

Industrial Phase-Transfer Catalysis

formerly Phase-Transfer Catalysis Communications

Top 10 Opportunities To Improve Process Performance and Profit Using Phase-Transfer Catalysis

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Summary: Phase-Transfer Catalysis offers dozens of benefits for more than 40 reaction categories. This article identifies and describes the "Top 10" opportunities and benefits most commonly achieved by organic chemical manufacturers using phase-transfer catalysis. The Top 10 were chosen based on frequency of occurrence, economic impact and technical probability of success.

As chemical markets fluctuate between good times and bad times, there is an observable shift in the manner in which organic chemical manufacturers seek cost savings and process improvement. The focus of cost reduction methods for survival is different than the focus of cost reduction methods to achieve higher bonuses. During much of the 1980's and 1990's, many organic chemical manufacturing facilities were operating at or near capacity. These facilities turned to phase-transfer catalysis primarily to reduce their reaction time and process cycle time to achieve productivity gains while avoiding capital investment. More recently, many organic chemical markets have been experiencing overcapacity and manufacturers are looking for cost savings at lower operating rates. Under these market conditions, organic chemical manufacturers turn to phase-transfer catalysis primarily to increase yield (increase raw material usage efficiency), reduce excess reactants and use less expensive raw materials (e.g., hydroxide instead of methoxide). Fortunately, phase-transfer catalysis provides the opportunity to achieve cost savings, higher quality, better environmental performance and enhanced safety to meet corporate goals under a variety of market conditions. This article will highlight the most common opportunities to achieve cost savings and higher process performance.

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Top 10 Opportunities

To Improve Process Performance and Profit Using Phase-Transfer Catalysis

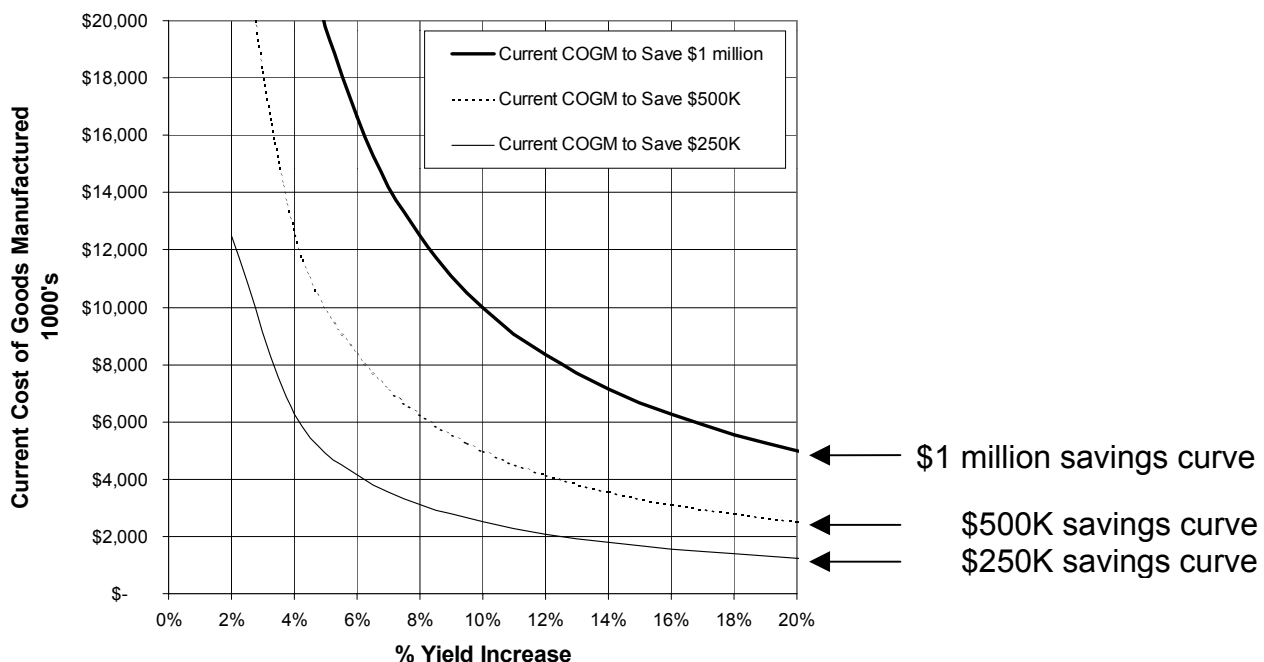
Opportunity #1

Increase Yield

Summary: PTC provides higher isolated yield due to higher selectivity achieved by taking advantage of the great flexibility in designing the microenvironment of the reaction. Typically, cost savings of \$250,000/year to \$3 million/year or more for specialty chemical manufacture warrant serious consideration of PTC retrofit. Applicable reactions can be found in the Table on page 14.

Regardless of market conditions, process scale or country of manufacture (including those with low labor cost), the ability to increase the isolated yield of a reaction is always a basic method to reduce cost, improve raw material usage and prevent pollution. Obviously, the magnitude of the cost savings is proportional to the volume of product produced, the yield increase which can be achieved and the amenability of the reaction to improvement by Phase-Transfer Catalysis (PTC). A list of reactions in which PTC excels is shown in the Table on page 14. A rule of thumb used by PTC Organics when evaluating process improvement opportunities is to assume that process improvement using PTC may result in an **increase in yield of 1/3 to 1/2 of the difference between the current yield and 100%**. For example, a 4-6% yield increase may be targeted for an existing commercial process with an average yield of 88% and a 10-15% yield increase may be targeted for an existing process with a 70% yield. PTC should almost always be considered for new process development for reactions shown in the Table on page 14. However, when retrofitting an existing commercial process with PTC, the driving force for changing the process must be significant and typically a yield increase resulting in incremental cost savings of \$250,000/year to \$3 million/year is appropriate for serious consideration of PTC retrofit. Figure 1 shows a graph of expected cost savings as a function of yield increase and the annual cost of goods manufactured.

Figure 1: **Deciding if PTC Yield Increase Is Worth Pursuing**



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Underlying Fundamentals of Yield Increase

Phase-transfer catalysis reactions often provide higher yield than non-PTC reactions due to several reasons which broadly fall into the categories of higher selectivity (minimizing side reactions) and easier workup.

Higher selectivity results from allowing the phase-transfer catalyst to regulate the reaction between two reactants located in a common phase (after phase-transfer) in a **controlled solvation environment** and at a controlled instantaneous concentration of the reactant being transferred. The controlled solvation environment is achieved by [1] solvating the reacting anion with a purposely controlled level of hydration (usually low), [2] pairing the reacting anion with a quat cation in a purposely controlled tight or loose ion pair, [3] solvating the ion pair with a purposely controlled polar or nonpolar solvent and [4] maintaining an ion pair concentration in the organic phase purposely controlled by the amount of catalyst. The extreme flexibility achieved by controlling the many permutations of these four factors in PTC systems provides the opportunity to greatly affect selectivity. The selectivity may take many forms including reducing hydrolysis of water-sensitive reactants, promoting kinetic control vs thermodynamic control by working at lower temperature (less hydration can translate into lower energy of activation), affecting the C-/O-alkylation ratio of ambident anions, enhancing monosulfonylation vs disulfonylation of N-H groups, and many more.

A corresponding non-PTC reaction may be performed at an interface or using a polar aprotic solvent. When performing the corresponding non-PTC reaction at an interface, the solvation of reactants and collisions between the reactants are in a much less controlled environment and often the brute forces of agitation and temperature are applied to promote the reaction. Non-PTC processes have less degrees of freedom than PTC processes for fine tuning reaction conditions to achieve the highest process performance.

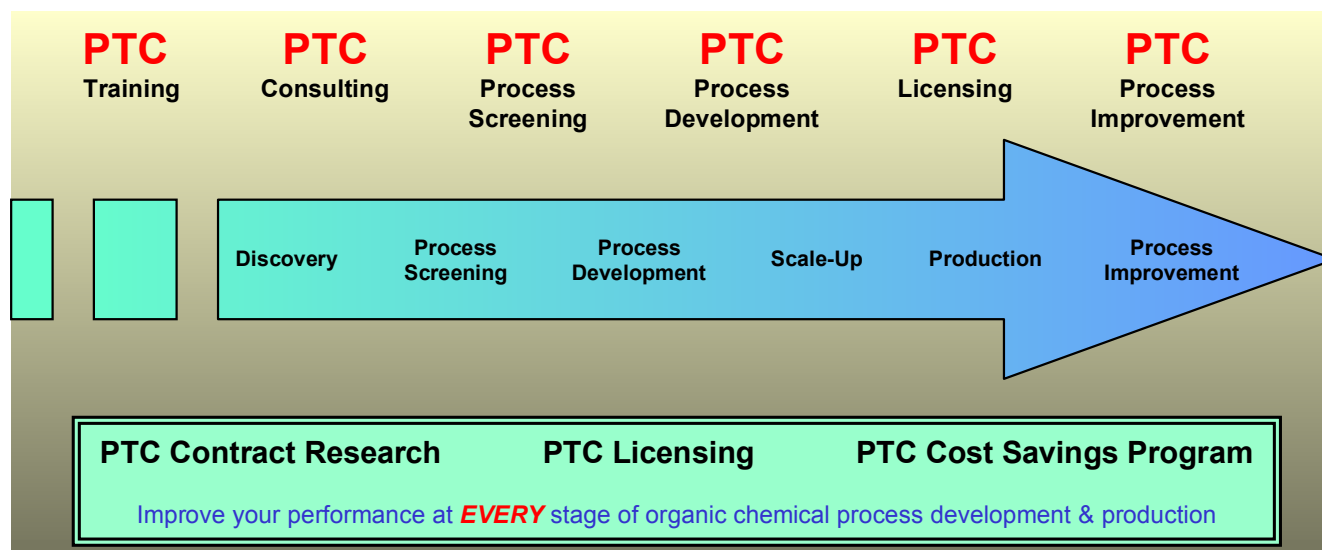
PTC often replaces the use of polar aprotic solvents (see Opportunity #9 below), especially for nucleophilic substitutions using inorganic anions (e.g., cyanide). The isolated yield of a PTC reaction will often be higher than the isolated yield of a DMSO reaction for example, due to advantageous workup. At the end of a reaction performed in DMSO, the polar high boiling solvent is often washed away from the product with water and sometimes the product is entrained in the wash (not to mention generating a difficult to treat waste stream). In a corresponding PTC system, performed in toluene for example, the workup begins with a simple phase cut and the product remains in the organic phase with little possibility for handling losses.

Opportunity #2

Replace Expensive Hazardous Strong Base with Inexpensive Inorganic Base

Summary: The use of PTC with inexpensive inorganic base (e.g., NaOH) can often replace the use of expensive and hazardous strong bases such as sodium methylate, potassium t-butoxide, sodium amide and sodium hydride and usually save between \$1,250/ton to \$18,000/ton depending on the base used. The biggest barrier to achieving these savings is often a strong resistance to even try PTC/base conditions due to common misperceptions that an inorganic base such as sodium hydroxide is not a strong enough base to perform the reaction and/or hydroxide will nucleophilically decompose sensitive reactants. In fact, PTC-inorganic base systems are very effective and beneficial.

The idea to use PTC with inorganic bases such as NaOH instead of NaOCH₃, t-butoxide, NaNH₂, NaH and Na metal seems to generate more skepticism than any other PTC process improvement idea. Highly skilled and experienced chemists usually have two reasonable objections to considering using PTC/NaOH (or other inexpensive inorganic base) instead of alkoxide, hydride or sodamide. These objections relate to BASICITY and COMPATIBILITY and will be discussed and overcome below.



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Basicity

In order to address the question of basicity, it is useful to consider the pKa's of the conjugate acids of strong bases. For example, the pKa's of both methanol (the conjugate acid of CH_3O^-) and water (the conjugate acid of OH^-) are both about 16. Thus, hydroxide and methylate have about the same inherent basicity. On the other hand, ammonia (the conjugate acid of NH_2^-) has a pKa of 34, which is 18 orders of magnitude less acidic than water! The key to understanding the power of basicity of hydroxide in PTC systems is hydration. When hydroxide is dissolved in water or located at a water-organic interface, there are many molecules of water which can hydrate the hydroxide and reduce its basicity. Once transferred into the bulk organic phase by a quat, the hydroxide can achieve near gas phase basicity and has been shown to deprotonate substrates up to a pKa of 38.4! To be sure, expert selection of reaction conditions must be performed to achieve effective reaction of organic compounds of "low acidity."

Compatibility

It is understandable that experienced highly qualified chemists would consider inorganic bases such as hydroxide to be incompatible with reactive species which are sensitive to nucleophiles. The two most common systems in which we encounter resistance by customers to considering PTC/base conditions are strong base reactions of esters and benzyl chloride derivatives. In fact, it is known that PTC/NaOH can be used very effectively to hydrolyze esters and it is known that one can produce dibenzyl ether from benzyl chloride and hydroxide in quantitative yield! Both of these reactions proceed through hydrolysis of the nucleophilically sensitive reactive group. On the other hand, there are hundreds of publications describing the use of PTC with 50% NaOH in alkylations using benzyl chloride. The key to understanding the success of these reactions is to know how to control the behavior of hydroxide as a base and as a nucleophile. It turns out that, when given the chance, hydroxide greatly prefers to act as a base rather than a nucleophile under PTC conditions. For example, the C-benylation of phenyl acetonitrile with benzyl chloride in the presence of 50% NaOH and a phase-transfer catalyst proceeds in quantitative yield. In the absence of the phase-transfer catalyst and the phenyl acetonitrile, dibenzyl ether is formed quantitatively. Similarly, PTC can be used to perform reactions of esters in the presence of aq. NaOH while avoiding hydrolysis. PTC Organics developed an etherification using NaOH to form an ether-ester in 97% yield with < 100 ppm hydrolysis. Expert selection of reaction conditions must be performed to achieve effective base-promoted reactions using nucleophilically-sensitive reactants.

Cost Savings

The magnitude of the cost savings which can be achieved by replacing a classical strong base with PTC and an inexpensive inorganic base depends on the identities, costs and mole ratios of the strong base being replaced, the replacement inorganic base and the phase-transfer catalyst. As a rule of thumb, the following are typical cost savings which may be expected.

<u>Strong Base to be Replaced</u>	<u>Typical Cost Savings</u>
sodium methylate (methoxide)	up to \$1,250 per ton of base replaced
sodium amide	up to \$2,500 per ton of base replaced
sodium hydride	up to \$6,000 per ton of base replaced
potassium t-butoxide	up to \$18,000 per ton of base replaced

If you have identified a challenging opportunity to replace expensive strong base with PTC and an inexpensive base, you can gain access to PTC Organics' expertise using the evaluation form on page 15.

From Concept to Commercialization

PTC Cost Savings Program

Pre-Screening



PTC Organics' Scientific Advisory Board determines the technical probability of success of potential customer process improvements using Phase Transfer Catalysis (under secrecy agreement). If "high," proceed to Development Agreement. Pre-screening is free of charge.

Development Agreement



Reach development agreement based on "Criteria For Success" defined by the customer and upon which process performance is measured during development and commercialization. Agreement is designed for alignment of interest.

Laboratory Development



PTC Organics commits its best efforts to develop a process in the laboratory with the goal of meeting the Criteria For Success. A commitment fee is paid by the customer at the outset of laboratory development. PTC Organics invests laboratory resources and expertise of leading PTC scientists.

Process Verification



After submission of a written report by PTC Organics describing a detailed procedure for meeting the Criteria For Success, the customer verifies the performance of the written procedure in its own laboratory. A Successful Laboratory Development Fee is paid after verification. The customer incurs no additional financial obligation if the Criteria For Success are not met.

Scale Up & Commercialization



At its discretion, the customer performs scale up and commercialization of the advantageous process. Technical support is provided by PTC Organics. The Commercialization Fee is typically 25% of the cost savings achieved.

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Opportunity #3

Etherification

Summary: PTC etherification provides high yield in short reaction time WITHOUT THE NEED TO PRE-FORM AND DRY THE ALKOXIDE OR PHENOXIDE or use it in large excess. The procedure is simple, uses inexpensive inorganic base and usually does not require an added solvent.

Phase-transfer catalysis is very often the best technique for performing the Williamson ether synthesis, which is the most common method for preparing ethers. Usually PTC etherification is performed by simply heating and stirring a mixture of the alcohol or phenol, an optional solvent, the alkylating agent (usually an alkyl halide), a phase-transfer catalyst and an inexpensive inorganic base (usually NaOH). PTC etherifications are usually rapid high yield reactions.

Major advantages of PTC etherification are based on the ability to perform the reaction **without pre-forming and drying the alkoxide**, without a large excess of alkoxide and using an inexpensive inorganic base. In one commercial application, PTC Organics was able to greatly improve an etherification reaction which previously reacted an aliphatic alcohol with sodium metal to form the dry alkoxide followed by reaction with an alkyl halide. The PTC etherification simply replaced the sodium metal with NaOH and a phase-transfer catalyst and quantitative yield was achieved after a very short reaction time. In another process improvement, the use of a phase-transfer catalyst was able to eliminate a very lengthy drying step (80% of the process time). Originally, the drying was performed after mixing the aliphatic alcohol and NaOH and before the addition of the alkyl halide. In the pre-retrofit system, the drying step was designed into the process to activate the alkoxide by eliminating its hydration shell. However, PTC essentially performs the function of stripping away most of the hydration of the alkoxide when it transfers the alkoxide into the organic phase. In addition, the PTC system provides for a loose ion pair between the bulky quat and the alkoxide which further enhances reactivity relative to using the pre-formed sodium salt. The PTC reaction takes place in the bulk organic phase and not at the interface, thereby further enhancing reactivity.

One pitfall in performing PTC etherification is the possibility for dehydrohalogenating the alkyl halide. Indeed, dehydrohalogenation is one of the most effective PTC reactions and would have been in the Top 10 list if more frequently encountered in commercial processes. In such cases, expert selection of reaction conditions must be performed to achieve the desired selectivity, yield and cycle time (see form on page 15 to gain access to PTC Organics' expertise). The key process parameters to be optimized include the identity of the base, identity and concentration of the catalyst, temperature, order of addition, choice of leaving group, solvent, optional co-catalyst and agitation (*less* is sometimes better).

Etherification is one of the most common PTC reactions and is applicable to a wide variety of alcohols, polyols (including carbohydrates) and phenols. PTC etherification is used in the commercial production of simple aliphatic ethers, aromatic ethers and polymers. PTC is used to produce several large scale products from bisphenol A including epoxy resins (reaction with epichlorohydrin), polycarbonate (reaction with phosgene) and polyetherimides (reaction with nitrophthalimide). PTC etherification is effective for both nucleophilic aliphatic substitution and nucleophilic aromatic substitution.

PTC thioetherification is an interesting subset of PTC etherification. PTC/base deprotonates mercaptans in-situ, then transfers and activates the mercaptide to achieve very high reaction rates without pre-forming the mercaptide salt. The reactions are fast enough to consider continuous processes for thioetherification and minimize the handling of the mercaptans by eliminating a separate salt formation step. PTC can also be used for the irreversible scrubbing of mercaptans. Reaction conditions must be carefully chosen to minimize attack of the nucleophilic mercaptide on the quaternary ammonium cation.

Opportunity #4

Specialty Esterification and Transesterification

Summary: Specialty PTC esterification is performed between a carboxylate and an alkyl halide as opposed to classical large volume esterification performed by dehydration using a carboxylic acid and an alcohol. PTC esterification should be employed when the compelling need for irreversible, high yield and fast reaction outweighs the difference in cost between the alkyl halide and corresponding alcohol. PTC transesterification is an effective technique for achieving impressive reductions in temperature relative to classical high-temperature non-PTC transesterification.

During the first 15 years after Starks' article in which he coined the term "Phase-transfer Catalysis," esterification was the most highly patented PTC reaction. Many of these patents were for pharmaceutical applications, such as the esterification of penicillin derivatives, since these applications required complete reaction and short cycle time to minimize heat history. Today, PTC esterification is used in many industries including pharmaceuticals, agricultural chemicals, flavors & fragrances, additives and polymers.

PTC esterification is usually performed by simply heating and stirring a carboxylate salt (or carboxylic acid and NaOH) with an alkyl halide in slight excess and a phase-transfer catalyst. There is usually no need to add a separate solvent, unless both the product and alkylating agent are solids or the liquid alkylating agent cannot be used in excess. The carboxylate anion is highly activated in the organic phase due to very low hydration, loose ion pairing with the phase-transfer catalyst and co-location with the alkylating agent in the bulk organic phase. The high reactivity provides for short reaction time. The reaction of the carboxylate with the alkylating agent is irreversible and provides a major advantage relative to dehydration of an acid with an alcohol which is limited by the physical ability to remove water from the system. PTC offers particular advantage for producing formate esters since they are very sensitive to water at high temperature. PTC Organics developed a rapid esterification to achieve 99.95% conversion to a formate ester.

The major disadvantage of PTC esterification is that the simple alkyl halides are almost always more expensive than the corresponding alcohols (except for benzyl chloride). In addition, esterification by nucleophilic substitution generates a mole of salt, versus dehydration which generates a mole of water. For these two reasons, commodity esters are rarely made using PTC. Specialty esterifications use PTC when the compelling benefits of high yield, short reaction time and irreversibility are more important than the cost of the alkylating agent and the generation of a mole of salt does not have undue environmental impact.

PTC transesterification is an obscure reaction. PTC Organics developed a transesterification which is performed at a temperature 100°C below the traditional non-PTC commercial transesterification. PTC transesterification is particularly useful when the starting alcohol and ester suffer from immiscibility problems. In such cases, expert selection of reaction conditions must be performed to achieve the best results which focus on minimizing heat history, primarily of the product ester. Complete the form on page 15 to gain access to PTC Organics' expertise.

Opportunity #5

Cyanation

Summary: High yield and short reaction time can be achieved using a very small excess of cyanide in PTC/cyanide nucleophilic displacements. Hazardous waste streams can be greatly minimized by appropriate choice of solvent which also facilitates easy workup.

As with most other anions, cyanide can be extracted by a well chosen phase-transfer catalyst from water and transferred into just about any organic liquid where effective subsequent reactions can be performed. Before the invention of PTC, polar aprotic solvents such as DMSO were often chosen to co-solublize the inorganic cyanide and the organic substrate, usually an alkyl halide or aryl halide. At the end of a typical cyanide/chloride displacement reaction performed in DMSO, the reaction is usually diluted with water to separate the product nitrile (if insoluble in water) from the DMSO solvent. Since an excess of cyanide is used, then a very hazardous waste stream of cyanide in DMSO/water is generated and is usually of large volume since multiple water washes are often needed to remove the DMSO from the product. The DMSO is usually not recoverable since the separation of DMSO and water is difficult and expensive.

In contrast, in a typical PTC cyanide/chloride displacement, a solvent is chosen which is immiscible with water, such as toluene (or no solvent at all if the product nitrile is a liquid) and workup consists of a simple phase cut and a water wash of low volume to assure the absence of cyanide in the vessel. In addition, PTC/cyanide reactions are very efficient and generally do not require a significant excess of cyanide for completion. A 2 mole% excess of cyanide is often adequate to achieve quantitative conversion of the alkyl halide. Of course, if the alkyl halide is inexpensive or readily available, then the alkyl halide can be used in excess to assure that no cyanide remains at the end of the reaction. However, this is not always possible, for example if the alkyl halide is a late stage intermediate in a multistep synthesis. Overall, cyanation reactions proceed rapidly and in high yield due to very low hydration of the cyanide ion, loose ion pairing with the phase-transfer catalyst and co-location with the alkyl or aryl halide in the bulk organic phase. A solvent such as toluene, if used, is generally very recoverable by distillation at a reasonable temperature

A challenge when performing certain PTC cyanations is that cyanide can act both as a nucleophile and as a base. In the reaction of cyanide with an alkyl halide, especially a secondary alkyl halide, significant amounts of dehydrohalogenation can be observed. For example, in the extreme case of the PTC reaction of aqueous sodium cyanide with 1-chloroethylbenzene, more than 30% styrene can be produced at the expense of 1-cyanoethylbenzene. Unlike PTC/hydroxide systems which favor hydroxide basicity over nucleophilicity, PTC/cyanide systems favor cyanide nucleophilicity over basicity. Expert selection of reaction conditions must be performed to achieve high selectivity of substitution versus elimination (see form on page 15 to gain access to PTC Organics' expertise).

Opportunity #6

Reduce Reaction Time

Summary: Very significant plant capacity increases can be achieved by retrofitting a commercial non-PTC process with PTC to reduce reaction time. These productivity gains are often achieved with little or no capital investment. Many existing PTC plant processes can be improved, especially those currently using tetrabutyl ammonium bromide. Faster reaction can also favorably affect selectivity, heat history and raw material usage.

As repeated several times in this article, PTC provides high reactivity due to very low hydration of the reacting anion, loose ion pairing with the phase-transfer catalyst and co-location of the reactants in the bulk organic phase. The higher reactivity achieved in PTC systems can be translated into a variety of benefits, but by far the most common is increasing plant capacity. When the world economy is strong (as it was in the late 1980's and mid- to late 1990's), many chemical production facilities operate at full capacity. In such market conditions, when sales forecasts exceed production capability, a choice is faced to debottleneck the plant or invest capital in a physical plant expansion. This is especially important for fully scheduled multi-purpose facilities where the opportunity cost may be great. In such cases, if the reaction under scrutiny is amenable to phase-transfer catalysis (see list of reactions on page 14), then it should be seriously considered

for PTC retrofit. The author has been involved in commercial PTC process improvements achieved by cycle time reduction worth more than \$100 million in incremental cost savings over a 10 year period, in which little or no capital was invested. In these cases, plant capacity increases of 20%, 40% and 100% were achieved well within a year of project initiation. Reduced reaction time is particularly important at companies in Western countries which compete with manufacturers in low labor cost countries. Cycle time reductions are less important in low labor cost countries because of the lower incremental investment required for a physical expansion of plant capacity. Process costs in Western countries are much more sensitive to throughput (initial reactor capital investment as well as variable labor cost) and should use PTC to enhance competitiveness by reducing cycle time.

Opportunity #7

Reduce Excess Expensive and/or Hazardous Reactants Especially Water-Sensitive Reactants

Summary: **Due to the efficiency of transfer and reaction of anions in PTC systems, it is very often possible to reduce excess reactant usage. The benefits are greatest when expensive and/or hazardous reactants are being used. Surprising reductions can be achieved in usage of water-sensitive reactants.**

As explained in “Opportunity #1 – Increase Yield,” PTC systems often provide higher selectivity due to the controlled microenvironment in the reaction phase. In many reactions, one of the reactants is used in excess to compensate for side reactions of the reactant or to drive the kinetics using higher concentration. PTC addresses both of these issues by minimizing side reactions and by enhancing reactivity. As a result, it is common in PTC systems to be able to significantly reduce the amount of the reactant in excess. For example, when replacing ethanolic borohydride with PTC/borohydride in the presence of water, the amount of the expensive borohydride excess can usually be reduced to under 5 mole% with yields above 97%. This is because borohydride is more stable in water than in ethanol. Since PTC can transfer and react borohydride in just about any organic liquid, including non-polar solvents, ethanol is no longer needed to dissolve the organic reactant. Hazardous reactants such as cyanide and phosgene have been reacted in commercial PTC systems using 2 mole% excess and achieving yields of > 98%, even in the presence of 50% NaOH!

The ability to **reduce the excess of water-sensitive reactants** and nucleophile-sensitive reactants is a particular strength of phase-transfer catalysis. Commercial success has been achieved using PTC in reducing the excess of water-sensitive reactants such as benzoyl chloride, phosgene, PCl_3 , $(\text{RO})_2\text{P}(=\text{S})\text{Cl}$, methanesulfonyl chloride, diethyl sulfate, acetic anhydride and others. The author played an active role in reducing the excess of several of these reactants in PTC reactions with O-H or N-H groups and in each case the cost savings in acylating agent or alkylating agent alone were greater than \$200,000/year each (above and beyond yield increases based on the limiting reactant).

Upon first thought, it is often surprising that water-sensitive compounds such as benzoyl chloride can be reacted very effectively in the presence of water while avoiding significant hydrolysis. The reason this can be achieved is because the labile reactant can be protected from the water by the fact that it is dissolved in an organic phase which is immiscible with water. In these systems, it is usually important to minimize agitation and **allow the phase-transfer catalyst to regulate the reaction in the organic phase and minimize non-catalyzed interfacial hydrolysis**. In any case, expert selection of reaction conditions must be performed to achieve effective PTC reactions using water-sensitive reactants in low excess. See the **Process Improvement Evaluation Form** on page 15 to gain access to PTC Organics’ expertise.

Opportunity #8

Highly Flexible Choice of Solvent

Summary: Almost any organic liquid can be used as a solvent in PTC systems. PTC provides the opportunity to choose solvent based on reactivity, recovery, environmental considerations, polarity, boiling point, selectivity and the ability to use the same solvent as used in a previous or subsequent step thereby avoiding solvent exchange and isolation of intermediates. Alternatively, “Solvent-Free” PTC conditions can be employed.

The flexibility in choosing solvent based on practical considerations is one of the great advantages of phase-transfer catalysis. By choosing the right process parameters, PTC can transfer just about any anion into just about any organic liquid (even as nonpolar as cyclohexane) and achieve successful reaction.

In many cases, the choice of solvent is dominated more by achieving easy workup, enhanced safety and environmental performance than by considerations to enhance reactivity, since the phase-transfer catalyst structure can be adjusted to affect reactivity. In most cases, though not all, a solvent is chosen which is essentially immiscible with water to allow for a simple phase cut to begin workup after the reaction. This is major advantage over the polar aprotic solvents which are used to promote reactivity by co-dissolving the organic reactants and nucleophilic anions (e.g., cyanide, azide, phenoxide, acetate, etc.). Even though DMSO, DMF, NMP and DMA are excellent solvents for the reaction, the post-reaction workup is usually difficult due to their miscibility with water and their high boiling points. Workup with polar aprotic solvents may involve a difficult distillation or water washes which generate large aqueous-organic waste streams which require further treatment and usually entrain valuable product. The recovery and recycle of polar aprotic solvents is also challenging, especially if they must be charged dry into the next reaction. In typical PTC systems, the organic phase consists of an easily recoverable solvent (e.g., toluene) and product, while the aqueous phase contains water and inorganic salts. The structure of the phase-transfer catalyst can be designed to wind up in either the aqueous or organic phase, depending on the easiest method of workup which in turn depends on the properties of the product. Overall, the flexibility in choosing combinations of solvent and catalyst structure in PTC systems provides additional degrees of freedom to achieve desired results.

Another major advantage of PTC is the ability to use the same solvent which may be optimal for a prior or subsequent step, thereby avoiding the isolation of intermediates. For example, chlorobenzene was once used as a solvent for a PTC methylthiolation because it followed two steps which both used chlorobenzene as the solvent (the first step used chlorobenzene to azeotropically dry the reaction). Handling losses are minimized and solvent exchange is avoided. If PTC were not considered, the methylthiolation would likely have been performed in a more polar solvent. In another different methylthiolation, a plant using acetone as solvent was retrofit with a PTC process using xylene because xylene was used in prior steps. Again, a solvent exchange was eliminated, handling losses were minimized and, most importantly, acetone emissions were eliminated.

When possible, “**Solvent-Free**” PTC conditions are employed. Solvent-free PTC is a good candidate when one of the reactants is a liquid and can be used in excess and recycled (e.g., many alkylating agents) and/or the product is a liquid. There are quite a few commercial PTC applications in which a liquid reactant is the “solvent” at the beginning of the reaction and the product is the “solvent” at the end of the reaction. In these cases, little or no excess of the liquid reactant is used. Solvent-free PTC usually affords low emissions and higher reactor volume efficiency since additional solvent does not use valuable and productive reactor space.

Opportunity #9

N-Alkylation, N-Acylation, N-Sulfonylation

Summary: PTC provides high yield and short cycle time for N-alkylation of N-H groups with a pKa of up to about 23, which includes a very wide variety of heterocycles. PTC also provides the opportunity to selectively obtain either mono- or di-substitution of -NH₂ groups (amides, sulfonamides, anilines, etc.) using acyl halides, anhydrides or sulfonyl halides. PTC also provides the opportunity to alter N- vs O-alkylation selectivity and sometimes N- vs N- selectivity in heterocycles.

The reaction of N-H groups with alkylating agents, acylating agent and sulfonylating agents is one of the most applied categories of PTC. The most common PTC N-alkylations use heterocycles with N-H groups with a pKa of up to about 23. These include pyrroles, indoles, carbazoles, imidazoles, triazoles, phthalimides, lactams, purines, pyrimidines and azepines. Expert selection of base can give by design either mono- or di-alkylation, acylation or sulfonylation of -NH₂ groups of amides, sulfonamides and anilines. Following mono-N-alkylation, acylation or sulfonylation, a second alkylating agent, acylating agent or sulfonylating agent can be effectively reacted under PTC conditions.

There are over 100 PTC N-alkylations with reported yields of > 90%, reaction times of 2-8 hours and temperatures up to about 80°C. There are a number of commercial processes which use PTC to achieve high yield as well as high selectivity for N-alkylation vs O-alkylation for pyridinol derivatives. Expert selection of PTC reaction conditions must be performed to achieve selective reaction of the N-H group while avoiding hydrolysis or dehydrohalogenation of the alkylating agents, acylating agent and sulfonylating agents (see form on page 15 to gain access to PTC Organics' expertise).

Opportunity #10

Halex Reactions

Summary: PTC has been used to successfully perform nucleophilic aromatic substitution for fluoride/chloride exchange and nucleophilic aliphatic substitution for almost every combination of fluoride/chloride/bromide/iodide exchange. By far the most difficult is fluoride/chloride exchange. Yields of up to 96% for aromatic fluoride/chloride exchange have been achieved by careful selection of PTC conditions.

PTC Halex reactions cover the scope from the very easy aliphatic bromide-to-iodide exchange to the very difficult aromatic chloride-to-fluoride exchange. Iodide is one of the easiest anions to transfer under PTC conditions and once transferred, its high nucleophilicity gives high reaction rates. Fluoride is thought to be the monoanion most difficult to transfer under PTC conditions and once transferred, the nucleophilicity of the fluoride ion is extremely sensitive to hydration and solvation factors. The keys to successful PTC aromatic fluoride/chloride exchange include solvation, solid salt effects, temperature and thermally stable phase-transfer catalysts under strongly basic conditions. Aromatic PTC/fluoride reactions are the only PTC reactions which consistently use high boiling polar aprotic solvents. Standard ammonium quats rarely provide high yields due to catalyst decomposition. Fluoride is particularly challenging because it can act as a base as well as a nucleophile and will do so at high temperatures. Despite the challenges, PTC aromatic fluoride/chloride exchange is feasible when the best reaction conditions are used. Aliphatic fluoride/chloride exchange has the extra challenge of dehydrochlorination, so brute force does not always work. In light of the importance of Halex reactions in pharmaceuticals and agrochemicals and the success PTC has achieved in Halex reactions, PTC should be seriously considered for these applications.

Summary

Phase-transfer catalysis is used in the manufacture of billions of dollars per year of organic chemicals and polymers because it really delivers enormous benefits in the crucial categories of productivity, raw material costs, environmental performance, quality, safety and plant operability. The “Top 10” opportunities to use PTC to achieve cost savings and process improvement exemplify these benefits. Many commercial PTC processes are currently enjoying the benefits of PTC, but many more have the potential to achieve these benefits. If your company is interested in achieving higher process performance and profit, we hope that you will be able to use this “Top 10” list as a starting point for considering new opportunities to enhance the growth and health of your company.

If you have any questions about the content of this article, please contact Dr. Marc Halpern at telephone +1 856-222-1146, fax +1 856-222-1124 or E-mail mhapern@ptcorganics.com

Final Comment

The History of a Commercial Process Makes a Difference

Sometimes process improvements and PTC retrofits have been performed hastily due to market pressures of increased demand in strong markets or survival cost cutting in weak markets. In these cases, PTC processes and non-PTC processes may have been commercialized which are far from optimal, even though they were beneficial enough to be justified. It is often worthwhile to revisit PTC process improvements and retrofits or have PTC Organics perform free pre-screening of opportunities to improve, develop or PTC-retrofit commercial processes. PTC Organics and its staff have played major roles in achieving very significant cost savings and improved process performance for commercial PTC and non-PTC processes. Please use the **Process Improvement Opportunity Evaluation Form** on page 15 to have PTC Organics perform free pre-screening of your potential opportunities.

Table: Reactions In Which Phase-transfer Catalysis Excels

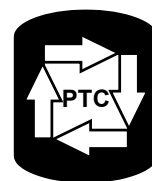
<ul style="list-style-type: none"> • Etherification • Esterification • Transesterification • N-Alkylation • C-Alkylation • S-Alkylation • Other Mercaptan Reactions • Dehydrohalogenation • Michael Addition • Aldol Condensation • Oxidation • Epoxidation • Chloromethylation • Hydrohalogenation 	<ul style="list-style-type: none"> • Hydrogenation • Borohydride Reduction • Chiral Reactions • Darzens Condensation • Carbene Reactions • Condensation Polymerization • Polymer Modification <p>Displacements Using:</p> <ul style="list-style-type: none"> • cyanide • fluoride, bromide, iodide • azide • thiocyanate, cyanate • sulfide • inorganic nucleophiles <p>Displacements Using:</p>	<ul style="list-style-type: none"> • benzyl chloride • allyl chloride • many alkyl halides • benzoyl chloride • other acyl halides • methanesulfonyl chloride • other sulfonyl halides • epichlorohydrin • PCl₃, POCl₃ • other phosphoro halides • anhydrides <p>Other reactions involving anions or anionic metal complexes</p>
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Industrial Phase-Transfer Catalysis

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Pre-Screening by PTC Organics, Inc.
The Industrial Phase-Transfer Catalysis Experts



Process Improvement Opportunity Evaluation Form

*(Do not disclose proprietary information unless a secrecy agreement
 has been properly executed between your company and PTC Organics, Inc.)*

Step 1: Draw the reaction you want to improve or develop

Include reactants, molar ratios, solvent, catalyst (if any), time, temperature, yield and key impurities (if important)

Reaction to be improved:

Step 2: Describe the performance parameter(s) you want to improve

add additional pages if necessary

Step 3: Fill out your name, company, address, phone, fax, E-mail

Name _____

Company _____

Address _____

Phone _____ Fax _____

E-mail _____

Step 4: Fax this form to Dr. Marc Halpern at PTC Organics: [+1 856 222 1124](tel:+18562221124)