

# Phase-Transfer Catalysis Communications

## Avoid Over-Agitation in PTC Systems to Reduce Excess Reactants and Improve Selectivity

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Summary: There are two common cases in which it is possible to hurt performance in PTC systems by over-agitation. These include [1] reactions which use water sensitive reactants (such as acylating agents and alkylating agents) and [2] cases in which the formation of the desired product and undesired by-products can both be enhanced by PTC. Over-agitation is common in PTC systems because of the natural tendency to strive to achieve intimate mixing of multi-phase systems. There are also cases in which PTC systems are under-agitated. The purpose of this article is to heighten the awareness of certain opportunities and pitfalls in addressing agitation in PTC systems.

## PTC Contract Research

### PTC Process Screening

- "proof-of-concept" in ~ 3 weeks
- Resource-efficient breakthrough PTC process innovation

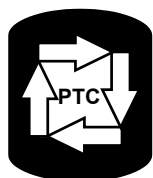
### PTC Process Development

- Define PTC process parameters to achieve a high-performance PTC process ready for scale-up.

## PTC Consulting

### PTC Consulting

- Effectively screen PTC process options in *YOUR* lab saving 50-90% of internal R&D resources



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## Avoiding Over-Agitation to Reduce Excess Reactants and Improve Selectivity

*cont'd from p.1*

“Shake well” reads the medicine bottle label. “Oil and water don't mix” says the elementary school teacher. Since childhood, we have been taught that it is imperative to strongly agitate two-phase systems. It is natural to strive to achieve intimate mixing of two or more phases in PTC systems. However, process chemists and especially process engineers, need to be careful not to over-agitate a variety of PTC systems. Unfortunately, it is not uncommon to see chemical companies increasing their raw material usage due to over-agitation. Even in the academic world, it is common to observe publications in which the authors are surprised that sonication, baffles or other special agitation measures, do not result in enhanced reactivity. This article will address the question of when it is prudent to minimize agitation in PTC systems, and when it is prudent to invest in elaborate agitation schemes in PTC systems.

The tendency to strongly agitate two phase systems, which do not involve PTC, is justified. For example, if one wants to hydrolyze (saponify) a fatty ester with aqueous NaOH, one approach would be to heat and very strongly agitate the two phase system and hope to achieve a reasonable rate of interfacial hydrolysis. Since it is recognized that this reaction is interfacial, anything we can do to increase the surface area of contact between the two phases as well as overcome other interfacial barriers, should enhance reactivity. Thus, heat and strong agitation would seem to be required. The addition of surfactants should reduce the interfacial tension and is also often used to increase reactivity. The use of co-solvents may also enhance reactivity.

In contrast, a system which uses Phase Transfer Catalysis is different in concept. In the PTC system, the phase transfer catalyst will physically transfer the hydroxide into the reaction phase (the organic phase or the interfacial region). In the case of saponification, the reaction phase is the bulk organic phase of the fatty ester. In the absence of the phase transfer catalyst, the microenvironment of the nucleophilic attack is heterogeneous and interfacial. In the presence of the phase transfer catalyst, the microenvironment of the

nucleophilic attack is homogeneous within the bulk organic phase (or interfacial region). Therefore, it may not be surprising to learn that the effect of agitation on a non-PTC hydrolysis may be different from the effect of agitation on a PTC hydrolysis.

When determining the reactivity and selectivity of PTC reactions, many factors need to be considered. These factors include the identity of the rate determining step and the identity of non-catalyzed side reactions. Although somewhat of an over-simplification, the rate determining step of most PTC reactions is either the transfer step or the chemical reaction in the organic phase, also called the intrinsic reaction. When the rate determining step is the transfer step, more effective agitation will indeed enhance the transfer rate which will result in an increase in the overall reaction rate. However, when the intrinsic reaction in the organic phase (or interfacial region) is the rate determining step, that means that the intrinsic chemical reaction is slower than the transfer step. In such a case, any activity which enhances the transfer step will not affect the overall reaction rate, because the intrinsic chemical reaction cannot consume reactant as fast as it is being supplied by the transfer step. Thus, the effect of agitation on a PTC system is closely linked to the identity of the rate determining step. In principle, when the rate determining step is purely the intrinsic reaction, increased agitation will have no effect on the overall reaction rate. When the rate determining step is purely the transfer step, increased agitation will significantly increase the overall reaction rate.

A common agitation pitfall in PTC systems occurs when one of the reactants, typically an alkylating agent or an acylating agent, is susceptible to hydrolysis. Most PTC systems actually protect alkylating agents and acylating agents from hydrolysis simply as a result of their dissolution in the organic phase, which protects them from interfacial hydrolysis. In an acylation, for example the PTC reaction of phenol with benzoyl chloride, hydrolysis does not occur to a significant extent because the phase transfer catalyst extracts almost exclusively phenoxide and not hydroxide. Therefore, in the absence of non-catalyzed interfacial hydrolysis, only the phenoxide is available for nucleophilic attack on the acylating agent, and not the hydroxide. Usually, relatively non-vigorous agitation would cause the reaction of phenoxide with benzoyl chloride to be limited in rate by the intrinsic chemical

reaction. This means that the reaction rate of acylation will reach a maximum at relatively low agitation efficiency. However, non-catalyzed interfacial hydrolysis may still occur. At low agitation efficiency, the non-catalyzed interfacial hydrolysis will be negligible. At higher agitation efficiency, the non-catalyzed interfacial hydrolysis may be significant. At extremely high agitation efficiency the non-catalyzed interfacial hydrolysis may in fact predominate. Again, once the requirement for mass transfer is met, the desired rate of acylation will not increase with increased agitation. If increased agitation does not enhance the desired reaction but does indeed promote the undesired non-catalyzed interfacial hydrolysis, then it should be obvious that increased agitation will simply result in **wasted raw materials, higher cost and greater pollution**. To maximize selectivity to the desired product and minimize the undesired hydrolysis, an optimum agitation efficiency may be found, and indeed should be sought, which will likely be at a relatively low agitation efficiency. For the benzylation of phenol, Figure 1 shows the three regimes (the disappearance of benzoyl chloride is being monitored): [1] at low rpm, the PTC reaction is transfer rate limited, [2] at medium rpm, the PTC reaction is organic phase limited and [3] at high rpm the non-catalyzed interfacial hydrolysis of benzoyl chloride predominates. Typically, in a 100-250 ml round bottomed flask with no baffles using a half moon Teflon blade, the maximum rate of the desired reaction can often be achieved at 200 to 700 rpm.

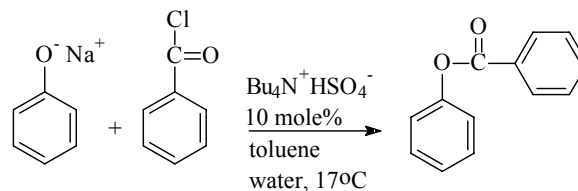
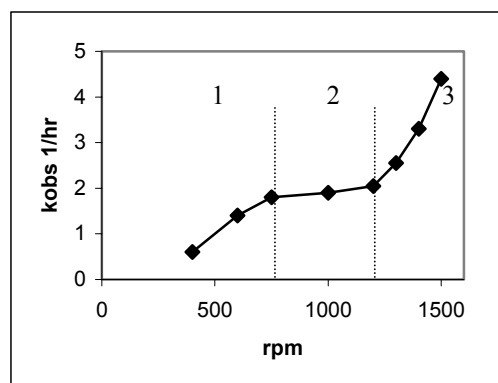
Some reactions, such as the benzylation of phenylacetone, are transfer rate limited even at very high rpm. These reactions exhibit strong dependence of reaction rate on agitation even at very high agitation efficiencies. In typical laboratory glassware, the overall reaction rate of transfer rate limited reactions can be observed to increase even at 2000 rpm. In such cases which are transfer rate limited even at very high rpm, maximum reactivity can only be achieved at these high agitation efficiencies. It may be necessary to find the optimum agitation efficiency at which the desired reaction rate is enhanced and the competing reaction(s) (e.g., interfacial hydrolysis) are minimized.

Occasionally, one may encounter PTC systems in which the desired reaction as well as the undesired side reactions are both catalyzed by the phase transfer catalyst. For example, if one is using 50% NaOH to

Figure 1: **Effect of Agitation on PTC Acylation** (disappearance of benzoyl chloride was measured)

- [1] transfer limited regime
- [2] intrinsic reaction limited regime
- [3] interfacial hydrolysis regime

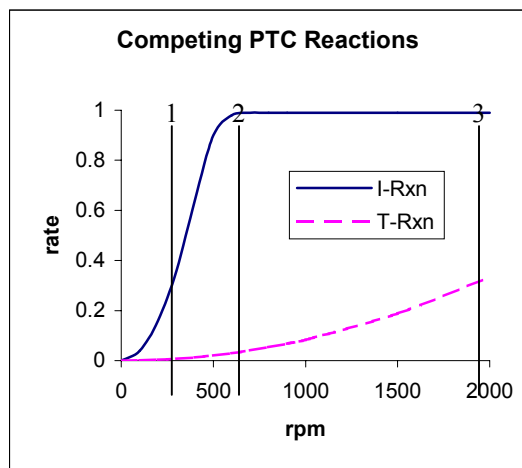
Lee, Y.; Yeh, M.; Shih, Y.; *Ind. Eng. Chem. Res.*, **1995**, *34*, 1572



promote the etherification of an aliphatic alcohol with an alkyl bromide, PTC may catalyze both the O-alkylation as well as the dehydrobromination of the alkyl bromide. If the desired PTC reaction is intrinsic reaction rate limited and the undesired PTC reaction is transfer rate limited, then it is very important to run the reaction at the agitation efficiency just above that needed for mass transfer. This is because additional agitation efficiency will NOT enhance the rate of the desired intrinsic reaction but WILL enhance the rate of the undesired transfer rate limited side reaction. Thus, additional agitation efficiency above that needed to satisfy the mass transfer requirement would result in poor selectivity without any offsetting gain in the rate of conversion to the desired product. This is illustrated in Figure 2. Vertical line 1 in Figure 2 shows an rpm at which both the desired reaction and the undesired reaction are mass transfer limited. The desired reaction at this rpm is slow, but no appreciable undesired reaction is observable. Vertical line 2 in Figure 2 shows the rpm at which the desired reaction achieves maximum reactivity and becomes intrinsic reaction rate

limited (“I-Reaction”). Vertical line 2 in Figure 2 also shows that the undesired reaction is still transfer limited (“T-Reaction”) and is still relatively slow. The rpm of line 2 is the lowest at which productivity is at a maximum and selectivity may be acceptable. Vertical line 3 in Figure 2 is an rpm at which selectivity is poor since we are not achieving additional productivity for the desired reaction, but we are increasing the rate of the undesired competing reaction. The rpm shown for line 3 would not be a good choice for running the reaction. Line 2 would be much better. Depending on the selectivity required, line 1 may be the best choice, in which case, we may want to tradeoff reactivity for selectivity.

Figure 2: **Controlling Selectivity**  
two competing PTC reactions with different rate determining steps



In summary, there are two cases in which over-agitation can be a major pitfall and result in reduced performance in PTC systems. In such cases, an optimal agitation efficiency exists, below which productivity suffers and above which either selectivity suffers or raw materials are wasted by interfacial decomposition processes. It is very important to seek and find the optimal agitation efficiency in these cases. These cases are:

[1] The desired reaction is a phase transfer catalyzed intrinsic reaction rate limited reaction and the undesired side reaction is non-catalyzed and interfacial (e.g., Figure 1).

[2] The desired reaction is a phase transfer catalyzed intrinsic reaction rate limited reaction and the undesired side reaction is a phase transfer catalyzed transfer rate limited reaction (e.g., Figure 2).

The pitfall of over-agitation is particularly easy to fall into since there is a natural tendency to want to strongly agitate two phase systems. This pitfall is also sinister because the process developers/owners usually never find out that they are working under non-optimal conditions.

**Recommendations:** It is strongly recommended that before proceeding to scale up, every PTC process being developed should be screened for agitation efficiency. A simple way to do this is to run the reaction under development at 200 to 700 rpm, in 100 rpm increments in the lab and monitor the disappearance of starting material and appearance of product. This should provide a profile from which you should be able to determine the transfer rate limited regime, the intrinsic reaction rate limited regime, and possibly detect any interfacial or transfer limited undesired side reactions. You may even conclude that your desired reaction is transfer rate limited. In all cases, you will be well prepared to determine the best agitation efficiency for your application. If you think that there may not be time to perform this agitation study, I recommend that you consider the economic impact of reducing your reaction time by 10-20% or reducing the excess reactant by 10-20 mole% or improving your selectivity. The realization of how much performance you may gain will probably help justify the added investment of R&D resource.

There is good news and bad news. The bad news is that agitation is one of a dozen special parameters which need to be optimized when developing or optimizing a commercial PTC application or synthesis (above and beyond non-PTC systems). The good news is that once you are aware of the opportunities in optimizing these special PTC parameters, you can achieve very high performance in your new PTC application. If you feel that developing a high performance commercial PTC application for your company's great benefit will require too much internal resource, then feel free to contact PTC Organics to develop the process for your company. For more information, contact the author, Dr. Marc Halpern of PTC Organics at tel +1 856 222 1146.