Abstract of the Thesis

Multiphase catalytic reactions have significant impact on the development of new synthetic routes and their scope has been expanding into diverse areas of applications for making value added products. Catalytic reactions in multiphase systems are prevalent in production of fuels, bulk and specialty chemicals, pharmaceuticals, food etc. The success of catalytic processing of multiphase systems has resulted from a synergetic approach to the problem by chemists and chemical engineers\(^1\). Making useful products, at economical yields and selectivities, from the diverse chemistries in such a broad range of applications requires the ability to quantify the interplay of transport phenomena and kinetics\(^1\,2\). Hydroformylation, oxidation, epoxidation, hydrogenation, carbonylation, oxidative carbonylation and amination are some of most important examples of multiphase catalytic reactions.

Liquid Phase Oxidation (LPO) and hydroformylation are two of the most prominent examples of multiphase catalytic reactions in industry. LPO has been employed for synthesis of a variety of industrial products such as aldehydes, ketones, alcohols, carboxylic acids etc. The conventional LPO processes have relied on classical stoichiometric oxidants, which are not acceptable from environmental considerations, as they generate large quantities of mineral wastes and employ toxic reagents. Oxidation of hydrocarbon and aldehydes using metal complex catalysts has emerged as an important tool for synthesis of a variety of drug intermediates and specialty products like aldehydes, alcohols and carboxylic acids. In case of liquid phase oxidation of hydrocarbons like alkyl benzenes, the products of commercial interest are the aldehydes or ketones, which are prone to over oxidation, lowering selectivity to desired product\(^3\). In this respect, selection of catalysts, solvents and reaction conditions is very important to achieve high yield and selectivity.

Hydroformylation is a well-known synthetic tool for the preparation of a wide range of organic molecules of high commercial value through aldehyde or alcohol products. It manifests the largest application of homogeneous catalysis in industry for the manufacture of oxo-alcohols. The process, now conventionally known as the oxo-
process, may be applied to linear as well as substituted olefins. Hydroformylation technology for linear olefins has advanced considerably in the last few decades with development of novel catalysts and ligands as well as better understanding of reaction mechanism. However, literature shows limited information on hydroformylation of substituted olefins with respect to kinetics and mechanism.

Tandem as well as sequential syntheses using cheaper feedstocks as starting materials have gained a lot of interest in an attempt to avoid the old generation multi-step syntheses and development of cleaner and cheaper alternatives. In this context, the sequential synthesis of important pharmaceutical products like dl-naproxen via 6-methoxy-2-vinyl naphthalene (MVN) hydroformylation-oxidation route and hydroxy propionic acids (HPAs) via vinyl acetate monomer (VAM) hydroformylation-oxidation-hydrolysis investigated in the present thesis may contribute to some extent.

Considering the status of developments discussed above, the following problems were chosen for detailed study in this thesis.

- Selective liquid phase oxidation of toluenes to benzaldehydes
- Selective oxidation of ethylbenzene using hydrotalcite like compounds as catalyst
- Hydroformylation of 6-methoxy-2-vinyl naphthalene as a potential route for the synthesis of naproxen
- Hydroformylation of vinyl acetate monomer as potential route for the synthesis of hydroxy propionic acids

The thesis will be presented in five distinguished chapters, the brief details of which are presented below.

Chapter 1, a detailed survey of the literature on catalysis and kinetics of multiphase catalytic reactions involving oxidation and hydroformylation is presented as well as the conventional, stoichiometric or catalytic processes for synthesis of aromatic aldehydes, ketones, arylpropionic acids and hydroxypropionic acids (HPAs).

The oxidation product of aromatic hydrocarbons like aromatic aldehydes and ketones are important intermediates in various synthetic procedures. Benzaldehyde, for example, is used in flavors, fragrances, as intermediates in manufacture of dyes, perfumes, pharmaceuticals and pesticides. Aromatic ketones like acetophenone are important
chemical intermediates in perfumery, drugs and pharmaceuticals. The conventional modes of manufacturing industrially important aldehydes or ketones involve reagent-based synthesis like vapor phase catalytic hydrolysis of benzyl chloride to benzaldehyde; and Friedel-Craft's acylation of aromatics. These procedures yield low selectivity and generate large amounts of wastes. The oxidation of hydrocarbons in liquid phase (LPO) is better alternatives considering cleaner synthesis and atom economy.

Several transition metal catalysts like iron, cobalt, manganese, copper, molybdenum or nickel as monometallic or their combinations as multimetallic catalysts promoted by bromides have been successfully investigated for LPO of toluene. Comparatively much lesser literature is available on selective acetophenone synthesis via ethylbenzene oxidation. The latter is reported in many instances for the synthesis of either ethylbenzene hydroperoxide or phenyl ethanol. The few reported catalyst systems for acetophenone synthesis include salts of cobalt, manganese etc in acidic solvents which report formation of byproducts like phenyl ethanol, benzaldehyde and benzoic acid. Provided that an economically viable, easily recoverable and reusable catalyst is designed, LPO offers better alternatives for the synthesis of such aldehydes and ketones.

Naproxen has been manufactured via multistep syntheses, e.g. acylation, ketalization, bromination, hydrolysis and reductive cleavage starting from nerolin; bromination, methylation and alkylmetal coupling reactions starting from naphthol and chiral syntheses involving chiral catalysts and ligands like (S)-BINAP. The multistep synthesis suffer from the lower yield of naproxen 50-60%. These routes suffer from use of hazardous chemicals, generation of wastes and high costs.

The industrial synthesis procedure for hydroxypropionic acids, 2-HPA and 3-HPA is achieved via fermentation of molasses, which employs high dilutions, mineral acids for work-up, and has lower reaction rates. The commercial synthesis of 2-HPA is also practiced by hydrocyanation of acetaldehydes followed by hydrolysis of cyanohydrin produced. This route produces cyanohydrin upon hydrocyanation of acetaldehyde using toxic HCN. The cyanohydrin produced is hydrolyzed with corrosive sulfuric acid, leading to waste salt generation. Attempts have been made for the synthesis of 2-HPA by hydroformylation of VAM in acidic solvents, followed by oxidation of corresponding 2
acetoxy propanal to 2 acetoxy propionic acid (2-APA) and the hydrolysis of 2-APA, yields 2-HPA. This route suffers from the lower yield of aldehydes in hydroformylation step\textsuperscript{13}. Moreover there is no literature on synthesis of 3-HPA, by synthetic route.

Chapter 2, a study on liquid phase oxidation of toluenes has been presented with the aim of achieving high selectivity to the aldehydes at optimum conversion of toluenes. Cobalt based catalyst systems are the most extensively explored for the oxidation of toluene to benzaldehyde. It was reported that the incorporation of Mn-acetate as an initiator in cobalt-catalyzed oxidation of toluene increases the activity and selectivity to benzaldehyde. In this study, Mn (OAc)\textsubscript{2} was chosen as the main catalyst along with FeCl\textsubscript{3} as a co-catalyst for liquid phase oxidation of toluene. It was found that the benzaldehyde selectivity (60.2\%) is significantly improved at good conversion of toluene (18.4\%) due to addition of FeCl\textsubscript{3}, which is a Lewis acid as a co-catalyst to Mn(OAc)\textsubscript{2}, catalyst. Moreover, the observed selectivity to benzaldehyde, benzyl alcohol and benzyl acetate with the Mn based catalyst system is higher than that reported in the literature. Screening of various Lewis acids like FeCl\textsubscript{3}, SnCl\textsubscript{2}, CuCl\textsubscript{2}, NiCl\textsubscript{2}, SbCl\textsubscript{3} etc was therefore carried out to investigate their effect on activity and selectivity in the oxidation of toluene.

The kinetics of liquid phase oxidation of toluene using Mn (II) acetate- FeCl\textsubscript{3}-NaBr catalyst was investigated in the temperature range of 383 to 403 K and pressure range of 2 to 5 MPa in acetic acid as solvent. Based on the data several empirical rate equations were evaluated and the best model was found to predict the concentration time profile in good agreement with the experimental data.

Chapter 3, selective synthesis of acetophenone via liquid phase oxidation of ethyl benzene was investigated using hydrotalcite-like compounds (HTlcs). Very few literature references are available on ethyl benzene oxidation using TBHP as oxidant, among which supported cobalt and copper are the best catalysts, giving > 80\% selectivity to acetophenone at a conversion of 36-50\%, along with byproducts like benzaldehyde and benzoic acid, which lower the selectivity. In the present study, Layered Double Hydroxides with various M(II) + M(III) combinations were screened for their catalytic activity for the liquid phase oxidation of ethylbenzene, using tert-butyl hydroperoxide.
(TBHP) as the oxidant. Excellent selectivity (> 95%) for acetophenone with good ethylbenzene conversion (>50%) was obtained using Co-containing hydrotalcites. The hydrotalcites are shown to be highly active and reusable catalysts for oxidation of ethylbenzene. The component balance was first established for TBHP oxidation of ethyl benzene using the best catalyst i.e. Co-AlHTlc.

The heterogeneous nature and reusability of the hydrotalcite catalysts was confirmed by carrying out the recycle experiments. The activity of the hydrotalcites remained unchanged upon three recycles. Negligible loss of metal in the reaction was observed by AAS studies of fresh and recovered catalyst (less than 0.1%). The hydrotalcite were fully characterized using XRD, IR, XPS, BET, AAS and SEM. The catalysts vary widely in their surface and bulk properties, depending on the divalent and trivalent metals used for their synthesis. The kinetics of liquid phase oxidation of ethyl benzene using hydrotalcite like compounds and TBHP as oxidant was investigated in the temperature range of 323 to 343 K. A model proposed was found to predict the concentrations in good agreement with the experimental data.

Chapter 4, A two-step route consisting of hydroformylation-oxidation was investigated for the synthesis of naproxen. The present synthesis of naproxen involves stoichiometric synthesis, which is non-ecofriendly in terms of waste generation. The alternative catalytic routes proposed employ chiral catalysts and reagents, which are costly and sensitive to reaction conditions. In the hydroformylation of substituted styrene using Rh catalyst, high selectivity to branched aldehydes (>95%) has been reported with quantitative conversions. The separation of enantiomers used to be the cost-centre in the past, which has evolved in recent years considerably, and the cost of resolution of optical isomers is drastically reduced. With this background, the catalytic synthesis of racemic naproxen holds immense significance. Accordingly, in this chapter, the hydroformylation of 6-ethoxy-2-vinylnaphthalene (MVN) to 2-(6-methoxy-2-naphthyl) propanal (2-MNP) using homogeneous Rh(CO)2(acac) as the catalyst with 1,2-bis-(diphenylphosphino)ethane (dppe) as a ligand was investigated to achieve high selectivity to the branched isomer, i.e. 2-MNP; followed by its oxidation to achieve high yields of the corresponding acid was studied as an alternative route for the synthesis of dl-naproxen.
A detailed study on the key MVN hydroformylation step was carried out and its feasibility was demonstrated. The roles of the catalyst, ligands, and solvents, and the effect of reaction conditions on the reaction rate and regioselectivity of the product 2-MNP was investigated. By using Rh(CO)\textsubscript{2}(acac) as a catalyst and dppe as a ligand, >98% selectivity to 2-MNP (an important precursor to \textit{dl}-naproxen) was achieved and this catalyst and ligand combination has been used for the further studies on the hydroformylation step. A detailed kinetic analysis was carried out using initial rate data of hydroformylation of MVN using NMP as solvents in a temperature range of 383-403 K.

In the second step in the proposed route for Naproxen, oxidation of 2-MNP to the racemic 2-(6-methoxynaphthyl) propanoic acid (\textit{dl}-naproxen) was studied using Na\textsubscript{2}WO\textsubscript{4} as a catalyst and an acidic phase transfer catalyst with H\textsubscript{2}O\textsubscript{2} as the oxidant. Screening of early transition metals like salts of tungsten, vanadium and molybdenum showed that Na\textsubscript{2}WO\textsubscript{4} gives the best performance for the oxidation step with >80% selectivity to 2-(6-methoxynaphthyl) propanoic acid (naproxen). Optimization of reaction parameters and condition was carried out for the synthesis of naproxen.

Chapter 5, a three step route involving of hydroformylation-oxidation-hydrolysis was investigated for the synthesis of hydroxy propionic acids. Conventionally 2- and 3-hydroxy propionic acids are synthesized by enzymatic route. Tinkar and co-workers have reported hydroformylation-oxidation-hydrolysis route for 2-hydroxy propionic acid, but the overall yields are very poor due to use of acidic solvents and also, the reaction conditions are harsh. Moreover, there is no synthetic route for exclusive synthesis of 3-hydroxy propionic acid. In this chapter, hydroformylation of VAM was studied as key step with Co\textsubscript{2}(CO)\textsubscript{8} as catalyst to give 2-acetoxy propanal (52%) and 3-acetoxy propanal (48%). The results show that this catalyst gives ~ 100% conversion of VAM and more than 94% selectivity to aldehydes. The detailed investigations of the liquid phase oxidation of these aldehydes were carried in a glass reactor. The screening of different supported transition metal catalysts was carried out and Co/C was found to be the best catalyst. The mixture of 2 and 3-acetoxy propanal was oxidized with a high selectivity (>98%) to 2- and 3-acetoxy propionic acids respectively; with high conversion (>95%) of the aldehydes, using molecular oxygen as oxidant and Co/C as catalyst. Hydrolysis
experiments were carried out using different acid catalysts and Amberlite IR 120 resin was found to be the best catalyst. The latter was found to give >90% conversion of 2 and 3-acetoxy propionic acids with high selectivity to the corresponding hydroxy propionic acids. The kinetics of the key hydroformylation step was investigated with Co$_2$(CO)$_8$ as catalyst. Various empirical rate models were considered to explain the trends observed. It was observed that rates predicted by the model were in excellent agreement with experimental rates.

Further, the liquid phase oxidation of 2-acetoxypropanal was investigated in detail to understand catalysis and kinetics involved, using Co/C catalyst and air as the oxidant, in the temperature range of 303 to 343 K.

References

1 Dudukovic, M.P.; Catalysis Today 1999, 48, 5
2 Mills, P.L.; Chaudhari, R.V.; Catalysis Today 1999, 48, 17
8 Suresh, A.K.; Sharma,M.M.; Shridhar, T; Ind. Eng. Chem. 2000, 39,3958
9 Sheldon, R.A.; Kochi, J.K.; Metal catalyzed oxidation of organic compounds academic press, New york 1881
10 Sanders, H.J.; Keag, H.F.; McCollough, H.S. ; Ind. Eng. Chem. 1953, 45,2
13 Tinkar, H.B.; US 4072709 1978

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