Phase-Transfer Catalysis Communications

The 60-Second Phase-Transfer Catalysis Test

Identifying Opportunities with High Probability of Success

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Summary: How can you know if your process can benefit from using phase-transfer catalysis and possibly save millions of dollars for your company? Your existing process or process under development must meet two criteria in order to be considered a candidate for phase-transfer catalysis. First, your process must require achieving **process performance** parameters which phase-transfer catalysis is capable of providing. Secondly, your process must be within the scope of **reactions** amenable to phase-transfer catalysis. If your process does not meet *both* criteria, it is not likely to be a good candidate for phase-transfer catalysis. If your process meets both criteria, you should *definitely* consider phase-transfer catalysis to enhance the profitability of your company's process.

Many companies are adding millions of dollars of profit to their bottom line by using phase-transfer catalysis, "PTC," in their commercial processes for the manufacture of organic chemical and polymers. Many companies are *wasting* millions of dollars by not using PTC in processes where they should. The reasons why companies miss profit opportunities by not using PTC when they should were outlined in an earlier article.[1] It is usually the process chemist who decides if PTC will be considered for the process or not. This decision by the process chemist can result in saving or costing his/her company a lot of money. This article will help process chemists overcome some of the simple barriers to commercializing PTC processes and profit opportunities. This article will provide practical tools and offer one service which will help process chemists (1) identify which processes should be PTC candidates, (2) obtain an estimated probability of success for the PTC process option and (3) overcome organizational resistance to change at the outset of process improvement or process development project.

[1] Halpern, M. *Phase Trans. Catal. Comm.*, **1996**, *2*, 33

The 60-Second Phase-Transfer Catalysis Test

Does your existing plant process or process in development meet any of the criteria in Steps 1 and 2?

STEP 1: *choose any that apply*

Desired Process Improvement

- **Increase Productivity**
  - ⇒ increase yield
  - ⇒ reduce cycle time
  - ⇒ increase reactor volume efficiency

- **Improve Environmental Performance**
  - ⇒ eliminate, reduce or replace solvent
    replace DMSO, NMP, DMF, DMA, EDC, methylene chloride, etc.
  - ⇒ reduce waste & waste streams

- **Replace Expensive Strong Base**
  - ⇒ replace NaOMe/OEt, t-butoxide, NaH, $NaNH_2$ with inexpensive inorganic base

- **Increase Quality**
  - ⇒ improve selectivity
  - ⇒ improve product assay

- **Enhance Safety**
  - ⇒ reduce excess hazardous reactants
  - ⇒ control exotherms

- **Reduce Other Manufacturing Costs**
  - ⇒ reduce excess expensive reactants
  - ⇒ avoid isolation of intermediates
  - ⇒ use water-sensitive reactants (e.g., PCl_3, acyl chloride, mesyl Cl) without drying

STEP 2: *choose any that apply*

Reaction

O-Alkylation (Etherification)
Esterification
Transesterification
N-Alkylation
C-Alkylation
S-Alkylation
Dehydrohalogenation
N-, O-, or S-Acylation
Displacement Using:
- Cyanide
- Fluoride
- Iodide
- Bromide
- Azide
- Hydroxide
- Thiocyanate, Cyanate
- Sulfide
- Alkyl, Acyl or Sulfonyl Halides

Other Nucleophilic Aliphatic & Aromatic Substitution
Hydrohalogenation
Chloromethylation
Oxidation
Epoxidation
Borohydride Reduction
Hydrogenation
Michael Addition
Aldol Condensation
Wittig
Darzens Condensation
Carbene Reactions
Thiophosphorylation
Carbonylation
Transition Metal Co-Catalysis
Other Reactions Involving Anions
Any Reaction Above for Polymerization
Any Reaction Above for Modifying Polymers

STEP 3: *IF* your new or existing process:

1. could benefit from at least **one desired process improvement** listed in Step 1

   AND

2. includes at least **one reaction** listed in Step 2

THEN

you should definitely consider **Phase-Transfer Catalysis** to improve process performance

STEP 4: *Initiate evaluation of the PTC option*

In order to initiate evaluation of the PTC process performance, it would be a wise investment of resource to first obtain an expert opinion about the *probability of success* of the PTC option. If the estimated probability of success is "high," then it is easier to justify investing R&D resource (to yourself and to management) to evaluate the PTC option, assuming that the potential economic impact of the enhanced process performance is significant. An expert opinion about the probability of success of the PTC option may be obtained, free of charge, by filling out the form on page 24 (approximately 10 min) and faxing/sending the form to PTC Organics.

Taking the 60-Second PTC Test and submitting a Process Improvement Opportunity Form allows process chemists to invest less than 15 minutes of their company's time to identify PTC profit opportunities and obtain an independent expert opinion which can be used to justify initiating a project to increase the company's profit and/or prevent pollution. Reducing cost of manufacture of organic chemicals and polymers and pollution prevention are two of the most powerful underlying driving forces in the chemical industry. Not taking the 60-Second PTC Test and not submitting the Process Improvement Opportunity form often allows significant organizational barriers to remain in place and negatively overcome the positive driving forces toward profitable commercialization of the better technology.

It is very simple to take the 60-Second Phase-Transfer Catalysis Test. If you support an existing plant for the manufacture of organic chemicals, you should really take this test *now*. The 60-Second PTC Test should also be applied to any processes you may be developing now or at the outset of future projects when considering options for new processes.

Description of Step 1: Process Performance Improvement Criteria

For an existing plant process or a process in development, Step 1 encourages you to ask the question, "can we benefit from *any* improvement in process performance?" Our experience has been that PTC is most often considered for existing or new high yield processes for which reduced cycle time and/or solvent reduction/elimination are recognized as bringing great profit, operability and environmental benefit to the plant. If the plant is already operational, it is likely already profitable. There are many such profitable "acceptable" processes onstream, which management would like to see more productive, with higher operability and which have substantial room for optimization. Some existing non-PTC plants are converted

to PTC processes in order to reduce excess and hazardous raw materials. The driving forces for other successful commercial PTC retrofits have included improving the selectivity of the reaction (mostly for pharmaceutical and agricultural chemical intermediates); controlling exotherms (using the two-phase nature of the system and operating under transfer-rate limited conditions); reducing the number and duration of workup unit operations; and increasing operability. Multiple consecutive PTC steps often provide the opportunity to totally avoid isolation steps.

Some PTC opportunities are easily flagged by the existing use of certain reagents and solvents. For example, the use of strong organic or inorganic bases in an existing or new process should always be considered as a candidate for conversion to PTC. The use of alkoxides, NaH and $NaNH_2$ is a strong signal for considering using NaOH or K_2CO_3 with a phase-transfer catalyst. The use of dipolar aprotic solvents in a plant may incur high recovery costs and are usually considered a hassle by plant engineers and operators. Phase-transfer catalysis provides the opportunity to choose solvents which are much easier to recover and recycle, such as toluene. Solvent-free PTC is also a popular retrofit target. Sometimes the combination of reagents and solvent are excellent triggers for considering PTC. For example, the use of NaH with DMF for difficult base-promoted nucleophilic substitutions should become a classic PTC retrofit situation in future years as the awareness of PTC spreads.

The psychological reactions of plant chemists, engineers and managers to Step 1 of the 60-Second PTC Test are sometimes very interesting. Some technical people think that Step 1 is a gimmick...after all, who doesn't want increased yield, reduced cycle time and reduced solvent? Step 1 is NOT a gimmick. The benefits listed in Step 1 are real and represent actual performance improvements being used in hundreds of PTC plants, many of which are in competition with onstream and less profitable non-PTC plants which may suffer from operability problems.

Step 2: Reaction Criteria

Step 2 is even easier to complete than Step 1. Simply look at the list of reactions in Step 2 and see if your reaction is listed. The list in Step 2, again, is not a gimmick. Step 2 is simply a list of the most common reactions (not even a totally comprehensive list) in which PTC excels by providing the benefits listed in Step 1. Note that Step 2 does not claim all of organic chemistry. In fact, most organic chemistry cannot be performed using PTC. Maybe one day, important commercial reactions such as Friedel-Crafts alkylation and nitration will be amenable to PTC, but to date these have not been published nor commercialized.

Step 3: PTC Go/No-Go Decision

Obviously, if your reaction is on the list of Step 2 AND could benefit from improved process performance listed in Step 1, you should definitely consider phase-transfer catalysis for your process. This does not yet mean that PTC will definitely work, it only means you should think about PTC for the process. For example, most commercial esterifications are dehydration reactions. PTC is not yet known to catalyze the dehydration of alcohols and acids to form esters. However, if you have a specialty ester which needs to be manufactured in high yield (pushed to completion) with short cycle time and you can tolerate the liberation of one mole of salt, (and possibly the higher cost of the corresponding alkyl halide vs the alcohol) then you have a very good PTC candidate.

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

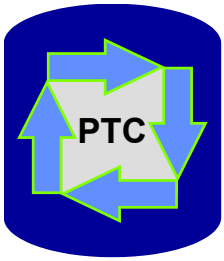
PTC Organics commits its best efforts to develop a process in the laboratory with the goal of meeting the Criteria For Success. A commitment fee is paid by the customer at the outset of laboratory development. PTC Organics invests laboratory resources and expertise of leading PTC scientists.

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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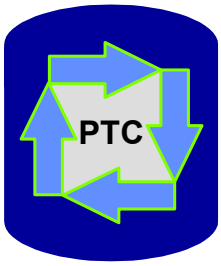
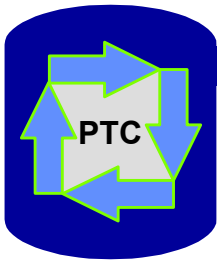
Process Improvement Opportunity Evaluation Form



FREE Evaluation from PTC Organics

The Industrial Phase-Transfer Catalysis Experts

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



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** (see 60-Sec PTC Test Step 1)

_____

_____

_____

add additional pages if necessary

Step 3: **Fill out your name, company, address, phone, fax**

Name _____

Company _____

Address _____

_____

Phone _____ Fax _____

E-mail _____

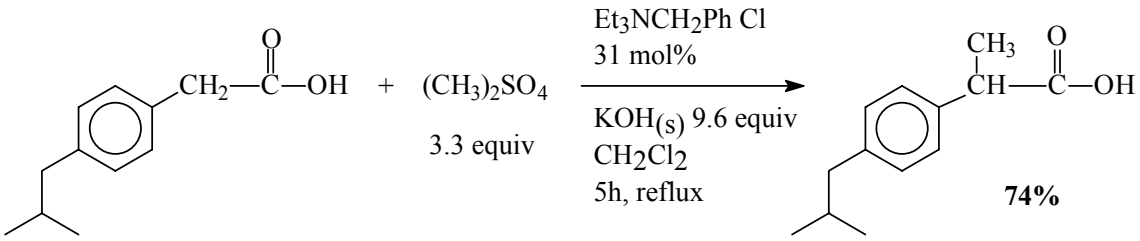
Step 4: **Fax this form to Dr. Marc Halpern at PTC Organics: +1 856 222 1124**

Process Improvement Opportunity Evaluation Form

Examples

Example 1: With Secrecy Agreement

Step 1: **Reaction to be improved** (reactants, product, solvent, catalyst, time, temp, yield, impurities, etc.):

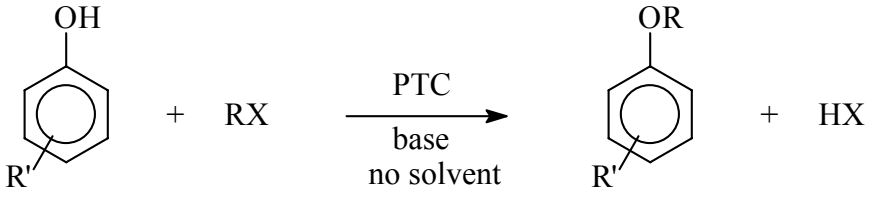


Step 2: **Describe the performance parameter(s) you want to improve**

1. Improve yield to at least 90%
2. Reduce catalyst charge
3. Replace methylene chloride with more environmentally acceptable solvent
4. Use safer methylating agent and reduce its excess

Example 2: Without Secrecy Agreement

Step 1: **Reaction to be improved** (reactants, product, solvent, catalyst, time, temp, yield, impurities, etc.):



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

1. High yield etherification with short cycle time
2. Use NaOH without side reactions (RX is water sensitive)
3. No added solvent

In today's corporate culture, it is politically correct to innovate cost reductions which can be measured and achieved rapidly. For this reason, it is particularly worthwhile for process chemists and engineers who support existing plants, to apply the 60-Second PTC Test to their processes. It really won't take more than 60 seconds to realize whether or not your process meets the two criteria. If your process qualifies, you may be able to commercialize a conversion to PTC within a few months of development and become a hero (or make your manager into a hero). It is ironic that if you develop a highly advantageous PTC process during the *first* commercialization of the process, you are considered just to be doing your expected job. But if you retrofit an existing non-PTC plant with PTC and show significant measurable incremental profit, you may receive an award for your achievement. The point is, that you can increase your company's profit by incorporating PTC into processes which may be in the plant right now or which are currently under initial development.

Not to be overlooked are opportunities in existing plants which already use PTC. For example, one large existing plant process for the manufacture of an agricultural chemical was using PTC with very good plant performance. In 1996, this plant achieved a very significant increase in plant capacity by combining the existing expertise of the manufacturing company with the expertise of an industrial PTC expert. If you operate an existing commercial PTC process, ask yourself the question: "Is it possible that my existing PTC plant process may be providing less than optimal performance?" If you cannot rule out this possibility, proceed to Step 4.

Step 4: PTC Opportunity Evaluation Form

If you think that your process meets the performance criteria of Step 1 and the reaction criteria of Step 2, then completing the PTC Opportunity Evaluation Form on page 24 may help you justify initiating projects for increasing profit by:

- **RETROFIT**: converting a non-PTC plant to PTC with better performance
- **OPTIMIZATION**: optimizing an existing PTC plant
- **DEVELOPMENT**: developing a new process (for a new product) using PTC achieving high performance

To evaluate your process, draw the reaction scheme you want to improve (in the box on page 24). Include reactants, product, by products, solvent, time, temperature, yield and catalyst. Then define, in order of priority, how much and which process performance parameters you want to improve (for an existing process) or achieve (for a new process). This information should take you several minutes to define and write for an existing process and somewhat longer for a new process. If your company already has a valid secrecy agreement in effect with PTC Organics, Inc., fax the form to PTC Organics at +1 856 222 1124. Example 1 shows a recommended format for completing the PTC Opportunity Evaluation Form. PTC Organics will offer an opinion regarding the probability of success of achieving the desired process performance, expressed as "high," "medium" or "low." If the probability of success is "high" and the potential economic impact is high then the PTC option probably warrants investigation under the PTC Cost Savings Program performed by highly specialized industrial PTC experts (or investment of internal R&D resource). If the probability of success is "low," then it is probably not warranted to invest development resource. If the probability of success is "medium" then it may require a very large potential economic impact to justify further work.

It is important to note, that if your company has not properly executed a secrecy agreement with PTC Organics, Inc., then company confidential information should **NOT** be disclosed to PTC Organics using this form. In order to benefit from the expert opinion of PTC Organics without disclosing confidential information, you can submit a generic functional group conversion such as that shown in Example 2. Consult with your management as to what may be appropriate to ask before submitting the form to PTC Organics for an opinion. If you want to initiate a secrecy agreement with PTC Organics, simply call (USA phone) +1 856 222 1146 or fax to +1 856 222 1124 or e-mail to mhalpern@ptcorganics.com.

Conclusion

The driving force for taking the 60-Second PTC test and submitting the PTC Opportunity Evaluation Form is achieving high process performance (reduced cost of manufacture and pollution prevention). Some commercial processes for the manufacture of organic chemicals are optimal, but let's face it, in the real world, most are not. As an employee of your company, you are

probably motivated to help increase your company's performance. The 60-Second PTC Test and the PTC Opportunity Evaluation Form are simple tools to help you identify and evaluate improvements. Invest a few minutes of your company's time (maybe over lunch) to apply these tools.

About the Author

Dr. Marc E. Halpern is a leading authority on **increasing profit** using phase-transfer catalysis (PTC) technology. Dr. Halpern is the founder of PTC Organics, Inc. the only company dedicated exclusively to enhancing customer profit and process performance by developing high-performance low-cost processes for the manufacture of organic chemicals using Phase Transfer Catalysis. Dr. Halpern helped companies save > $150 million in process improvements and has provided PTC services at > 150 industrial sites in the US, Europe, the Middle East and Asia.

Dr. Halpern has authored or co-authored the classic books and training programs "*Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*" (Chapman & Hall, 1994) "*Phase-Transfer Catalysis: Mechanism and Syntheses*" (ACS Symposium Series #659, 1997), "*Practical Phase-Transfer Catalysis*" (320 chemists trained in the US, UK, Germany, Switzerland and Italy). Dr. Halpern founded PTC Communications, Inc., publisher of the journal "Phase-Transfer Catalysis Communications." PTC Communications, Inc. distributes this journal free of charge to industrial customers. Dr. Halpern innovated the guidelines for evaluation and optimization of new PTC applications and invented the accessibility parameter for characterizing the effect of phase-transfer catalyst structure on reactivity and selectivity. Dr. Halpern has an impressive track record as an Organic Process Chemist, a Supervisor of Process Chemistry Research and Director of Research and Development over a 18 year period in the chemical industry. Dr. Halpern currently dedicates his full time to phase-transfer catalysis.

Dr. Halpern would appreciate your comments and questions about this article and about industrial phase-transfer catalysis.

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All correspondence and change of address should be sent to this address.

Proper safety precautions must always be taken when performing chemical reactions, including phase-transfer catalysis reactions.

