions are present, PTC can also be used for base-induced β -elimination of HX from haloalkanes, particularly when cocatalysts such as some alcohols or phenols are used [1,7].



It should be also stressed that PTC has found wide application in organometallic chemistry, for example in metal-catalyzed carbonylation of alkyl or aryl halides [8].

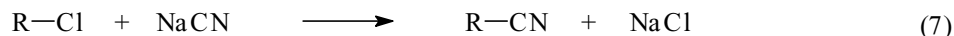
This very limited list of examples of application of PTC in organic synthesis is evidence of its generality and effectiveness.

Since in PTC reactions concentration of the reacting anions in the organic phase cannot exceed that of the catalyst, in a great majority of cases they can be carried out without an organic solvent.

Indeed, when the starting materials and products are liquid they can act as solvents for the reacting species and form the organic phase when used neat, into which the reacting anions are introduced by the catalyst. Taking into account that the catalyst is used in amounts ca. 1% molar, the reactions proceed in diluted system in respect to the reacting anions, although no solvent is used. Since anions associated with tetraalkylammonium cations exhibit high activity and since concentration of the partner reacting with the anions (when it is used neat) is high, the reactions proceed in good rates. Due to this situation PTC reactions proceed usually in high yields and selectivity, whereas undesired side-products are produced in low quantities.

Application of PTC instead of traditional technologies for industrial processes of organic synthesis provides substantial benefits for the environment. These benefits are best presented when particular examples are discussed. The discussion here will be limited to two representative examples.

Cyanation of alkyl chlorides—a major way to produce nitriles according to eq. 7.

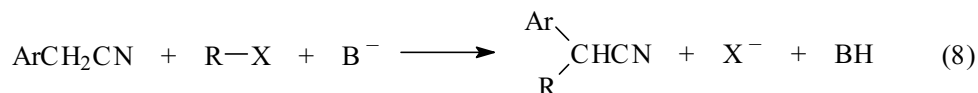


Since R-Cl and NaCN are mutually immiscible, traditionally solvents are used for homogenization (at least partial) of the system necessary for the reaction to proceed. The process is usually carried out in lower alcohols—water mixtures, where, due to strong solvation of the anions, the reaction is rather slow and requires prolonged heating. Isolation of the product needs separation from the solvent, which should be recovered, and wastes, which are produced in substantial quantities, destroyed and disposed. The reaction proceeds much faster in dipolar aprotic solvents such as DMF or DMSO, but isolation of the product and recovery of the solvents is even more troublesome.

In the PTC methodology neat alkyl chloride containing ~1% molar of the catalyst is stirred with saturated solution of NaCN in water. Upon completion of the reaction the organic phase, which is often the pure product, is separated and the product can be subsequently purified or used in the further steps as such. The aqueous phase upon separation of solid NaCl formed, and introduction of fresh NaCN can be used again for the reaction with R-Cl, so the only waste is solid NaCl.

Alkylation of arylacetonitriles to produce α -arylalkanenitriles is an important process for pharmaceutical industry. It proceeds in general according to eq. 8.

Traditional technologies for this transformation are multistep processes. First, the starting nitrile dissolved in a strictly anhydrous solvent (e.g., toluene) is treated with a strong base such as NaNH_2 or NaH to produce intermediate carbanion in the form of its salt with Na^+ . This preformed sodium derivative (carbanion) treated with an appropriate alkyl halide gives the final product. Isolation of the product needs treatment of the mixture with water and removal of the solvent, which should be subsequently regenerated. The overall process needs large investment—also connected with safety requirements due to work with NaNH_2 or NaH , and the necessity to keep anhydrous conditions consumes much energy and large quantities of wastes are produced.



The same process executed using PTC technology as shown in eq. 2 consists of vigorous stirring of neat ArCH_2CN and R-X with 50% aqueous NaOH and ca 1% molar of the catalyst. It proceeds with moderate exothermic effect and upon completion the product is isolated just by simple separation of the phases, eventually upon slight dilution with water. This methodology needs much less investment, consumes much less energy, and wastes are produced to much smaller extent, particularly taking into account that due to high selectivity of the process, yield of the final products are usually much higher than when traditional methodology is used.

One should stress that the first industrial application of this green technology for alkylation of the nitrile was in a Polish pharmaceutical factory in the early 1960s; it was subsequently used in many other companies.

These two representative examples of application of PTC in industrial processes disclose substantial advantages in comparison with traditional technologies. There are hundreds other industrial applications of PTC for a variety of processes of organic synthesis. Always these technologies require less investments, consume less energy, and generate much less industrial wastes as compared to the traditional ones. It is obvious that all measures which save energy and investments offer directly or indirectly

substantial benefits to the environment. Of great importance is direct effect—generation of smaller volume of wastes. Major advantages of PTC in industrial applications are listed below.

- elimination of organic solvents
- elimination of dangerous, inconvenient, and expensive reactants (NaOH, KOH, K_2CO_3 , etc. instead of NaH, $NaNH_2$, t-BuOK, R_2NLi , etc.)
- high reactivity and selectivity of the active species
- high yields and purity of products
- simplicity of the procedure
- low investment cost
- low energy consumption
- possibility to mimic counter-current process
- minimization of industrial wastes

These numerous and important advantages of PTC are easily recognized in the given examples. One shall stress that when a new synthetic process is developed, the possibility to apply PTC should be considered first. Due to the specific features of PTC and its advantages presented above it should be considered as a most efficient and general green technology.

REFERENCES

1. M. Makosza and M. Fedorynski. *Adv. Catal.* **35**, 375 (1987); E. V. and Dehmlow, S. S. Dehmlow. *Phase-Transfer Catalysis*, 3rd ed.; Verlag Chemie, Weinheim 1993; C.M. Starks, C. L. Liotta, M. Halpern. *Phase Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman & Hall, New York (1994).
2. M. Makosza and M. Fedorynski. In *Handbook of Phase Transfer Catalysis*, Y. Sasson, R. Neumann (Eds.), Chapman & Hall, London (1995).
3. M. Makosza and A. Jonczyk. *Org. Synth.* **55**, 91 (1976).
4. V. Bocchi, G. Casnati, A. Dossena, V. Villani. *Synthesis*, 414, 124 (1976).
5. M. Makosza and M. Wawrzyniewicz. *Tetrahedron Lett.* 4659 (1969).
6. M. Makosza. *Pure Appl. Chem.* **43**, 439 (1975); A. Jonczyk, A. Kwast, M. Makosza. *Chem. Comm.* 902 (1977); R. Solaro, S. D'Antone, E. Chielline. *J. Org. Chem.* **45**, 4179 (1980); M. Makosza and I. Krylova. *Tetrahedron* **55**, 6395 (1999).
7. M. Makosza and W. Lasek. *Tetrahedron* **47**, 1283 (1991). M. Makosza and A. Chesnokov. *Tetrahedron*, **56**, 000 (2000).
8. H. Des Abbayes, A. Buloup, G. Tanguy. *Organometallics* **2**, 1730 (1983).
9. C. M. Starks. *J. Am. Chem. Soc.* **93**, 195 (1971).