

Strategies of conducting reactions on a small scale. Selectivity engineering and process intensification*

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Abstract: Advances in conducting reactions, new catalysts, and reactors have made manufacturing on a small scale very facile and even efficient. Selectivity engineering and process intensification permit minimalization of the chemical industry, and some demanding chemistry can be handled in a facile way.

USE OF HETEROGENEOUS ACIDIC/BASIC CATALYSTS

The availability of a variety of cationic and anionic ion exchange resins, zeolites, heteropolyacids, clays (including pillared clays), hydrotalchites, etc. permit just about any reaction requiring acidic or basic catalysts, such as alkylation, etherification, aldol condensation, Michael addition, etc., to be carried out in a clean way, avoiding washing of the reaction product [1–3]. Further, the use of cyclodextrins can allow stereo-, regio-, and optical-selectivity.

Macroporous resins, such as Amberlyst-15, have been extensively used for esterification of a variety of acids with different alcohols, etherification of different alcohols with isobutylene/isoamylene, etc. The availability of supported Nafion as nanocomposites has not only allowed reactions to be carried out up to temperatures as high as 280 °C, but also difficult reactions such as alkylation of *p*-xylene with benzyl alcohol, which does not occur with Amberlyst-15. Nafion nanocomposites have been used to acylate anisole with a variety of acyl chlorides [3].

Na/K alloys, sodium carbonate/potassium carbonate supported, have been successfully used to have side-chain alkylation of toluene with propylene to give isobutylbenzene. In the recent past, some difficult isomerizations and side-chain alkylation of *o*-xylene with butadiene have been carried out industrially.

PHASE-TRANSFER CATALYSIS (PTC)

A variety of liquid–liquid and liquid–solid reactions have been intensified and made selective by using simple phase-transfer (PT) catalysts such as quats, polyethylene glycol-400, etc., which allow ionic species to be ferried from aqueous phase to organic phase. Thus, the problems associated with extremely low solubility of the organic reactants in the aqueous phase can be overcome. In the pesticide and pharmaceutical industries, PTC is used extensively and has changed the fundamentals of business. Figure 1 shows the mechanism of PTC.

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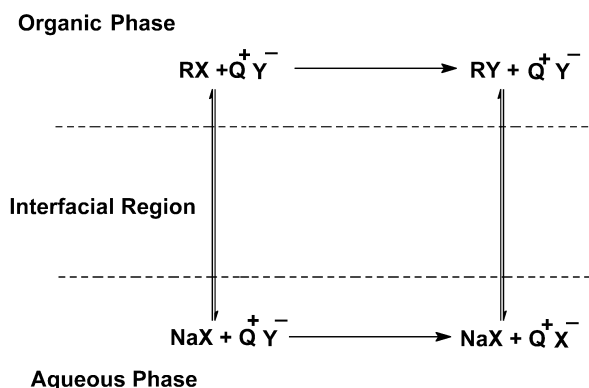


Fig. 1 Mechanism of PTC.

An early example was conversion of benzyl chloride to benzyl acetate/benzoate with sodium acetate/benzoate with benzyl triethylammonium chloride as a catalyst. Now we have widespread uses, such as conversion of benzyl chloride/*p*-chlorobenzyl chloride to the corresponding $-\text{CN}$ compound with aqueous NaCN . A variety of *C*- and *N*-alkylations are commercially practiced. Primary–tertiary alkyl bisperoxides have been made by reacting, for instance, tertiary hydroperoxides with bromoalkanes [4].

We often benefit by deliberately converting homogeneous reactions to liquid–liquid reactions using PTC to adopt cheaper reagents (e.g., aqueous NaOH vs. CH_3ONa), milder operating conditions, higher yields, etc. Consider the case of making tricresyl phosphate, which has been efficiently carried out by using simple water-immiscible solvents to dissolve POCl_3 and reacting with aqueous alkaline solution of cresols, with even PEG 400 as a PT catalyst [5]. Even *O*-, *H*-, and *C*-alkylations have been steered by manipulating operating conditions.

IONIC LIQUIDS

Ionic liquids are receiving much attention as a benign alternative to organic solvents because these can be used repeatedly. Even PTC can be adopted. Ionic liquids do not burn, and there is no problem of emissions.

PHOTOCHEMICAL REACTIONS

The well-known examples of selective side-chain chlorination of toluene, xylenes, and substituted derivatives provide the right backdrop. These reactions can be safely conducted on a small scale. Even photooxygenations have been conducted.

An early example was chlorination of benzene to give the well-known agrochemical benzene hexachloride (BHC). Photochemical oximation of cyclohexane to make the oxime, with NOCl , has been successfully conducted. Photoisomerization of *cis*- to *trans*-vitamin A acetate has been carried out [6]. Photochemical reactions can be further improved through the use of micelles, microemulsions, cyclodextrins, etc.

ULTRASONOCHEMISTRY (U/S)

Sonic wavelengths in liquids are typically 0.1–100 nm, well beyond molecular dimensions. Ultrasonication can speed up reactions remarkably even in mechanically agitated reactors. Solid–liquid reactions such as Grignard reaction, Barbier reaction, etc., benefit due to the creation of “cleaner” surfaces.

U/S works through one or more of the following effects: mechanical and dispersive effect on porous solids; generation of free radicals; promotion of electron transfer; or removal of chemical and biological contamination from surfaces and liquids [7]. A variety of examples, demonstrating a marked intensification of reaction and sometimes even changing the selectivity, have been reported. Consider the case of the reaction between 60 % HNO₃, octanol, and 3-bromo-2,3-dimethyl propanol, which proceeds slowly requiring 12 h for completion. Adoption of U/S gives quantitative yield in just 20 min [8]. Hydrodynamically generated cavitation effects can be gainfully employed to realize comparable results for a variety of reactions [9,10].

MICROWAVE-ASSISTED REACTIONS

Domestic microwave ovens, which use a magnetron to generate microwaves with wavelengths of around 12.2 cm, have been used to carry out a variety of reactions, such as synthesis of dioxolanes, dithiolanes, oxathiolanes, etc., in a remarkably short time and in an efficient way. Microwaves heat the liquid by inducing rotation of polar molecules to align and relax, at a given frequency. Thus, “kitchens” can be adopted to make hazardous chemicals. Attempts have also been made to have on-line continuous-flow systems [11].

BIOCATALYSIS

Biological catalysts allow many important transformations to be carried out under close-to-ambient conditions, and very high regio- and stereospecificity have been realized [12]. Hydrolytic enzymes such as lipases and esterases are widely used. Lipases are ubiquitous enzymes belonging to the esterase class of hydrolases. In many cases, the activity and selectivity of lipases are influenced by many factors related to the reaction medium, pH, and microphase created by salts. (*R*)-cyanohydrins have been made from aldehydes and hydrogen cyanide (HCN) with an (*R*)-hydroxy lipase; (*S*)-enzyme has also been developed to give (*S*)-cyanohydrins. Some examples of difficult conversions are: benzene to dihydrocatechol; beta nicotinic acid to 6-hydroxy nicotinic acid. The biocatalytic route for 7-amino desacetoxy cephalosporinic acid (7-ADCA), by Dutch State Mines (DSM), is very impressive and appears to be the first full-scale application of metabolic pathway engineering. In some cases, enzymes can increase the rate of reaction by up to 10¹² times. Rasor and Voss have given an overview of enzyme-catalyzed processes in pharmaceutical industry and hence have shown how chemo- and regioselectivity is realized [13].

SOLID SUPPORTED REAGENTS

The use of a highly porous support, polymeric or nonpolymeric, for reagents provides a large effective area for the reactions to be conducted in a facile way, besides making separations of product simpler. A recent example refers to nitration of 4-hydroxy benzaldehyde with Fe-nitrate and K-10 montmorillonite, in which nuclear nitration was preferentially realized and practically no oxidation of aldehyde occurred. Metallic nitrates, supported on clays, have been used for nitrations and oxidations. Insoluble supports may provide powerful “handles” to facilitate synthesis [14]. Monoacylation of diols, such as 1,4-butanediol, 1,2-cyclohexanediol adsorbed on silica gel, with acetyl chloride, has been reported [15].

MEMBRANE REACTORS

A range of sophisticated membranes, which can withstand aggressive conditions, are available, and thus, equilibrium-limited reactions can be conducted with reactions and separations being incorporated in the same system. Polymeric membranes can be used for lower temperatures, and zeolites can be used at higher temperatures.

In the recent past, adsorptive chemical reactors have been considered where the chemical reaction, with gaseous or liquid reactants, is carried out in the presence of a solid adsorbent capable of selectively adsorbing the components of the reaction mixture.

DISTILLATION COLUMN REACTORS

It is quite feasible to use laboratory distillation columns in a combo-mode and thus make many products in a convenient way. Here it is possible to usefully employ the exothermicity of the reaction, and both the capital cost and recurring cost associated with steam consumption can be substantially reduced. The well-known example of making methyl acetate by Eastman Chemical may be cited. The manufacture of methyl *tert*-butyl ether (MTBE) is the single largest example, but a number of fine chemicals like methylal, dioxolane, etc., have been made.

ELECTROCHEMICAL PROCESSES

The ease with which oxidations and/or reductions can be carried out with the practically mass-free “clean” electrons makes electrochemical processes well suited for such jobs, including paired synthesis. A variety of lab models are available, which can be conveniently adopted to make wanted chemicals. High specificity is realized [16].

Some industrially important examples are: conversion of *p-tert*-butyl toluene to *p-tert*-butyl benzaldehyde and of *p*-methoxy toluene to *p*-anisic aldehyde; naphthalene to naphthaquinone; fluorinations; and hexafluoropropylene oxide from hexafluoropropylene. An industrially successful example of paired synthesis is of phthalide and *p-tert*-butyl benzaldehyde by using phthalic anhydride and *p-tert*-butyl toluene.

ADOPTION OF CONTINUOUS REACTORS

Due to the low inventory of reagents, hazardous reactions, such as nitrations, can be conducted in a safe way in continuous reactors, and even high pressures, including supercritical conditions, can be adopted. Even a 1-cm³/s flow rate may result in the production of 30 tons per annum of a specified product. Microchannel reactors have further improved the versatility of this strategy. The use of static mixers and monolithic catalysts has further improved the utility of such reactors. Continuous reactive chromatography, adopting simulated moving beds (SMBs), has further strengthened our toolbox to carry out reactions and separations, through adsorption, in an elegant way, particularly for temperature-sensitive substances. Laboratory models of SMBs can give respectable throughputs.

Examples include: Hoffmann rearrangement of cyclopropyl carboxamide to cyclopropylamine; synthesis of diazomethane; conversion of –OH, in a furfuryl alcohol derivative, to –Cl, with SOCl₂ and subsequent conversion to –CN; alendronate where phosphonation of H₂NCH₂CH₂COOH with H₃PO₃ and PCl₃ is carried out; nitration of glycerine; nitration of a pyrimidine derivative; and production of POCl₃ [17].

CONCLUDING REMARKS

It is possible to carry out a variety of hazardous reactions in a safe and an efficient way in a so-called small-scale set-up without being “noticed”. Multistep batch processes are amenable to microprocessor-based control systems.

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