Process Engineering

Production of Industrial Pharmaceuticals and Fine Chemicals

by Ganapati D. Yadav

The principles of selectivity engineering can be applied to a variety of important reactions in pharmaceutical and fine chemical industries with reference to environmental issues and a few examples, covering phase transfer catalysis and solid acid catalysis, are cited to illustrate these aspects. The process engineering and reactor engineering aspects are also briefly outlined.

In pharmaceutical and fine chemical industries, as also speciality, dyestuff, agrochemical and fragrance industries, multi-step and multi-phase batch reactions are frequently encountered which involve several cumbersome and expensive separation/purification stages which result into poor atom economy. Pharmaceutical and drug industry typically produces 80-100 kg of by-product or waste per kg of desired product. A challenging aspect of multi-stage synthesis, particularly of bio-active compounds, is that the complexity of the process goes on increasing with each additional stage thereby affecting the desired selectivity because the number of functional groups and the number of chemically reactive centres in the molecule increase, steric hindrances influence, and thermal stability of compounds decrease. Furthermore, recovery and reuse of solvents and/or reactants add to the costs.

Sources of pollution

The basic building blocks in multi-step synthesis are mostly aromatic compounds with incorporation of such groups as halo, -NH$_2$, -OH, -NO$_2$, -SO$_3$H, alkyl, acyl, aryl etc. which change the reactivity of the cyclic compound and sometimes the color and odor of the final compound. Multi-step synthesis is typically done via routes which do not take into account the atom economy or the amount and nature of co-products or by-products. Catalysis, if any, is limited to homogeneous catalysis involving highly corrosive substances posing disposal problems. Use of solvents is also very common. Low boiling, halogen containing or hazardous inflammable solvents are used. Some of the important precursors used in these industries are: aniline, acetanilide, benzyl chloride, benzoic acid, monochlorobenzene, chloronitrobenzenes, cresols, cresylic acid, cumene, cyclohexane, cyclohexanone, dichlorobenzenes, dihydroxbenzenes, dimethyl sulfate, ethylbenzene, bisphenol-A, α-methylstyrene, nitrobenzene, nonylphenol, xylenes, phenol, phthalic anhydride, pyridine, picolines, salicylic acid etc. Most of these are hazardous to handle and wasted during separation or washings. Irrespective of the best solutions to reduce waste at source, it may not be totally avoided and in such cases, it should provide an impetus to convert the waste as an asset and the plant engineers should look for integrated facility to convert the liabilities into an assets.

The environmental challenges faced by these industries during the 21st century will be:

(i) development of theoretically zero waste (or minimum waste) processes;
(ii) minimisation of hazardous products and green house gases;
(iii) replacement of corrosive and non-reusable catalysts;
(iii) evolution of sustainable systems; zero energy input processes;
(iv) development of single-pot or cascade engineered processes;
(v) reduction in number of steps;
(vi) minimum use of solvents, environmentally benign solvents or solvent-free synthesis;
(vii) design of eclectically engineered systems (catalysts, different forms of energies, ultrasound; microwave radiation);
(viii) replacement of petroleum feedstock by renewable resources.

Selectivity engineering principle

From the process economics and environmental view points, the intensification of reaction rates and enhancement of selectivities can be achieved through selectivity en-

---

Ganapati D. Yadav, Chemical Engineering Division - University Department of Chemical Technology (UDCT) - University of Mumbai - Matunga - Mumbai - 400019 - India.

gineering principle [1, 2] which adopts the following strategies:

a) in a biphasic reaction, addition of a third solid phase (porous or non-porous and/or catalytic or non-catalytic), with particle size smaller than diffusion film thickness. The triphasic system can lead to an enhancement in rates by orders of magnitude with reference to the original gas-liquid, and liquid-liquid systems (microphase catalysis);
b) converting a liquid-liquid reaction into liquid-liquid-liquid or liquid-liquid-solid phase transfer catalysis;
c) heterogenising a homogeneous catalyst;
d) cascade engineering or single pot synthesis;
e) eclectically engineered composite catalysts;
f) deliberate incorporation of mass transfer and/heat transfer resistance;
g) on a larger scale, integration of different plants on the same site to achieve environmental goals.

Some of these ideas are discussed in this paper including process engineering aspects.

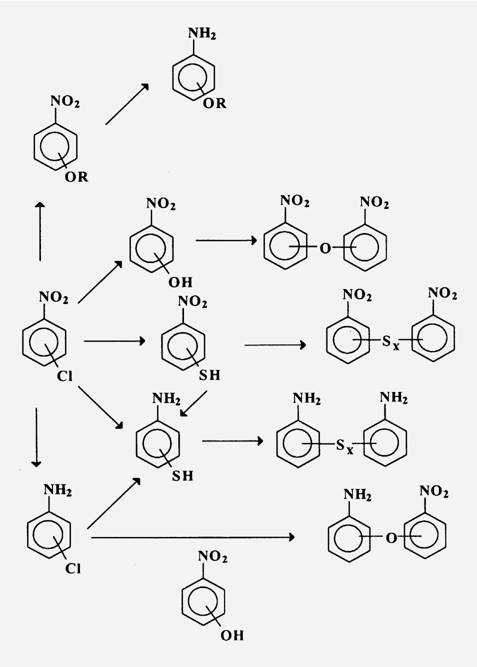

Figure 1 - Cascade engineered PTC: chloronitrobenzene based products

Use of third phase: solid particles

The desired selectivity of the product can be improved by using an inert solvent or an adsorbent or a membrane leading to the generation of a third phase which can remove the product or co-product to improve the conversion. In cefoxitin process, in the acylation step with acetyl chloride, HCl is selectively removed by using powdered molecular sieves (3Å/4Å). In the alkylation of hydroquinone, phenol and aniline with MTBE or *tert*-butanol, yields were improved by using these adsorbents [3].

Creation of a third liquid phase: L-L-L PTC

Phase transfer catalysis (PTC) is now a mature technique for conducting multi-phase reactions. In liquid-liquid-liquid phase transfer catalysis (L-L-L PTC), the third liquid phase is the main reaction phase. The advantages of L-L-L PTC over normal PTC are:

(i) increase in reaction rates by orders of magnitude;
(ii) easier catalyst recovery and reuse;
(iii) the catalyst need not be bound to a solid support;
(iv) better selectivity, hence the attendant difficulties of reduced activity and mechanical strength associated with liquid-liquid-solid (L-L-S) PTC can be avoided.

The disadvantages of L-L-L PTC are:

(i) more amount of catalyst is required, which is expensive;
(ii) the method is not applicable for systems where a very high temperature is required to carry out the reaction.

As the temperature increases, the stability of third liquid phase decreases. However, if the catalyst is stable, then by lowering the temperature at the end of the reaction it could be easily separated into a third phase for recovery and reuse.

Synthesis of *p*-nitroanisole (PNA), *p*-nitrophenetole (PNP) and *p*-butoxynitrobenzene from *p*-chloronitrobenzene (PCNB), sodium hydroxide and methanol, ethanol, *n*-butanol, respectively was found to be very selective and efficient with tetrabutylammonium bromide (TBAB) as catalyst under the L-L-L PTC systems [4, 5] in comparison with the bi-liquid PTC. The nature and concentration of catalyst and the amount of sodium hydroxide are important factors which influence the formation of the third liquid phase (catalyst-rich middle phase) and distribution of catalyst.

It was observed that the third liquid phase was the main reaction phase but at a certain critical concentration of the catalyst, sodium hydroxide was formed as the third phase. The reuse of the third phase is important from economical point of view and it is found that the third phase can be reused effectively.

Cascade Engineered Phase Transfer Catalysis (CEPTC)

Another related term is the so-called *Cascade Engineering* which embraces the single pot (reactor) wherein more than one steps, involving complex reactions, are combined elegantly to produce the desired products by minimising both the by-product formation and separation stages. It could be used to produce different products as well, starting from the same precursor but under different mode of operation. Cascade engineering inher-

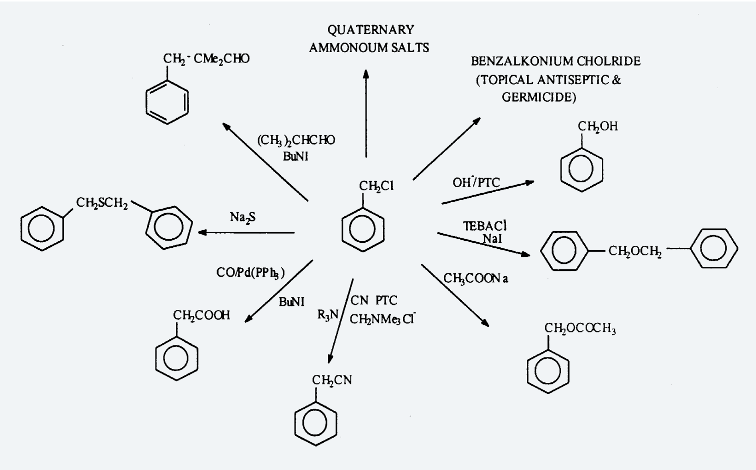

Figure 2 - CEPTC: benzyl chloride based products

ently or tacitly assumes the role of catalysts. In the realm of PTC, the technique can be used under L-L, L-S (reactant), L-L-S (bound catalyst) and L-L-L phase transfer catalysis for certain molecules such as chloronitrobenzenes or benzyl chloride to produce a variety of chemicals [6, 7]. For instance, chloronitrobenzenes are amenable to a variety of chlorine substitution and nitro reduction reactions. In order to study cascade engineering with phase transfer catalysis, chlorobenzenes could be used as the starting materials.

Both the chloro and nitro groups could be manipulated to obtain a variety of products, all having commercial values (Figure 1). Reduction of chloronitrobenzenes could lead to chloroanilines, aminophenols, aminothiophenols or substituted diphenyl sulphides or polysulphides or mixture thereof in the presence of Na_2S under alkaline condition using a suitable PTC. The PTC could be used under L-L, S-L, L-L-L and L-L-S (catalyst) and depending on the type of the system used, the product selectivity could be varied [6, 7].

Benzyl chloride is used in a number of PTC reactions (Figure 2). Of these, the reaction with sodium cyanide leading to phenylacetonitrile has a lot of commercial significance. Since sodium cyanide and potassium cyanide are hazardous chemicals, it is safer to take them as limiting reactants, whereby the final reaction mixture would contain only the unreacted benzyl chloride (b.p. 179 °C), phenylacetonitrile (b.p. 233.5 °C) and the dissolved catalyst. These could be separated by distillation under vacuum. In order to avoid the handling of unreacted metal cyanide, if benzyl chloride is taken in excess, then it can be subjected to further reaction under PTC conditions without separation of the catalyst. For instance, benzyl chloride can be transferred to benzyl alcohol under alkaline conditions as well as phenylacetonitrile hydrolysed to phenylacetic acid. In these reactions under alkaline conditions, instead of phenylacetic acid and benzyl alcohol, C-alkylations of phenylacetonitrile might take place leading to different products which are even otherwise useful in pharmaceutical industry for the preparation of pentapiperdine, idoxifen (nonsteroidal antiestrogen), oxelodine, phenoperidine and *d*-cylonine. Even the higher acetonitriles, namely, benzyl phenylacetonitrile and dibenzyl phenylacetonitrile can also be used for this purpose. Furthermore, the formation of benzyl ether will be there because benzyl chloride hydrolysis leads to benzyl ether as a by-product. In this reaction, phenylacetic acid, used in the synthesis of Penicillin G, could be extracted *in situ* as the sodium salt (Figures 1 and 2).

Process hazards

Industrial accidents are reported to have occurred mostly in batch processes involving hazardous reactants, solvents and exothermic reactions.

Nitrations, oxidations, alkylations, polymerisations, halogenations and hydrogenations are important unit processes, the risk being in that order approximately. Reagents such as phosgene, dimethyl sulfate, formaldehyde/hydrogen chloride (for chloromethylation), sodium azide, hydrogen fluoride, hydrogen cyanide, methyl isocyanate, bromine and for that matter chlorine are hazardous to handle and their use calls for special precautions. Some of these reagents can be replaced by catalytic options such as carbonylation instead of phosgenation, solid superacids for HF etc.

Table 1 - Alkylation of aniline with *tert*-butanol

No.	Catalyst	Conversion (%)	Selectivity (%)[c]
1.	HMS	No conversion	-
2.	ZrO_2	No conversion	-
3.	Sulfated - ZrO_2	5	98
4.	UDCaT-1(i)[a]	20	99
5.	UDCaT-1(ii)[a]	13.9	99
6.	UDCaT-1(i)[b]	30	99

Reaction conditions: aniline:tert-butanol 1:4, catalyst loading: 1 g, temperature: 250 °C, reactant feed rate: 6.5 ml/hour; a: nitrogen flow rate: 30 ml/min., b: nitrogen flow rate: 15 ml/min., c: 4-tert-butylaniline

Eclectically engineered catalysts

In certain cases, it is possible to combine two different functionalities synergistically to get better activity and selectivity. A synergistic combination of sulfated zirconia and mesoporous molecular sieve catalyst (UDCaT-1) [8, 9] with high surface area and acidity is prepared by forming *in situ* deposition of zirconium hydroxide in a mesoporous molecular sieve (HMS) and then promoting its acidity by sulfating agents. UDCaT-1 was found to be an active catalyst for the vapour phase alkylation of aniline with *tert*-butanol to give 4-*tert*-butylaniline selectively (Table 1) [10].

UDCaT-1 is also found to be highly active for the alkylation of *p*-cresol with MTBE as seen from Table 2. The high acidity and controlled activity of UDCaT-1 makes it a truly desirable catalyst. Furthermore, its being an inorganic solid can be employed at higher temperatures in comparison to ion exchanger resin catalysts. The kinetic study shows that all species are weakly adsorbed and the rates are governed by typical second order kinetics [11].

Another such catalyst is based on the sulfated zirconia and carbon molecular sieves. Table 3 shows the effect of different catalysts on conversion and *p:o* selectivity in nitration of chlorobenzene and toluene. S-ZrO_2 yielded high selectivity for *para-* isomer in the nitration of chlorobenzene and no *meta-* isomer or dinitrated by-products were observed. Modification of S-ZrO_2 by coating it with carbon molecular sieve (CMS) to yield UDCaT-2 [12], further enhanced the selectivity for the *para-* isomer though there was no considerable change in conversion.

Table 2 - Activity of various catalysts for the alkylation of *p*-cresol with MTBE

Catalyst	% Conversion	% Selectivity of 2-tert-butyl-p-cresol
1. UDCaT-1	45	97
2. Indion 130	39	92
3. Filtrol-24	19	96
4. Sul. Zirconia	15	91
5. K-10	12	96
6. HPA/K-10	30	96

Reaction conditions: MTBE (220 mmol), p-cresol (220 mmol), catalyst loading: 3.5% of reaction mixture, temperature: 100 °C, speed: 700 rpm, reaction time: 3 hours; by-products formed are: isobutylene, diisobutylene, triisobutylene and methanol

Table 3 - Nitration of substituted benzenes

Catalyst	*Conversion of acetyl nitrate (%)*		*p:o ratio*	
	Chlorobenzene	*Toluene*	*Chlorobenzene*	*Toluene*
No catalyst	No conversion	60	-	0.55:1
S-ZrO_2	47	98	10.6:1	0.75:1
20%DTP/K-10	-	73	-	0.80:1
UDCaT-2	45	98	13.2:1	0.86:1
5%DTP/S-ZrO_2	41	92	8.6:1	0.74:1
5%DTP/S-ZrO_2/CMS	21	95	10.2:1	0.80:1

Reaction conditions: chlorobenzene:nitric acid 2:1, temperature: 30 °C; catalyst loading: 0.029 g/cm³; toluene:nitric acid 2:1, temperature: 20 °C, catalyst loading: 0.012 g/cm³; speed 2,500 rpm, flow rate of nitric acid 1.85×10^{-5} mol/s, reaction time 90 min.

This can be attributed to the fact that the CMS around S-ZrO_2 acts as a barrier for the bulkier *ortho*- isomer and hence favouring the formation of kinetically smaller *para*- isomer.

By the use of eclectically engineered catalyst, UDCaT-2, in nitration of chlorobenzene and toluene, the use of mixed acids was completely eliminated which also facilitated easy separation of the products. UDCaT-2 was found to be highly selective catalyst for nitration of aromatic compounds, chlorobenzene, in particular. The *p:o* ratio of nitro-substituted chlorobenzene and toluene was found to be dependent on the pore size of the catalyst and was found to increase with decrease in the pore size of the catalyst. Also, UDCaT-2 was found to be highly reusable with very small decrease in activity after every use.

The synergism between heteropolyacids (HPA) and K-10 clay was found to be an excellent catalyst for condensation, etherification, alkylation etc. Due to the problems associated with unavailability, transportation and handling of *iso*butylene, particularly for usage in low-tonnage fine chemical and speciality manufacture, it is advantageous to generate pure *iso*butylene *in situ*. Two attractive sources of *iso*butylene are *tert*-butanol and methyl-*tert*-butyl ether (MTBE). *Tert*-butanol is available as a by-product in the Arco process for propylene oxide. MTBE is a good source for the generation of pure *iso*butylene and the byproduct, methanol, is also a very important raw material in chemical industry. On the contrary, the dehydration of *tert*-butanol *in situ* leads to water as a co-product in the alkylation reaction and thus different yields of the alkylated product are expected *vis à vis* MTBE as the alkylating agent. Synthesis of MTBE from *tert*-butanol and methanol has been studied in this laboratory by using a variety of solid acids [13].

Table 4 - Efficacies of different catalysts in alkylation of aniline with *tert*-butanol

No.	*Catalyst*	*% Conversion of aniline*	*% Product selectivity*	
			2-TBA	*4-TBA*
1.	DTP/K-10	34	50	50
2.	DTP/Filtrol-24	31	64	36
3.	K-10	19	58	42
4.	Filtrol-24	22	50	50
5.	DTP	31	61	39
6.	DTS	28	57	43
7.	Al pillared clay	21	66	34
8.	KSF	21	58	42
9.	S-ZrO_2	14	51	49
10.	Na montmorillonite	10	55	45

Reaction conditions: aniline: tert-butanol 1:4 mol, temperature 150 °C, catalyst loading 0.05 g/cm³, speed 1,000 rpm, time: 4 hours, autogeneous pressure: 200 psi, autoclave: 100 ml

Table 5 - Efficacies of different catalysts in alkylation of aniline with MTBE

No.	*Catalyst*	*% Conversion of aniline*	*% Product selectivity*		
			2-TBA	*4-TBA*	*2,4-DTBA*
1.	DTP/K-10	70	53	31	16
2.	DTP/Filtrol-24	51	54	28	18
3.	DTP/KSF	56	56	32	12
4.	DTP/SWy2	47	53	36	11
5.	Filtrol-24	35	43	41	16
6.	K-10	40	44	37	19
7.	Al pillared clay	37	67	26	7
8.	DTP	52	63	29	8
9.	DTS/K10	56	58	34	8
10.	DTS	48	60	31	9
11.	$AlCl_3$/$FeCl_3$/K10	41	54	36	10
12.	S-ZrO_2	26	53	36	11
13.	KSF	24	45	45	10
14.	Na montmorillonite	18	45	42	13

Reaction conditions: aniline:MTBE 1:4 mol, catalyst loading: 0.05 g/cm³, temperature: 175 °C, speed: 1,000 rpm, time: 4 hours, autogeneous pressure: 350 psi, autoclave: 100 ml

Heteropoly acids (HPA) supported on clays have shown superior activity as catalyst in comparison to others in the alkylation and etherification reactions (Tables 4-8) [14].

MTBE was found to be a very effective *tert*-butylating agent *vis à vis tert*-butanol 20% DTP/K10 was found to be the best catalyst for the alkylation of aniline.

The alkylation of hydroquinone was studied with MTBE and *tert*-butanol as alkylating agents with a variety of catalysts amongst which 20% w/w dodecatungstophosphoric acid on K10 (DTP/K-10) was found to be the best catalyst. The rate of alkylation of hydroquinone with MTBE was much faster than that with *tert*-butanol. The reaction mechanism involves weak adsorption of MTBE on the catalyst followed by surface reaction with hydroquinone leading to typical second order kinetics at a fixed catalyst loading.

Reactors and process engineering

Innovation in processes could be achieved through reactor design and making the processes continuous and in contrast to the traditional stirred tank, several other combinations appear promising in pharmaceutical and fine chemical industries; for instance, fixed bed of catalysts with film flow or flooded, loop reactors, fluidized beds, moving beds, multi-stage suspended beds, pipeline reactors with static mixers, distillation column reactors for equilibrium limited reactions, catalysts in tea-bags, catalysts coated structured packings, honey-comb catalysts etc. The conventional stirred tank reactor can be modified in several ways to improve mass transfer and heat transfer rates, via new designs of energy saving impellers, leading to drastic reduction in batch times, favourable mixing environments for microbes and enzymes without affecting their activity and selectivity. Spargers have been efficiently designed to aid mass transfer rates and reactors and separators have been combined (Combo-reactors); for instance, reactive distillation, membrane reactors for overcoming thermodynamic barriers on conversions and yields.

Table 6 - Effect of different catalyst on alkylation of phenol with MTBE

Catalyst	*% Conversion of phenol*	*% Selectivity of butylated phenol* *2-TBP*	*4-TBP*	*2,4-DTBP*	*2,6-DTBP*	*2-/4-ratio*
DTP(20%)/K10	68	38	38	22	2	1.0
DTP	55	4	5	86	5	0.8
K10	52	33	39	25	3	0.84
S-ZrO$_2$	30	40	48	10	2	0.83
ZnCl$_2$(20%)/K10	32	38	42	19	1	0.90
Na montmorillonite	23	53	47	-	-	1.12
Al exchanged K10	20	48	45	7	-	1.06
Zr exchanged K10	14	52	45	3	-	1.15
Cr exchanged K10	11	59	41	-	-	1.43

Reaction conditions: phenol:MTBE 1:2 mol, catalyst loading: 0.04 g/cm^3, temperature: 150 °C, speed: 1,000 rpm; time 4 hours, autogeneous pressure: 200 ps

The role of mixing and micro-mixing are not properly understood in several reactions which are typically conducted in laboratory in round bottom flasks without proper suspension of catalyst or dispersion of immiscible liquids in multiphase reactions. The data so collected are invariably inadequate for scale-up and lead to lower yields or different product distribution altogether on plant scale. In fact, a multipronged approach is essential in process development with a proper flow-sheet and optimization of a number of variables simultaneously starting from a micro-reactor, bench-scale prototype, pilot plant, and commercial reactor, which takes into account reaction chemistry, kinetics, molecular modeling, hydrodynamics, safety, hazard and process control, wherein the role of computers for control and optimization and computational fluid dynamics will be very critical. For making pharmaceutical and specialty chemicals in a multi-product plant, retro-synthesis, chemical tree building and batch scheduling will also be the key elements, where experience gathered in handling hazardous but atom efficient routes will come handy.

Table 7 - Effect of alkylating agent on alkylation of phenol

Alkylating agent	*% conversion of phenol*	*% Product distribution* *2-TBP*	*4-TBP*	*2,4-DTBP*	*2,6-DTBP*	*2-:4- ratio*
MTBE	68	38	38	22	2	1.0
Tert-butanol	55	50	43	7	-	1.16

Reaction conditions: phenol:MTBE or tert-butanol 1:2 mol, catalyst: 20% DTP/K10, catalyst loading: 0.04 g/cm^3, temperature: 150 °C, speed: 1,000 rpm, time: 4 hours;
DTP: dodecatungstophosphoric acid; TBP: tert-butylphenlol; DTBP: di-tert-butylphenol

Ecofriendly solvents

The use of solvents has to be properly understood and a variety of ecofriendly solvents including water and supercritical carbon dioxide should be considered. Water is the nature's solvent and nothing comes closer to it in terms of benignity, abundance, and cost. The role of micro-emulsions with water is also a beneficial way of conducting reactions. Various ecofriendly solvents are aqueous blends, oxygenates, terpenes, *N*-methyl-2-pyrrolidone, propylene glycol, methyl isopropyl ketone and methyl amyl ketone, ethyl acetate, *n*-butyl, isopropyl and *n*-propyl acetate, hybrid aqueous-non aqueous solvents, γ-butyrolactone, terpene *d*-limonene (citrus-peel derived), tropical derived esters, aliphatic and cycloaliphatic hydrocarbons, isopropyl alcohol, butyl acrylate, 3-ethoxy propionate, butyl propionate, pentyl propionate, pentyl propionate, dimethyl glutarate, dimethyl succinate, dimethyl adipate and methylal.

Continuous processes

The continuous processes are inherently safer not only due to low inventory of the reactants but also due to improvements in selectivity. Stirred reactors and tubular reactors of small capacity provide high heat transfer rates, withstand high pressures, can be stopped easily and in some cases can be operated adiabatically without leading to run-away situations by introduction of pre-cooled reactants.

In the manufacture of intermediates for Vitamin A, a nozzle reactor has been used adiabatically. Limitations of thermodynamic equilibrium have been over-

Table 8 - Alkylation of hydroquinone with MTBE

Catalyst	*% Conversion*	*% Selectivity of* *2-TBHQ*	*2,5-DTBHQ*
DTP(20%)/K10	46	72	28
TSA(20%)/K10	42	42	58
K10 montmorillonite	29	100	-
ZnCl$_2$(20%)/K10	25	100	-
S-ZrO$_2$	26	100	-
DTP/ZnCl$_2$/K10	24	89	11

Reaction conditions: hydroquinone:MTBE 1:3 mol, catalyst loading: 0.014 g/cm^3, temperature: 150 °C, speed: 1,000 rpm, solvent: 1,4-dioxane, reaction time: 4 hours; autogeneous pressure: 150 psi;
DTP: dodecatungsto phosphoric acid; TSA: tungsto silicic acid;
TBHQ: tert-butylhydroquinone; DTBHQ: di-tert-butylhydroquinone

come in multi-stage sparged reactors, *e.g.* in the manufacture of phthalimide from molten phthalic anhydride and NH_3. The production of hazardous peroxy esters from the corresponding acid chloride and hydroperoxide is much safer in a continuous mode as also the production of 4,4'-bipyridyl from pyridine. The miniature technology has been exploited by using micro-reactors, which are 3-D structures imbedded like microchip circuits. The principle advantages of micro-channel reactors are enhanced heat and mass transfer rates, suitable for highly exothermic and hazardous reactions with mass transfer limitations leading to unstable products. Some laboratory trials have been reported in literature on nitration of benzene and fluorination with F_2 gas.

Zero discharge processes

Replacement of a large number of liquid acids by solid acid catalysts in alkylation, acylation, isomerisation, esterification, nitration, hydration has been now widely studied leading to zero discharge processes.

Reduction of nitro compounds with hydrogen rather than iron/acid, and epoxidations with H_2O_2 or hydroperoxides rather than using chlorohydrin route or peracetic acid route lead to practically zero discharge.

m-Phenoxybenzaldehyde can be made using a safer and cleaner process based on *m*-phenoxytoluene, which in turn is obtained by vapour phase dehydration of *m*-cresol and phenol, instead of the polluting process based on bromination of benzaldehyde followed by Ullmann reaction with phenol in the presence of copper catalyst. 2,4-Dihyroxyacetophenone can be synthesised from resorcinol and acetic acid in diisopropyl ether over Amberlyst-15. The synthesis of *para*-acetamol is typically done starting from *p*-chloronitrobenzene or phenol in 3-4 stages involving high raw material cost and effluent costs. Instead, the oximation of *p*-hydroxy acetophenone followed by rearrangement by the Celanese process looks attractive.

The Friedel-Crafts acylation of aromatics is the method of choice in today's organic chemistry for synthesising aromatic ketones as reactive intermediates for the production of fine chemicals. The conventional method of preparation of these aromatic ketones is the homogeneous Friedel-Crafts acylation of aromatic hydrocarbons with carboxylic acid derivatives using Lewis acids ($AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$, $TiCl_4$, $ZrCl_4$) or Brönsted acids (polyphosphoric acid, HF). For this purpose, stoichiometric to excess amounts of the catalyst are required for the reaction to proceed.

On the industrial scale, the use of metal halide type of acids, which are preferred catalysts, creates work-up and effluent problems. Indeed, during the work-up of acylation mixtures, catalysts are destroyed which produce relatively large amounts of hydrochloric acid in the off-gas or in the effluent. This hydrochloric acid, which is to be disposed of, originates both from the catalyst and from acyl chloride employed for the acylation. In addition, to this disposal as a considerable environmental problem, the corrosion problem, due to the hydrochloric acid, must be solved.

Table 9 - Effect of different substrates

Acid	*% Conversion*
Phenylacetic acid	74
Benzoic acid	39
Butyric acid	11
Iso-butyric acid	10
Anthranilic acid	15
Acetic acid	30
Propionic acid	21
Heptanoic acid	11

Reaction conditions: acid:cyclohexene 1:3 mol, time: 6 hours, catalyst: Amberlyst-15, solvent: cyclohexane, catalyst loading: 0.015 g/cm³, temperature: 100 °C, speed: 1,000 rpm

Pressure from legislative and environmental bodies together with a growing awareness within the chemical industry led to a search for new eco-friendly processes to replace unacceptable outdated reactions. Therefore, a process that could be environmentally friendly and inexpensive, with respect to the disadvantage indicated, is clearly desirable. Solid acids that give the desired level of activity but which can be easily removed from the reaction mixture with no residual inorganic contamination of the organic products offer obvious advantage over existing methods.

A 100% atom economical process for the preparation of cyclohexyl esters from the carboxylic acids and cyclohexene over ion exchange resin catalysts where all atoms of the reactants are utilised without any by-product formation is reported by Yadav and Goel as seen from Table 9 [15]. The preparation of perfumery esters such as cyclohexylphenyl acetate, cyclohexyl acetate, cyclohexyl anthranilate, cyclohexyl benzoate, cyclohexyl butyrate, cyclohexyl *iso*butyrate, cyclohexyl heptoate, and cyclohexyl propionate is covered. A complete theoretical and experimental analysis is presented for the model studies with phenylacetic acid and cyclohexene.

Esterification

For the esterification of phthalic anhydride with various alcohols such as *iso*amyl alcohol, *n*-butanol and 2-ethylhexanol, a large number of catalysts have been reported; for instance, H_2SO_4, *p*-toluenesulfonic acid (PTSA), methanesulfonic acid (MSA), hydrochloric acid and phosphoric acid, which are all liquid-phase catalysts. Dialkyl phthalates have been prepared from the reaction of phthalic anhydride with alkanols by Yadav and co-workers (1992, 1999) by using various solid acids [16, 17]. Esters of salicylic acid such as methyl salicylate and *iso*amyl salicylate are known to be very good perfumery products used in industry. Methyl salicylate was prepared from methanol and salicylic acid by using ion-exchange resins as the catalyst [18].

Ultrasound-promoted acylation of yara-yara in the presence of solid-acid catalysts

Acylation of 2-methoxynaphthalene with acetic anhydride was carried out by using different solid acid catalysts such as zeolites, acid activated clays, ion-exchange resins, sulphated zirconia and triflic acid supported zeolites under irradiation by sonic waves. The product obtained was 2-acetyl-1-methoxy naphthalene. Acylation of anisole gives products, which are extremely useful in fine chemical industry. Acylation of anisole with acetic anhydride was carried out by using triflic acid supported on mesoporous molecular sieve (HMS), under irradiation by sonic waves. The product obtained was 4-acetyl-1-methoxy benzene and the selectivity towards *para-* product is more than 95% [19].

Conclusions

The principles of selectivity engineering coupled with process engineering can be advantageously used to develop ecofriendly processes in pharmaceutical and fine chemical industries. It should be mentioned here that the paper has addressed some of the aspects of selectivity engineering of a majority of reactions studied in the author's laboratory and several other examples could not be included due to paucity of space.

References

[1] G.D. Yadav, P.H. Mehta, *Cat. Lett.,* 1993, **21,** 391.

[2] M.M. Sharma, Selectivity Engineering, CSIR Distinguished lecturer series, New Delhi, 1990.

[3] G.D. Yadav, N.S. Doshi, *Cat. Today,* 2000 (in press).

[4] G.D. Yadav, S.S. Naik, *Cat. Today,* 2000 (in press).

[5] G.D. Yadav, C.A. Reddy, *Ind. Eng. Chem. Res.,* 1999, **38,** 2249.

[6] G.D. Yadav, S.S. Naik, unpublished work, 1998.

[7] G.D. Yadav, S.S. Sengupta, Y.B. Jadhav, *Org. Proc. Res. Dev.,* 2000 (in press).

[8] G.D. Yadav, M.S. Krishnan *et al., Brit. U.K. Pat. Appl.* GB 2,332,155, (Cl. B01J35/10), 16 June 1999, in *Appl.* 1997/DE 3,595, 12 Dec. 1997, (Eng.); *CA,* 1999, **131,** 132136g.

[9] G.D. Yadav, M.S. Krishnan *et al., Ger. Offen.* DE 19,857,314, (Cl. B01J29/89), 3 Feb. 2000, in *Appl.* 1997/3,594, 12 Dec. 1997 (Ger.); *CA,* 2000, **132,** 139087w.

[10] G.D. Yadav, M.S. Krishnan, M.S.M. Mujeebur Rahuman, Recent Trends in Catalysis, V. Murugesan, B. Arabindo, M. Palanichamy (Eds.), Narosa Publishing House, 1999, 100.

[11] G.D. Yadav, A.A. Pujari, A.V. Joshi, *Green Chemistry,* 1999, **1**(6)**,** 269.

[12] G.D. Yadav, J.N. Jayesh, N. Vikas, *Ger. Offen.* DE 19,857,313, (Cl. B01J27/053), 3 Feb. 2000, in *Appl.* 1997/3,595, 12 Dec. 1997 (Ger.).

[13] G.D. Yadav, N. Kirthivasan, *JCS, Chem. Comm.,* 1995, 203.

[14] G.D. Yadav, V.V. Bokade, *Appl. Cat. A: General,* 1996, **147,** 299.

[15] G.D. Yadav, P.K. Goel, *Green Chemistry,* 2000, **2,** 71.

[16] T.S. Thorat, V.M. Yadav, G.D. Yadav, *Appl. Cat. A: General,* 1992, **90**, 73.

[17] G.D. Yadav, M.S.M. Mujeebur Rahuman, Recent Trends in Catalysis, V. Murugesan, B. Arabindo, M. Palanichamy (Eds.), Narosa Publishing House, 1999, 453.

[18] G.D. Yadav, M.S.M Mujeebur Rahuman, unpublished work, 2000.

[19] G.D. Yadav, M.S.M Mujeebur Rahuman, unpublished work, 2000.

Ingegneria di processo. Produzione di prodotti per l'industria farmaceutica e della chimica fine

I principi della selettività possono essere applicati a numerose reazioni dell'industria farmaceutica e della chimica fine con particolare riguardo alle applicazioni ambientali. Per illustrare questi aspetti vengono citati alcuni esempi riguardanti la catalisi in trasferimento di fase e la catalisi solido-acido. Vengono inoltre brevemente sottolineati alcuni aspetti dell'ingegneria del processo e del reattore.