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Review

Fluorous phase transfer catalysts: From onium salts to crown ethers

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ABSTRACT

Fluorous quaternary ammonium and phosphonium salts, as well as fluorous macrocyclic ligands, such as crown and aza-crown ethers, have been gradually emerging as viable alternatives to classical phase transfer catalysts. The major results thus far obtained in this burgeoning field will be the focus of this review.

Contents

1. Introduction

Phase transfer catalysis (PTC) was first introduced in the 1960s, as a tool to efficiently perform reactions between water soluble inorganic reagents and organic substrates, dissolved in mutually immiscible liquid phases [1–3]. Since that period, PTC has received widespread attention, and it still has attracted considerable scientific and practical interest. Moreover, the term PTC encompasses several different techniques characterized by operational simplicity, mild conditions, high reaction rates, high selectivity, and the utilization of inexpensive reagents. These techniques have been widely applied in industry for the synthesis of pharmaceuticals, perfumes, flavorants, dyes, agricultural chemicals, monomers, polymers, and for many other applications [4,5].

PTC processes still have great potential for waste reduction and catalyst reuse. Indeed, removal of traditional phase transfer (PT) catalysts from the reaction mixture can be achieved by solvent extraction, distillation, adsorption, or simply by washing the organic phase with copious amounts of water. In most cases, such PT catalysts have not been recovered from the effluents, or, once recovered, they have not been pure enough, and have been disposed of as waste, thus increasing the process costs and reducing the otherwise remarkable environmental benefits of the PTC approach. Heterogeneous PT catalysts, bound to either an insoluble polymer or an insoluble inorganic support, have been developed in order to overcome these problems [6]. They can be

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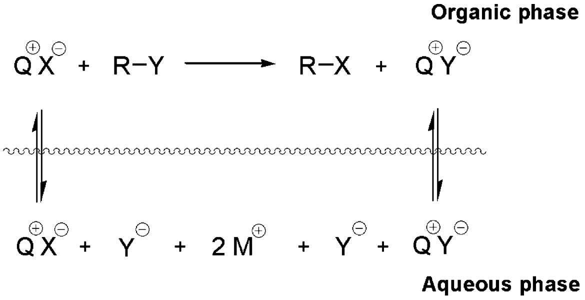
easily separated from reaction products by simple filtration and then reused; but unfortunately, their broad application has been limited by the fact that most PTC reactions are much slower with insoluble catalysts due to mass transfer limitations. More importantly, most solid-bound catalysts have not been found to be mechanically robust enough to survive repeated reaction/separation cycles. As an alternative, immobilization of PT catalysts on soluble polymers, such as poly(ethylene glycol)s (PEGs), has been proposed [7]. Reactions can be performed under standard PTC conditions, after which, selective precipitation of the supported catalyst was induced by thorough dilution of the organic phase with an additional solvent, showing little affinity for the polymer matrix (e.g. Et_2O in the case of PEGs). This method showed some limitations as well, in particular, large amounts of extra solvent have been required in the precipitation step, and also for the efficient washing of the crude precipitate.

In this review, the recent advances on the ease of recovering and recycling PT fluorous catalysts will be discussed. Potential advantages associated with the use of an additional fluorous liquid phase in PTC will also be a focus of this review.

2. Basic PTC concepts

Although the mechanisms and a manifold of applications for PTC were illustrated in detail in several comprehensive books [4,5,8,9] and reviews [10–18], some important key issues are worth further discussions. Many organic reactions entail anionic reactivity, which, especially on the laboratory scale, were enhanced by using dipolar aprotic solvents, such as hexamethylphosphoramide, dimethylsulphoxide, or dimethylformamide. These solvents have been found to be excellent for most organic substrates and, at the same time, they are able to dissolve inorganic salts by selectively solvating the cation, while the unsolvated anion becomes highly reactive [19]. However, dipolar aprotic solvents can be highly toxic and generally exhibit high boiling points and water solubility, making their recovery and the separation of products rather difficult. In PTC, anionic activation was achieved by decreasing the coulombic interaction with the cation, but also through solubilization of the reactive ionic couple in a low polar environment, usually a solution of the organic substrate in a halogenated or hydrocarbon solvent, or the neat liquid substrate itself. The PT catalyst fulfills both functions by forming organophilic ion-pairs, Q^+X^-, in which Q^+ was either a bulky organic cation (e.g. tetraalkylammonium or tetraalkylphosphonium), or the positively charged alkali metal complex of a neutral ligand (e.g. crown ether, PEG), while X^- was the reactive anion. The large size accounts for the low charge density on the surface of the cations: accordingly, interactions with the anion were strongly reduced. The extent of anion extraction into the organic phase, and its reactivity, has depended on a combination of many parameters, including the nature of the anion; for example, charge, size, polarizability, etc. Moreover, the concentration of the inorganic salt in the aqueous phase, the dielectric constant of the organic solvent, the separation between cation and anion in the ion-pair, and the number of water molecules associated with the anion in the organic phase, were also found to be important parameters.

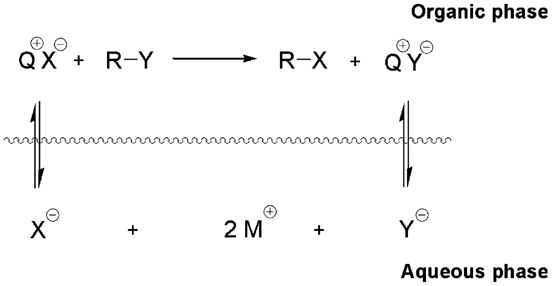
In typical PTC reactions, anions were introduced in a multiphase system under the form of inorganic salts, or they could be generated from an organic precursor possessing an acidic X–H bond under the action of a base. The first general PTC mechanism (Scheme 1) was proposed by Starks, who studied a representative liquid–liquid, aqueous–organic PTC process; namely, the reaction of 1-chlorooctane (RY) and aqueous NaCN (MX) in the presence of $(C_6H_{13})_4N^+Cl^-$ (Q^+Y^-). [3] It was assumed that the PT catalyst, Q^+Y^-, partitioned between the two immiscible liquid phases, should first react in the aqueous phase with CN^- to provide the active species, $(C_6H_{13})_4N^+CN^-$ (Q^+X^-). In this manner, the reacting anion, CN^-, was transferred from the aqueous to the organic phase, where the reaction occurred, and the catalyst was regenerated. The product anion, Cl^-, was then released into the aqueous phase (Scheme 1).



Scheme 1.

It is important to note that this was not the exclusive pathway through which PTC reactions could proceed. Indeed, depending on the nature of the catalyst, the multiphase system employed, and the reaction under investigation, other mechanisms must be taken into account. As an example, Montanari and coworkers demonstrated that under a given set of reaction conditions, the catalytic efficiency of a quaternary onium salt in liquid–liquid PTC increased with its solubility in the organic phase [20]. Based on this observation, and on the independent work of Brändström [21], a revision of the original Starks mechanism was proposed (Scheme 2). Accordingly, the anion transfer does not necessarily require the partitioning of the quaternary cation, while the electroneutrality in the organic and aqueous phase was ensured by the quaternary and the metal cations, respectively [22]. In this case, the anion exchange between the catalyst, Q^+Y^-, and the source of reacting anion, M^+X^-, occurred at the interface, and the following reaction between Q^+X^- and the substrate RY occurred in the bulk organic phase. This modified PTC mechanism can also be applied when lipophilic cyclic and acyclic polyethers were used as catalysts under liquid–liquid PTC conditions.

An interfacial reaction mechanism proposed by Mąkosza was also generally thought possible for liquid–liquid PTC reactions, where aqueous solutions of alkali hydroxides, M^+OH^-, were used to generate the reactive organic anions from weakly acidic substrates, SH (Scheme 3) [23]. As confirmed by extraction experiments, the transfer of OH^- into the organic phase by lipophilic onium salts was hampered by the exceedingly high hydrophilicity of the anion. Alternatively, abstraction of a proton at the aqueous–organic interface was possible, but the resulting ion-pair, M^+S^-, was unable to leave the phase boundary, since M^+ cannot be extracted into nonpolar organic solvents, while solubility of S^- in the concentrated M^+OH^- solution was negligible. The ion exchange with a PT catalyst allowed the formation of a



Scheme 2.