Phase-Transfer Catalysis Communications

Replace Methoxide (Methylate) and Other Strong Bases with Hydroxide!

Big Cost Savings Opportunities, Myths, Questions and Answers

Summary: Significant benefits and **cost savings** may be achieved by using Phase Transfer Catalysis with inexpensive inorganic base in place of expensive and hazardous sodium methoxide, sodium amide, sodium hydride or t-butoxide. It is often surprising and possible that inexpensive inorganic bases, such as sodium hydroxide (and/or others), under carefully chosen phase transfer catalysis conditions, can [1] provide sufficient basicity [2] with minimal hydrolysis [3] at **low cost** [4] while avoiding handling of the flammable solid $NaOCH_3$ dust or volatile methanol solution. The advantages are compelling!

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PTC Organics Expands Lab and Staff

PTC Organics, Inc. expanded its Willingboro, New Jersey laboratory for custom development of high performance processes for the manufacture of organic chemicals using phase transfer catalysis. "PTC Organics is first-to-market as the only company dedicated exclusively to developing advantageous processes using phase transfer catalysis to improve customer performance," said Dr. Halpern, President of PTC Organics. "We are executing a strategic plan and committing resources to assure that we maintain our leadership position in providing industrial PTC services to improve customer performance. This includes offering enhanced process cost savings programs to customers (e.g., for Six Sigma programs), adding leading industrial PTC scientists to our Scientific Advisory Board, expanding our laboratory, hiring PTC process development chemists and joining SOCMA." The laboratory is managed by Dr. Darrell Crick who joined PTC Organics in January 2001. The laboratory expansion will accommodate additional Ph.D. organic process chemists which PTC Organics plans to hire in the near future.

Replace Methoxide (Methylate) and Other Expensive Strong Bases with Hydroxide!

Big Cost Savings Opportunities, Myths, Questions and Answers

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"Replace methoxide with hydroxide in *OUR* process...YOU CAN'T DO THAT!" This is one of the most common statements heard when suggesting to use PTC with NaOH instead of sodium methoxide. We all learned in our first organic chemistry course that inorganic bases, such as NaOH, especially in the presence of water, will hydrolyze water-sensitive compounds. As discussed below, this is not necessarily true. In addition, chemists will naturally choose a strong, "dry" base to perform reactions which require deprotonation of a weakly acidic compound which may also be water-sensitive. Expensive dry strong bases commonly chosen include sodium methoxide methylate), potassium t-butoxide, sodium amide, sodium hydride, sodium metal, LDA or others. If the reactant or product is very sensitive to nucleophiles (reactants such as phosgene, acyl chlorides, sulfonyl chlorides, phosphoryl chlorides, anhydrides, epoxides), then bases such as NaH or sodium metal are often chosen. In many cases involving water-sensitive or nucleophile-sensitive reactants and/or products, choosing sodium hydroxide or other inexpensive inorganic bases as the base may mistakenly be considered foolish for reasons of reactivity, hydrolysis and possibly other factors. Following are some myths and truths about strong base PTC reactions. *con't on p. 4*

Low Cost and High Performance Using PTC with Inexpensive Base

System Capability	Strong Base (e.g., sodium methoxide, $NaNH_2$, NaH, t-butoxide)	Phase Transfer Catalysis & Inexpensive Inorganic Base (e.g., sodium hydroxide)
Low cost	No	√√√ **YES** √√√
Do not have to keep dry	No	**YES**
Not flammable or explosive	No	**YES**
Minimize emissions (VOC, NH_3, H_2)	No	**YES**
Avoid hydrolysis/work with water-sensitive compounds *ability to design system to eliminate or minimize hydrolysis (e.g., work with esters, anhydrides)*	**YES**	**YES**
Can work with nucleophile-sensitive compounds *(e.g., phosgene, PCl_3, benzoyl Cl, sulfonyl Cl's)*	No, for methoxide/$NaNH_2$	**YES**
Base strength – pKa up to 24 *can deprotonate organic substrates and perform C-alkylation, N-alkylation, O-alkylation on compounds with pKa up to 24 (including activated methylene compounds; ketones, aldehydes, nitriles, esters, sulfones, imines)*	**YES**	**YES**
Base strength – pKa up to 38 *can perform selected base promoted reactions with substrates up to pKa 38 (e.g., oxidation with oxygen, dehydrohalogenation, deuteration)*	**YES**	**YES**

Does mixing water-sensitive compounds with aqueous NaOH

SOUND CRAZY ?!?!?!?

If so, then

Call PTC Organics

The Industrial Phase-Transfer Catalysis Experts

PTC Organics has surprisingly replaced expensive hazardous strong base with inexpensive inorganic base in many applications

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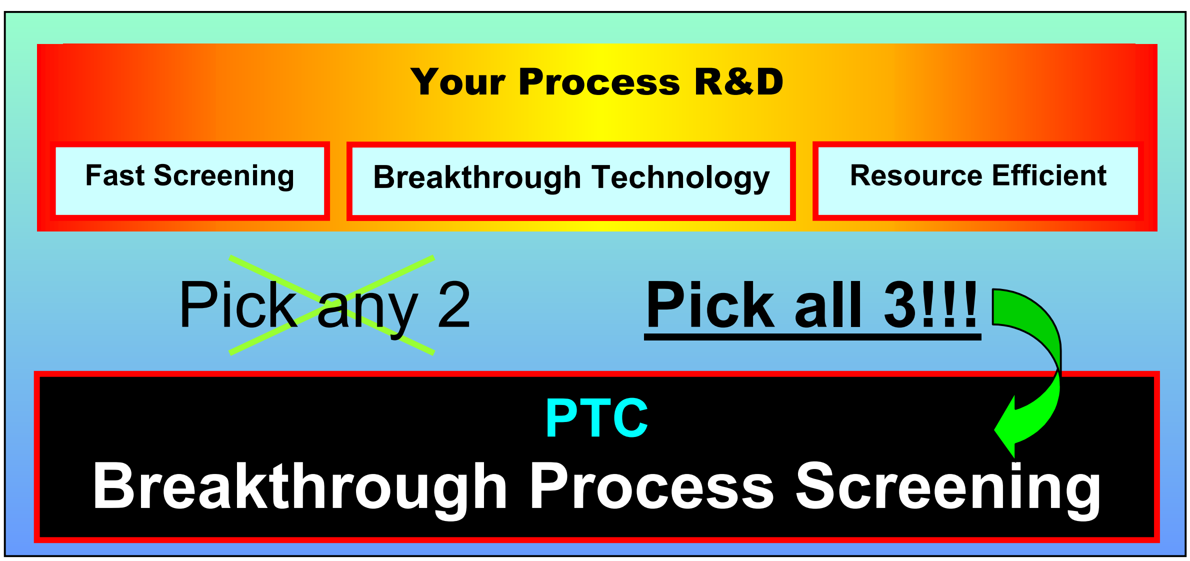

Despite healthy skepticism and intuition that it may not prudent to mix NaOH with water sensitive compounds...is it possible anyway?!?

Hydrolysis

Myth *Sodium hydroxide hydrolyzes esters and other water-sensitive compounds under most phase transfer catalysis conditions.*

Truth *Careful selection of PTC conditions, including solvent, ionic strength, catalyst, agitation, physical form of the base and other process parameters allows the use of sodium hydroxide in the reaction of esters and other water sensitive compounds while avoiding/minimizing hydrolysis.*

You can perform reactions of esters using PTC and base without hydrolysis. If you choose, you can use PTC to purposely perform hydrolysis of esters. It all depends on the reaction conditions chosen. It is more obvious to use PTC to hydrolyze esters very effectively. For example, Dehmlow reported that diethyl adipate can be hydrolyzed effectively with PTC and 50% NaOH in 1 hour at room temperature (J. Chem. Res. S, **1979**, 238). However, it is also possible to suppress hydrolysis of water-sensitive compounds under PTC conditions, primarily in systems in which hydroxide (or other base) has a choice between acting as a base or as a nucleophile. The PTC system can be designed so that the hydroxide (or other base) acts predominantly as a base. The fundamental concept is to use the phase boundary to "protect" the ester (or much more water-sensitive compounds, such as phosgene) from the base and water, to minimize non-catalyzed interfacial hydrolysis and regulate the desired reaction using the phase transfer catalyst. An elegant and somehwat counter-intuitive example of using PTC with 50% NaOH while reducing phosgene excess from 30 mole% to 2 mole% is found in US patent 5,391,682. Another surprising success is the PTC reaction of benzoyl chloride with phenol in the presence of basic water with minimal hydrolysis of the benzoyl chloride (Water Environ. Res., **1998**, *70*, 4). Another example of using PTC with a water-sensitive compound in the presence of water is an etherification using ethyl chloroacetate (reacted at the Cl atom) with high yield and minimal hydrolysis (US 3,969,360).

Often, the design of such systems is not easy and usually requires significant expertise (extensive trial-and-error experimentation may not be effective) to carefully choose the right combination of solvent, ionic strength, catalyst, agitation, physical form of the base and other process parameters. It should be noted that other inexpensive inorganic bases can be used besides sodium hydroxide. PTC Organics specializes in developing very challenging PTC processes using water-sensitive reactants and products using inexpensive inorganic bases in place of the classical expensive "dry" strong bases.

Base Strength

Myth *Sodium hydroxide is not a strong enough base to perform many of the useful organic base promoted reactions which can be performed using sodium methoxide, t-butoxide, sodium hydride, sodium amide and other strong bases.*

Truth *NaOH has been used under PTC conditions to perform deprotonations of substrates with pKa up to 38 (thiophene α-proton), oxidation of methylene groups up to pKa 33 (e.g., diphenylmethane to benzophenone) and alkylations of substrates up to pKa 24.*

When hydroxide is transferred to a non-polar environment by a phase transfer catalyst, enormous enhancement of basicity can be achieved, which may approach gas phase basicity. Enhanced basicity can be achieved with other inexpensive inorganic bases. For example, PTC can be used with inexpensive inorganic bases to perform alkylation of many heterocycles, ketones, aldehydes, nitriles, sulfones, esters, imines and other activated methylene groups. One of the more impressive publications is the replacement of LDA in dry THF with PTC and aqueous NaOH to perform a Michael addition of an iminoester to an α,β-unsaturated ester, with a simultaneous 19% yield improvement (to 85%) and minimal hydrolysis of any of the esters (J. Fluorine Chem., **1996**, *80*, 27).

Cost Savings

Question How much money can be saved by replacing strong bases, such as sodium methoxide, sodium amide, sodium hydride and potassium t-butoxide with a phase transfer catalyst and an inexpensive inorganic base?

Answer The answer depends on the identities, amounts and current prices of catalyst and base, but following may be used as guidelines:

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Being pushed to reduce cost?!?

PTC Breakthrough Process Screening

PTC Cost Savings Program

Breakthrough Process Improvement Using Phase Transfer Catalysis

Call PTC Organics
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- Replace sodium methoxide (methylate)
  save up to $1,250 per ton
- Replace sodium amide
  save up to $2,500 per ton
- Replace sodium hydride
  save up to $6,000 per ton
- Replace potassium t-butoxide
  save up to $18,000 per ton

Other Process Advantages

Question What other process advantages may be achieved by using phase transfer catalysis with inorganic base in place of expensive dry strong base?

Answer

- Avoid Special Handling
  Strong bases such as sodium methoxide, sodium hydride and sodium amide are very moisture sensitive and must be kept dry. These bases are often sold as a fine powder and the dust may represent a respiratory hazard. The inorganic bases typically used with PTC (e.g., NaOH, others), may be easily handled as a liquid (aqueous solution), in bead or granular form.
- Flammability & Explosivity
  Strong bases such as sodium methoxide, potassium t-butoxide and sodium amide are considered flammable. Sodium hydride can generate hydrogen gas and can be explosive. The inorganic bases typically used with PTC, such as NaOH, are neither flammable nor explosive.
- Emissions
  Sodium methoxide is sometimes purchased as a solution in methanol which is a volatile organic solvent, requiring emission controls. The inorganic bases typically used with PTC are supplied as solid or aqueous solutions with no VOC potential.

The PTC vs Methoxide Decision

Question Why isn't PTC used much more to replace expensive strong dry base with inexpensive inorganic base?

Answer There are two overcomable "reasons":

1. Perception

Let's face it...it still may be hard to believe that you can avoid hydrolysis of esters or phosgene in the presence of concentrated aqueous NaOH! Therefore, many chemists may simply not seriously consider using NaOH as a base when working with water-sensitive compounds. This is understandable. On the other hand, try to recall some of the times you have used methanolic KOH or the fact that the isocyanate MDI (used in polyurethanes) can be used in aqueous systems. Not all water-sensitive compounds are as sensitive as we may perceive as long as they are protected by an appropriate interface.

2. Expertise

In defense of the skeptics, it should be noted that quite often, the challenge is not trivial to choose the proper PTC process conditions to perform the desired base-promoted reaction with an inexpensive inorganic base while minimizing hydrolysis. Given the high workload of many chemists, it is usually difficult to screen and optimize the myriad of process parameters required to develop and fully commercialize a PTC-base process within tight deadlines. PTC Organics is the only company dedicated exclusively to developing high performance PTC processes and PTC Organics has the expertise to develop PTC-base reactions in a timely manner with a high likelihood of commercial success.

Summary

PRO

The benefits are *very compelling* for replacing sodium methoxide and other expensive strong bases with phase transfer catalysis and inexpensive inorganic bases. The benefits include significant cost savings, easier handling, lower emissions and enhanced safety.

CON

One must overcome chemical intuition and natural resistance to considering using NaOH and other inexpensive inorganic bases in the presence of water-sensitive compounds. Significant expertise is often needed to successfully develop PTC-base reactions with high performance *and* in a timely manner.

ARE YOU WILLING TO CONSIDER?

Are you open to considering the possibility of using PTC with inexpensive inorganic base instead of classical expensive strong base? It's your choice.

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.

PTC

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