Mechanism of Phase-Transfer Catalysis & Relevance to PTC Process Development

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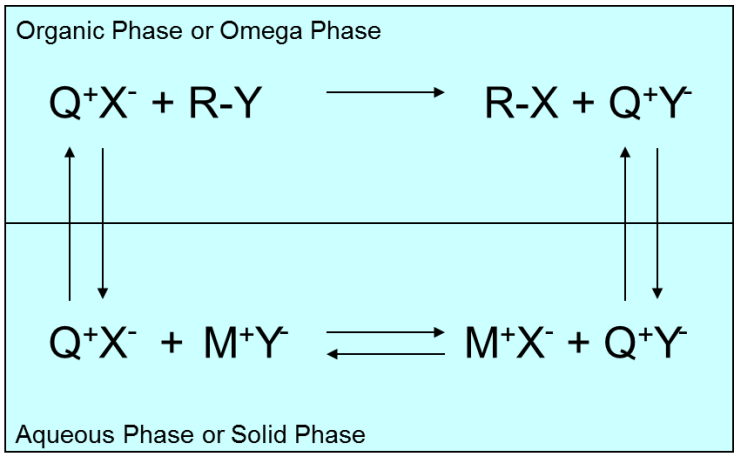
It is important to understand the mechanism of phase-transfer catalysis not only because it is academically interesting but because optimal choice of PTC reaction conditions to achieve the highest process performance is determined by the identity of the rate determining step. Let's examine the mechanism of phase-transfer catalysis to assure resource-efficient process R&D.

The simplified mechanism of a typical PTC reaction (a nucleophilic substitution) is shown in Figure 1. This mechanism was first published by Charles Starks, an industrial chemist at DuPont, in 1971. Dr. Starks coined the term "phase-transfer catalysis"" and he called this mechanism the "Extraction Mechanism."

Figure 1: The Extraction Mechanism of Phase-Transfer Catalysis[1]



In the extraction mechanism shown in Figure 1, a substitution reaction is being performed between a nucleophilic anion, X^-, and an organic substrate R-Y to form the product R-X and a leaving group, Y^- which is a waste material.

Since the source of many nucleophilic anions, bases, oxidants and reductants is very often an inorganic salt that does not readily dissolve in organic solvents, it is often difficult or sometimes nearly impossible to successfully react X^- with R-Y. Two classical non-PTC solutions to the problem of phase immiscibility are [1] use undesirable co-solvents such as DMSO, DMF or NMP that are hard/expensive to recover/recycle and [2] use emulsifiers to increase interfacial surface area to promote reaction at the interface, but that suffers from emulsions at the end of the reaction that are hard to break and often render the process not feasible due to the inability to separate the product from the messy reaction matrix.

The elegant solution of phase-transfer catalysis is to use a phase-transfer catalyst, often a quaternary ammonium cation, Q^+, such as tetrabutyl ammonium (Bu_4N^+) that has many carbons that impart organophilicity to the ion pair with X^-. The somewhat organophilic ion pair Q^+X^- can then distribute between the aqueous phase and organic phase in an equilibrium process. Once a portion of the X^- in the system is transferred into the bulk organic phase by the Q^+, it reacts with enhanced reactivity with R-Y due to three reasons (reverse order of importance): [1] Q^+X^- is often a much looser ion pair than the Na^+X^- source of the anion, [2] X^- is located right next to R-Y in the organic phase and does not have "jump" through an interface to react and [3] when X^- is transferred into a non-polar organic phase, its reactivity is

[1] Starks, C. J. Amer. Chem. Soc., **1971**, *93*, 195

not hindered by hydration (hydrogen bonding) that is usually the #1 factor that reduces the nucleophilicity of nucleophiles, the basicity of bases and the general accessibility of oxidizing agents and reducing agents to the substrates in redox reactions.

In the vast majority of PTC reactions, the reaction in the organic phase is irreversible. This is true for direct nucleophilic substitutions such as cyanide-chloride exchange; most base-promoted reactions such as C-, N-, O-, S-alkylations, dehydrohalogenations, Michael or aldol condensation; most oxidations such as hypochlorite oxidation of alcohols and most reductions such as borohydride reduction of ketones.

When examining the diagram of the extraction mechanism, it becomes clear that there are several possibilities for the identity of the rate determining step of the entire phase-transfer catalysis process. From a practical standpoint, it turns out that the vast majority of PTC reactions are limited by either the **transfer** of Q^+X^- from the aqueous or solid phase or by the **intrinsic reaction** of Q^+X^- with R-Y in the bulk organic phase. When the reaction is transfer rate limited, we call the PTC reaction a "T-Reaction". When the reaction is intrinsic reaction rate limited (i.e., the rate determining step is the productive chemical collision in the bulk organic phase), we call the PTC reaction an "I-Reaction."

While understanding the rate determining step of a PTC system may seem like an academic mental exercise, the reality is that it has very significant ramifications on the magnitude of the profit of a commercial PTC process. Recognizing the identity of T-Reactions and I-Reactions also has impact on the development cycle time which is so crucial to achieve effective and resource-efficient R&D. Sometimes, the lack of understanding of the rate determining step of a PTC process leads to nearly random choices of reaction conditions which in turn sometimes results in incorrectly concluding that the PTC process option is not feasible with a final outcome of companies missing huge profit opportunities.

The Importance of Leveraging PTC I-Reaction vs PTC T-Reaction

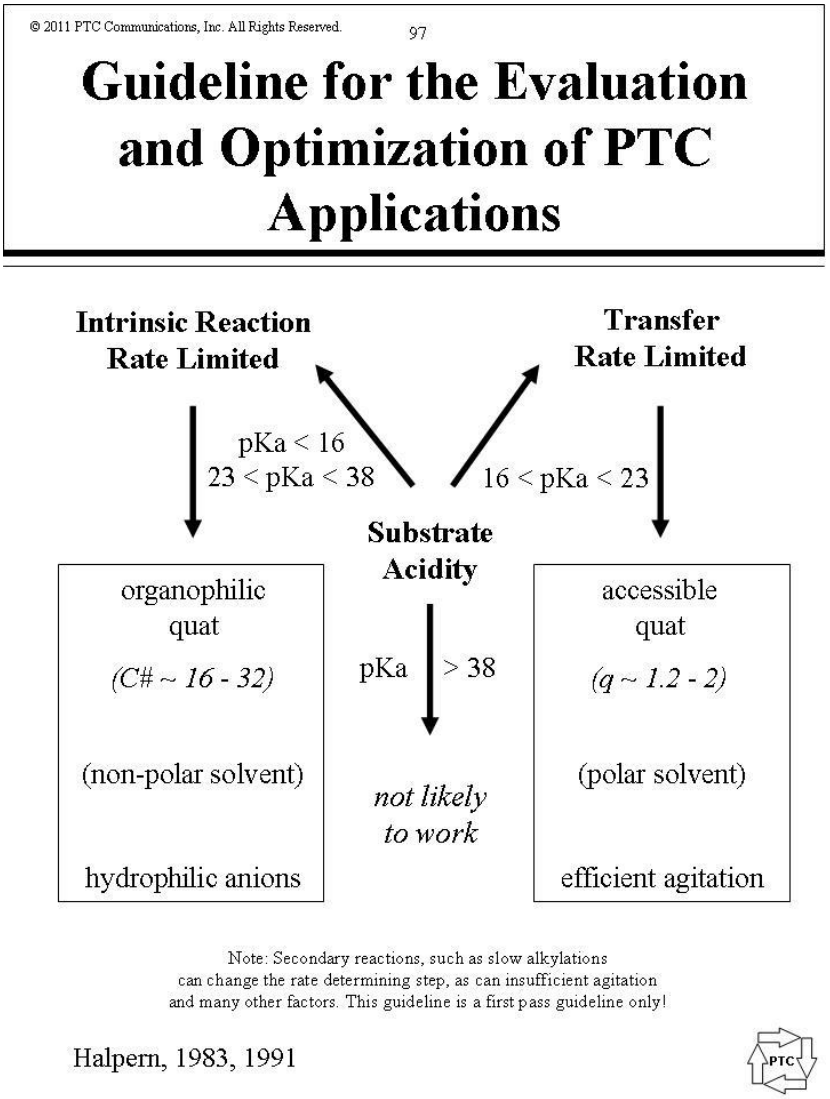
The optimum conditions for a given PTC reaction to achieve the highest performance are often opposite for I-Reactions and T-Reactions. This can be a very crucial concept and it is very often overlooked. According to the "Halpern pKa Guidelines for Evaluation and Optimization of PTC Applications",[2] I-Reactions benefit from more organophilic quats, less polar solvents that reject water, using leaving groups that are more hydrophilic and are not sensitive to agitation efficiency above a relatively low minimum required for minimal mass transfer and sufficient heat transfer. In contrast, according to these guidelines, T-Reactions benefit from more "accessible" quats,[3] especially those containing one methyl group (one only) with three butyl groups or larger or 2-3 ethyl groups with 1-2 butyl groups or larger, very efficient agitation to increase interfacial surface area, more polar solvents that form two phases with water and less sensitivity to the identity of leaving groups.

The pKa guidelines further suggest that one should look at the pKa of the conjugate acid of the anion being reacted to get a first pass estimate of whether the PTC reaction is likely to be a T-Reaction or an I-Reaction, even before running the first reaction or doing a comprehensive kinetic study. For example, if one is performing a base-promoted reaction such as C-alkylation in which the substrate before deprotonation has a pKa in the range of 16-23 (such as methylene groups activated by ketones, sulfones, nitriles, certain benzylic groups, many heterocycles, etc.), then the reaction is likely (not guaranteed) to be a T-Reaction. This means that screening should begin with the set of conditions suggested for T-Reactions such as using "accessible" quats,[3] non-polar solvents and very efficient agitation. In contrast if one is performing a nucleophilic substitution with common inorganic anions such as cyanide or anions formed by deprotonation of acidic O-H groups, such as phenoxide from phenol or carboxylate from carboxylic acids, then these PTC reactions are between anions from conjugate acids with pKa's of under 16 and are likely to be I-Reactions. This means that screening should begin with organophilic non-accessible quats, non-polar solvents, care to avoid over-agitation (especially if water-sensitive compounds are used or generated!) and avoid highly polarizable leaving groups such as iodide and tosylate.

[2] Halpern, M.; Ph.D. Dissertation, **1983**, Hebrew University of Jerusalem
[3] Halpern, M.; Sasson, Y.; Rabinovitz, M.; *Tetrahedron*, **1982**, *38*, 3183

Many chemists choose middle-of-road PTC reaction conditions when they are not aware of the pKa guidelines. This often means choosing a quaternary ammonium phase-transfer catalyst such as tetrabutyl ammonium, that is not overly organophilic nor bears an overly accessible positive charge on the central nitrogen. They choose whatever solvent is convenient and use whatever agitation happens to be comfortable in the lab and don't give much more thought to agitation since it will change anyway upon scale up. All too often, this leads to non-optimal performance and lost profit opportunity.

Figure 2: Halpern pKa Guidelines for the Evaluation and Optimization of PTC Applications



When multiple consecutive PTC reactions are used, which is a great way to streamline processes and reduce cost of manufacture, it is helpful to recognize whether the PTC reactions are all T-Reactions or I-Reactions. If they are, then PTC reactions are easier to choose. If they are not, adjustments and compromises must be made.

There are other considerations to take into account when choosing PTC process parameters, especially choices that affect catalyst separation and isolation of product during workup (e.g., choice of reaction solvent, catalyst organophilicity, etc.) and catalyst stability in the reaction matrix. These considerations are usually addressed in the stage of development that follows the initial screening experiments.