

# Process Intensification from a Chemist's Perspective

J. Cihonski and G. Dolbear

## Introduction and Focus

The concept of Process Intensification (PI) is largely credited to Professor Colin Ramshaw, University of New Castle Upon Tyne. Ramshaw's approach initially focused on the ability to significantly improve mass transfer related processes such as chemical reactions and separations to reduce reactor size by using high gravity processing fields such as centrifugal force. This approach led to the development of the Spinning Disk and HiGee (Rotating Packed Bed) reactors. Related to PI is the concept of reactive mixing (Bourne, 2003), which considers the consequences of bringing reactants together at different mixing scales and how this can influence the reaction environment, rate, conversion and selectivity. Although this reactive mixing concept was initially developed using stirred tank reactor principles, it has been expanded to provide insight into a number of mixing devices for process improvement and PI. The application of PI to chemicals and materials processing can have broad technical and economic impact, ranging from large volume petroleum scale processes to nano-scale pharmaceutical applications. PI is also considered to be an enabling tool for green and sustainable opportunities.

Process Intensification (PI) is a broad topic, too broad to address in depth in this short introduction. Our goal is to provide sufficient information and insight to permit a chemist to understand the rudiments of PI and to determine if PI is a technically viable option for his or her application. Since the chemist is usually the first to evaluate potential process chemistry, it is important to think about mixing and processing options early on. In the absence of early consideration of PI, process engineers tend to choose either a stirred tank reactor (STR) or a plug flow reactor (PFT) because these systems have a long history of successful commercial use and there is a high level of technical understanding and comfort. This conservative approach can be an economic mistake that can result in long-term higher process costs.

In this document we will define PI, discuss some of the more significant PI reactor equipment options for chemicals synthesis, provide chemical and material processing examples, and offer some insight and considerations into the potential applicability and benefits of PI. We will not specifically address the application of PI to separation issues

although this is a viable application area. We will also ignore engineering related issues. However, Hessel, et al. (2003) and Keil (2007) address both of these topics.

## **PI - Definition and Levels of Applicability**

Process Intensification (PI) is the significant improvement of a unit process with the goal of improving product quality, reducing equipment size, and reducing process costs. PI has implications regarding reaction rate, conversion, selectivity, separation rate and efficiency, safety and overall process economics. A unit process is a reaction or process step that relies on mass, momentum and/or heat transport; examples are mixing, evaporation, liquid-liquid extraction, crystallization, and various mechanical-physical separations. In some ways any process enhancement program can be considered to be process improvement. From our perspective, process improvement moves into the realm of PI when the goal of an improved rate, conversion, selectivity or separation is not attainable using conventional technology. As a rule of thumb, this improvement often entails an order of magnitude of improvement to a feature of the process. Examples include a rate improvement of 10x or larger or a decrease in an impurity concentration by 10x or more.

This definition of PI is admittedly somewhat arbitrary and what constitutes PI can vary significantly from one application to another. The key is the ability to provide a significant economic and processing advantage over conventional technology. For our discussion here “conventional technology” will be limited to STRs, PFRs and their modifications. Stankiewicz and Moulijn (2002) provide insight into the benefits of PI and on the barriers to implementation of PI mainly from a chemical engineering perspective.

When considering significant process improvements to a chemical or material synthesis, one can identify several levels of PI. We shall consider four of these in turn.

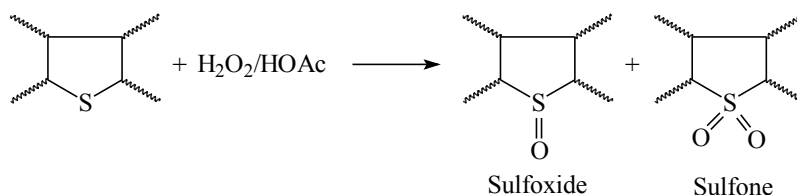
*Similar chemistry, selectivity and conversion but a faster reaction rate* From literature reports it is often possible to improve the rate of a process from one to three orders of magnitude by improving the mass or heat transport through improved mixing efficiency. Obviously, if the reaction is inherently slow and heat and mass transport are not issues, PI will likely have very little impact on the process. Increasing reaction rates with no changes in selectivity can be important in many areas of performance chemicals, where a product's utility is more a function of its reproducibility than its purity. Examples are corrosion inhibitor blends, pigments and lubricants. However, when mass or heat transfer is improved

over a conventional process, it is not surprising to find that the selectivity is often altered as well. This potential issue needs to be considered in those areas where it is important NOT to change the product composition or overall properties. Pharmaceutical applications are good examples where one usually does not want to (or is not legally permitted to) alter the species present or their relative amounts.

*Similar chemistry and selectivity but increased conversion and faster reaction rate* The goal here could be the complete reaction of a reactant or other unwanted material in a process stream or product. Or it may be to eliminate a process step. For example, in solvent free polymerizations a complete monomer conversion would result in the elimination of the polymer devolatilization step designed to remove unreacted monomers. This higher conversion would result in more product being formed and less organic waste being generated.

*Similar chemistry but increased conversion, selectivity and faster reaction rate* An example is the synthesis of single isomer chiral compounds, the preferred form for new pharmaceutical products. This also applies to high purity and fine chemical applications where purity is of critical importance either for making a pure product or for selectively and completely removing an impurity from a product.

An example from our experience is the selective oxidation and removal of sulfur from petroleum or a fuel product stream. Peracetic acid is an oxidant used to react selectively with the sulfur derivatives in the feed to form the sulfoxide and sulfone derivatives. These polar



species can then be removed by selective sorption or extraction (Gore et al., 2003).

Refinery streams used in diesel applications typically contain more than 0.5 wt% sulfur, in the form of various substituted benzo- and dibenzothiophenes. In the US today, that sulfur must be removed down to <15 ppm to meet the current U.S. diesel fuel specifications. This sulfur removal is essentially quantitative as we usually define it, greater than 99.9 %. In an even more demanding case, petroleum based hydrocarbon fuels that are suitable for use with fuel cell technology must have the sulfur removed down to the ppb range.

The oxidation takes place in a two-phase system, oil and aqueous acetic acid. At the interface, oxidation is rapid, and a batch STR can give very high conversions in less than an hour. Formation of the sulfone requires twice the amount of oxidant as the sulfoxide, but both species can be removed through sorption. Selective formation of the sulfoxide with little or no sulfone being co-generated would provide an economic advantage by cutting the consumption of peroxide in half. Cihonski and Dolbear (2001) found that high shear mixing improved the oxidation rates more than 50 fold in a mixture of thiophenes, while also shifting the products to the more desirable sulfoxides.

*Novel processing environments to promote currently difficult or impractical chemical reactions* PI makes it possible to rapidly generate uniform and promising novel reaction environments that can provide unique chemical and processing opportunities. Significant research and development areas that fall into this category are the use of supercritical carbon dioxide (ScCO<sub>2</sub>) as a reaction medium, the use of water as a medium for organic reactions, and the use of ionic liquids, especially when used in conjunction with improved mixing and heat transport techniques. An example of this level of PI using an ionic liquid will be covered later in this report.

### **Technical basis for PI**

It is reasonable to ask what is happening in the reactor that makes the results so different from conventional mixing and reactor technology. The answer to this question is complex since the fluid dynamics can be difficult, especially in multiphase systems. Fortunately, it is possible to gain a qualitative but useful feel for what is likely occurring in a mass transport limited system beginning with the Arrhenius rate equation and then considering what process changes must occur to obtain a significant rate, conversion or selectivity improvement.

$$Rate = \kappa e^{-E_a/RT} [A] [B] \quad \text{where } \kappa = zp$$

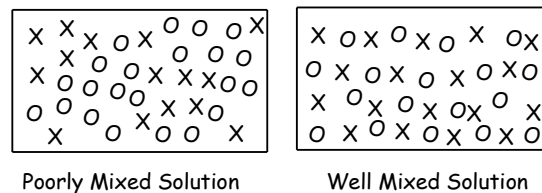
For this form of the rate equation, the *Rate* is the rate of product generated or reactant removed that is required to attain the commercial goals of the process.

The pre-exponential factor,  $\kappa$ , is essentially a constant for a given reaction, reactor type and configuration and set of reaction conditions. However, even if  $\kappa$  is optimized for an STR its value can be low by orders of magnitude when compared to what PI equipment and methods can provide. Looking at  $\kappa$  a bit closer we see that it has two components –  $z$  and  $p$ , both are weaker functions of temperature than the exponential component of the rate equation.

- $z$ , the collision frequency, is an estimate of the number of collisions between the reactant species A and B and
- $p$ , the collision efficiency, is largely a function of reactant steric factors.

The collision frequency,  $z$ , assumes a uniform and well-mixed reactant solution with diffusion being the dominant micro-scale mechanism for a collision to occur. The reactant distribution uniformity assumption is usually not true, but for slow reactions in most conventional processes it is a safe approximation. To ensure that the maximum reaction rate is attained we need to select mixing technology that provides *rapid mixing* on an appropriate scale to ensure the *high dispersion* and *uniform distribution* of the reactants throughout that reactor volume.

The  $p$  term, collision efficiency, is usually considered to be a function of the reactant geometry. For simple small spherical reactants the value of  $p$  should be close to unity. However, as reactant molecules become more complex only a small portion of the molecule is available for reaction, the part where the reacting function is located. This means that the collision efficiency will decrease and in turn  $\kappa$  will decrease over what would be expected based on  $z$  alone. Also by default, the inefficiency of mixing will also be incorporated into  $p$  since if the reactants are not uniformly distributed at the molecular level then many of the anticipated collisions will not be productive since collisions will occur between A and A or B



and B but not between A and B. The illustrating figure above assumes a single-phase solution. It should be evident that as one moves to a multiphase system it will be more difficult to attain a well mixed solution, which in turn will decrease  $p$  and in turn decrease  $\kappa$ . Improving the rate of reactant dispersion and the reactant uniformity of distribution through more efficient mixing should increase the  $p$  value and in turn increase  $\kappa$ .

The activation energy,  $E_a$ , depends on the nature of the reactants, products, the presence of a catalyst, and on solvent effects. For a given reaction system  $E_a$  will not usually be a critical consideration for PI once a system is set. However, it can become an important consideration if there are significant options for altering the process chemistry, e.g. using water,

supercritical CO<sub>2</sub> or an ionic liquid as the reaction media instead of an organic solvent (assuming an organic reaction). Related to this term is the process temperature. The higher the process temperature the faster the reaction rate, but the energy requirements will be higher and the chance of unwanted side reactions and/or product decomposition will increase. With PI, if the reaction rate is improved essentially through improved mixing then it may be possible to actually reduce the reaction temperature and still have a viable reaction rate. This can have positive or negative effects on selectivity, depending on relative activation energies,  $E_a$ , for side reactions. Several PI reactor options, especially the microreactors, have specifically addressed heat input and removal for superior temperature control and in turn product quality and safety.

Reactant concentrations of A, [A], and B, [B], are significant since they in part determine the mixing mechanism and the reaction conditions that are likely to be required to attain the process goals. A high concentration relieves some of the stress of the mixing requirements and under PI conditions the reaction is easier to enhance. However, at low reactant concentrations the overall reaction rate will be slower. The reaction rate can be increased by:

- increasing the concentration of one or more of the reactants,
- increasing the reaction temperature, or
- enhancing the mixing efficiency.

Based on this discussion it is possible to estimate what the improvement to  $\kappa$  needs to be based on the reactant concentrations. Then it is a matter of determining which PI technology might work best. If this approach does not provide the desired results then methods that influence  $E_a$  should be considered.

### **Impact of Mixing on PI**

Although mass, momentum, and heat transfer are interrelated, in this section we will focus on mixing and its impact on mass transfer, reaction rate and selectivity. The mixing rate and mixing scale can impact the reaction rate since these are often key components in selecting the appropriate PI options for chemical reaction enhancement. Reaction rate depends on efficient mixing occurring in a timely manner. In conventional equipment the mixing, assumed to be turbulent, occurs from the top down – large to small eddies. Large eddies generate a rapid but non-uniform total volume dispersion of the reactants. The large eddies decay into smaller eddies that further disperse the reactants on a smaller scale until the smallest eddies disperse the reactants at the  $\mu\text{m}$  scale. The reactants are then ultimately

distributed at the sub micron scale by diffusion. While diffusion occurs throughout this process, it is most significant at this smallest scale where it has the greatest impact on the reaction rate and often the selectivity.

Bourne (2003) assumes turbulent mixing in a STR or PFR with a complete range of mixing scales and mixing times. He breaks the mixing scales down into three levels:

- Macro, where the length scale is  $>mm$  and the mixing half-life time can be in seconds. The larger the reactor, the larger the eddies and the longer the time required for efficient mixing to occur. One estimate for a STR is that the largest eddies can be up to 20% of the tank diameter and the eddy life can be long, many seconds based on the half-life mentioned. These large scale eddies are important for dispersing the reactants throughout the reactor volume, but they are poor at providing an overall uniform distribution of the reactants that would lead to the maximum reaction rate.
- Meso, where the length scale is from mm down to a few  $\mu m$ , and the mixing half-life estimate is in milliseconds. At this time scale we see rapid mixing and remixing of reactants so large reactant concentration gradients should be quickly alleviated.
- Micro, where the length scale is smaller than  $\mu m$ . This includes the Kolmogorov length scale (Harnby, et al., 1985), which is the smallest eddy size that can exist before it is dissipated due to viscosity forces. After the eddy dissipates the fluid is in a small-scale laminar flow regime. This mixing half-life is also in milliseconds.

The mixing rate is limited, like in any kinetic process, by the slowest step; in a STR that step is the macro-scale mixing. The difference between the macro and meso- or micro-scale mixing can easily be 1,000x, so we need to overcome the problems with the macro-scale mixing to achieve an improved reaction rate. The challenge then becomes how to improve the mixing efficiency and decrease the overall mixing time. It seems reasonable that it should be possible to accomplish this by decreasing the eddy size in the mixer by using a smaller mixing chamber. This also should shorten the mixing half-life and quickly lead to a well-distributed and uniform reactant solution. This ability to improve the mixing rate leads to faster initial mixing as well as continued rapid remixing of unreacted molecules to ensure a continued fast reaction, with the possibility of greater conversion in a short time and the opportunity to alter the process selectivity. However, this improved reaction rate does come at a price: since eddy sizes are restricted, the equipment size is likely also to be smaller, which reduces the volume of material processed in a given time. This leads to a need to

understand what scale of mixing is required for the process and the need to address scalability issues.

Bourne (2003) provides an example that illustrates the ability to control selectivity through an improved understanding and application of mixing levels and mixing times. In the nitration of benzene and toluene, rates measured separately show that the toluene should react 18-26 times faster than benzene. However, in a comparative nitration run in a simple stirred beaker toluene reacts only about 3 times faster. This implies that the reactants are not uniformly dispersed at the molecular level so that a packet of the nitrating reagent and one of the benzene remain in contact too long thus skewing the observed selectivity results. However, using a Vibromixer in place of a stirring bar the toluene shows an improved relative reactivity of 13.2 versus benzene due to enhanced mixing efficiency. A Vibromixer is a rotating and vibrating shaft that transmits force to a perforated mixing plate attached at the end of the shaft. As the plate vibrates up and down, liquid jets are generated (Rütten, 2008). This example demonstrates that by improving the mixing at the micro level it is possible to significantly alter product selectivity.

### **Selected PI Reactor Technologies and Applications**

PI technology can be separated into two categories: equipment and methods. Equipment constitutes stand-alone hardware that provides the desired significant improvement. Methods are associated techniques that may provide the “intensification”, but more often they need to be used in conjunction with one of the equipment methods. These categories are further defined and covered by Stankiewicz and Moulijn (2000). Examples of PI-enhancing equipment addressed here include microchannel reactors, spinning disk, static mixer, rotor/stator, and jet impinger systems. Other equipment that can be useful for chemicals synthesis but not covered here include: rotating packed beds (Hi-Gee), monolith reactors, loop reactors, oscillating flow reactors, Venturi based systems, membrane reactors and reactive distillation.

In the section that follows, we will address three examples of PI enhancing methods - ultrasonics, microwaves and the use of ionic liquids.

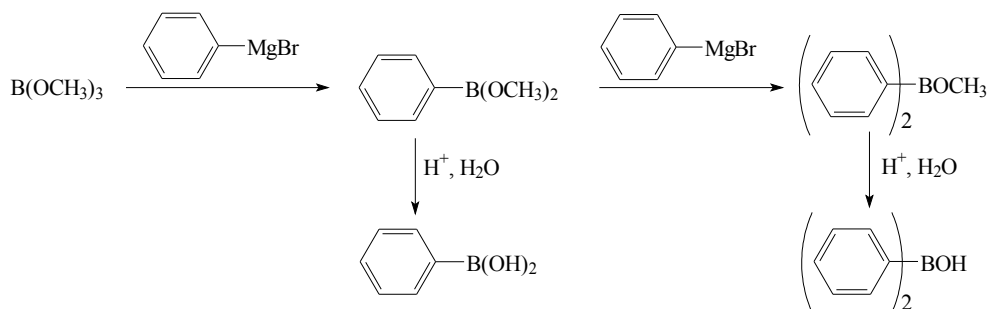
*Microreactors* – This group of reactors is presented first since it probably represents the largest number of PI reactors being evaluated and used for chemical and material synthesis. The open literature clearly shows the popularity of this type of reactor, and especially the microchannel

configuration. The simplest reactor configuration is just a 10 to 1,000- $\mu\text{m}$  diameter tube either as a stand alone tube or as a multitube configuration having hundreds to thousands of channels. These reactors are commonly machined from metal or etched into silicon or glass. The capillary or tube can have either a straight or a curved configuration, and this can impact the fluid dynamics and thus the reactor performance. In the simplest case, thin streams of miscible reactants are injected into the capillary and they flow like ribbons through the tube. Because of the narrow width of the capillary the time for diffusion between the reactant streams is short compared to the fluid residence time in the reactor. The result is an improved reaction rate. Multiphase systems can present special challenges for this technology.

Two important advantages of a microchannel reactor are its modular nature and excellent heat transfer characteristics. The modular nature permits the reactor to be readily scaled by increasing the number of channels. Since all the channels can have the same characteristics, it is a simple matter to increase reactor size without incurring scale-up issues. However, a disadvantage related to this scalability is that an extensive reactant distribution system may be required and this can increase the reactor system cost as the number of channels increases. Since the surface area of the capillary tube to liquid volume is high, the heat transfer efficiency is also high. This makes it a good choice for highly endo- and exothermic reactions that are difficult to control by conventional technology. This type of reactor is also well suited for high throughput testing and small-scale production.

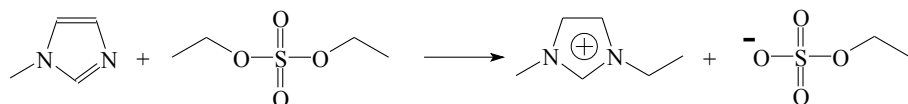
If the sole criterion for success is an improved reaction rate, other PI equipment and methods might be more suitable. Much work has been done to determine what chemistries are most suitable for this approach with a major limiting trait being the ability to handle solid reactants or products without fouling. Thayer (2005) and Mason et al. (2007) provide good overviews of the potential of microchannel reactor technology.

As an example, phenyl boric acid can be prepared with improved purity using microchannel technology (Yoshida, et al., 2005). The phenyl product is used in pharma, ag and polymerization catalyst applications. Loss to the unwanted diphenyl derivative can be significant, as the



monophenyl intermediate reacts with a second phenyl Grignard. The side reaction is rapid at higher temperatures, making good temperature control important. In the batch process, the phenyl derivative forms in ~71% yield with a diphenyl impurity yield of ~14%. In a microchannel reactor the phenyl derivative yield is improved to ~94% and the diphenyl component is decreased to <1% yield.

The synthesis of ionic liquids is another example of the need for effective heat removal and temperature control. Renken, et al. (2007) describe the synthesis of 1-ethyl-3-methylimidazolium



ethylsulfate in both a 6 mm diameter tube reactor and a 600  $\mu\text{m}$  tube diameter IMM (Institut für Mikrotechnik Mainz) microchannel reactor. In the 6mm tube the reaction initially started at 40°C but quickly lead to a thermal runaway. However, in the microreactor the temperature was well controlled and lead to a 50x decrease in residence time and a 3 order of magnitude improvement in productivity.

Nippoh Chemicals Co. announced the commercial production of 1,000 mt/y of 1,1,1-trimethoxyethane, a pharma precursor, from acetonitrile (see Ondrey, 2006) using microreactor technology. The reaction is highly exothermic, making efficient heat transfer and temperature control an important issue. The process has been run in a 100 mt/y pilot unit and the final plant size is anticipated to require about 1/5 of the floor space that a conventional process would require.

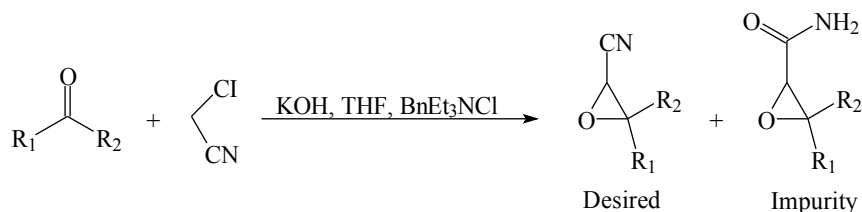
On scaling up, two multichannel reactor options that can provide good mass and heat transport are the HEX reactor (Heat Exchange Reactor), and the multichannel reactor by Velocys. Both are documented in patent and open literature.

*Spinning Disk Reactor (SDR)* – This reactor is one of the original PI reactors developed by Ramshaw, and several generations of improvements have followed. A simple SDR is a disk rotating at a high speed with the reactants metered onto the center of the disk, where they spread outward via centrifugal force as a highly sheared thin film. The disk can have either a smooth surface or a raised pattern designed to promote desired fluid dynamic characteristics that impact the mixing mechanism. A gas can be added to this system and the diffusion time to penetrate the thin liquid layer is shorter than the residence time of the fluid on the disk surface. This leads to improved mass transfer and a faster reaction rate. SDR systems have

also been designed with good heat transfer efficiency so highly exothermic or endothermic processes can be controlled. An advantage of this system is that the open disk surface makes it easier to remove volatile byproducts and drive a reaction to completion. An example of where this could be useful is in loss of water to drive an esterification or growth of a condensation polymer such as a polyester or polyamide.

The spinning disk reactor also makes it easy to do photo assisted processing such as uv initiated free radical polymerization. This device is easy to use at scales from the lab through small-scale commercial production (10-20 tons/year) level. However, it may not be practical for large volume chemical or material processes.

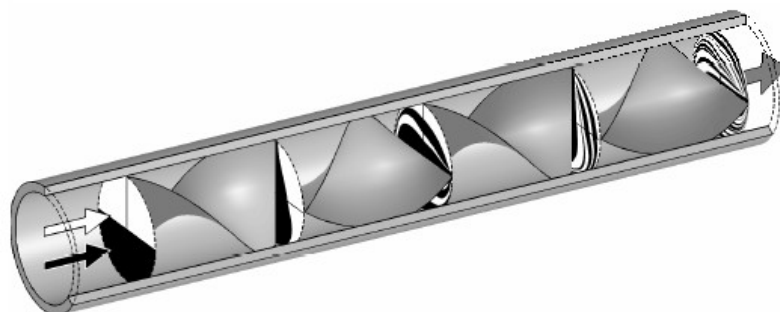
A good example of a SDR application is the phase transfer catalyzed Darzen reaction. The chemistry is:



Comparing the SDR results to a batch process shows that the reaction time was decreased from ~1 hour to about 1 second in the much smaller SDR system (~99% smaller), the reaction temperature could be increased from 0°C to 20°C, so less cooling is required and there was no detrimental effect on the product. Not surprisingly, as the disk rotation rate was increased the conversion increased as well. In both processes the conversion was approximately 90%. The unwanted amide impurity, due to exposure of the desired product to KOH, decreased from 1.5% selectivity in the batch process to <0.1% in the SDR. This work is discussed by Oxley, et al. (2000) along with several other interesting pharma related applications of SDR technology.

*Static Mixers* – Static mixers, also called motionless mixers, are easy to use, inexpensive, and provide cost effective mixing. The mixing environment is well defined and uniform, ideal for chemical processing. Static mixers can be thought of as a PFR with a series of mixing elements inserted – as illustrated. These elements are designed to control the amount and type of mixing that occurs. There are several manufacturers, and they all can provide good technical support for their devices, including the ability to select an optimal internal element

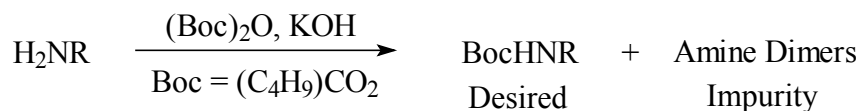
design and operating conditions for an application along with the ability to scale-up the reactor and process.



Static mixers can be used in either a laminar or a turbulent flow regime, and the mixing properties are different, as one would expect. For example, turbulent flow is best for intense mixing of low viscosity reactants, while for high viscosity materials the laminar flow approach will likely be the best choice for energy requirement and mixing mechanism reasons. In the turbulent flow mode, depending on the mixing element design, the mixer is capable of controlling the eddy size distribution, as discussed above. This alteration favors meso- and micro mixing while retaining the dispersing benefits of macro mixing. This in turn should lead to improved reaction kinetics, conversion and selectivity.

In the laminar flow mode, the more viscous reactant streams are repeatedly re-oriented, stretched and cut, as illustrated above for a Kenics KM static mixer. In the above picture there are six mixing elements and each will cut and fold the fluid in half, for a total of 64 folds in this short length of mixer. In a way it behaves like a high efficiency taffy-pulling machine. So, depending on the diameter of the mixer, its length, and the number and design of the mixing elements a significant amount of mixing of difficult-to-mix components can be effectively accomplished in a short time. Bourne, et al. (1992) considered the mixing scales in static mixers and his results provide valuable insight into the use of static mixers for chemicals synthesis applications.

A good example of the use of a static mixer by Brechtelsbauer and Ricard (2001) involves the protection of an amine group using Boc-anhydride. The reaction takes place in IPA/water



with KOH as the catalyst. This example was chosen because it is multiphase and as such requires significantly improved mixing in order to improve mass transfer. The reaction is also

highly exothermic; if the temperature is not well controlled, an unacceptable level of amine dimer impurities form. The static mixer used here is a Sulzer SMV, with a different mixing element configuration from the Kenics mixer illustrated above. The static mixer results compared to a batch process showed that the conversion was similar in both cases at about 98% but the static mixer process was run in 13 minutes compared to about 4 hours being required in the batch process. The 13-minute residence time in this example is atypically long for a static mixer and is due to the need to balance heat removal while achieving high conversion; it is this balance that results in slow flow rates and laminar flow. The static mixer selectivity was considerably better with 99.9% of the protected amine being formed, compared to 97% in the batch process largely because of the improved temperature control.

An interesting related study also of a Boc related amine protection reaction by Choe, et al. (2003) shows a similar temperature and residence time required as above for slow flow through a Kenics mixer. They discovered that their highest yields were achieved at residence times greater than 10 minutes or less than 10 seconds. This can be explained by the greatly improved mixing in the turbulent flow for the short residence time runs.

*Rotor/Stator Reactors* – Rotor/stator devices are characterized by a rotating member that is matched to a stationary member, with a controlled gap between the two components. A simple form is a solid cylinder (rotor) spinning inside an open cylinder. By varying the gap and rotor rotation speed the shear rate applied to the fluids present in the gap can be controlled. An advantage of this type of mixing system is that the largest eddies that can form in the reactor cavity, depending on the specific rotor/stator equipment configuration, are not likely to be larger than the rotor/stator gap. This means that we can limit the eddy sizes generated to favor the meso and micro scale.

These reactors tend to have very little backmixing, so care is needed to ensure that the proper reactant ratio is uniformly provided. This requires careful selection of reactant pumping and metering devices.

Rotor/stator mixers have a long history of improving mixing, especially in the rapid preparation of high quality and well-controlled emulsions. Emulsion preparation information is readily available from most of the rotor/stator equipment suppliers. In a way we can consider the preparation of emulsions in rotor/stator mixers as a long standing and widely accepted PI application if we consider STR based preparation as the conventional technology.

A specific example here involves oligomeric methylaluminoxane (MAO), used as an olefin polymerization catalyst component. The preparation is the reaction of trimethylaluminum (TMA) with water in a hydrocarbon solvent to form  $[\text{OAl}(\text{CH}_3)]_n$  the oligomeric product. It is a difficult material to prepare and its performance depends on its properties, especially its solubility in hydrocarbons. The reaction is very fast, and it should be evident that if mixing is slow and incomplete (non-uniform distribution of reactants) then insoluble aluminum oxides will preferably form. Graefe, et al. (1995) used a rotor/stator mixer to rapidly premix the reactants before the product solution was put into a STR. This pre-reaction of the TMA-water mixture improved the yield and product quality. In a batch reactor, the MAO yield is ~42-44%; in the rotor/stator enhanced system the yield is at least 20% higher, and the reaction can be run at room temperature.

Silver (1983) describes a process for converting cellulose from a pulp plant into simple sugars by hydrolysis using an enzyme based process. He used a modified STR where stator disks were horizontally incorporated around the side of the tank, like horizontal baffles, and rotor disks were installed on the shaft. The rotors and stators overlapped to provide a gap of 5-10 mm. The shear rate could be controlled by varying the rotation speed of the shaft/agitator. The level of shear rate was varied and the hydrolysis rate measured. For an enzyme concentration of 2.5 units/ml, increasing the shear rate doubled the hydrolysis rate. It's important to note that in biological systems the shear rate can easily be high enough to destroy biological materials and so must be controlled. This means that we may not see the large rate improvements in biological based processes that we can see in chemical applications where the reactant and product stabilities are shear insensitive.

As a last example, AET Group (2008) offers a rotor/stator reactor under the name of Raptor. We believe this is a rotor tube with discs or fins attached, placed in a stator housing that fits around the rotor and fins. The gap between the rotor and stator can be adjusted. By controlling the gap, rotor rotation rate, and the flow rate of the reactants, a uniform and controlled mixing environment and residence time can be attained. Two example reactions run with this reactor are the hydrogenation of an alkylated phenol and the methanation of an alcohol with methylchloride to form the methyl ether. For the phenol reduction the batch process took ~4-5 hours, required a solvent, and had a final yield ~95%. For the rotor/stator reaction, no solvent was required, the yield was >99%, and reaction time was less than 3 minutes. The batch methanation process took 6 hours and the final product was yellowish while the rotor/stator run was completed in ~2 minutes and the product was colorless.

*Jet Mixers (T or Y Reactors/Mixers)* These devices all work on a simple jet or injector principle. Here we will focus on a two jet T-reactor. The two jet streams are directed so they collide to provide fast and effective mixing predominately at the meso and micro scale. In most T-reactors the total volume of the mixing chamber is small, resulting in short residence times for high flow rates. This short residence time can be a disadvantage where the chemistry is fast but not fast enough to be completed within the residence time. In this situation, the process can be modified by converting the system into a processing loop to extend and control the residence time. An example of this approach is the Buss loop reactor, which uses a Venturi mixer instead of a simple jet. This loop system is good for gas-liquid-solid reactions such as hydrogenations and selective oxidations, which have mass and heat transfer issues. To illustrate this area we will consider two examples of solid synthesis and processing using impinging jet technology.

Mitake, et al. (2001) describes the preparation of ZnS particles by mixing ZnSO<sub>4</sub> and Na<sub>2</sub>S solutions in a batch reactor with the agitator run at 5,000 rpm to yield a solid having a mean particle diameter of 1.4 μm (10% diameter/90% diameter is 0.31/4.52). However, using a two-jet configuration with the reactant streams colliding head-on at 25.5 m/s with a flow volume of 600 ml/s the product solid has a mean diameter of 0.07 μm (10% diameter/90% diameter is 0.03/0.09), which is a significantly smaller and more tightly controlled particle size distribution. Adjusting the stream velocity and the reactant concentrations controls the mean particle size.

As an organic application (Midler, et al., 1994), the drug simvastatin, a hypolipidemic sold as Zocor, can be readily crystallized using solvent differentiation to produce a product with the desired particle size (so milling will not be required) and surface area, greater purity and improved stability. Here the simvastatin was dissolved in methanol as the first reactant stream with water being the second. The streams were injected together using a 1mm ID jet nozzle with a flow rate of 1.1 L/min, and a linear velocity of 23 m/sec. The resulting well-mixed stream was rapidly added to a 4 liter stirred flask with seed crystals and this solution was aged for 5 to 20 minutes prior to isolation. In this case the crystal size was well controlled and the product was purer (99.0% from jet vs. 98.7% from batch), had less of an undesirable form of simvastatin (<0.1% in jet vs. 0.7% in batch) and the jet product had the desired surface area.

Two final comments on using this mixing jet approach to PI:

- In rapid processing using jets, it is possible to use multiple injection ports to combine process steps, e.g. preparing quantum dots (QD) via jet mixing followed by the injection of an additional component to either protect the QD from further growth or agglomeration or to provide a performance coating required for the QD application.
- Depending on the application, it may be necessary to consider the impact of agglomeration or deagglomeration on the product in this intense mixing environment.

## Selected PI Methods and Applications

We will provide three examples of PI Methods. A more extensive list is presented by Stankiewicz & Moulijn (2000).

*Ultrasonic Assisted PI* – Ultrasonics uses sound in the 0.1 to 100 nm wavelength range to enhance mixing and chemical reactions. Two levels of sonics are in common used: a low level with sufficient energy to enhance mixing but not sufficient to perform or directly assist the chemical reaction and a high level that imparts significantly more energy. The high level creates voids, acoustic cavitation, and this cavitation results in bubbles being formed. When the bubbles collapse they generate a micro jet of fluid and a high-energy environment that can enhance the reaction rate. From a review covering the use of sonics in synthesis by Cains, et al. (1998) we will consider two examples of this enhancing method.

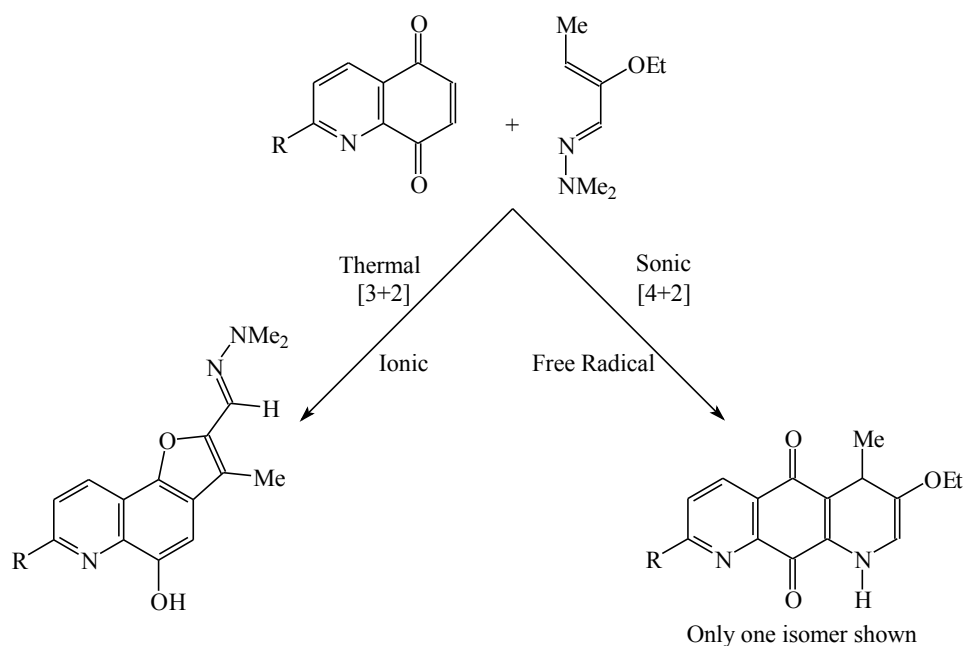
The first is a phase transfer catalyzed (PTC) benzylation of a secondary amine. The reaction



was enhanced by the use of sonics over the thermal preparation. In this reaction a phase transfer catalyst (polyethylene glycol methyl ether) was used and the reaction rate was found to be dependent on the base concentration and its transfer efficiency. By using sonication, a 20-40% yield enhancement over the thermal-only batch reaction was found. However, the use of sonics did not lead to a similar order of magnitude rate improvement as we saw with other PI mixing technologies. This implies that a coupling of a PI enhanced mixing technique with sonics should be a further enabling technique. In effect we see this in some comparative crystallization results from Accentus (McCausland and Reay, 2008 and related patents) where they compare the use of their high shear sono-enhanced vortex mixer to a Y-Jet mixer and a CSTR to prepare crystals of a pharmaceutical by the anti-solvent method. Their enhanced vortex mixer resulted in a narrow crystal size range of ~3 to 5  $\mu\text{m}$ , the Y-mixer ~3 to 17  $\mu\text{m}$  and

the CSTR yielded ~3 to 32  $\mu\text{m}$  particles. No specific product identity or process details were provided.

The second example is a Diels-Alder cyclization. Two different mechanisms are possible – ionic and free radical for the reactants shown below. The use of sonication permitted the mechanism to be altered from the ionic to the free radical and thus to show chemistry that might be difficult to perform using more conventional techniques. The reaction rates were not provided, but that was not an important part for the study, and the selectivities were low – both products form with about 45% selectivity.

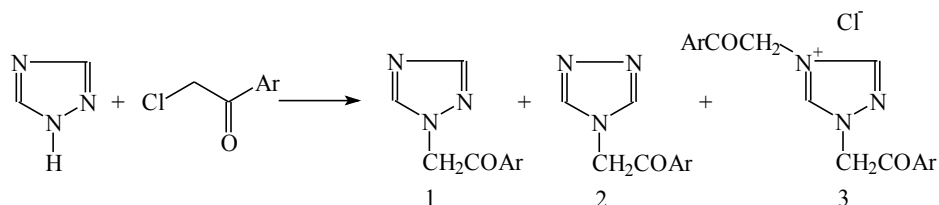


*Microwave Assisted PI* – Microwave technology uses the electromagnetic radiation spectrum in the 0.3 GHz to 300 GHz region. Microwaves can interact with materials in several ways. They can:

- be absorbed by polar molecules and materials that in turn heat the surroundings,
- be reflected by metals, or
- pass through an insulating material.

Microwave devices can be stand-alone or incorporated into a reactor system, and product literature for various applications and configurations is readily available.

Here we consider an example of the use of microwave technology that improves product selectivity and the possibility of eliminating the need for a solvent. Loupy, et al. (2001)



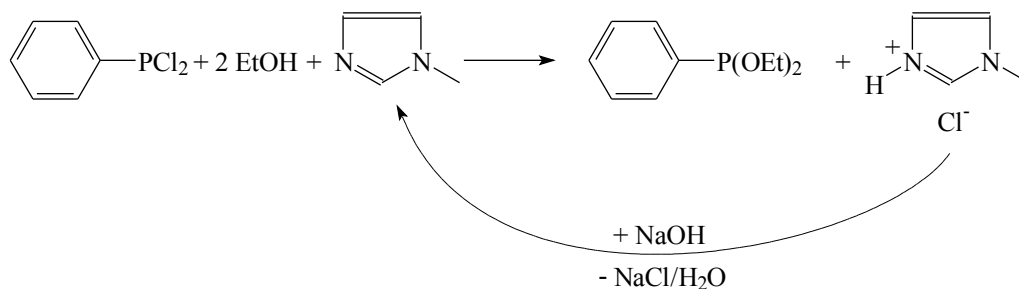
compared the product selectivity for the illustrated condensation reaction run as a thermal and a microwave driven reaction with various solvents. The results, Table 1, show that with a polar solvent, which absorbs microwaves, the results are similar to what is seen in the thermal reaction. However, with a non-polar solvent, or with no solvent, the selectivity is significantly enhanced over the thermal reaction analog. Both the ability to improve selectivity with microwave technology and the possibility of eliminating or decreasing solvent use are advantages.

**Table 1**  
**Comparison of Microwaves to Conventional Thermal Methods**

Solvent	Reaction Mode	% Conversion	% Selectivity, 1/2/3
Pentanol or DMF	Microwave	90	95/5/0
	Thermal	90	95/5/0
o-Xylene	Microwave	82	100/0/0
	Thermal	95	32/28/40
No Solvent	Microwave	92	100/0/0
	Thermal	100	36/27/27

Though not mentioned in the reference, it is likely that the reactor in this effort was a simple stirred vessel and it would be interesting to perform the same chemistry in a PI enhanced mixing environment with and without the microwave enhancement.

*Ionic Liquids* – An excellent example of the use of ionic liquids is found in BASF's BASIL process. The preparation is for a phosphine-based photo-initiator.



This is a very simple but elegant use of ionic liquid chemistry to improve the process productivity by 4 orders of magnitude. The inherently fast reaction generates HCl as a

byproduct that must be removed. The N-methylimidazole reacts readily with the HCl to form an ionic liquid. This ionic liquid rapidly separates into a second easily removed phase for regeneration of the getter. This attractive feature is broadly applicable to related chemistries where a strong acid by-product needs to be removed quickly. However, the regeneration of the N-methylimidazole does constitute an additional process step. This example of ionic liquids, along with several other interesting ionic liquid applications, is covered in an overview article by Short (2006).

### **Application Areas and Opportunities**

Numerous opportunities exist for applying PI to chemical and material synthesis and processing. While the selection of PI equipment and enhancing methods can be somewhat of an art, it should be possible to identify as least a couple of approaches with potential for any process. We have assembled a list (Table 2) of areas that we consider to be some of the better market and application areas for PI.

Opportunities for PI may be found for any reaction or process that has mass and/or heat transfer issues that cannot be resolved through conventional technology. Two key questions for selecting an appropriate PI approach are:

- Is the mixer/reactor and any associated method well suited for chemical PI opportunity?
- Is it scalable for large-scale commercial applications?

A few considerations we have found to be useful in addressing the above two questions are:

- Are product composition changes that can occur with PI conditions a commercial problem? As we have mentioned several times, selectivity changes can be marked. Such changes can also provide valuable insight into the chemistry.
- Is the effect of mixing on the individual process step and byproduct rate constants known? When considering relative reaction rates based on known, non-PI, rate constants, remember that the rate constant can change by several orders of magnitude from the STR or conventional value. Also, the rate constant changes with PI will usually be a strong function of the degree of mass transport limitation. This means that reaction rates will not necessarily improve proportionally with PI and in fact they likely will not. The larger the mass transport limitation the larger the potential for PI to improve the reaction rate assuming the chemical reaction itself is not inherently the limiting factor.

- Is the process to be batch or continuous? Conventional wisdom is that a continuous process is more cost effective and can provide the highest quality product. Sometimes, however, for nontechnical or economic reasons a batch process may be “required” unless there is a change in the way a product is accounted for. An example of this is the use of lot numbers in pharmaceutical production. How does a continuous process convert to a lot number and what is an acceptable approach?
- Is there a reasonable way to scale-up the process? For the equipment discussed in this document, some options are more easily scaled to a desired level than others. A successful scale-up will depend in part on the ability to maintain the test reactor’s micro mixing environment on a commercial scale.
- Is an existing technology a candidate for retrofit? Options here include completely new equipment, retrofitting a current process by adding a PI reactor to improve the product and boost output, and simply inserting steps for pretreating or premixing the reactant stream to shorten the overall process time.
- Is appropriate support equipment available? With short reaction times and often with little back mixing occurring in most PI equipment it is critical to have consistent and uniform reactant flows. For example, the fluctuating stream from a peristaltic pump generates an unsteady flow that can easily translate into non-uniform reaction mixtures passing through the reactor. This usually assures poorer results than are attainable with consistent flows.
- Is it reasonable to replace a conventional reactor by a PI reactor? Doing so may generate mismatched processing that would make other process parts unusable or require significant process alteration elsewhere. Luyben and Hendershot (2004) provide valuable insight into this and other concerns for incorporating PI into a process.

**Table 2.****Process Intensification – Applications and Advantages**

<b>Chemicals</b>	<b>Advantages:</b> improved reaction kinetics, conversion, selectivity, safety, enhanced ability to use water, ScCO <sub>2</sub> and ionic liquids as viable reaction media and may permit the use of novel and less costly feeds <b>Applications:</b> organic, inorganic, specialty, pharma and agricultural chemicals - e.g. hydrogen peroxide, methanol, chiral compounds, total destruction of toxic materials such as bio or chemical weapons, desulfurization of fuels
<b>Polymers</b>	<b>Advantages:</b> improved kinetics and control of molecular weight and distribution, ability to process immiscible components <b>Applications:</b> copolymers with immiscible monomers, immiscible polymer alloy preparation, random copolymerization, in-situ composite synthesis and polymer modification - e.g. nonlinear optical polymers, novel materials and composites for solar energy technology
<b>Solids &amp; Advanced Materials</b>	<b>Advantages:</b> improved particle size, size distribution and morphology control, multi-step coated material synthesis <b>Applications:</b> nanomaterials in general, nonstoichiometric synthesis, morphology control and specialty colloid preparation - e.g. quantum dots (memory, solar cell, blue laser, white light and imaging applications); pharmaceutical morphology as well as time release products, magnetic nanomaterials, catalysts, fuel cell and battery materials, superconductor powders, thermoelectric materials, novel MEMS materials and powdered metal and ceramic precursors
<b>Biocatalysis &amp; Biomaterials</b>	<b>Advantages:</b> Improved fermentation cell growth rates, deagglomeration and mass transfer, controlled nanoscale flow to optimize reactions without cell lysing or enzyme degradation, improved nonaqueous bioprocessing options <b>Applications:</b> fermentation (antibiotics, enzymes, amino acids, vitamins, and xanthan gum) and large volume chemicals such as ethanol for fuel use. Suspension cell culture for stem cell production, monoclonal antibody and gene expression
<b>Mixing/Blending</b>	<b>Advantages:</b> rapid and uniform blending of multiple components and phases with different viscosities, densities or miscibilities at the micro to nano scale <b>Applications:</b> compounding and processing, efficient blending of immiscible materials with widely differing viscosities and densities - e.g. emulsions, polymer composites, inks, cosmetic formulations, solar cell “active material” composites, reactive coating materials
<b>Separations</b>	<b>Advantages:</b> improved phase contacting, product extraction and impurity removal rates and efficiency <b>Applications:</b> liquid-liquid, liquid-gas, liquid-solid extractions - e.g. purification of products via extraction with immiscible solvents, off gas purification, extraction of natural products from complex mixtures

## Summary

Process Intensification shows great potential for improving existing and new chemical processes by taking advantage of new mixing and processing methods. The result is often a sharp increase in reaction rate, more than 10x, with resulting reductions in process volumes and equipment sizes. Along with the rate increases there are often marked changes in process selectivity, allowing simplifications in product workup and reductions in byproduct waste volumes. This is a relatively young area, with ongoing active development of equipment and methods. At this point, applications tend to be limited by a paucity of established techniques for scale-up beyond relatively modest sizes. This is, however, somewhat of an artificial limitation often based more on a lack of understanding than on real equipment constraints. It is also unfortunate that many of the best PI examples are not in the open literature but, hopefully, this will change as more suppliers see the value of marketing the PI benefits of their equipment and as more patents are issued for PI applications. We are confident that many new PI methods and applications will emerge over the next few years, rewarding those who apply the concepts of Process Intensification to their process developments.

## References

AET Group SAS, [www.aetgroup.com](http://www.aetgroup.com); viewed June, 2008.

Bourne, J. R., Lenzner, J., Petrozzi, S., *Ind. Eng. Chem. Res.*, **31**, 1216 (1992). Micromixing in Static Mixers: An Experimental Study

Bourne, J. R., *Org. Proc. Res. Dev.*, **7**, 471 (2003). Mixing and the Selectivity of Chemical Reactions

Brechtelsbauer, C., Ricard, F., *Organic Process Research & Development*, **5**, 64 (2001). Reaction Engineering Evaluation and Utilization of Static Mixer Technology for the Synthesis of Pharmaceuticals

Cains, P. W., Martin, P. D., Price, C. J., *Org. Proc. Res. Dev.*, **2**, 34 (1998). The Use of Ultrasound in Industrial Chemical Synthesis and Crystallization, Part 1. Applications to Synthetic Chemistry

Choe, J., Kim, Y., Song, K. H., *Org. Proc. Res. Dev.*, 7, 187 (2003). Continuous Synthesis of an Intermediate of Quinolone Antibiotic Drug Using Static Mixers

Cihonski, J. L., Dolbear, G. E., unpublished results (2001).

Gore; W.; Bonde; S.; Dolbear; G. E.; Skov, E. R.; US Patent 6,506,914 (2003) Petrostar. Method of desulfurization and dearomatization of petroleum liquids by oxidation and solvent extraction

Graefe, J., Gurtzgen, S., Müller, K. H., Schneider, J., Schrader, R., US Patent 5,427,992 (1995) Witco. Process for Preparing Solutions of Oligomeric Methylaluminumoxanes

Harnby, N., Edwards, M. F., Nienow, A. W., *Mixing in the Process Industries*, Butterworths, London (1985)

Hessel, V., Moulijn, J., Vatcha, J., *Process Intensification in Chemicals Production and Refinery Processes*, The Catalyst Group Resources, Inc. (2003)

Keil, F. J., *Modeling of Process Intensification*, Wiley-VCH, NY (2007)

Loupy, A., Perreux, L., Liagre, M., Burle, K., Moneuse, M., *Pure Appl. Chem.*, 73, 161 (2001). Reactivity and selectivity under microwaves in organic chemistry. Relation with medium effects and reaction mechanisms

Luyben, W. L., Hendershot, D. C., *Ind. Eng. Chem. Res.*, 43, 384 (2004). Dynamic Disadvantages of Intensification in Inherently Safer Process Design

Mason, B. P., Price, K. E., Steinbacher, J. L., Bogdan, A. R., McQuade, *Chem. Rev.*, 107, 2300 (2007). Greener Approaches to Organic Synthesis Using Microreactor Technology

McCausland, L. J., Reay, D., US Patent 7,326,294 (2008) Accentus. Preparation of Small Crystals. Also, see related patents.

Midler, M., Paul, E.L., Whittington, E. F., Futran, M., Liu, P. D., Hsu, J., Pan, S-H., US Patent 5,314,505 (1994) Merck & Co. Crystallization Method to Improve Crystal Structure and Size

Mitake, K., Miyake, F., Yasuda, F., Yazaki, T., Toda, M., US Patent 6,227,694 (2001) Genus Corporation and Hokusui Tech. Co. High Speed Collision Reaction Method

Ondrey, G., *Chem. Eng.*, 13, May 2006. A commercial breakthrough for microreactors

Oxley, P., Brechtelsbauer, C., Ricard, F., Lewis, N., Ramshaw, C., *Ind. Eng. Chem. Res.*, 39, 2175 (2000). Evaluation of Spinning Disk Reactor Technology for the Manufacture of Pharmaceuticals

Renken, A., Hessel, V., Löb, P., Miszczuk, R., Uerdingen, Kiwi-Minsker, L., *Chem. Eng. Proc.*, 46, 840 (2007). Ionic liquid synthesis in a microstructured reactor for process intensification

Rütten Engineering AG, [www.rutten.com](http://www.rutten.com); viewed June 2008.

Short, P. L., *C&EN*, page 15, April 15, 2006. Out of the Ivory Tower

Silver, R. S., US Patent 4,409,329 (1983) Gulf Research and Development. Saccharification Method

Stankiewicz, A. I., Moulijn, J. A., *Chem. Eng. Prog.*, January, page 22 (2000). Process Intensification: Transforming Chemical engineering. See figure outlining PI equipment and methods

Stankiewicz, A. I., Moulijn, *Ind. Eng. Chem. Res.*, 41, 1920 (2002). Process Intensification

Thayer, A. M., *C&EN*, 83(22), 43 (2005). Harnessing Microreactors

Yoshida, J-I., Nagaki, A., Iwasaki, T., Suga, S., *Chem. Eng. Technol.*, 28, 259 (2005). Enhancement of Chemical Selectivity by Microreactors

## The Authors

John Cihonski ([jeihonski@juno.com](mailto:jeihonski@juno.com), phone 408/629-7718) is a consultant in San Jose, CA, with more than 30 years of experience as a creative and entrepreneurial technical and commercial development professional. He has the ability to identify, evaluate, and direct significant pioneering opportunities in the chemicals, catalysis, electronics and advanced materials areas. He has a knack for identifying commercially viable technology and product options in technically demanding emerging areas. John has contributed to several Catalyst Group projects in the past.

John's broad expertise can be attributed in part to his industrial experience at El Paso Products, Engelhard, Catalytica and Holl Technologies/Kreido Laboratories where he was VP Commercial Development for this pioneering process intensification firm. He was a founding partner of VentureWest Technologies, an international technical, commercial development and licensing firm. John has also taught advanced undergraduate and graduate level chemistry and materials science courses at the University of Texas of the Permian Basin.

Geoff Dolbear ([geoff@gedolbear.com](mailto:geoff@gedolbear.com), phone 909/837-8109) is a process chemist with 40 years of industrial experience, 20 years as principal of G.E. Dolbear & Associates. In his career, he has developed catalysts and processes for several petroleum refining applications. His work in coal chemistry includes a project to develop a process for manufacturing polymer- grade terephthalic acid from coal. He is an internationally recognized expert on hydroprocessing of petroleum, and the chemistry and reactions of residual oils. He is co-author with Dr. John Magee of the well-received book, *Petroleum Catalysis in Non-technical Language*. Dolbear is inventor on ten issued U.S. Patents and more than 10 others currently pending. Geoff has contributed to more than 20 reports for the Catalyst Group.