San Jose State University
SJSU ScholarWorks

Master's Theses | Master's Theses and Graduate Research

2000

Industrial organic chemistry : a review

Lana Alshvang
San Jose State University

Follow this and additional works at: https://scholarworks.sjsu.edu/etd_theses

Recommended Citation

Alshvang, Lana, "Industrial organic chemistry : a review" (2000). *Master's Theses*. 1968.
DOI: https://doi.org/10.31979/etd.486g-nfaj
https://scholarworks.sjsu.edu/etd_theses/1968

This Thesis is brought to you for free and open access by the Master's Theses and Graduate Research at SJSU ScholarWorks. It has been accepted for inclusion in Master's Theses by an authorized administrator of SJSU ScholarWorks. For more information, please contact scholarworks@sjsu.edu.

INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

INDUSTRIAL ORGANIC CHEMISTRY: A REVIEW

A Thesis

Presented to

The Faculty of the Department of Chemistry

San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

by

Lana Alshvang

May 2000

UMI Number: 1399772

UMI®

UMI Microform 1399772

Copyright 2000 by Bell & Howell Information and Learning Company.
All rights reserved. This microform edition is protected against
unauthorized copying under Title 17, United States Code.

Bell & Howell Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

© 2000

Lana Alshvang

ALL RIGHTS RESERVED

APPROVED FOR THE DEPARTMENT OF CHEMISTRY

3/31/00

Dr. Stephen E. Branz
Professor of Chemistry

Date

Maureen Scharberg

31 mar 2000

Dr. Maureen Scharberg
Associate Professor of Chemistry

Date

Alto Benedicto

31 March 2000

Dr. Alto Benedicto
Assistant Professor of Chemistry

Date

APPROVED FOR THE UNIVERSITY

William

Date

ABSTRACT

INDUSTRIAL ORGANIC CHEMISTRY: A REVIEW

by Lana Alshvang

This thesis addresses a new approach to studying industrial chemistry by conducting a parallel analysis of laboratory syntheses and industrial syntheses for major classes of organic compounds. To illustrate the industrial economic issues, the costs of various synthetic routes (mostly raw materials costs) are compared. The rationale for choosing specific processes and catalysts is shown for specific examples. The thesis emphasizes the major objectives of the chemical industry, its economic, environmental, and operational differences from laboratory synthesis, and the importance of choosing and optimizing a synthetic route in industry.

Most of this thesis is devoted to two types of reactions most widely used, oxidation and hydrogenation. Other fundamental reaction types familiar to undergraduates such as aromatic substitution, dehydrogenation, hydration, halogenation, and etherification are discussed as well. In addition, significant recent improvements and research findings for each process are discussed. The thesis gives an overview of petrochemical processes. Special attention is paid to understanding the role of catalysis in the economics of industrial processes, in achieving high conversion and selectivity, and in developing new processes. Finally, major directions for current and future industrial development are presented.

Acknowledgments

I take this opportunity to express sincere gratitude to my research advisor. Dr. S.E. Branz. for suggesting this inspiring topic for my project and for his guidance throughout.

On the personal level, I want to thank my friend Zakhary Alper for his love and encouragement, and my children, Lena and Julia, for their understanding and moral support all along this journey.

Table of Contents

Glossary

Common Name	IUPAC Name
Acetaldehyde	Ethanal
Acetic Acid	Ethanoic Acid
Acetic Anhydride	Ethanoic Acid Anhydride
Acrylic Acid	Propenoic Acid
Acrylonitrile	Propenonitrile
Adipic Acid	1,6-Hexanedioic Acid
Adiponitrile	1,4-Dicyanobutane
Bisphenol A	4,4-Isopropylidenediphenol
Butadiene	1,3-Butadiene
Butyraldehyde	Butanal
Caprolactam	2-Oxohexamethyleneimine
Cumene	Isopropyl Benzene
Ethylene Glycol	1,2-Ethanediol
Ethylene Oxide	Oxirane
Formaldehyde	Methanal
Methyl Formate	Methyl Methanoate
Propylene	Propene
Propylene Glycol	1,2-Propanediol
Propylene Oxide	Methyloxirane

Salicylic Acid	2-Hydroxybenzoic acid
Styrene	Ethenylbenzene
Terephthalaldehyde	1,4-Benzenedicarboxaldehyde
Terephthalic Acid	1,4-Benzenedioic Acid
Toluene	Methylbenzene
Vinyl Acetate	Ethenyl Ethanoate
Vinyl Chloride	Chloroethene
p-Xylene	1,4-Dimethylbenzene

Note:

Prices shown are average prices of bulk chemicals per Chemical Marketing Reporter, Dec. 1998 - Jan.1999. Although prices of the reagents used in research laboratory might be significantly higher due to the lower volume purchased, bulk prices are used for comparison purposes.

Introduction

Many chemistry students who begin their careers in a chemical industry are involved in industrial synthesis or a process development scale-up. Therefore. knowledge of standard industrial processes and understanding goals and principles. as well as needs and current limitations of the chemical industry is crucial for chemistry students. The content of this thesis will help to prepare students for a successful start in industry and is a follow-up to the undergraduate organic chemistry course.

Since no book or review article has been found that specifically analyzes organic synthesis in industry versus laboratory synthesis for major functional groups. the primary purpose of this work is to present a new approach to studying industrial chemistry by conducting a parallel analysis of laboratory synthesis and industrial synthesis for major classes of organic compounds and giving a side-by-side comparison of organic chemistry in industry versus organic chemistry in academic laboratory where possible. In addition to discussions of organic synthetic routes and processes. this thesis emphasizes the major objectives of the chemical industry. its economic. environmental. and operational differences from laboratory synthesis. and the importance of choosing a valid synthetic route in industry. In this thesis. industrial organic chemistry refers to very large scale "bulk" organic synthesis. not "fine chemical" synthesis used. for example. in the pharmaceutical industry.

Finally, the thesis gives an overview of industrial catalysts, a topic unfamiliar to an average chemistry student, and outlines major avenues of current and future development in industrial organic chemistry. This will familiarize students with major issues and concerns of modern chemical industry. The idea of the importance and the key role of catalysts in an industrial organic reaction penetrates the majority of the course, as modern industrial chemistry, for the most part, is designed and driven by catalyst development. Another purpose of the present work is to review new findings and processes that make a major impact on the production of industrial organic chemicals, in both environmental and cost savings aspects.

Of all the processes for large-scale preparation of organic compounds, oxidation and hydrogenation are the most widely used. For that reason, most of this thesis is devoted to these two types of reactions. Other fundamental reaction types familiar to undergraduates such as aromatic substitution, dehydrogenation, hydration, halogenation, and etherification are discussed as well. In addition, most significant recent improvements and research findings for each process are discussed, to highlight for the reader the continious search for better processes. There is still much room for research and development in industrial chemistry.

A direct side-by-side comparison of industrial and laboratory synthetic routes, emphasizing differences between bulk catalytic and small-scale noncatalytic processes is done for some chemicals. To illustrate the industrial economic issues. the costs of various synthetic routes (mostly raw materials costs) are compared. The rationale for choosing specific processes and catalysts is shown for specific examples.

Even though the primary purpose has been to analyze industrial synthetic processes, this could not begin without an overview of petrochemical processes. since petrochemical feedstock is the origin for almost all organic molecules. Major developments in this area are summarized from the recent literature.

Since virtually all industrial reactions carried on the large scale are catalytic reactions. the thesis devotes significant attention to understanding the role of catalysts in the economics of industrial processes. in achieving high selectivity and yield. and in developing new processes. This work will familiarize students with major types of industrial catalysts and recent revolutionary catalyst-based developments in industrial organic chemistry.

The thesis will attempt to answer the following questions:

- What are the conditions. limitations. and major reasons for choosing a reaction pathway in industry versus the laboratory?
- Why are equilibrium. heat transfer. and kinetic considerations so much more important in industrial synthesis compared to synthesis on the laboratory scale?
- What are major economic and environmental considerations in industrial processes?

Why are they so critical?

- Why do almost all industrial synthetic processes, unlike reactions on the small scale, involve catalysts?
- What are the current demands facing modern chemical industry? What are the most promising alternatives to existing industrial processes?

Goals and Objectives of the Chemical Industry

A. Differences between Industrial and Laboratory Processes

An important step in preparing chemistry students for work in industry is giving them a basic understanding of the chemical industry, its objectives and principles, and general differences between laboratory and industry processes. There are significant differences between laboratory synthesis and synthesis on the large industrial scale. Even if the net chemical equations are similar, the actual operations and reaction conditions may be drastically different. For example, let's compare the hydration of alkenes to form alcohols. In the laboratory alkenes are hydrated by either oxymercuration (treatment with mercuric acetate following reduction by sodium borohydride) or hydroboration (addition of borane is followed by treatment with basic hydrogen peroxide).[1] Both procedures work well on a small-scale but involve costly reagents. They are also two-step processes, which are less economical than single step processes.

When the industrial process for ethylene hydration was first developed, it was based on the laboratory reaction which involved bubbling ethylene into concentrated sulfuric acid and then diluting and warming the reaction mixture to hydrolyze the sulfate ester byproduct (Eq 1). In the current industrial process a stream of ethylene is mixed with steam at elevated temperature and pressure and passed over a solid catalyst consisting of phosphoric acid on a solid support (Eq 2).[2]

The current industrial process is a significant improvement, both environmentally and economically. Corrosion problems are eliminated, and unreacted ethylene is separated and recycled. In addition, the modern industrial process is carried out in a continuous flow fashion that is advantageous over a batch process.

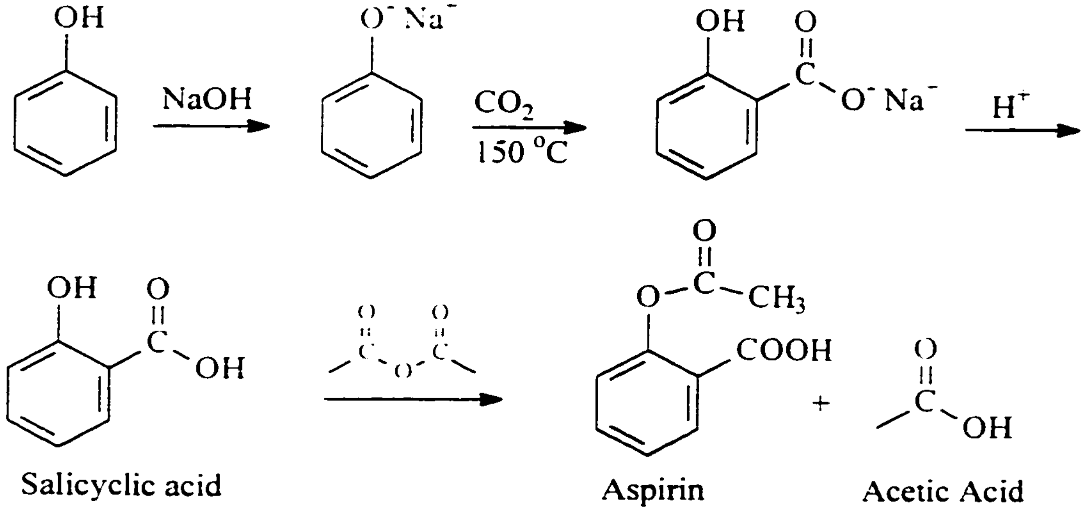
$$H_2C{=}CH_2 + H_2SO_4 \longrightarrow C_2H_5O{-}SO_3H \xrightarrow{H_2C=CH_2}$$

$$(C_2H_5O)_2SO_2 \xrightarrow[H_2C=CH_2]{H_2O} C_2H_5OH + (C_2H_5)_2O + SO_3 \qquad (1)$$

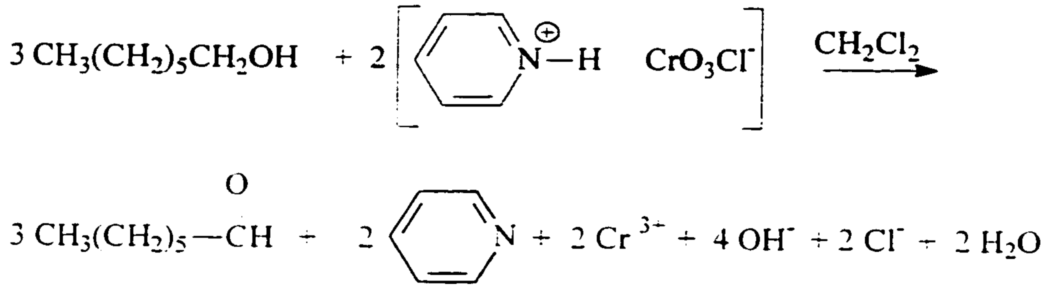
$$H_2C{=}CH_2 + H_2O \xrightleftharpoons{[cat.]} CH_3CH_2OH \qquad (2)$$

Another example is the manufacture of aspirin, the only drug manufactured on the scale of industrial chemicals with over 20 million lb/yr produced in the U.S. An industrial synthetic route for the manufacture of aspirin is shown in Scheme 1. Even though the final step is the same in the industrial process and laboratory process, the starting material used for the laboratory synthesis of aspirin is salicylic acid (\$1.21/lb), whereas in industry aspirin is synthesized from phenol (\$0.39/lb).[3] The difference in raw material cost, therefore, is \$.82 /lb. To manufacture 20 million lb of aspirin per year, a minimum of 20 million lb of starting materials is needed. Therefore, the economic advantage of manufacturing aspirin directly from phenol is close to \$16.4 million annually. Such comparisons are only an approximate, because only raw material costs but not process costs are compared. However, this is a workable approximation, since raw materials costs typically account for the major part of the production cost for the product. Clearly, the measure of success in industrial process is its effectiveness and low cost. It's obvious why phenol, and not salicylic acid, is the preferred starting material in this industrial synthesis.

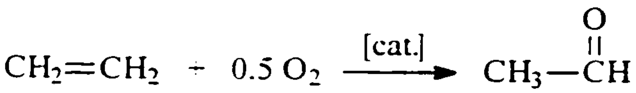
Scheme 1



For most industrial organic synthetic processes, the reactions are not even similar to familiar classical reactions that are used on the laboratory scale. For example, aldehydes are commonly prepared in the laboratory by oxidation of primary alcohols with pyridinium chlorochromate (PCC) in methylene chloride.[4] The industrial synthesis of acetaldehyde is based on oxidation of an alkene (ethylene) over a solid catalyst in the gas phase (Eqs 3 and 4).[5]



(3)



$$CH_2{=}CH_2 + 0.5\,O_2 \xrightarrow{[cat.]} CH_3{-}\overset{\overset{\Large O}{\|}}{C}H \quad (4)$$

The obvious differences in processes illustrate that an approach to industrial synthesis is driven primarily by economic and environmental considerations. First. these reactions use gaseous oxygen or air as the oxidant instead of PCC ($14/lb) or another popular oxidative agent potassium permanganate ($1.20/lb) to avoid high cost and disposal problems. Since the cost of waste disposal. often fairly high. is a part of the total cost. it affects the profitability of the process. Therefore. the environmental concern of industrial synthesis becomes an economic concern and leads to minimizing air and water pollution from gases and process waste streams.

Industrial processes, unlike laboratory reactions, utilize selective heterogeneous and less common homogeneous catalysts. They often utilize much higher temperatures and pressures than small-scale reactions. Solvents are rarely used on the large industrial scale, thereby reducing the costs for raw materials, separation and purification of the solvent for reuse, and equipment (by maximizing the effective reactor volume). Finally, industrial scale reactions can be carried out in both batch and continuous fashion and may involve reactants in both solution and vapor phases. Laboratory reactions familiar to chemistry students are batch processes only and, as a rule, contain reactants in solution phases only.

The major differences described above reflect the different objectives for industrial and laboratory processes. In commercial processes, the goal is to manufacture a product to produce maximum profit. Most often, this translates to having a low production cost. The scale of any process is optimized to generate the maximum economic return. In addition to the cost of raw materials, total cost includes capital costs and so-called overhead costs - utilities, maintenance, and labor. As will be discussed later in this thesis, an industrial process with the minimum total cost might not generate the product in highest yield.

Direct costs are the largest component of total cost, and raw material costs are largest component of direct costs. Therefore, minimizing raw materials cost is a major concern for any industrial process development. In the small scale laboratory, the objective is usually to synthesize a compound in the highest yield possible. Reaction conditions on the laboratory scale are limited in temperature and pressure by the glassware and equipment commonly available. Anything that can help meet this objective will be used, such as reagent grade chemicals, expensive or hazardous solvents, or lengthy reaction times. Only after the reaction demonstrates some potential are large-scale issues and economic questions considered.

B. The Economics of an Industrial Process

It is very important to select the best process for scale-up development. The process assessment is based on a rough economic analysis. which compares the economics of all possible routes to the product. and a technical feasibility assessment based on a general knowledge of similar reactions. The main consideration that determines whether a project will be worth pursuing is its return on investment. Return on investment is defined as the average annual profit divided by total capital investment. Because the success of an industrial process is determined by initial capital investment versus profit generated. students need to have a basic understanding of capital costs and factors that affect them. Capital cost is the cost involved in building a plant. and the simpler a process is. the cheaper will be the plant required running it.[6]

The factors contributing significantly into an increase of capital costs are listed below:

- Multiple step processes - Each separate reaction requires a separate reactor in a large plant.
- Extensive separation - Separation of product from byproducts (both stoichiometric and from unwanted side reactions). unreacted starting materials. and solvents involves separation equipment. e.g. distillation columns and filters. The more separation that have to be done. the more time. equipment. and expense is required.
- Use of extremes of temperature and pressure -The further removed are the operating

temperature and pressure from ambient conditions, the higher the capital cost of the plant will be. Compressors, pumps, and pipes are required for increased pressure. The use of expensive refrigeration equipment is needed for low temperatures. Achieving temperatures above ~ 950 °C has special engineering problems associated with it, leading to extremely high capital costs.[7]

- Use of corrosive materials - The use of corrosion-resistant equipment usually added great expense to any process.
- Solid handling - The capital costs associated with handling solids mechanically are much greater than those for the handling of liquids or gases.

Due to the large size and complexity of a modern chemical plant, all projects and processes involve significant capital investment. The chemical industry has a higher investment of current capital than any other industry.[8] Because of their capital intensive nature, chemical processes are very sensitive to economies of scale. For most processes the capital cost per annual unit of capacity, and therefore the production cost, decrease as the scale of operation is increased. There is a gap between the break-even price of products (when price is equal to total cost) and the lower price at which it's rational to shut down the plant. Since economies of scale are only realized if a plant operates at or near its full capacity, it's far more economical to run a plant at full capacity even if it means cutting prices.[6]

In order for a process to be profitable the total revenue from the product must be sufficient to cover all of the costs and generate some profit. Obviously, to maximize profit, total expenses have to be minimized. The total costs are separated into categories of direct and indirect costs. Indirect costs include, for example, general administrative expenses. Direct costs are directly associated with a product and include direct raw materials, direct labor, and direct overhead. In chemical industry raw materials account for as much as 70-90% of total cost.[9]

Another important classification of process costs involves fixed versus variable costs. Fixed costs, such as capital expenditures, are determined by the whole production facility and remain constant regardless a particular project operation. It was noted above that capital costs are extremely high in the chemical industry. In addition, energy costs are also high. For example, compression of gases and heating of reactants consumes large amounts of energy, as does the operation of strongly endothermic reactions. It might be a surprise to chemistry students, but in the chemical industry energy is produced primarily by burning either natural gas, heavy fuel oil, or coal.[10] In contrast, electrical energy is the primary source of energy used by chemists in laboratory experiments. Therefore, chemical companies are very concerned about rising fuel costs and are very interested in developing chemical processes that consume the lowest amount of energy.[10]

Costs of major importance to a chemist developing an industrial process are variable costs, which - as the name implies - vary directly with production rate. The predominant part of variable costs is the cost of the raw materials. When profitability of the plant is a concern, both variable and fixed costs have to be considered. However, in a discussion concerning the profitability of a particular process or reaction, only variable costs are relevant.

C. Basic Concepts of Industrial Operations

This portion of the course is intended to introduce the importance of heat transfer and waste disposal issues in industrial operations, since they are harder to deal with than in the laboratory setting. Moreover, better understanding of these factors can lead to the development of more efficient processes. Likewise, the undergraduates will be better prepared for the 'real world', if they understand the advantages of continuous flow over batch processes, and the conversion versus yield.

It is interesting to see how similar operations in industry and the laboratory create completely different concerns. For example, whereas heating and cooling are easily dealt with in the laboratory, on the large scale they present quite major problems. Also, in the laboratory where batch-type reactions are performed, chemicals are generally transferred in solution by physically pouring from one container to another. In industry the transport of fluids from one location to another occurs through pipes or tubing. Therefore, principles of mass transfer and heat transfer that are not discussed in chemistry courses are studied in detail in chemical engineering courses. These principles are described by complex calculations involving many variables since industry, unlike the laboratory, deals with open systems. In open systems where materials flow into and out of the process equipment, heat needs be added if the reaction is endothermic, or removed in case of an exothermic reaction. The complete accounting of all mass and energy in such chemical processes is referred to as a material and energy balance.

Heat Transfer Requirements of Chemical Reactants

Even though chemistry students learn principles of thermodynamics, they are often not aware of the significance of heat transfer in industrial processes. In the laboratory reactions typically are run in 50 to 500 mL flasks, where the surface area of the reaction vessel is large relative to the volume of the reaction mixture. In such cases the heat of reaction is dissipated through the walls of the reaction flask without any difficulty, and principles of heat transfer are usually ignored. In order to maintain control of the temperature in large scale industrial reactions, the addition or removal of heat from the chemical reactor is necessary.

Chemical reactions in industry are usually carried out in large vessels. Surface area to volume ratios are reduced significantly during scale-up. Therefore, temperature control is much more difficult. A significant increase in temperature in the reaction vessel can cause serious problems. It is well known that the reaction rates typically double for every 10 °C increase in temperature. An increase in reaction rate increases temperature, and this increases the reaction rate to an even higher level, leading to a loss of temperature control.

Heat transfer is not only important during the reaction, but also when the products of a reaction are removed from the reactor. First, the products have to be cooled down to the temperature of the surroundings before they leave the plant. Additionally, separation of the product from unconverted reactants and byproducts is required. All of the major separation processes, such as distillation, crystallization, and absorption, involve the addition or removal of energy in the form of heat.

Kinetics

In industry, kinetics is directly related to finding the optimum conditions for achieving commercially feasible rates. These conditions are so important because they determine the final flow design, equipment requirements, and economics of the process. For example, the residence time, temperature, and catalyst requirements determine the type and dimensions of the reactor required.[11] The ultimate goal of chemical kinetics in industry is to develop a fundamental rate equation that fits the rate data.

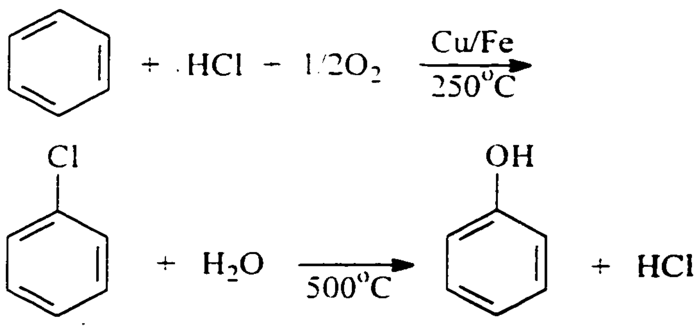
Many of the reactions in the laboratory are carried out in homogeneous systems. However, most industrial processes involve heterogeneous systems with the reactant streams passing over a solid catalyst surface. Solid matrices used as catalysts or as insoluble supports for the catalysts can modify the reaction kinetics due to the additional processes of diffusion and adsorption. Relative to homogeneous catalysis, there are changes in the activation energy resulting from the modified reaction path. This changes the kinetics: a well-understood laboratory scale reaction may lead to different products. Therefore, the properties of solid catalysts and the methods for their preparation are of utmost importance for the kinetics in an industrial process.

Continuous Flow versus Batch Process

The majority of laboratory reactions are carried out in glass flasks. These are batch operations as opposed to industrial processes, which are typically performed in a continuous fashion. Because continuous flow operations are predominant in industry, they deserve some attention in this thesis. Continuous flow, a process of passing a mobile chemical reagent phase over a stationary catalyst (bed), is used in the majority of industrial operations. Because continuous flow methods allow for the manufacture large amounts of compounds, they are used whenever possible. Examples include industrial scale reactions ranging from petroleum feedstock production to the relatively small scale manufacture of fine chemicals. Another significant advantage of the continuous flow method is the reduction in energy costs compared with batch processes. However, batch processes still find use in industrial chemistry. In general, continuous processing is preferred for large scale manufacture and for gas phase reactions on any scale, and batch processing is used for small scale manufacture except for gas phase reactions.[6] Examples of syntheses of organic compounds performed under continuous flow conditions include such well known industrial processes as the Fischer-Tropsch synthesis of alkanes or the synthesis of ethanol from synthesis gas (a mixture of H_2 and CO), and those oxidation, hydrogenation, and other processes performed with gas phase reagents.

Byproduct and Waste Disposal Issues

From laboratory experience, organic chemistry students learn that almost any synthetic procedure is accompanied by undesirable byproducts. Byproducts may be difficult or expensive to remove. For example, the monochlorobenzene process for phenol gives a high yield of phenol, but is inefficient from the point of view of raw materials usage. In addition to phenol, low value sodium chloride is produced (Eq 5).

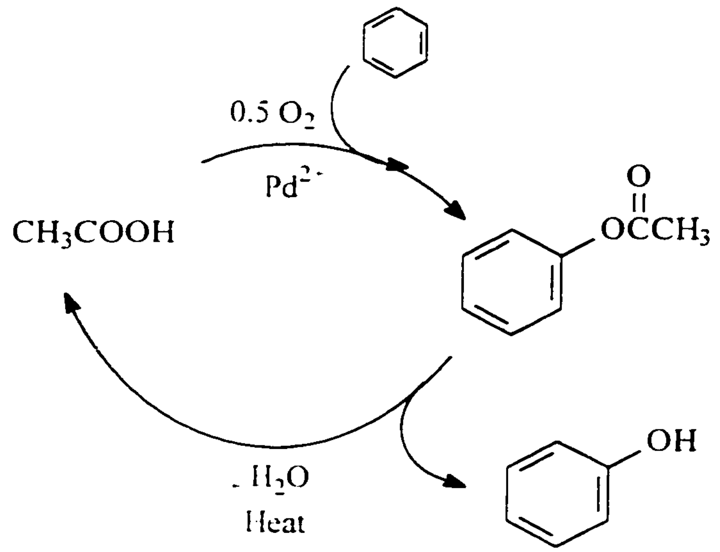


(5)

Addition reactions are more atom-economical than substitution reactions, since there are no stoichiometric products formed in addition reactions. Addition reactions incorporate all of the atoms of the reactants into the product and, therefore, are highly atom-economical. Atom economy refers to maximizing a number of raw materials that end up in the product. Trost[12] emphasizes the necessity of efficient syntheses that minimize the depletion of raw materials and the generation of waste by maximizing atom economy. Because of the ability of transition metals to add to nonpolarized unsaturated systems, transition metal catalysts permit development of a large variety of catalytic processes with high atom economy. For example, a more economical method of phenol synthesis involves direct air oxidation of benzene in the presence of acetic acid catalyzed by Pd(II) (Scheme 2). The reaction proceeds via formation of phenyl acetate which is hydrolyzed to phenol and acetic acid. Acetic acid is recycled, and the net result of this reaction is an addition of an oxygen atom to benzene. No atoms are wasted.

Historically, atom economy was not a major concern for the chemical industry. With increasing costs for waste disposal, it is inevitable that atom economy will become a more important design consideration in the future.

Scheme 2



Today the environmental consequences of chemical production are considered right from the beginning of every new process development. To satisfy the environmental requirements of federal and state regulations, separations and/or waste treatments need to be performed, since waste streams can no longer be simply discarded into the air or water near the plant site. A synthesis that results in extremely poisonous byproducts, even in small amounts, is often abandoned, since the risks and costs in handling these compounds in commercial quantities may be too high.[13] These problems may be avoided by using catalysts in place of hazardous reagents that generate waste streams and cannnot be recovered easily. For example, palladium (Pd) catalysts in industrial hydrogenation reactions can substitute for lithium aluminum hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$) reducing reagents that generate significant waste streams.

Finally, in addition to the reaction byproducts, unreacted starting materials can also generate a waste stream, if the reaction does not go to completion. Starting materials can be separated from the product and recycled, but this requires additional capital costs.

Conversion, Selectivity, and Yield

The relationship between conversion, selectivity, and yield is critical and deserves explanation. In undergraduate laboratory synthesis, obtaining the highest yield is the major goal. In industry, the objectives are to get the highest possible selectivities. Because yield is defined as the mathematical product of the conversion and the selectivity, it will be maximized when conversion and selectivity are maximized.[14] Conversion measures the extent of reaction (on a scale of 0.0 to 1.0) and is defined as a fraction of the starting mateiral that has been converted to product. Selectivity measures the purity of the product (also on a scale of 0.0 to 1.0) and is defined as a ratio between the quantity of the desired product and the total quantity of the products synthesized.

It is important to remember that there is no right or wrong balance of selectivity, conversion, and yield. It all depends on the production goals and is driven by maximizing the economic return of the production plant. For example, in situations of high sales demand it might be more beneficial to produce as much product per day as possible for the expense of low conversion, causing considerable waste of raw materials. Still, in the majority of cases. chemical plants operate at highest conversion conditions to minimize costs of raw materials.

High selectivity is often achieved at the expense of low conversion. or high conversion is achieved at the expense of low selectivity. Conversion might be sacrificed to produce a pure product. and a product with impurities will be obtained if high conversion is needed. Traditional synthetic organic chemistry seeks to maximize both conversion and selectivity (thereby maximizing yield) by optimizing the ratio of reactants. selecting a more favorable solvent. or applying low temperatures. even if this would mean long reaction times. Catalysts may be used. but usually they are homogeneous. Typically, industry uses heterogeneous catalysts with high activity and high selectivity. Heterogeneous catalysts may cost more to develop and may be less general than homogeneous catalysts. but they are easily recovered and better suited for industrial reaction conditions.

Summary: Steps in Development of an Industrial Synthetic Process

Since chemists are involved in the development of a reaction from a laboratory scale to an industrial process. the industrial economic and operational principles discussed earlier will be summarized.

First, the reaction conditions for a sufficiently high production rate per unit volume must be found. Then, a reactor type that can be used on a large scale needs to be found. Reactor conditions have to be optimized with respect to conversion and selectivity. Next, the best purification routes and means of byproduct disposal have to be determined. Sometimes byproducts can be converted into useful compounds, or they can be converted into harmless wastes such as carbon dioxide and water. An important design decision is whether to carry the reaction to (virtually) complete conversion, which is common practice in the laboratory, or to choose an intermediate degree of conversion in order to obtain a higher selectivity. Only after all these steps have been completed can the costs for the process be estimated.[15] Recall that such costs include capital, raw materials, utility costs, maintenance, and labor costs.

The economic value of a product will have a significant influence on the design and operation of the chemical process. Even the selection of the separation methodology will be strongly influenced by the economic value of the products being isolated. For example, for production of n-butane with price of $.10/lb, expensive equipment for the separation process can't be used. Generally, the lower the economic value of the product, the more important it is to select a process with the lowest possible energy consumption and lowest possible purification costs.

II. Fundamentals of Industrial Catalysts

Chemistry students usually learn little about heterogeneous catalysts in their coursework and are not completely aware of the role of catalysts in modern synthetic organic processes. To give the readers an idea what really drives the field of industrial chemistry, catalytic function, types of catalysts used in industry, and how catalytic research and development is solving problems in modern industrial processes will be discussed. Rather than explaining mechanisms of catalysis in depth, which is actually a prerogative of organometallic/inorganic chemistry, we will attempt to give a general overview of catalysis sufficient for good understanding of the most important industrial organic reactions.

The definition and a major role of catalysts in an organic reaction is well known. Catalysts are substances that are recovered unchanged at the end of the reaction and affect the reaction by increasing the rate of the overall reaction and providing a reaction path with a lower activation energy. It is important to remind ourselves that the free energy profile in the presence of a catalyst is different than the uncatalysed reaction, because the catalyst introduces the new pathway that changes the mechanism of the reaction (Figure 1).

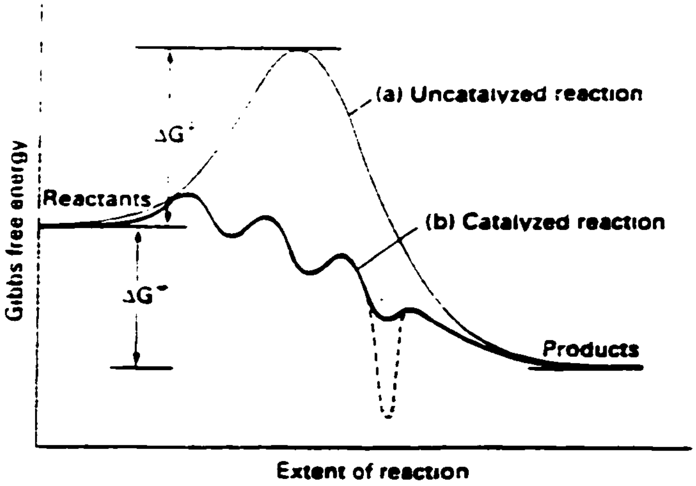


Figure 1. Energy diagram for catalyzed and uncatalyzed reactions. Reprinted from ref. 16. Copyright 1994 Shriver. $\Delta G^{\neq}$ - Gibbs energy of activation: $\Delta G^{\ominus}$ - Gibbs free energy of reaction.

The major functions of a catalyst can be illustrated with carbonylation reactions as an example (Figure 2). The rhodium (I) complex which serves as a catalyst coordinates to methyl iodide obtained from methanol, the starting material for the reaction.[17] Figure 2 shows the conversion of methanol and CO to acetyl iodide, which hydrolyzes to acetic acid in the next step. After the rearrangement occurs and another CO molecule coordinates to rhodium, acetyl iodide dissociates, leaving the metal fragment free to bind a new molecule of substrate and go around the catalytic cycle again and again. The regeneration of catalyst is the feature that distinguishes it from a simple reagent. A mole of catalyst may typically convert up to thousands of moles of starting material into the product, before the catalyst is destroyed in a side reaction. For both economical and environmental reasons, catalysts that do not generate waste streams are used in place of expensive and often hazardous laboratory reagents.

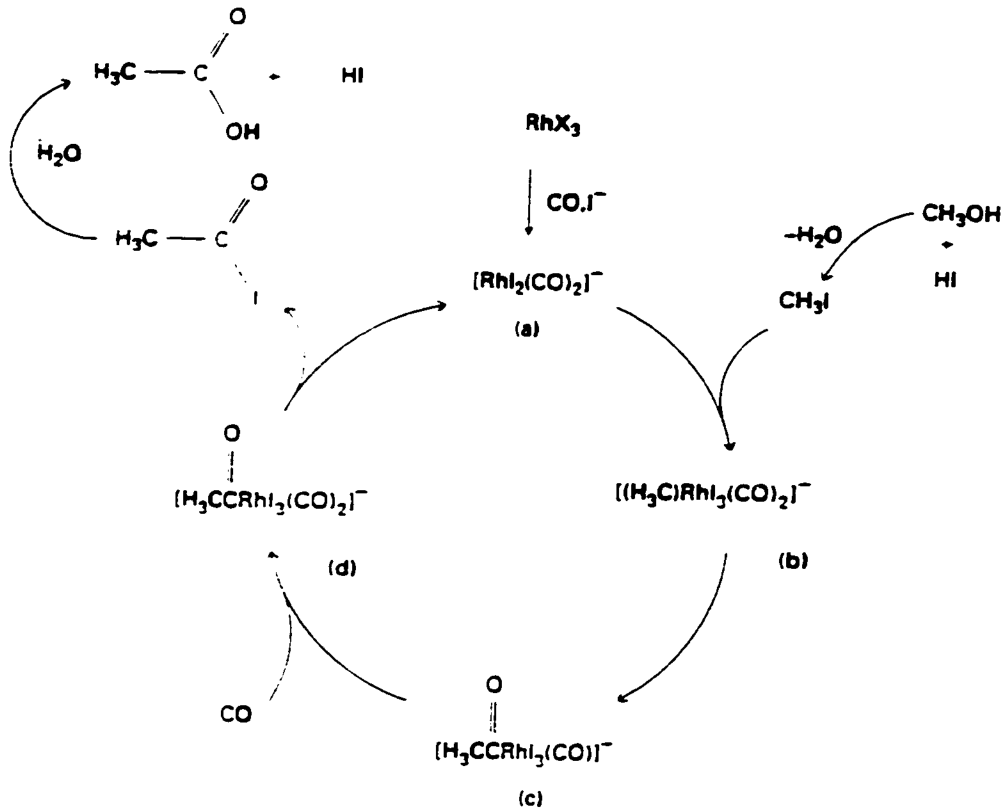
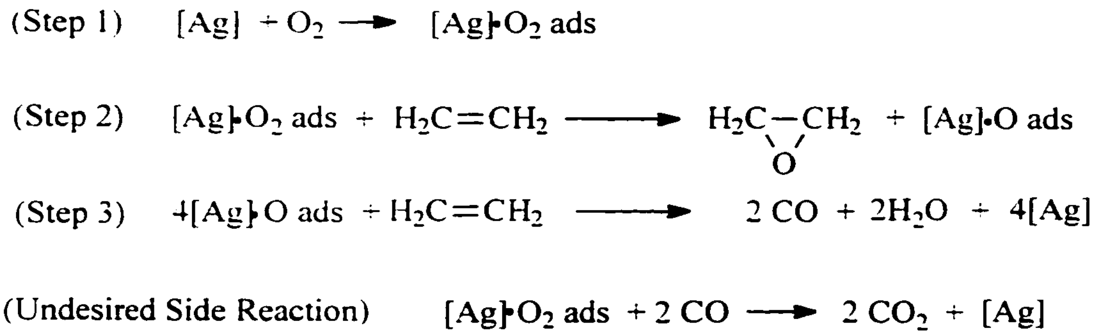


Figure 2. Formation of acetic acid by carbonylation of methanol. Reprinted from ref. 16. Copyright 1994 Shriver.

Unlike raw materials for industrial processes which are chosen primarily for their low cost, the cost of catalysts usually is not an important consideration.[18] Catalysts are chosen for their conversion of starting material(s), their selectivity for a desired product, and their longevity.[18] The lack of selectivity can increase the raw material consumption, as in the case of oxidation of ethylene to ethylene oxide by metallic silver (Scheme 3). Initially, molecular oxygen is adsorbed on the silver and reacts in this form with ethylene to yield ethylene oxide. The atomic oxygen generated normally cannot be regenerated back to molecular oxygen or produce more ethylene oxide. As shown in Scheme 3, step 3 consumes 20% of ethylene in order to regenerate Ag metal. Therefore, maximum possible yield of ethylene oxide (based on ethylene) in this reaction cannot exceed 80%. In addition, formation of CO_2 in a side reaction is more thermodynamically favored than formation of ethylene oxide. Thus, a reasonable commercial yield can be achieved only due to the development of an efficient catalytic system with strong selectivity for ethylene oxide.[19]

Scheme 3



(Step 1) $[Ag] + O_2 \longrightarrow [Ag]\text{-}O_2 \text{ ads}$

(Step 2) $[Ag]\text{-}O_2 \text{ ads} + H_2C{=}CH_2 \longrightarrow H_2C{-}CH_2 (\text{-}O\text{-}) + [Ag]\text{-}O \text{ ads}$

(Step 3) $4[Ag]\text{-}O \text{ ads} + H_2C{=}CH_2 \longrightarrow 2\,CO + 2H_2O + 4[Ag]$

(Undesired Side Reaction) $[Ag]\text{-}O_2 \text{ ads} + 2\,CO \longrightarrow 2\,CO_2 + [Ag]$

The increasing use of catalysts has a tremendous impact on the industrial economy. Of the 700 billion pounds of chemicals produced annually in the US, more than 60% are produced with the aid of catalysts. On average, 1 lb of catalyst produces about 1500 lb of chemicals. In 1997 the total world market for catalysts was more than $10 billion, with the US share of more than $3 billion.[20]

There are three important types of industrial catalysts in the US. They are used for petroleum refining, chemical processing, and for the control of automobile emissions. Petroleum refining catalysts are the cheapest and are dominated by acid catalysts used, for example, for alkylation. The acid catalysts account for 90% by weight, but only for 30% of the cost of all catalysts sold annually. It should be noted that the new solid acid catalysts developed to satisfy environmental demand are more expensive.[18,20]

Acid-base catalysis is one type of catalysis that might be already familiar to the reader. Acid catalyzed reactions are so important in industry that a significant portion of contemporary catalytic development has been directed to solid acid and superacid catalysts for major industrial processes. Well-known acid-catalyzed reactions include the Friedel-Crafts alkylation of benzene, hydration of alkenes, and esterification. Some of this development work is discussed in the last part of this thesis.

The majority of the modern acid-catalyzed industrial reactions utilize heterogeneous catalysts. The acid-base reactions occur at solid surfaces with high surface area to volume ratios. Widely used examples are silica/alumina catalysts. They can act as both Bronsted and Lewis acids. Remember that Lewis acids are defined as electron pair acceptors, and Bronsted acids are defined as proton donors. Even though silica surfaces themselves are not Lewis acidic sites. Lewis acidity increases tremendously when Al atoms replace some of the Si atoms in SiO_2. An aluminum atom in an aluminosilicate is an electron pair acceptor, because it has only six electrons in the outer shell and has room for eight. For example, the cracking catalyst, SiO_2/Al_2O_3, is a strong Lewis acid.

Because aluminum occurs as Al (III), its presence in place of tetrahedrally coordinated Si (IV) in an aluminosilicate creates an excess of negative charge. This excess of charge is neutralized by cations such as Na^+ or Ca^{2+} attracted to the surface. If the cation is H^+, the aluminosilicate can become a Bronsted acid with acidity as strong as that of concentrated H_2SO_4 (Figure 3).[21] Such catalysts have replaced sulfuric acid in many industrial reactions, eliminating the problems of hazardous waste disposal and corrosion of reactor materials.

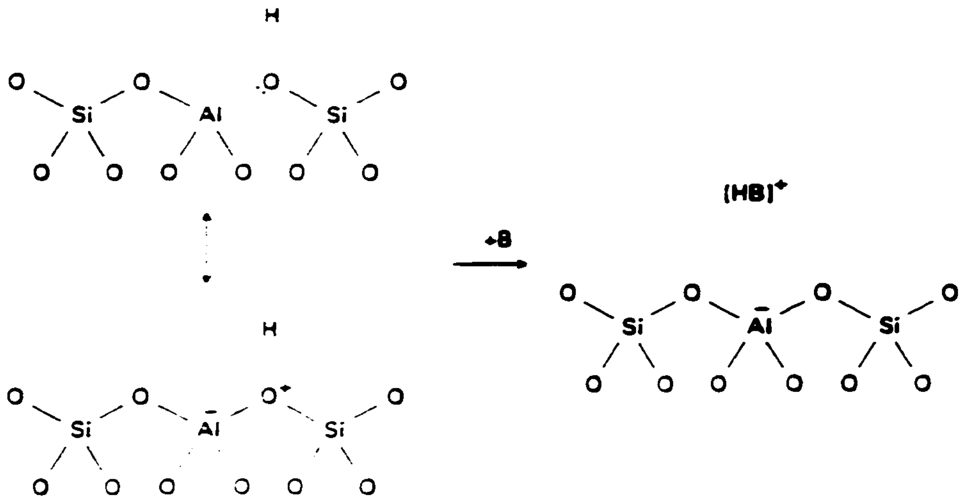


Figure 3. Bronsted acid sites in zeolites. Reprinted from ref. 16. Copyright 1994 Shriver.

Zeolite catalysts are the most powerful of all silica/alumina catalysts. Their alumosilicate framework encloses 3-dimensional cages and tunnels with cations of group (I) or (II) trapped inside. Zeolites form in nature from the reaction between volcanic glass and saline water, but natural zeolites have high degree of contamination and cannot be used as catalysts. Over 150 synthetic zeolite types have been prepared and characterized, each having specific internal configuration and specific chemical properties on the inner surface of the cages.[22]

The zeolite-based catalysts play an important role in the reactions of hydrocarbons and the alkylation of aromatics as well as in redox reactions. A new zeolite ZCM 5 with a unit cell of 288 atoms is one of a new class of sophisticated catalysts with high activity. Three-dimensional crystal structure of ZCM-5 consists of intersecting channels (Figure 4). The high selectivity of ZCM 5 is attributed to the shape of its channels where reactive intermediates are oriented in a certain way which favors specific product formation. In the isomerization of m-xylene to p-xylene. for example. ZCM-5 acts as a Bronsted acid catalyst by donating a proton for carbocation formation and is highly selective for p-xylene (1,4-dimethylbenzene) (Eq 6). ZCM-5 also catalyzes the conversion of methanol to gasoline and the synthesis of aromatic hydrocarbons from saturated hydrocarbons.[23]

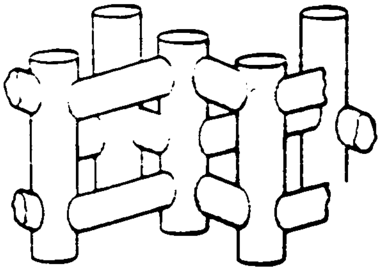
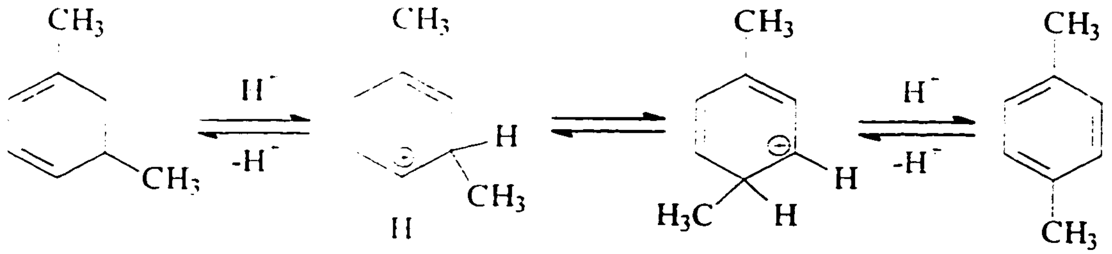


Figure 4. Intersecting channels in ZCM-5. Reprinted from ref. 16. Copyright 1994 Shriver.


(6)

Catalysts may be classified as either homogeneous or heterogeneous, depending on whether they operate in a single phase or at a phase boundary. Heterogeneous catalysts are used extensively in industry for several reasons. Many of the solid catalysts are robust at high temperatures and, therefore, are stable under a wide range of operating conditions. In addition, unlike homogeneous catalysts that can be added easily to a reactant system but may be difficult to remove from the products, heterogeneous catalysts have the great advantage of being easily separated from the reactant systems. Catalytic effect for heterogeneous catalysts is determined not by the amount added, as in case of homogeneous catalysts, but by surface area which is relatively easy to enlarge due to microporous structure.

Most discoveries in catalytic processes were made in the laboratory with homogeneous catalysts. Heterogeneous catalysts were substituted, where possible, for the industrial scale-up. To satisfy environmental requirements, recent research effort is directed to developing more effective heterogeneous catalysts to replace hazardous and corrosive homogeneous catalysts. For example, in the proton-catalyzed hydration of ethylene, where sulfuric acid has long been used as a homogeneous catalyst. phosphoric acid adsorbed into porous matrix celite is now used instead.[24]

Heterogeneous catalysts cannot just be mixed into reaction mixture. as in the case with homogeneous catalysts. Heterogeneous catalysts require a certain reactor design. Usually fixed or fluidized beds are used. Fixed bed reactors simply utilize a catalyst packed into a column. Fixed beds are practical when the catalyst has a long lifetime. If the catalyst has to be removed for frequent regeneration. the shutdown of production can become rather costly. In this case fluidized bed catalysts are used. In the fluidized bed a catalyst is present in the powder form and is fluidized by the gas flow. Therefore. the heterogeneous catalyst in these systems behaves and is handled as a liquid. It can be mixed easily and withdrawn from the reactor for regeneration in continuous flow. Fluidized beds are valuable in exothermic or endothermic reactions where accurate control of temperature is important. The catalyst particles move rapidly. helping to dissipate the heat and establish constant temperature throughout the entire reactor.[25]

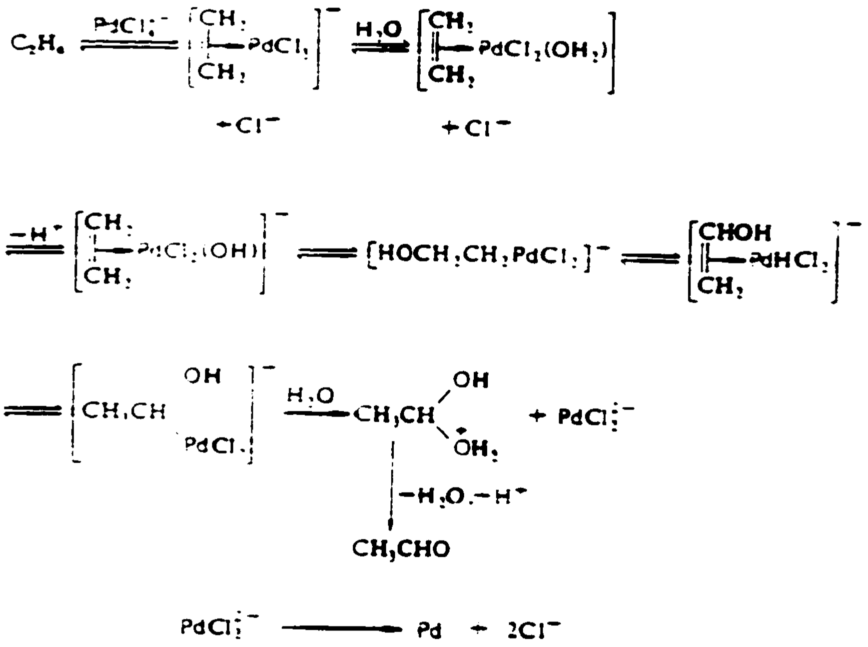
Metals or metal oxides catalysts represent the majority of heterogeneous catalysts. Metals catalyze both reduction and oxidation reactions by alternating between two oxidation states (Cu^{2+}/Cu^{+}. Co^{3+}/Co^{2+}. Mn^{3+}/Mn^{2+}. and Pd^{2+}/ Pd^{0}). Most advances in this type of catalysts involve improvements in selectivity. For example. first ammoxidation (oxidation in the presence of ammonia) catalyst for acrylonitrile gave 6% yields (Eq 7).

This was later increased by bismuth phosphomolybdate to 65%. This improvement made the process economically viable. A further increase in yield to 80% was achieved by using a uranium oxide catalyst. New proprietary catalysts have raised the yield even further.[26]

$$CH_2{=}CH{-}CH_3 + NH_3 + 3/2\,O_2 \xrightarrow{[cat.]} \underset{\text{Acrylonitrile}}{CH_2{=}CH{-}C{\equiv}N} + 3\,H_2O \qquad (7)$$

Transition metal catalysts represent a class of coordination catalysts. Transition metals catalyze reactions by forming coordinated complexes with ligands. The most active among coordination catalysts are rhodium catalysts. Rhodium phosphine complexes catalyze carbonylation of methanol to acetic acid, which is believed to proceed via a rhodium/iodine/carbon monoxide complex (Figure 2, p. 27).[17] The new rhodium catalyst has made the process commercial, reducing costs tremendously by allowing the reaction to occur at much lower pressure. In general, coordination catalysts may be either homogeneous or heterogeneous in such major industrial processes as oxidation, carbonylation, or hydrogenation. Wacker oxidation of ethylene to acetaldehyde catalyzed by Pd(II) is a good example of a process first developed for the homogeneous reaction (Scheme 4). An understanding of the homogeneous reaction mechanism then allowed for the development of a heterogeneous catalyst.

Scheme 4



Reprinted from ref. 27. Copyright 1979 Applied Science Publishers.

Overall, the importance of catalysts to society is based on their great financial impact in the production of broad range of products that are vital to our quality of life. In addition, they play an increasingly important role in the search for alternative sources of energy and the search for improvements in environmental protection and control. Catalysts are one of society's most important strategic tools for the science and technology of the future.

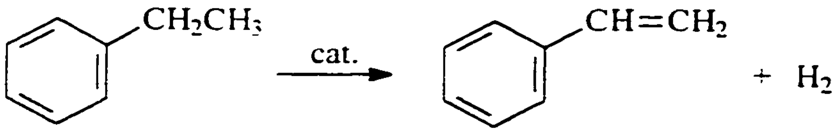
III. Synthetic Processes for the Top Volume Organic Chemicals

A. Highest Volume Organic Chemicals

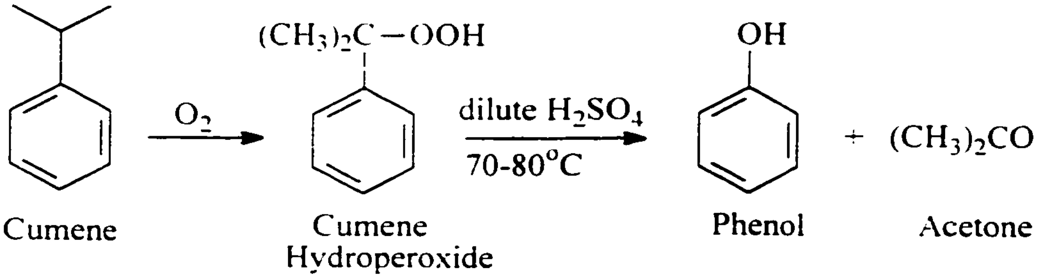
Out of total of 750 billion pounds of top 50 chemicals produced annually, the total organic volume was 286 billion pounds in 1997.[8] Thirty of the top 50 chemicals and 68 of the top 100 chemicals are organic.[8] These chemicals form the backbone of the so-called heavy organic chemical industry. They are large volume commodity chemicals such as ethylene and propylene as opposed to specialty chemicals such as pharmaceuticals and dyes. Many of the highest volume organic chemicals are monomers, including ethylene, propylene, vinyl chloride, styrene, terephthalic acid, formaldehyde, ethylene oxide, ethylene glycol, phenol, butadiene, propylene oxide, acrylonitrile, vinyl acetate, adipic acid, and caprolactam.

Some of the chemicals have only one major use. For example, ethylene dichloride is the synthetic precursor of vinyl chloride used as a monomer for widely used polyvinyl chloride (PVC) (Eq 8), and ethylbenzene is used to make styrene (Eq 9). p-Xylene is converted primarily into terephthalic acid used for polyester fiber production (Scheme 5). Cumene is converted to phenol and acetone (Eq 10). Cyclohexane is used primarily to make adipic acid (Scheme 6) and caprolactam (Eq 11) for manufacture of nylons.

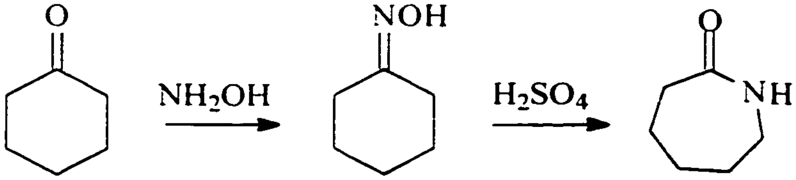
$$CH_2{=}CH_2 + Cl_2 \longrightarrow ClCH_2CH_2Cl \longrightarrow H_2C{=}CHCl + HCl \qquad (8)$$



(9)

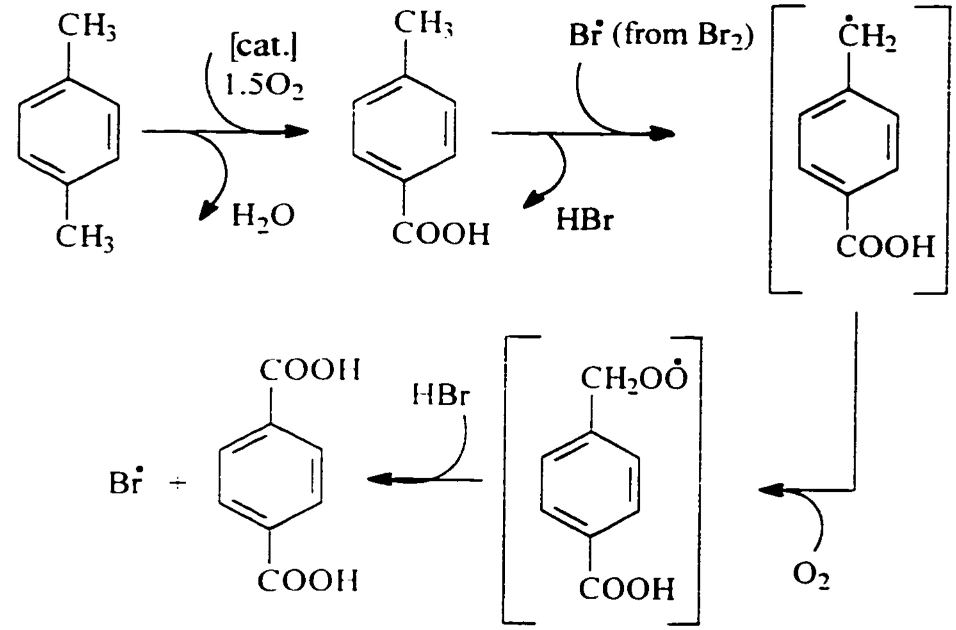


(10)

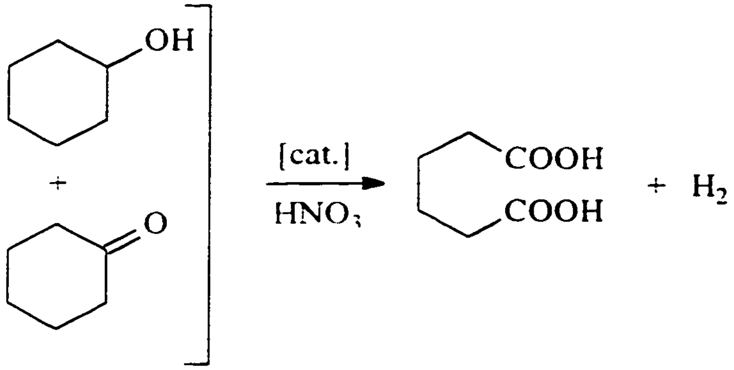


(11)

Scheme 5



Scheme 6



The two most important organic chemicals. ethylene and propylene. occupy positions four and nine on the "Top 50 list" with annual production of 51 and 27.5 billion pounds respectively. Benzene. the third most important building block. occupies position number sixteen with 16 billion pounds produced.[8,26] Ethylene. propylene. and benzene are produced in such high volume. because they are used in production of the major organic chemicals shown in Table 1.

Table 1. Ethylene. benzene and propylene and their major derivatives

Compounds derived from ethylene	Compounds derived from benzene	Compounds derived from propylene
Acetaldehyde	Aniline	Acetone cyanohydrin
Acetic Anhydride	Bisphenol A	Butyraldehyde
Ethanol	Cumene	Hexamethylenediamine
Ethanolamines	Cyclohexanol	Propylene glycol
Linear alpha olefins	Ethylbenzene	Cumene
Perchloroethylene	Linear alkylbenzenes	Propylene oxide
1.1.1 -Trichloroethane	Nitrobenzene	Acrylonitrile
Acetic Acid	Phenol	Acetone
Ethylene dichloride	Cyclohexane	Isopropyl alcohol
Ethylbenzene	Maleic anhydride	
Ethylene Oxide		
Ethylene glycol		
Styrene		
Vinyl chloride		
Vinyl acetate		

Like ethylene and propylene, some of the top 68 major organic chemicals are produced in petroleum refinery reactions. Other top organic chemicals are manufactured by such familiar chemical reactions as oxidation, hydrogenation, hydration, aromatic substitution and halogenation.

Both standard and novel reactions and processes for top U.S. organic chemicals are discussed in this section along with recent breakthroughs in development driven mostly by economic and environmental factors. The industrial processes are compared to classical laboratory synthetic reactions, and the reasoning behind significant differences in processes is thoroughly analyzed.

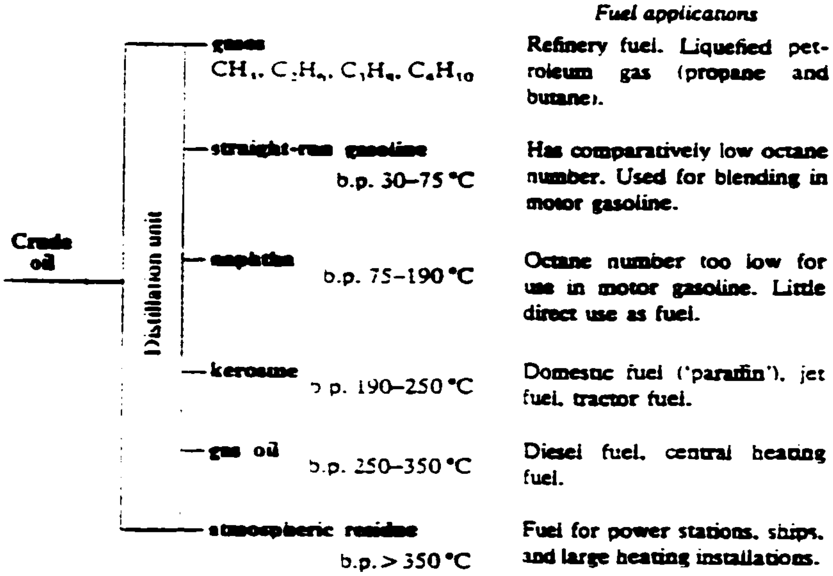
B. Raw Materials for Chemical Industry (Overview of Petroleum Refining Reactions)

Approximately 90% (by weight) of the organic chemicals used worldwide are produced from petroleum and natural gas. Others come from coal, fats, oils and carbohydrates, and natural products (examples are sterols and alkaloids).[26] Since the majority of raw materials for chemical industry are petroleum-based, a basic overview of petroleum refinery reactions should be presented to the reader.

Refining is a combination of physical and chemical processes by means of which crude oil is converted into useful products. The chemical industry consumes only 6% of refinery products in the US. The rest serves the gasoline industry.[28] A major objective of a petroleum refinery is to raise the octane number of gasoline to prevent knocking. Octane number is measured on a "knockmeter" scale under the engine test conditions, along with isooctane and n-heptane which are used as reference fuels. The octane rating of the fuel reflects the ability of the unburned gases to resist spontaneous autoignition. The autoignition is caused by the products of pre-flame reactions and happens before the normal combustion occurs. The reactions are initiated by formation of alkyl radicals that create unsaturated oxygen-containing intermediates and eventually lead to formation of hydroxyl and atomic oxygen radicals that start the autoignition. Since secondary C-H bonds are weaker than the primary C-H bonds of methyl groups, straight chain alkanes undergo pre-flame reactions more easily than branched alkanes with a large number of methyl groups. This explains why resistance to knocking increases with branching but decreases with increasing chain length or ring size. Octane number is the lowest for unbranched alkanes (~0) and the highest for aromatics (>100). Therefore, major refinery products for gasoline industry are branched and aromatic hydrocarbons, which are mixed with straight chain alkanes to satisfy octane number of 90-100 required for modern engines.[29]

Refining begins with fractional distillation of the crude oil. The resulting fractions are shown in Figure 5. The gasoline fractions are then subjected to a number of reactions, most important of which are steam cracking, catalytic cracking, catalytic reforming, isomerization, and metathesis.

Steam cracking of alkanes is a process of major importance for the chemical industry, since it produces the basic starting materials (ethylene, propylene, and C_4 olefins such as butadiene) for a wide range of organic chemicals (Figure 6). Steam cracking is a major source for ethylene, which is required in the quantity of approximately 40 million tons annually worldwide.[30] The cracking proceeds via free radicals and involves the steps shown in Scheme 7 for the formation of ethylene.



Fuel applications

Refinery fuel. Liquefied petroleum gas (propane and butane).

Has comparatively low octane number. Used for blending in motor gasoline.

Octane number too low for use in motor gasoline. Little direct use as fuel.

Domestic fuel ('paraffin'), jet fuel, tractor fuel.

Diesel fuel, central heating fuel.

Fuel for power stations, ships, and large heating installations.

Figure 5. Distillation of crude oil. Reprinted from ref. 27. Copyright 1979 Applied Science Publishers.

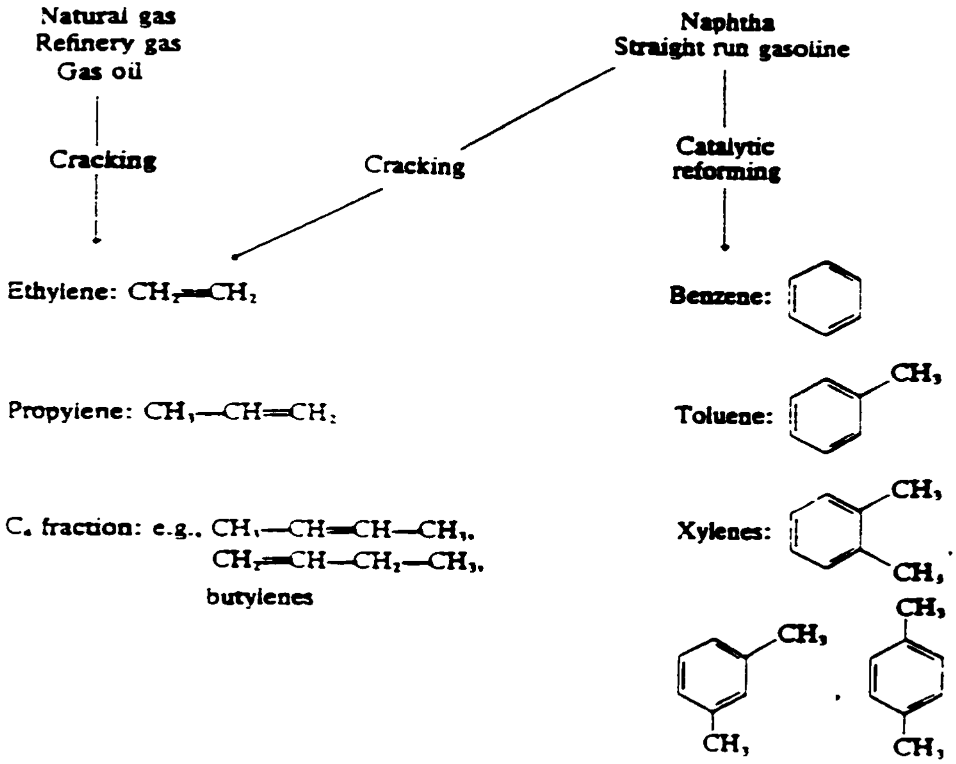


Figure 6. Cracking and catalytic reforming. Reprinted from ref. 31. Copyright 1993 Wiley-Interscience.

Scheme 7

$$\left.\begin{array}{l} CH_3CH_3 \longrightarrow CH_3^{\cdot} + CH_3^{\cdot} \\ CH_3CH_3 + CH_3^{\cdot} \longrightarrow CH_4 + CH_3CH_2^{\cdot} \end{array}\right] \text{Initiation}$$

$$\left.\begin{array}{l} CH_3CH_2^{\cdot} \longrightarrow H_2C{=}CH_2 + H^{\cdot} \\ H^{\cdot} + CH_3CH_3 \longrightarrow H_2 + CH_3CH_2^{\cdot} \end{array}\right] \text{Propagation}$$

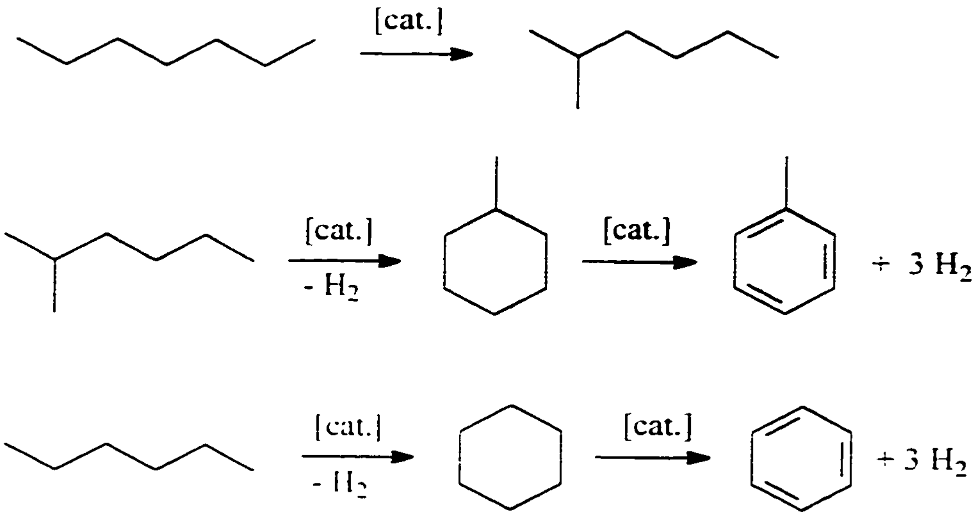
$$\left.\begin{array}{l} 2CH_3CH_2^{\cdot} \longrightarrow CH_3CH_2CH_2CH_3 \\ CH_3CH_2^{\cdot} + H^{\cdot} \longrightarrow CH_3CH_3 \end{array}\right] \text{Termination}$$

Unlike steam cracking, catalytic cracking is only a minor source of ethylene and mainly produces molecules with five to twelve carbon atoms (suitable for gasoline) from larger molecules. Catalytic cracking is not a major route to petrochemicals, but it is a primary source of gasoline.[31] Acidic zeolites are used as catalysts for catalytic cracking. Besides providing acid catalysis, the catalysts also facilitate formation of branched chain and aromatic molecules in this reaction. Catalytic cracking is an excellent example of the important contribution catalysts can make to the improvements of conversion and selectivity. For example, owing to introduction of new synthetic zeolites of ZCM-5 type, the "residue" fraction from the vacuum distillation of crude oil, which previously was wasted since it deactivated the catalysts, now is used as feedstock for catalytic reforming.[18] This has led to tremendous improvement in the economics of the catalytic cracking process.

Basic aromatics (benzene, toluene, xylenes) are produced from petroleum by catalytic reforming. Catalytic reforming dehydrogenates both straight chain and cyclic aliphatic hydrocarbons to aromatics to improve the octane number of the gasoline. It is the most widely used refinery reaction in the U.S., supplying aromatic hydrocarbons for chemical industry as well. A dual function catalyst, platinum-on-alumina, is used.[32] It has both acidic and hydrogenation-dehydrogenation properties. Platinum is the hydrogenation-dehydrogenation component, and the alumina treated with HCl or HF acts as an acid component. The two most important reactions are dehydrogenation and isomerization (Scheme 8). Isomerization converts linear alkanes to branched alkanes. Dehydrogenation converts linear alkanes to cyclic alkanes and cyclic alkanes to aromatics with formation of molecular hydrogen (the former is called dehydrocyclization). The dual function catalyst is essential here. The dehydrocyclization equilibria are driven to the product side by the subsequent aromatization reactions. Resonance stabilization thermodynamically drives the aromatization. The dehydrocyclization is a rate-determining step.

Both cracking and reforming processes can be technically considered dehydrogenation reactions, and, as such, make dehydrogenation the most important reaction carried out industrially.

Scheme 8



Isomerization is used to convert straight chain to branched-chain compounds for subsequent use in alkylation reactions. n-Butane is converted to isobutane over aluminum chloride and hydrogen chloride as catalysts. This catalytic combination creates a very strong hydride-abstracting agent to generate a carbocation (Eq 12). The overall reaction is a chain reaction. only small amount of carbocation needs to be generated. The reaction favors isobutane formation. since branched alkanes have greater thermodynamic stability than linear alkanes. Isomerization of C_5 and higher alkanes is carried out over platinum-on-alumina catalysts similar to those used in catalytic reforming.[29]

$$C_4H_{10} + HCl + AlCl_3 \longrightarrow C_4H_9^+ + AlCl_4^- + H_2 \qquad (12)$$

Metathesis is used to disproportionate, then recombine alkenes from longer carbon chain to shorter carbon chain, e.g. to convert cheap propylene into higher value ethylene and butylene (Eq 13). Since the reaction is reversible, it makes it possible to interchange between major alkenes. For example, if there were a shortage of propylene, the process could be run in reverse with the same catalysts and yield propylene by combining 2-butene and ethylene. The shift of equilibrium to the left may be achieved by using a large excess of ethylene, in accord with Le Chatelier's Principle.[33] The ethylene must, of course, be recycled if it is used in excess.

$$2\,\underset{\text{Propylene}}{CH_2{=}CHCH_3} \rightleftharpoons \underset{\text{Ethylene}}{CH_2{=}CH_2} + \underset{\text{2-Butene}}{CH_3CH{=}CHCH_3} \qquad (13)$$

C. Reactions

Oxidation

Here the term 'oxidation' is used in the traditional organic chemistry meaning, e.g. a reaction that either decreases the hydrogen content or increases the oxygen, nitrogen, or halogen content. Once again, there is a significant difference between larger scale industrial oxidation and smaller scale conventional laboratory oxidation reactions. Even pharmaceutical preparations resemble laboratory processes utilizing potassium permanganate, sodium dichromate, chlorine, or sodium hypochlorite as reagents. However, if hundreds of thousand of tons of a chemical are produced annually, it is more reasonable to spend more on research and development of other methods of manufacture to find cheaper reagents and methods of synthesis.

Air is the cheapest oxidation reagent and is used for many industrial large-scale processes. Oxygen is used only in processes where air cannot be used, since oxygen, unlike air, is not free. Its cost includes the cost of cryogenic condensation of air and the subsequent (fractional) distillation of oxygen from the liquid air. There are two major types of oxidation by air or oxygen in industry, free radical liquid phase oxidation and non-free radical liquid phase or gas phase oxidation. The range of gas phase heterogeneous oxidation reactions has been broadening tremendously in the recent years with the development of environmentally friendly heterogeneous catalysts.

Both types of oxidation are represented below with the examples of processes for the top U.S. organic chemicals. Examples of oxidation by a free radical mechanism include the syntheses of phenol from cumene, cyclohexanol/cyclohexanone from cyclohexane, adipic acid and caprolactam from cyclohexanol/cyclohexanone, and terephthalic acid from p-xylene. Large scale processes proceeding by non-free radical mechanism are illustrated by the Wacker oxidation of ethylene to acetaldehyde or vinyl acetate, the oxidation of ethylene to ethylene oxide, the oxidation of propylene to propylene glycol and acrylonitrile, and the oxidation of toluene to phenol.

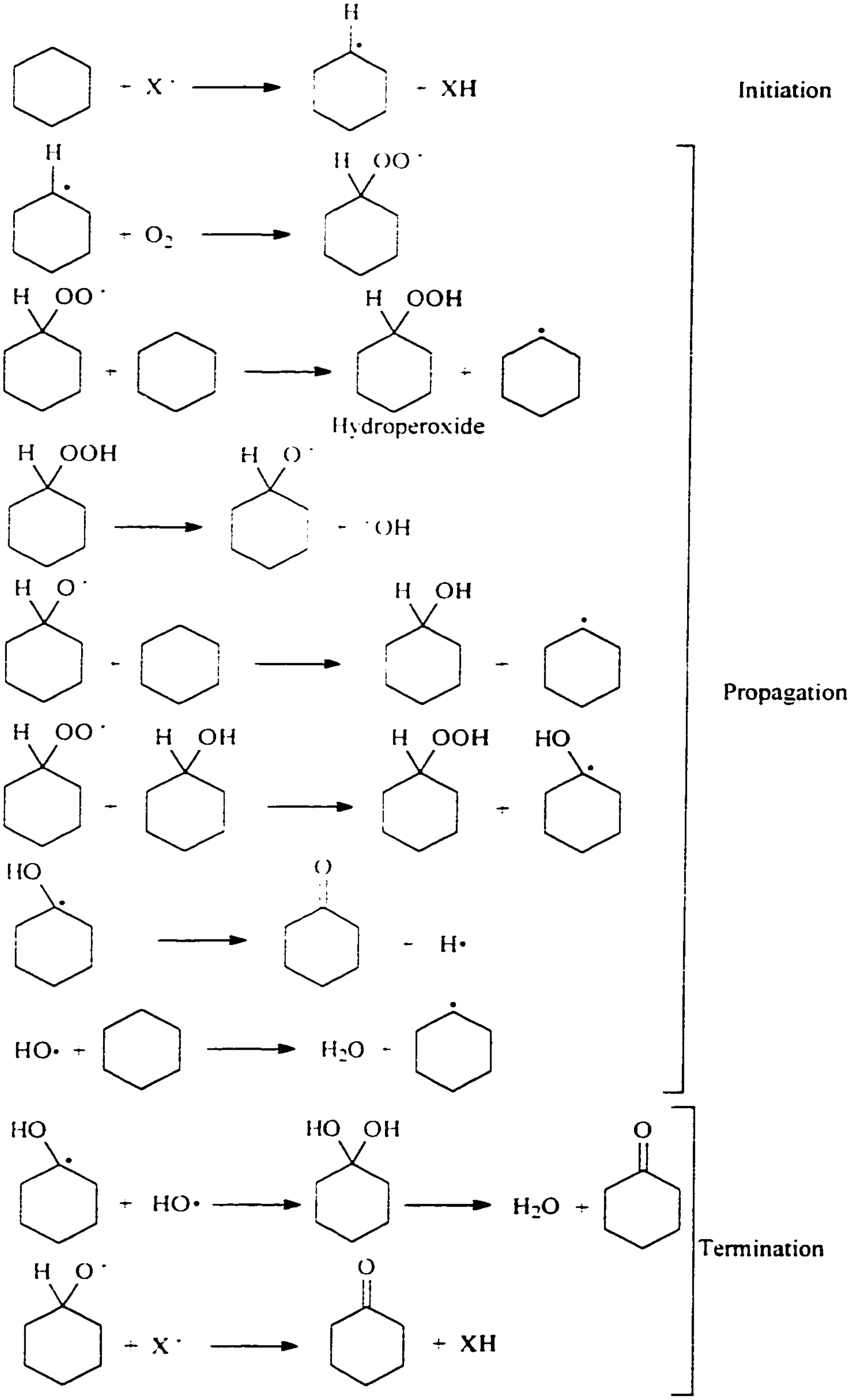
Free radical oxidation belongs to the most important class of free radical reactions, chain reactions. Chain reactions consist of three types of reactions, initiation, propagation, and termination. The propagation steps occur in cyclic fashion thousands or even millions of times for every initiation or termination step. Gas-phase free radical oxidation is much less selective than liquid phase oxidation and gives a mixture of products rather than a dominant product in a high yield. Therefore, all free radical oxidation reactions discussed below proceed predominantly in a liquid phase. In addition to direct oxidation, alternative carbonylation routes are discussed for some processes in this part of the thesis, since carbonylation can be considered an oxidation reaction (if the oxidation state of the carbon monoxide is ignored).

Alcohols and Ketones

Many materials in industry are oxidized in the liquid phase by oxygen (usually as air) which acts by a free radical mechanism. Even though these processes can proceed without a catalyst, homogeneous catalysts, typically metal salts, are usually used in industrial processes to accelerate the reaction. The oxidation of cyclohexane to a mixture of cyclohexanol and cylcohexanone is an example of the industrial process for manufacture of alcohols and ketones from saturated hydrocarbons.

The production of cyclohexanol/cyclohexanone mixtures is usually carried out as a part of an operation to make adipic acid or caprolactam for the manufacture of nylon 66 (polyhexamethylenediapamide) or nylon 6 (polycaprolactam) respectively. Nylon 6, produced by caprolactam self-condensation, is widely used in clothing and for molded plastic parts. Nylon 66 is the starting material for fibers used in the textile industry as well as other industries. The numbers used to designate nylons refer to the number of carbon atoms in the diamine and the acid monomers, as in the case of Nylon 66. If only one monomer is used, then only a single digit descriptor is necessary.

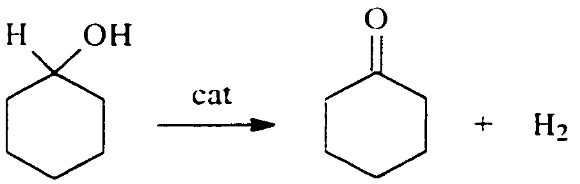
Scheme 9



(•X is radical initiator)

The chain reaction proceeds via formation of hydroperoxide (Scheme 9).[34] The free radical produced in the initiation step combines with oxygen. resulting in formation of the peroxy radical. In the propagation step the peroxy radical abstracts hydrogen from another molecule of cyclohexane. leading to formation of hydroperoxide and cyclohexyl radical. The oxygen-oxygen bond in hydroperoxide is weak and easily undergoes cleavage. Hydroperoxide undergoes further propagation reactions to form cyclohexanol and cyclohexanone. At the termination stage free radicals are destroyed.

The products of cyclohexane oxidation. cyclohexanol and cyclohexanone. are oxidized more readily than cyclohexane. In order to minimize further oxidation and achieve the maximum selectivity. cyclohexane conversion is limited to 10%. The excess of cyclohexane is recycled. Oxidation is carried out with air. at 150 -160 °C and 8-9 atm pressure in the presence of a cobalt salt catalyst. Low conversion allows to achieve up to 85% of the cyclohexanol and cyclohexanone selectivity (in ratios ranging from 1:1 to 2:1). Cylohexanol may be further dehydrogenated to cyclohexanone at 425 °C and atmospheric pressure with metallic catalysts such as zinc or copper (Eq 14).[34]



(14)

It is worth mentioning here that, in addition to oxidation from cyclohexane, cyclohexanol and cyclohexanone are also produced by hydrogenation of phenol.[35] The low cost of raw materials (the bulk price of cyclohexane is $0.13/lb, and that of phenol is $0.40/lb) and the high production volume make the process highly economical. Commercial prices of $0.73/lb for cyclohexanone and of $0.83/lb for cyclohexanol easily cover raw materials costs and process costs and still generate profit.

Unlike industrial reactions for alcohol formation, small scale syntheses of alcohols do not utilize alkanes as starting materials. The low reactivity of alkanes under ordinary lab conditions is the fundamental problem. On the small scale alcohols are usually obtained from halides by hydrolysis or from alkenes by hydration. Other laboratory methods for alcohol formation include the reduction of aldehydes, acid chloride, ketones, carboxylic acids, and other expensive starting materials. These reduction reactions use expensive and often hazardous laboratory reagents, such as sodium borohydride ($NaBH_4$, $19.10/lb) or lithium aluminum hydride ($LiAlH_4$, $314.00/lb) in the presence of solvents. Some of these reactions are analyzed below in the part of the thesis devoted to hydration.

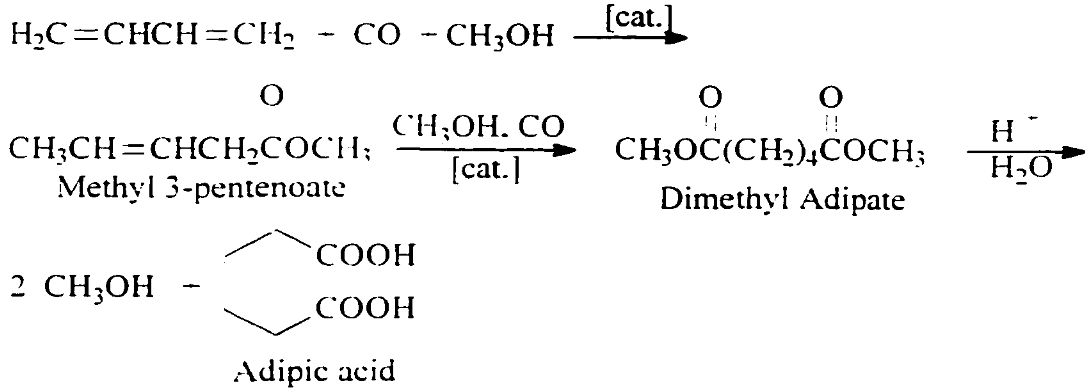
Ketones are synthesized in the laboratory from secondary alcohols using bleach (sodium hypochlorite) or more expensive Jones reagent, CrO_3 in aqueous sulfuric acid ($11.20/lb). The least expensive raw materials for ketone synthesis in the laboratory are alkenes that are converted to ketones via oxidative cleavage by ozonolysis or potassium permanganate

(Mn^{VII}).[1] The permanganate reactions are typical of many laboratory reactions in that they result in formation of waste byproducts in stoichiometric amounts (Mn^{IV}).

Carboxylic acids

Like caprolactam, adipic acid manufacture also proceeds through a cyclohexanol/cyclohexanone mixture. The synthesis of adipic acid (hexanedioic) is an example of a two-step oxidation: the first step, oxidation of cyclohexane, was already described above. The second step involves oxidation of the 'mixed oil', a mixture of cyclohexanol and cyclohexanone, with 40% nitric acid under a few atmospheres pressure. The selectivity for adipic acid is up to 96%.[36] Even though air is a more economical oxidant, free-radical oxidation by air is less advantageous because of the large number of side reactions and byproducts. Here it is helpful to stress the importance of considering not only the cost of the raw materials for industrial reactions, but also process and byproduct costs. As a result, adipic acid synthesis is the only industrial process for manufacturing a major organic chemical utilizing nitric acid as an oxidant (Scheme 6, p. 39).

A new carbonylation process is based on the ability of butadiene to react with CO to form aldehydes and ketones that can be treated further to give adipic acid.[37] Although this reaction had been known since the early 1950s, the industrial process was developed more than twenty years later when highly selective catalysts became available. In general, carbonylation reactions benefit from use of coordination catalysts, such as cobalt (III) or rhodium (I) complexes, although platinum (II) and palladium (II) catalysts are also used.[38] The carbonylation to adipic acid is carried out in the presence of methanol which, along with carbon monoxide, is involved in the formation of the ester functionality. Regenerated methanol is recycled. The yield of adipic acid in this process is 72% based on butadiene. The reaction sequence includes the migration of a double bond (Eq 15). Even though the costs of raw materials for the oxidation and carbonylation processes to adipic acid are similar, a big advantage of the butadiene process is that corrosive nitric acid is not needed.



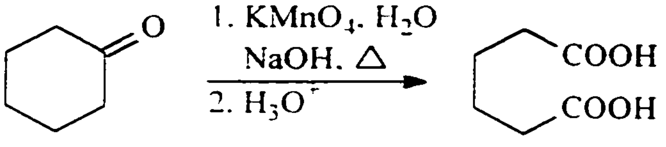
$$H_2C{=}CHCH{=}CH_2 + CO + CH_3OH \xrightarrow{[cat.]}$$

$$\underset{\text{Methyl 3-pentenoate}}{CH_3CH{=}CHCH_2\overset{O}{C}OCH_3} \xrightarrow[\text{[cat.]}]{CH_3OH,\ CO} \underset{\text{Dimethyl Adipate}}{CH_3O\overset{O}{C}(CH_2)_4\overset{O}{C}OCH_3} \xrightarrow[H_2O]{H^+}$$

$$2\ CH_3OH + \text{Adipic acid}$$

(15)

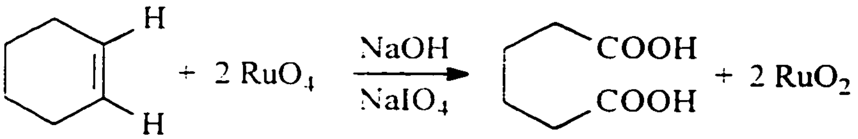
For comparison, laboratory oxidative cleavage of alkenes (or less commonly, ketones) to carboxylic acids is accomplished with potassium permanganate, osmium tetroxide/periodate, ozone, or RuO_4. The permanganate reaction involves the formation and decomposition of a cyclic manganate intermediate. Adipic acid is commonly synthesized in the laboratory in 79% yield from cyclohexanone in a slow cleavage reaction with transition metal oxidants (hot alkaline $KMnO_4$ or acidic CrO_3) via 2-hydroxycyclohexanone and 1,2-cyclohexanedione intermediates (Eq 16).[39]



(16)

The cost of $KMnO_4$ is \$1.20/lb; that of CrO_3 is \$11.20/lb. The cost of cyclohexanone is \$.73/lb which is \$.60/lb higher than the cost of cyclohexane from which adipic acid is manufactured in the industrial process. Therefore, the cost of raw materials to make one pound of adipic acid would vary from approximately \$2 to \$12 depending on the reagent used, not considering the cost of waste disposal. The commercial price of adipic acid, prepared by nitric acid oxidation, is \$.70/lb. Note, however, that in recent years, many lab scale reaction systems have been developed in which a cheaper oxidant is used to reoxidize a catalytic amount of the transition metal catalytic oxidant.

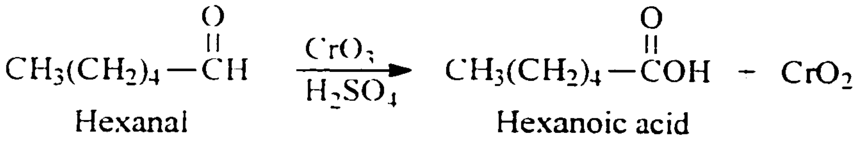
Adipic acid can be also synthesized on a larger scale in the laboratory by the oxidative cleavage of the double bonds of cyclohexene under alkaline conditions (Eq 17). The reaction proceeds in 86-96% yield when the oxidant is ruthenium tetroxide. The initial step of this reaction is the direct electron transfer to form a radical cation-perruthenate complex. The RuO_4 serves as a catalyst, rather than a stoichiometric reagent. Sodium periodate (\$110/lb) serves as the bulk oxidant by rapidly oxidizing ruthenium dioxide back to ruthenium tetroxide.[40] The cost of adipic acid is determined mostly by the cost of cyclohexene (\$3.50/lb). Although the price of ruthenium tetroxide is high (\$16.7/lb), its cost per pound of product is negligible because it is a catalyst.



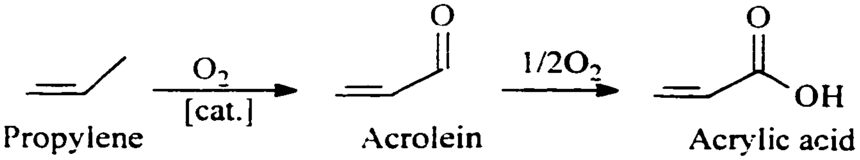
(17)

Note that in the cost analyses for this thesis, only raw material costs are compared, since they constitute approximately 70% of all variable costs. Remember that for more accurate calculations a capital cost, which is typically high for chemical industry, needs to be considered as well. Part of the capital (or equipment) cost is fixed, which means that its value will not be affected by the particular process. Because very high volumes are produced, capital costs contribute much less than raw materials costs to the final cost of the product. Based on this consideration, cost calculations will be limited to the raw material costs in most cases.

Aldehydes can also be starting materials for carboxylic acid synthesis. In the laboratory carboxylic acids are synthesized from aldehydes by oxidation with Mn(VII) or Cr(VI) (Eq 18).[39] For comparison, the industrial synthetic process for acrylic acid involves oxidation of the aldehyde acrolein which, in turn, is formed from propylene (Eq 19).[38] In place of expensive laboratory oxidants, oxygen (from air) serves as the sole oxidant for both steps. The low cost of propylene and the availability of active and selective heterogeneous catalysts for allylic oxidation made this route economically viable. Molybdenum-based alumina supported catalysts consisting of a variety of metal oxides are predominantly used for both acrolein and acrylic acid formation steps. The oxidation of propylene to acrylic acid is an example of a heterogeneously catalyzed gas phase oxidation. Reactants and oxygen are adsorbed on the catalyst surface and interact there to produce the product.



$$\underset{\text{Hexanal}}{CH_3(CH_2)_4-\overset{\overset{O}{\|}}{C}H} \xrightarrow[H_2SO_4]{CrO_3} \underset{\text{Hexanoic acid}}{CH_3(CH_2)_4-\overset{\overset{O}{\|}}{C}OH} + CrO_2 \qquad (18)$$



Propylene Acrolein Acrylic acid

(19)

Oxidation of propylene to acrylic acid is normally carried out as a two-step continuous process without isolation of the intermediate acrolein. Propylene is oxidized to acrolein in the first reactor. The resulting mixture of acrolein and water is then passed to the second reactor where acrolein is oxidized to acrylic acid. For the first stage (320 °C) propylene conversion to acrolein is 97%. The second stage (220 °C) gives a 30-60% aqueous solution of acrylic acid. The selectivity for acrylic acid is 98%. The lower operating temperature for the second step was chosen to maximize selectivity.[38]

Acrylic acid is essential for the production of widely used acrylic esters, which in turn serve as monomers for emulsion polymerization. Polymers in the form of emulsion are major components of water-based paints (accounting for 30-35% of the use of all acrylates) and are used in solvent-based coatings.

The conversion of p-xylene to terephthalic acid (1,4-benzenedioic acid) is another commercially important oxidation process. Terephthalic acid is currently produced in a quantity of 8×10^6 tons annually worldwide, with a half of this quantity produced in the U.S. It is required in large quantities to manufacture polyethylene terephtalate for polyester fibers. At first it was difficult to carry this oxidation with air, because p-toluic acid, formed as an intermediate, was resistant to oxidation. The electron-withdrawing effect of the carboxyl group increased the difficulty of abstraction of a hydrogen atom from the second methyl group. The oxidation was accomplished with nitric acid prior to the development of direct oxidation conditions.[41]

The direct oxidation of p-xylene to terephthalic acid proceeds at 200 °C and 15 atm (Scheme 5, p. 39).[41] Toluic acid formed in the first stage of oxidation contains a methyl group that is resistant to further oxidation, because the carboxyl group is electron withdrawing. To promote further oxidation the reaction is carried out in the presence of catalytic amounts of manganese (II) or cobalt (II) acetates with a bromine promoter. These catalytic systems are widely used in industry for oxidation of hydrocarbons via radical mechanisms. The bromine radical initiates the chain reaction by converting the methyl group to a free radical which is then easily oxidized. It has been suggested that in this reaction the cobalt cation assists in an electron abstraction from the aromatic molecule converting it into a free radical, which is then converted to a peroxy radical by reaction with oxygen. The latter maintains the chain reaction by hydrogen abstraction. The hydroperoxide reacts further to give terephthaldehyde, which is then oxidized to terephthalic acid. This method is used widely in industry for oxidation of other aromatic hydrocarbons to acids.

Acetic acid is required for the synthesis of vinyl acetate and many other esters. Beginning in 1911 it was produced by direct oxidation of acetaldehyde. However, due to increased acetaldehyde cost, methanol carbonylation (Eq 20) has now replaced direct oxidation.

$$CH_3OH + CO \longrightarrow CH_3COOH \qquad (20)$$

The outstanding feature of this reaction is that it has the highest yield of all reactions in industrial organic chemistry (99+% yield of acetic acid, based on methanol).[42] The reaction is catalyzed by metal-carbonyl complex of rhodium (I), $(RhI_2(CO)_2)^-$, at 200 °C and 1-3 atm pressure, and proceeds through insertion of carbon monoxide. The catalyst is regenerated after reductive elimination of acetyl iodide, which is then hydrolyzed to acetic acid (Figure 2, p. 27).[43]

This process became commercial in 1960s when the previously used cobalt (II) catalysts were replaced by rhodium (I). It is a very good example of a process in which a change in catalysts increased yield dramatically, while at the same time significantly reducing the capital cost. The capital savings resulted from the lower pressures (3 atm) required for the rhodium-catalyzed process than for the cobalt-catalyzed process (60 atm). An additional advantage of the methanol carbonylation route is the fact that methanol is obtained from synthesis gas and leads to a future possibility of synthesizing acetic acid from synthesis gas directly, without isolating methanol.

Recently British Petroleum announced a new acetic acid technology called Captiva. Captiva uses methanol and carbon monoxide as raw materials in combination with a new iridium-based active catalyst system with proprietary promoters.[7] The catalyst has higher reaction rates than the existing carbonylation process, it makes less propionic acid byproduct, and involves lower purification and energy costs. This process is the most significant development in acetic acid production in the past 25 years and potentially could lead to a 10-30% decrease in production costs compared with the existing rhodium-catalyzed carbonylation method. This leads to significant savings for acetic acid producers. Current global acetic acid demand is estimated to be 5.5 million metric tons per year (4.7 billion pounds is the annual consumption in the U.S., 50% of which is used in the manufacture of vinyl acetate).

Potentially, acetic acid can also be made from inexpensive petroleum C_4-C_8 fractions and butane from natural gas. However, capital processing costs are too high, and large quantities of byproducts are generated. Another promising route is based on methyl formate (Eq 21), which is derived from synthesis gas (obtained either from methane reforming or gasification of coal).[44] Methyl formate can isomerize to acetic acid in a reaction catalyzed by salts of many transition metals such as rhodium (I), cobalt (II), or palladium (II) in the presence of an iodide ion. In addition to the catalytic components, the activities and selectivities depend on the solvent and carbon monoxide pressure necessary to stabilize the catalysts. Selectivity for acetic acid is good, with methyl acetate being the major byproduct. However, economic advantages over current acetic acid process are not yet clear, and companies may need to have specific use for formic acid derivatives to use this method of manufacture.

$HCO_2CH_3 \longrightarrow CH_3CO_2H$ (21)

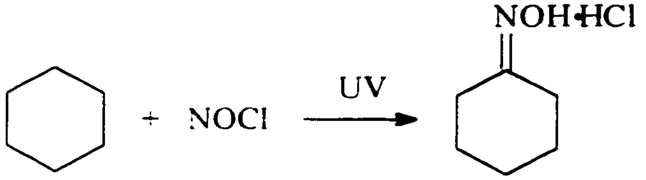
Lactams

Usually primary amides are synthesized in the laboratory from acid chlorides or anhydrides and ammonia. The synthesis of cyclic amides, or lactams, is not generally taught in introductory organic courses. Oxidation of cyclohexanone via formation of cyclohexanone oxime is the major process for commercial manufacture of caprolactam. This reaction, the Beckmann rearrangement, is also used in the laboratory. Formation of cyclohexanone oxime is accomplished with a salt of hydroxylamine, usually the sulfate, at 85 °C (Eq 11, p. 38). In order to displace the equilibrium in favor of cyclohexanone oxime formation, NH_3 must be continuously introduced to maintain a pH of 7.

Cyclohexanone oxime is converted to caprolactam via a Beckmann rearrangement. In a process developed at BASF, the oxime solution, acidified with sulfuric acid, is passed through a reaction zone that is kept at the rearrangement temperature of 90-120 °C. The resulting caprolactam sulfate is converted into the free lactam with NH_3 in a neutralization vessel. The caprolactam is separated from the saturated ammonium sulfate solution as an oily layer, then purified. The selectivity for the final product of this step is up to 98%.[45]

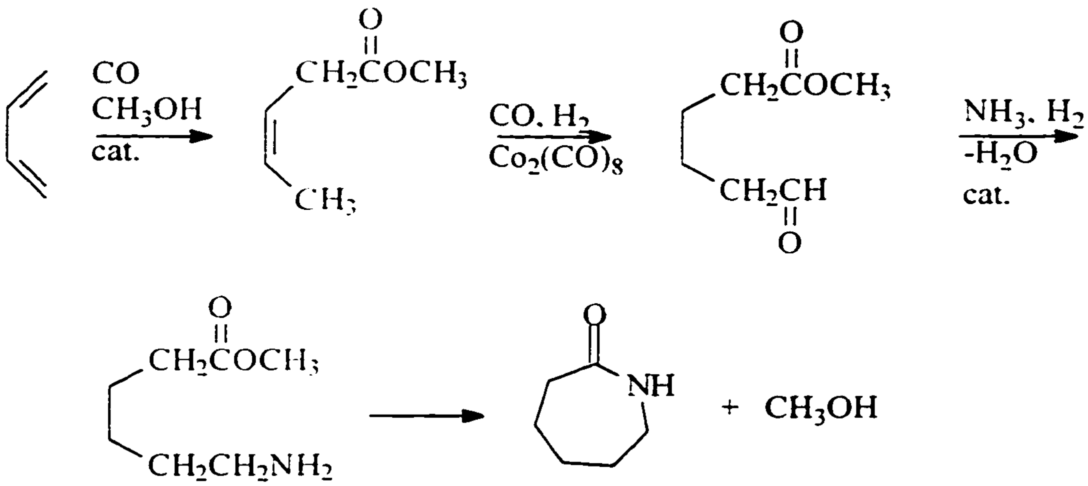
The greatest disadvantage of the caprolactam process is the co-production of 5 kg ammonium sulfate per kilogram caprolactam. Even though ammonium sulfate is used as a fertilizer, still it makes the process less economical. Most process improvements are therefore focused on saving sulfuric acid (H_2SO_4). Sulfuric acid was replaced with phosphoric acid to effect the Beckmann rearrangement, because ammonium phosphate has greater value as a fertilizer than ammonium sulfate. This process was further improved with a strongly acidic ion-exchange resin in DMSO at 100 °C. In this process caprolactam has lower production costs than in the classical route.[46]

The Toray process provides an alternative synthesis of cyclohexanone oxime that avoids salt generation. Cyclohexane, nitrosyl chloride, and hydrogen chloride react photochemically to give cyclohexanone oxime hydrochloride. This process is wasteful of chlorine since the hydrochloride salt must be converted to the free oxime. Still, this process has the lowest raw material costs of all the competing processes. Process costs, however, are considerably higher than rival processes due to the cost of the mercury (Hg) lamps and their high energy consumption (Eq 22).[45]



(22)

Finally, a revolutionary synthetic method producing caprolactam without the simultaneous production of ammonium salts has been designed. This very economical process is based on the carbonylation of butadiene in the presence of methanol. Cobalt catalyzed allylic insertion of CO yields the aldehyde. Following reductive amination with ammonia and cyclization caprolactam is formed (Eq 23). Methanol released in the last step is recycled.[47] Of all known caprolactam processes this process is the most efficient, since it does not use corrosive reagents and does not generate byproduct waste. Note that the first step in this caprolactam synthesis is identical to the first step in the synthesis of adipic acid (Eq 15, p. 57).



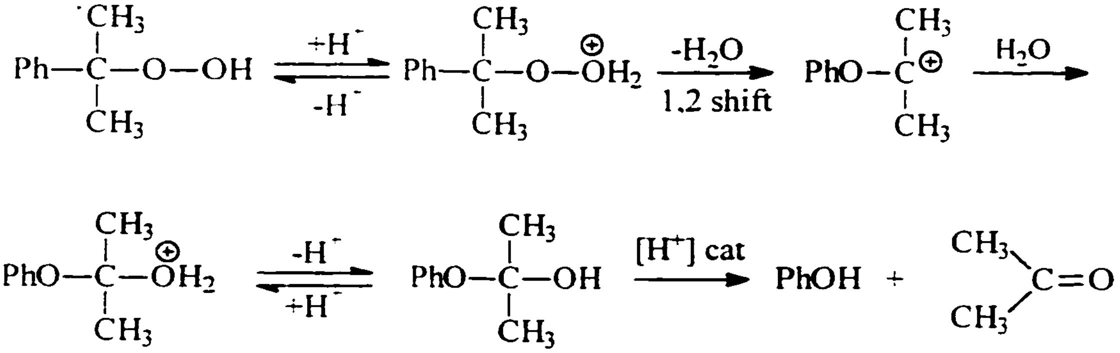
(23)

Phenol

A major use of phenol is for the synthesis of phenolic resins. the polycondensation products of phenol with formaldehyde. These resins are used in manufacture of paints. adhesives. foam plastics. and molding materials. Phenol is also used for synthesis of many organic molecules. the most important of which are bisphenol-A and caprolactam.

The major phenol process. oxidation of cumene (isopropyl benzene). proceeds via formation of cumene hydroperoxide (Eq 10. p. 38).[48] Cumene hydroperoxide is formed via a radical chain mechanism. initiated by abstraction of the easily removed benzylic hydrogen. The hydroperoxide then undergoes cleavage to phenol and acetone via treatment with dilute sulfuric acid. a reaction discovered accidentally in 1944. This reaction is also a major source of acetone. The cleavage proceeds via phenyl shift driven by the formation of a tertiary carbocation. The shift results in formation of the phenyl-oxygen bond of phenol. Reaction with water gives a hemiketal which readily forms acetone and phenol (Scheme 10).

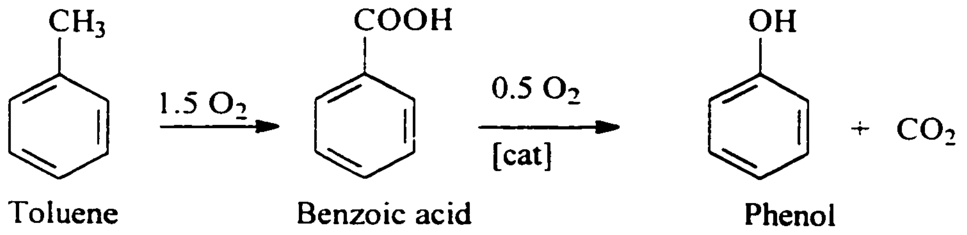
Scheme 10



The cumene process gives a 93% yield of phenol based on cumene and accounts for more than 95% of the phenol produced worldwide. Reaction conditions are mild, and utility costs are low. It has clear advantages over older phenol processes which used chlorine, sodium hydroxide, or large excesses of sulfuric acid. The process generates acetone as well, and demand for acetone is growing faster than demand for phenol, eliminating a major problem of byproduct disposal.[49] The only drawback of the cumene process is that demand must exist for both phenol and acetone in the ratio in which they are produced. Market disruptions during the mid-1980s motivated research for a new process that produces phenol only.

There has been research on direct oxidation of benzene to phenol. The reaction of benzene with acetic acid in the presence of palladium and oxygen yields phenyl acetate (Scheme 2, p. 21). The phenyl acetate can be hydrolyzed to phenol and acetic acid, which is recycled to the first step of the process.[49] However, the direct oxidation of benzene is not used on the industrial scale, because it is so far less economical than the current cumene hydroperoxide process.

In addition to manufacturing phenol from cumene and benzene, there is another process developed by Dow Chemical leading from toluene to phenol. (Eq 24).[50] This reaction is based on the oxidative ability of the Cu(II) catalyst. Cupric benzoate oxidizes the benzene ring and gets reduced to cuprous benzoate. Cu(I) is oxidized by O_2 back to Cu(II). Conversion of toluene to benzoic acid by free-radical oxidation is followed by passing an air stream into molten benzoic acid with cupric benzoate. Magnesium benzoate acts as a promoter. Phenol distills out as it is formed at the high reaction temperature. This process is usually operated when there is surplus of toluene from catalytic reforming. Both toluene and benzene are lower cost starting materials than cumene (the cost of cumene is $0.15/lb compared to $0.08/lb for toluene and $0.10/lb for benzene). Still, the cumene process is considered more economically attractive, mainly because it results in the coproduction of acetone.

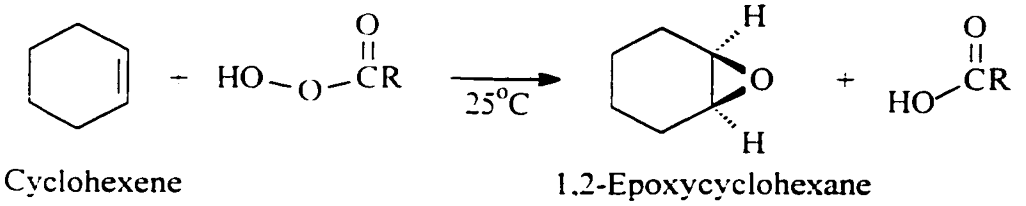


(24)

Epoxides

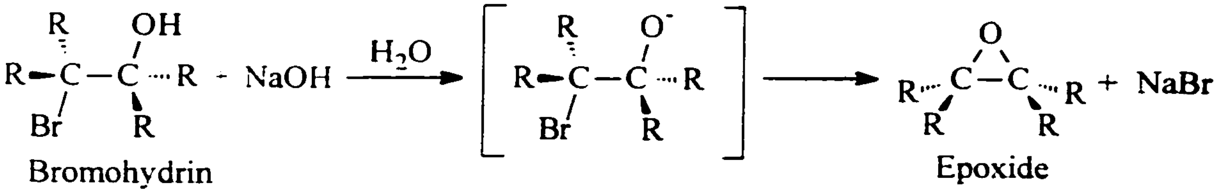
It is known that epoxides are set apart from other ethers (both cyclic and acyclic) due to the highly strained 3-membered ring that increases ether reactivity and requires unique methods of synthesis.

Peroxyacids are the most common reagents for alkene epoxidation in the laboratory. For example, cyclohexene can be transformed to 1,2-epoxycyclohexane by m-chloroperoxybenzoic acid (MCPBA) or potassium hydrogen peroxysulfate (Eq 25).[51] This is a one step reaction, but the cost of reagents is high (the cost of MCPBA is $124/lb), and the reagents require a special procedure for disposal.



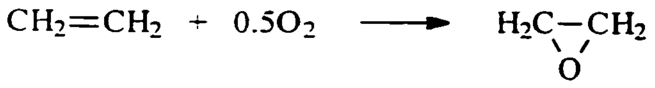
(25)

Another familiar synthetic route for epoxides starts from halohydrins made by the hydrohalogenation of alkenes.[51] This process (which is actually an intramolecular Williamson ether synthesis) does not utilize expensive reagents. Still, the halohydrin process is not economical for industrial use. Halogens tend to be avoided for industrial scale syntheses for reasons described later. Furthermore, epoxidation of alkenes via halohydrin formation is a two-step process (Eq 26).



(26)

In fact, the first industrial synthetic process for ethylene oxide became possible only after the discovery of chlorohydrin formation in 1930s, but this process is now obsolete due to development of other more economical processes. Today ethylene oxide is one of the most important chemicals prepared from ethylene. It is made in quantities of 10 million tons annually with approximately a half of this quantity (8.2 billion pounds) produced in the United States. Ethylene oxide is used primarily for the production of ethylene glycol. Contrary to the more complex and hazardous laboratory reactions, nowadays ethylene oxide is easily manufactured on the industrial scale from ethylene in the gas phase (Eq 27).[52] Oxidation of ethylene to ethylene oxide is an example of a heterogeneous gas-phase oxidation that uses metal or metal oxide catalysts. As in any heterogeneously catalyzed oxidation reaction, the reactants and oxygen are adsorbed on the catalyst surface and interact there to produce the product. Since all air oxidation reactions are exothermic, one of the major problems in the engineering of such oxidations is the removal of heat (of reaction) from the catalyst bed. This is necessary, since overheating will lead to reduction in yield and catalyst destruction.



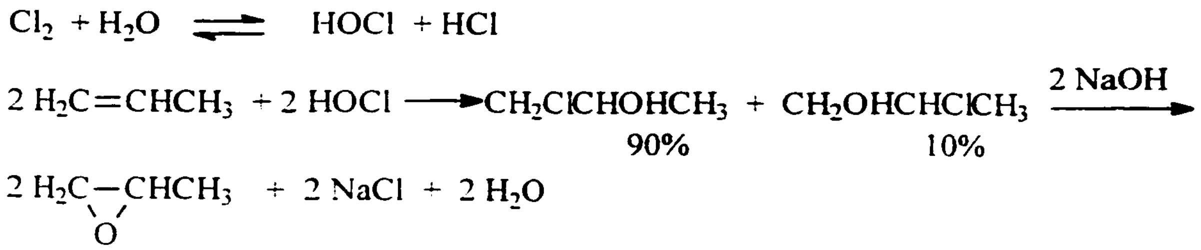
$$CH_2{=}CH_2 + 0.5O_2 \longrightarrow H_2C{-}CH_2 \text{ (with O bridging)} \qquad (27)$$

The catalyst for ethylene epoxidation is alumina-supported metallic silver.[52] Silver achieves epoxidation of ethylene uniquely; other catalysts are relatively or totally ineffective. The specific oxygen activation on the metal surface of the silver is the fundamental reason for its catalytic activity and high selectivity for ethylene oxide. (Scheme 3, p. 28).[53] The excess of ethylene is necessary for the formation of ethylene oxide, since a significant portion of ethylene undergoes combustion. The economics of the ethylene oxide process are determined primarily by the cost of ethylene, which is about 70% of the total cost. Because of high raw material costs, improvement in catalyst selectivity is necessary.

The manufacturing process and the type of heterogeneous support primarily influence the activity and selectivity of the catalyst for ethylene oxide production. In recent years, research has improved ethylene oxide production from an initial selectivity of 65% to 86%. Improvement of the catalysts was made by treating them with small quantities of nickel. Previously catalytic selectivity declined over time, and catalysts required replacement in less than a year. The nickel treatment solved this problem.[17] The annual saving from an increase in ethylene oxide yield for a 250.000-ton ethylene oxide plant is equivalent to \$1.4 million at the current ethylene oxide price of \$616/metric ton. Recently developed rubidium and cesium cocatalysts are reported to increase selectivity for ethylene oxide to 94%.[54] The power of such cocatalysts to improve selectivity is attributed to their ability to catalyze the recombination of atomic oxygen from the metal surface to regenerate free silver metal. Therefore, step 3 of the process (see Scheme 3, p. 28) utilizing 20% of ethylene is no longer necessary for free metal surface regeneration.

Propylene oxide serves as a precursor in propylene glycol synthesis, but its major use is in the production of polyurethanes and polyesters. Oxidation of propylene to propylene oxide is a more complicated process. Unlike ethylene oxide, for which allylic oxidation is impossible, propylene oxide cannot proceed by direct oxidation, due to the formation of numerous oxidation byproducts and low selectivity of the existing catalysts. The byproducts are formed because allylic radical reactions compete with the direct oxidation of the alkene π-system. Propylene oxide has for a long time been synthesized by the reaction of propylene with hypochlorous acid, generated in situ from chlorine and water (Scheme 11).[55] The intermediate chlorohydrin was treated with calcium or sodium hydroxide to affect dehydrochlorination. This process gave a 94% yield based on propylene and was wasteful of chlorine, because only 50% of the chlorine starting material could be converted to hypochlorous acid. Therefore, much research has been devoted to discovering new oxidation routes.

Scheme 11

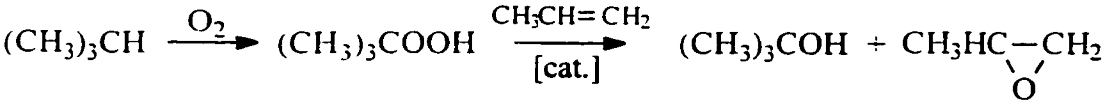


$$Cl_2 + H_2O \rightleftharpoons HOCl + HCl$$

$$2\,H_2C{=}CHCH_3 + 2\,HOCl \longrightarrow \underset{90\%}{CH_2ClCHOHCH_3} + \underset{10\%}{CH_2OHCHClCH_3} \xrightarrow{2\,NaOH}$$

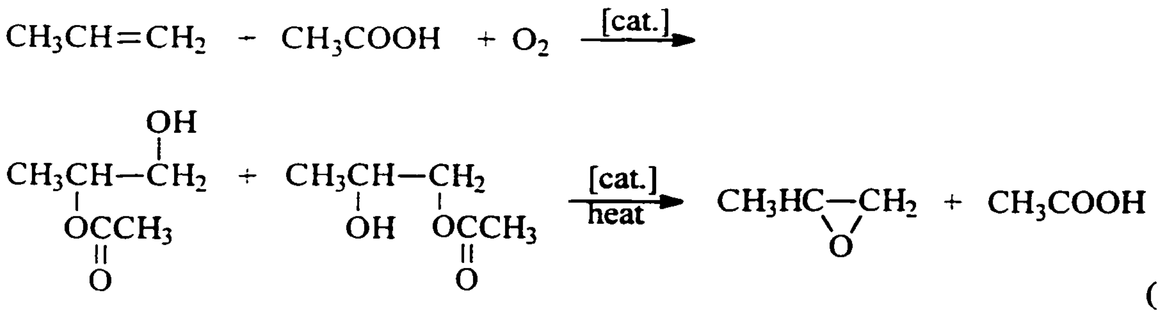
$$2\,H_2C\underset{O}{-}CHCH_3 + 2\,NaCl + 2\,H_2O$$

Currently, the predominant route to propylene oxide is the reaction of an organic hydroperoxide with propylene (Eq 28). Either t-butyl hydroperoxide or ethylbenzene hydroperoxide is used as the oxidant in this epoxidation. The hydroperoxides are produced by the liquid phase air oxidation of isobutane or ethylbenzene respectively. The reaction is run at 70 °C under 17-67 atm pressure, in the presence of a soluble molubdenum catalyst. The yield of propylene oxide based on propylene is greater than 95%.[56] However, the yield of propylene oxide based on hydroperoxide is less because of side reactions such as decomposition of the hydroperoxide during epoxidation. Therefore, an excess of the hydroperoxide must be used.



$$(CH_3)_3CH \xrightarrow{O_2} (CH_3)_3COOH \xrightarrow[\text{[cat.]}]{CH_3CH=CH_2} (CH_3)_3COH + CH_3HC\underset{O}{-}CH_2 \qquad (28)$$

To reduce the byproducts. another route to propylene oxide was introduced. The two-step route proceeds via the intermediate 1.2-propylene glycol monoacetate (PGMA) (Eq 29).[57] The intermediate decomposes to yield propylene oxide and acetic acid. Previously the attempt to synthesize propylene glycol monoacetate based on a soluble catalytic system (homogeneous catalysis) was unsuccessful. In the present method PGMA formation is catalyzed by heterogeneous palladium catalysts suspended in acetic acid solutions of nitric acid.



$$CH_3CH{=}CH_2 + CH_3COOH + O_2 \xrightarrow{[cat.]}$$

$$CH_3\underset{\underset{\underset{O}{\|}}{OCCH_3}}{CH}{-}\overset{OH}{CH_2} + CH_3\underset{OH}{CH}{-}\underset{\underset{\underset{O}{\|}}{OCCH_3}}{CH_2} \xrightarrow[heat]{[cat.]} CH_3HC\underset{O}{-}CH_2 + CH_3COOH \qquad (29)$$

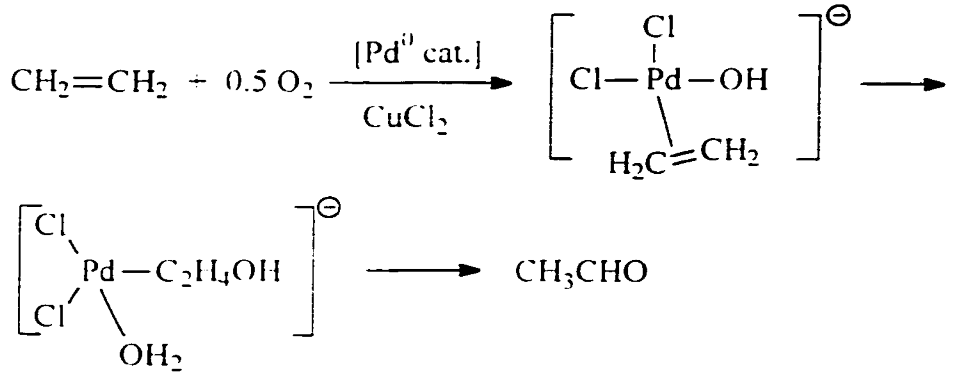
The two different methods for propylene oxide synthesis discussed above are both indirect oxidation processes. Costs are dominated by the necessity to dispose of large amounts of unwanted co-products. From the atom economy concept those processes are less efficient than direct addition reactions. The direct oxidation of propylene to propylene oxide is not commercialized on a large scale yet, but seems very promising from the standpoint of raw materials cost, if the selectivity could be improved. There is currently a major research effort directed toward this goal.[58]

Aldehydes

Familiar syntheses of aldehydes in the laboratory include oxidation of primary alcohols by pyridinium chlorochromate (PCC), oxidative cleavage of alkenes by ozonolysis, and reduction of esters with diisobutylaluminum hydride (DIBAH) at -78 °C.[59] Although yields are good for these reactions, the major economic disadvantage is, again, the costs of the reagents ($14.00/lb for PCC and $35.5/L of 20% DIBAH solution in toluene).

The industrial analog is acetaldehyde, the most commercially important aldehyde, the majority of which is used in the manufacture of acetic acid and alcohols such as n-butyl alcohol and 2-ethylhexanol. A major industrial oxidation process for acetaldehyde preparation is the well-known Wacker Chemie process developed in the 1950s.The Wacker process has replaced the old process of acetaldehyde preparation from acetylene, since ethylene is a less expensive raw material.

The oxidation of ethylene to acetaldehyde is based on the observation made in 1894 that platinum metal salts oxidize ethylene selectively to acetaldehyde in stoichiometric fashion, while themselves being reduced to the metal.[60] The industrial oxidation to acetaldehyde became possible only after industrial chemists at Wacker Chemie in Germany were able to convert the palladium salt from a stoichiometric to a catalytic component by adding cupric chloride, oxygen, and hydrogen chloride to the reaction mixture (Eq 30). This allowed rapid oxidation of palladium to palladium chloride by cupric chloride and rapid oxidation of cuprous chloride to cupric chloride by oxygen in dilute hydrochloric acid.



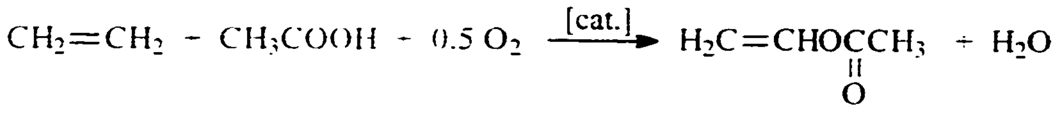
(30)

$PdCl_2$ begins its catalytic cycle by forming a π-complex to ethylene. The ethylene-palladium chloride complex is attacked by water upon formation. The subsequent β-hydride elimination forms the enol complexed to palladium. Finally, acetaldehyde is released from the hydrate, which readily loses water (Scheme 4, p. 36). A further modification of the Wacker process makes acetaldehyde by oxidation of ethylene over a palladium-on-charcoal catalyst. More recently, a two-stage process has been developed in which air is used instead of oxygen, further reducing costs.[61] Money also can be saved by using an ethylene-ethane mixture instead of purified ethylene. It should be noted that acetaldehyde is one of the few industrial chemicals whose production volume has reduced in the past decades, probably due to the replacement of acetylene-based routes to major organic chemicals with lower cost raw materials and processes.

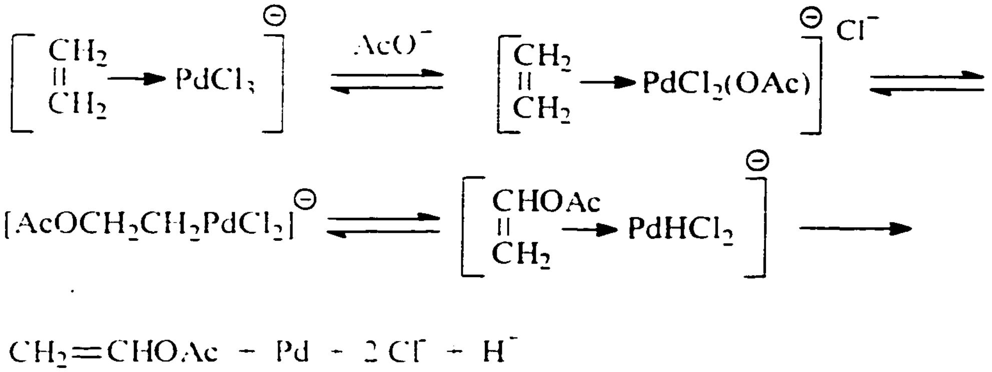
Esters

Among many esters synthesized for needs of various industries (for example, for use in perfume industry), only acetate and acrylate esters are prepared by direct esterification on a relatively large industrial scale. What is the reasoning behind such restricted use of the direct esterification reaction in industry? This question can easily be answered if one takes a look at the economics of the Fisher esterification reaction. For example, in the preparation of diethyl hexanedioate, the costs of ethanol (for Fisher esterification) and ethylene are comparable. The difference lies in the types of reactions. Fisher esterification is an equilibrium controlled substitution reaction. A large excess of ethanol is needed for high yields. Recycling of starting materials and the separation and removal of water, the stoichiometric second product, are costly. The addition reaction of a carboxylic acid and ethylene is inherently more efficient since no other product is formed.

Vinyl acetate, the highest volume ester and the only ester among top 100 chemicals in the U.S., is produced in an annual volume of 3 billion pounds.[8] Therefore, an economical process is required for its manufacture. The industrial process for vinyl acetate is based on oxidation of ethylene in the presence of acetic acid under conditions used in the Wacker process (discussed above) (Eq 31). After the development of the ethylene route to acetaldehyde, it was discovered that the palladium-catalyzed oxidation of ethylene could also lead to the formation of an enol ester, if the reaction is run in acetic acid in the presence of sodium acetate (Eq 32).[62] Acetate ion acts as a nucleophile, attacking the ethylene-palladium chloride π-complex with subsequent formation of vinyl acetate.



$$CH_2{=}CH_2 + CH_3COOH + 0.5\,O_2 \xrightarrow{[cat.]} H_2C{=}CHO\underset{\substack{\| \\ O}}{C}CH_3 + H_2O \qquad (31)$$



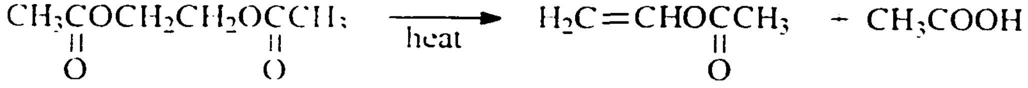
$$\left[\begin{matrix}CH_2\\ \| \\ CH_2\end{matrix}\rightarrow PdCl_3\right]^{\ominus} \xrightleftharpoons{AcO^-} \left[\begin{matrix}CH_2\\ \| \\ CH_2\end{matrix}\rightarrow PdCl_2(OAc)\right]^{\ominus} Cl^- \rightleftharpoons [AcOCH_2CH_2PdCl_2]^{\ominus} \rightleftharpoons \left[\begin{matrix}CHOAc\\ \| \\ CH_2\end{matrix}\rightarrow PdHCl_2\right]^{\ominus} \longrightarrow CH_2{=}CHOAc + Pd + 2\,Cl^- + H^+ \qquad (32)$$

Palladium is reduced to the metallic state, but, as in the Wacker process for acetaldehyde manufacture, the stoichiometric reaction was converted into a catalytic process when Pd^{2+} is regenerated from Pd^0 by oxygen, the stoichiometric oxidant. The current industrial process is carried in acetic acid solution with the co-catalyst $CuCl_2$, which is itself oxidized by the $PdCl_2$ catalyst. The reaction takes place at 120 °C and 40 atm of pressure, with a vinyl acetate yield of 93% based on acetic acid.[63]

In the liquid phase, acetaldehyde and hydrogen gas are formed in a secondary reaction of ethylene with water. Chloride ions and formic acid formed from the reaction of H_2 and CO_2 make the reaction solution very corrosive, so that expensive titanium must be used for the plant construction. For this reason the vinyl acetate process is carried out in the gas phase almost exclusively at the present time. In the gas phase process non-corrosive palladium or chlorine-free palladium salts can be used as catalysts. In the gas phase mainly vinyl acetate and only negligible amounts of acetaldehyde are produced. Therefore, almost no corrosive formic acid byproduct is formed. Thus, the gas phase process does not involve noticeable corrosion problems and the use of stainless steel is sufficient for the plant constuction. The gas phase process currently accounts for 80% of the world's production of vinyl acetate.[62]

High purity of the final product is important for vinyl acetate production, because it is required for polymerization to polyvinyl acetate (PVA), the major outlet for vinyl acetate. A supported palladium acetate catalyst developed recently improves the activity and selectivity of the vinyl acetate process.[64] High purity is achieved by multi-step distillation, which results in 99.9% purity, with some traces of methyl acetate and ethyl acetate. The cost of the Wacker vinyl acetate process has a strong raw materials dependency. Since acetic acid accounts for 70% by weight of vinyl acetate, its price basically determines the price of vinyl acetate. Therefore, the less expensive acetic acid becomes, the more attractive the gas-phase ethylene acetoxylation process appears.

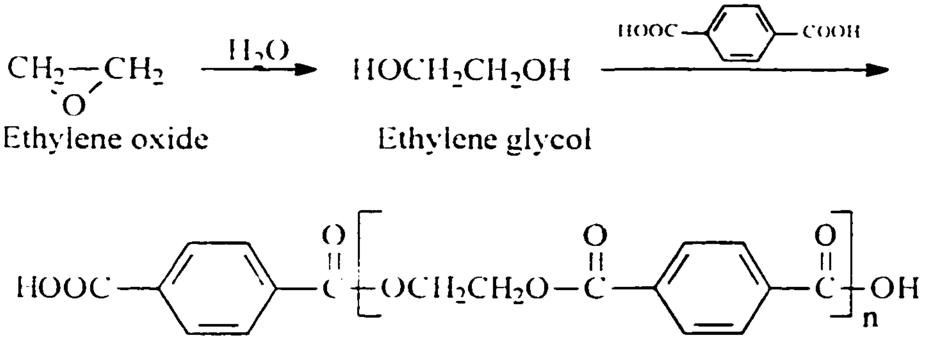
In addition to the Wacker process, new manufacturing routes for vinyl acetate are being developed. Among the most interesting is an integration of vinyl acetate and ethylene glycol manufacture. Since some manufacturers produce ethylene glycol by the catalytic oxidation of ethylene with acetic acid (see below), it became possible to manufacture vinyl acetate by the thermolysis of 1,2-diacetoxyethane, the intermediate in this reaction (Eq 33).[63]



$$CH_3\underset{\underset{O}{\|}}{C}OCH_2CH_2O\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow[heat]{} H_2C{=}CHO\underset{\underset{O}{\|}}{C}CH_3 + CH_3COOH \qquad (33)$$

Glycols (Diols)

Ethylene glycol is required in large quantities as antifreeze in automobile radiators as well as for the synthesis of one of the most important polyester polymers, polyethylene terephthalate (Eq 34).



Poly(ethylene terephthalate) (34)

Ethylene glycol is produced by the Halcon process. Ethylene reacts with acetic acid, a low cost raw material ($.38/lb), and oxygen at 160 °C and 28 atm in the presence of a catalyst system consisting of tellurium and bromide (Eq 35).[65] The proposed mechanism shown in Scheme 12 proceeds via diacetate formation from the displacement of bromide ion followed by hydrogen bromide oxidation to elemental bromine by the catalyst Te(IV). The catalyst is then subsequently oxidized by elemental oxygen to Te(VI) at the end of the reaction. This oxidation process gives a high yield and is economical, since the acetic acid is recycled. However, because the catalysts and acetic acid are corrosive, the Halcon process is not widely used. The hydrogenation route to ethylene glycol is discussed later in this thesis.

$$CH_2{=}CH_2 + 2\,CH_3COOH + 1/2\,O_2 \xrightarrow[\text{[cat.]}]{} CH_3CO_2CH_2CH_2O_2CCH_3 + H_2O$$

$$CH_3CO_2CH_2CH_2O_2CCH_3 + 2\,H_2O \longrightarrow 2\,CH_3COOH + HOCH_2CH_2OH \qquad (35)$$

Scheme 12

$$CH_2{=}CH_2 + Br_2 \longrightarrow BrCH_2CH_2Br$$

$$BrCH_2CH_2Br + 2\,CH_3CO_2H \longrightarrow CH_3CO_2CH_2CH_2O_2CCH_3 + 2\,HBr$$

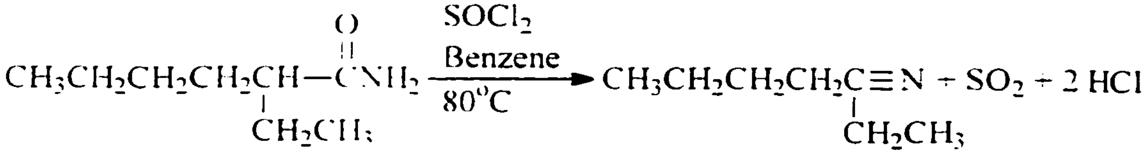
$$Te^{VI} + 2\,HBr \longrightarrow Te^{IV} + Br_2 + 2\,H^+$$

$$Te^{IV} + 1/2\,O_2 + 2\,H^+ \longrightarrow Te^{VI} + H_2O$$

In contrast, the laboratory oxidation to diols is achieved by hydroxylation of alkenes with potassium permanganate $KMnO_4$ or osmium tetraoxide OsO_4 ($84.00/g). (The conversion of cyclohexene to cyclohexanediol via formation of a cyclic intermediate is an example). When OsO_4 is used, the reaction becomes a two-step process, since the cyclic osmate intermediate is not reactive enough to undergo cleavage without a reagent.[66] Using $KMnO_4$ or OsO_4 in the oxidation allows research chemists to reach a major goal of laboratory synthesis - achieving high yield for a wide variety of substrates. The fact that the reagents are toxic and expensive is only a secondary concern in laboratory synthesis, where small quantities of materials are used. Still, improvements in this area has been made, and OsO_4 is now used as a catalyst in the laboratory.

Nitriles

Nitriles are commonly synthesized on a small scale by dehydration of an amide utilizing thionyl chloride (Eq 36).[67] Another method is the S_N2 displacement of a primary or secondary alkyl halide with cyanide ion. Both of these methods are unsuitable for industrial synthesis due to the problems of handling of the poisonous raw materials and disposal of hazardous waste gases (sulfur dioxide and hydrogen chlorides in the thionyl chloride route). Frequent use of the cyanide anion in the laboratory is justified by its versatility and reactivity as a nucleophile. S_N2 displacement proceeds easily and without the formation of gaseous byproducts.[68]



$$\mathrm{CH_3CH_2CH_2CH_2\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}H-\overset{\displaystyle O}{\overset{\|}{C}}NH_2 \xrightarrow[80^{\circ}C]{\substack{SOCl_2\\ Benzene}} CH_3CH_2CH_2CH_2\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}\equiv N + SO_2 + 2\,HCl}$$

2-Ethylhexanamide 2-Ethylhexanenitrite (36)

The highest volume industrial nitrile, acrylonitrile, is widely used as a monomer or co-monomer for acrylic fibers, plastics, and nitrile rubbers. In addition, acrylonitrile is used in the manufacture of adiponitrile, a precursor for hexamethylenediamine (HMDA). Industrially acrylonitrile is prepared by one of the most important industrial oxidation reactions, ammoxidation of propylene (Eq 7, p. 35). This is the second most important use of propylene. The manufacture of polypropylene is first. The term 'ammoxidation' refers to reactions in which a methyl group is converted into a nitrile group upon treatment with ammonia and oxygen.

The ammoxidation to acrylonitrile was a revolutionary process when it was developed in 1950s by Sohio (Standard Oil of Ohio). It quickly replaced all previous processes of acrylonitrile manufacture and now accounts for all manufacture of acrylonitrile in the world. The novelty of this process was in the formation of the C-N bond using an ammonia - catalyst system, an unprecedented reaction at the time (Figure 7).[69]

The ammoxidation to acrylonitrile is carried in a continuous fashion in the gas phase. A mixture of propylene and ammonia is oxidized with air over a solid catalyst at 500 °C. After extensive work on catalyst development, the yield was improved from 56% with the original bismuth molybdate catalyst to 87% with a proprietary catalytic system of silica-supported oxides of selenium, iron, and tellurium at 320 °C.[70] Although the industrial process was discovered in 1949, the ammoxidation to acrylonitrile only became commercialized after high efficiency catalysts were developed. The ammoxidation reaction is highly exothermic and is carried out in a fluidized bed to ensure effective heat exchange and temperature control.

Significant worldwide attempts are being made to reduce the raw material cost by replacing alkenes with alkanes. Recently developed processes for manufacturing acrylonitrile from propane are the first successful example of such replacement. One of these processes was made possible by new catalysts based on V-Sb or V-Bi-Mo oxides.[71,72]

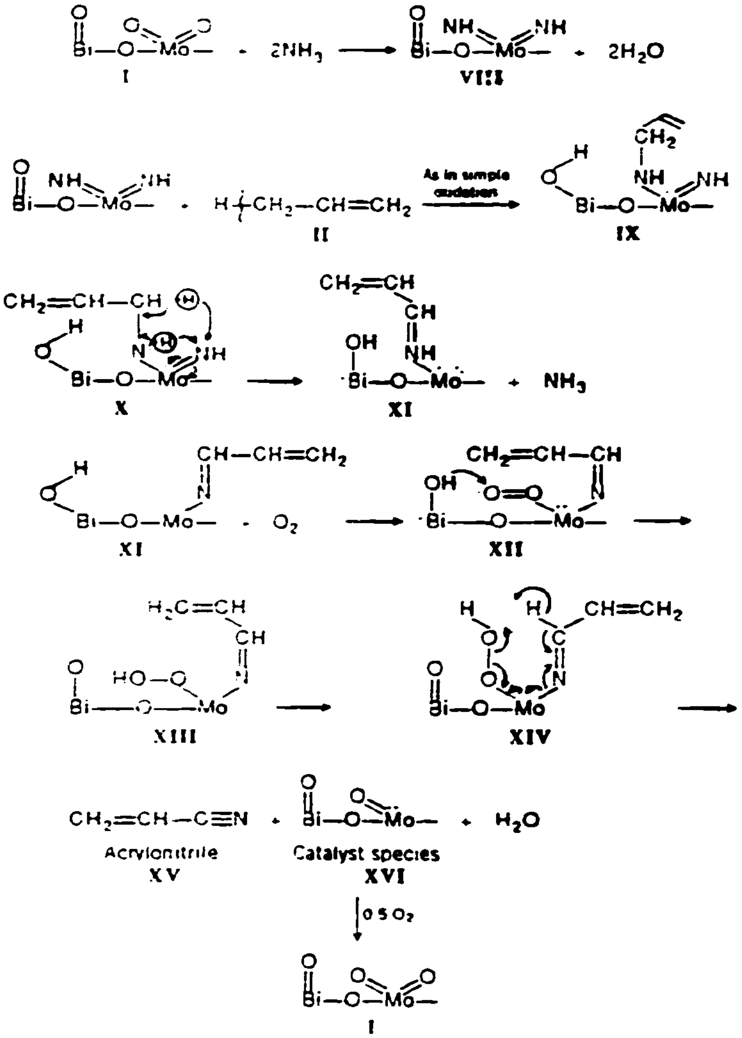


Figure 7. Mechanism of acrylonitrile formation. Reprinted from Witcoff. Reuben (1993). Copyright 1993 Wiley-Interscience.

Although the new process has a considerably lower selectivity for acrylonitrile. the lower cost of propane (one-half to one-third that of propylene) makes the process economically feasible. The selectivity problem is associated with the first step. the conversion of propane to propylene, in which unwanted side products are generated. The difference in reactivity is attributable to the relatively weak allylic C-H bond(s) found in propylene but not in propane. Obviously, the selectivity of the catalyst has to increase in order to commercialize a process based on propane as the starting material.

BP Chemical Company has already demonstrated a pilot plant production of acrylonitrile from propane, ammonia, and oxygen in one step catalytic process.[73] The propane method can cut at least 20% of the production costs of BP's widely used 40 year old propylene route. The cost saving is fairly significant, considering that annual U.S. production volume of acrylonitrile is as high as 3.3 billion pounds. Considering these advantages, the company hopes to base all of its new acrylonitrile plants on the propane ammoxidation process.

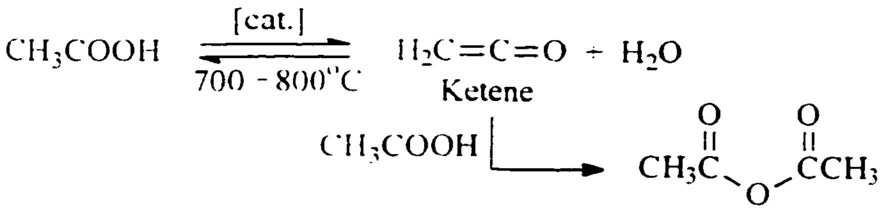
In addition, UK BOC Gases has developed the same process of propane ammoxidation using a new catalyst from Mitsubishi Chemical with higher selectivity for acrylonitrile.[74,75] Separation of unreacted propane from the product will be done by a proprietary process developed by BOC.

Anhydrides

In the laboratory acid anhydrides are rarely synthesized. Common anhydrides, such as acetic anhydride, are purchased. If they must be prepared, then they are made by nucleophilic acyl substitution reaction of an acid chloride, using a carboxylate anion as the nucleophile.[68] The acid chloride and the carboxylate anion need to be prepared first, which makes anhydride synthesis a three-step process. In the laboratory the anhydride synthesis generates sodium chloride as a stoichiometric byproduct. The synthesis of acid chlorides involves the use of expensive and hazardous reagents such as thionyl chloride, $SOCl_2$ or phosphorous trichloride, PCl_3. Additionally, all of these reaction steps proceed in the presence of solvents, which is typical for small-scale synthetic reactions, but rarely applied on the large scale.

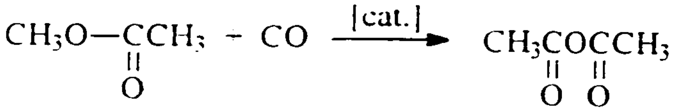
The highest volume anhydride, acetic anhydride, is manufactured from the corresponding acid. Acetic anhydride is primarily required for the esterification of cellulose to cellulose acetate. In addition, acetic anhydride is used as an acetylating agent in a variety of esterification reactions in the pharmaceutical industry, such as the esterification of salicylic acid to acetylsalicylic acid (aspirin).

The Wacker process in which acetic anhydride is produced by dehydration of acetic acid via ketene ($CH_2=C=O$) completely replaced an old acetic anhydride process based on acetaldehyde oxidation (Eq 37).[76] The thermodynamically unfavorable dehydration of acetic acid to ketene (ΔH = 147 kJ/mol) is forced to proceed at very high temperatures (700-800 °C) and reduced pressure in the presence of triethyl phosphate. Ketene is a very high energy intermediate. The reverse reaction of ketene with water back to the acid is thermodynamically favored over the reaction of ketene with acetic acid to give the anhydride. Triethyl phosphate is used as dehydrating agent to shift the equilibrium to the right by absorbing water forming in the first step. Therefore, the equilibrium is significantly shifted toward formation of ketene. In order to drive the equilibrium further to the right, the resulting H_3PO_4 is neutralized with 30% aqueous ammonia solution while still in the gas phase. The gas is then quickly cooled with simultaneous separation of higher boiling acetic anhydride, acetic acid, and water.[76]



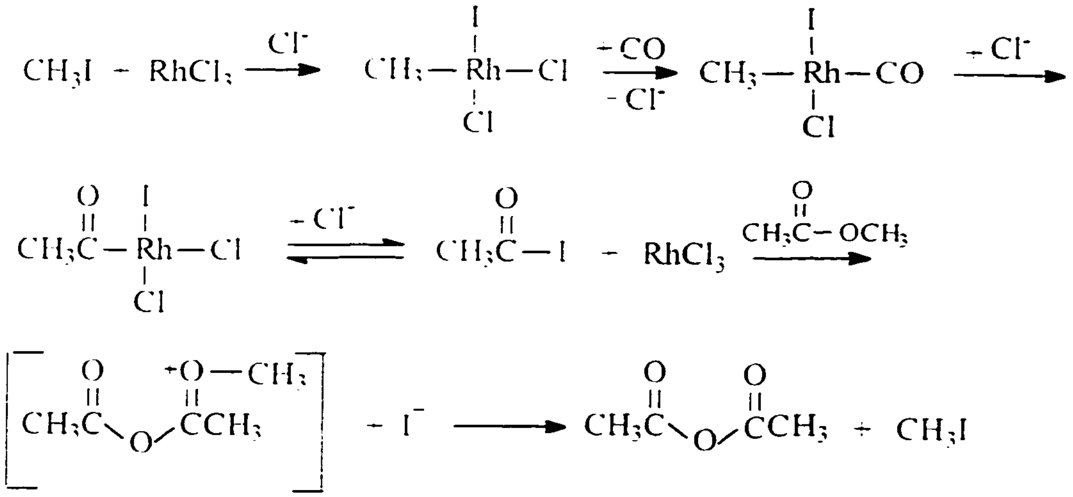
$$CH_3COOH \underset{700-800^{\circ}C}{\overset{[cat.]}{\rightleftharpoons}} \underset{\text{Ketene}}{H_2C{=}C{=}O} + H_2O$$
$$\xrightarrow{CH_3COOH} CH_3\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}CH_3 \qquad (37)$$

In 1983, acetic anhydride manufacture took another step forward. It is now produced by a more economical carbonylation reaction of methyl acetate in the presence of a rhodium salt catalyst and promoters, as a followup step to the methanol-based synthesis of acetic acid (Eq 38).[77] In this process methyl iodide acts as a promoter, assisting in a formation of the catalyst, a four-coordinate rhodium (I) complex. The initially formed acetyl iodide reacts with methyl acetate yielding acetic anhydride and regenerated methyl iodide (Eq 39). Eastman succeeded in the development of a catalytic system achieving rhodium recovery of better than 99.99%. Hydrogen acts as a reducing agent in the process in order to return to the rhodium (I) active state.[78] As a result of the economical method of production. the commercial price of acetic anhydride is presently fairly low ($.50/lb).



$$CH_3O-\underset{\underset{O}{\|}}{C}CH_3 + CO \xrightarrow{[cat.]} CH_3\underset{\underset{O}{\|}}{C}O\underset{\underset{O}{\|}}{C}CH_3$$

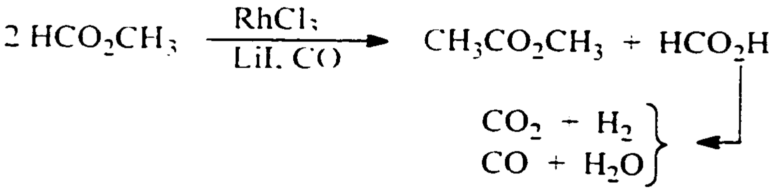
(38)



(39)

The historical significance of Eastman-Halcon carbonylation process is that it is the only process today in which synthesis gas (and. therefore. coal) has replaced petroleum. Methyl acetate is formed by a Fisher esterification reaction of methanol with acetic acid. Methanol comes directly from coal via manufacture of synthesis gas. a mixture of carbon monoxide and hydrogen. If the plant's location is close to coal mines. costs of the operation are significantly reduced. Even though the cost of raw materials is low, the capital investment for coal gasification is fairly high. Nonetheless, the process operates very successfully. There is reason to believe that synthesis gas from coal might someday replace natural gas and petroleum reservoirs, which are quite limited compared to existing reservoirs of coal.

A new industrial process for production of acetic anhydride is based on methyl formate in the presence of a rhodium-iodide catalyst. This process is currently in the initial stages of investigation. The conditions are similar to those used in the methyl formate-based preparation of acetic acid. Selective synthesis of methyl acetate from methyl formate has been reported recently, suggesting a possibility of direct synthesis of acetic anhydride from low-cost methyl formate.[79] This reaction does not occur at standard conditions, however. Acetic anhydride is only produced from methyl formate upon addition of methyl iodide to the reaction medium. A two stage procedure is necessary, as two subsequent reactions have to occur under different conditions. The first stage is the homologation of methyl formate into methyl acetate with formation of CO, CO_2, H_2 and H_2O. An alkaline iodide, such as LiI, is used with an accurate LiI/Rh ratio in order to avoid acetic acid production (Eq 40a). The second stage is similar to the conventional acetic anhydride process. Methyl iodide is required to convert methyl acetate into acetic anhydride (Eq 40b).



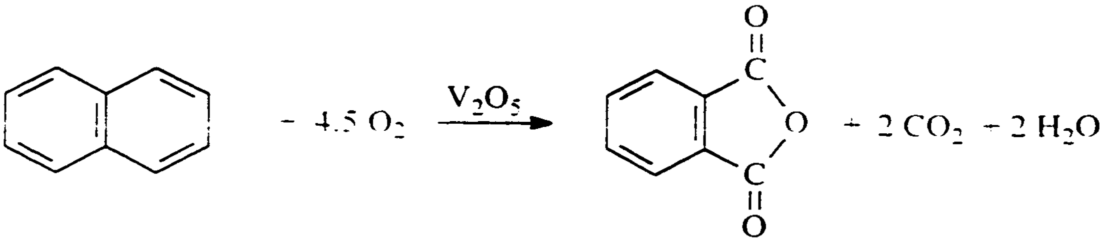
$$2\,HCO_2CH_3 \xrightarrow[LiI,\ CO]{RhCl_3} CH_3CO_2CH_3 + HCO_2H \rightarrow \left.\begin{matrix} CO_2 + H_2 \\ CO + H_2O \end{matrix}\right\}$$

(40a)

$$CH_3CO_2CH_3 + CO \xrightarrow{Rh\text{-}CH_3I} (CH_3CO)_2O$$

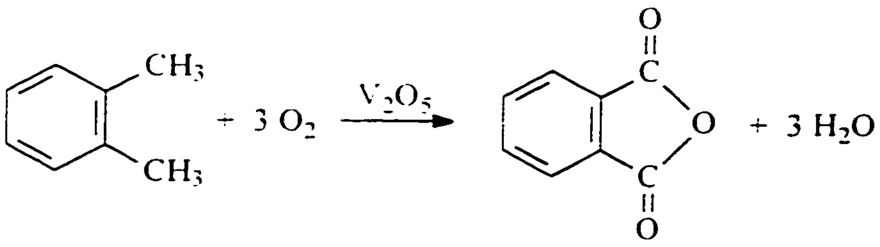
(40b)

The last oxidation process of major importance is an oxidation of o-xylene or naphtalene to phthalic anhydride, which is used in the production of phthalate esters for the manufacture of plasticizers. This oxidation is carried out with air in a liquid-phase over a soluble catalyst (acetates or naphthenates of Co, Mn, or Mo are used) or a supported vanadium pentoxide catalyst in a gas-phase reaction at 400 °C (Eqs 41 and 42).[44] Since 1960, o-xylene replaced naphtalene as the more economical and a readily available material. There are several economic advantages to this reaction. The number of carbon atoms is the same in the starting material and the product when ortho-xylene is used. In addition, less oxygen is required than in naphthalene process. The drawbacks of the process are the number of side reactions and the low yield (<80%).



Phthalic anhydride

(41)



(42)

Reduction in Industry: Hydrogenation

This portion of the thesis is devoted to reduction reactions in industry, the majority of which are hydrogenation reactions. It is useful here to review the conventional definition of reduction in organic chemistry. These are reactions that either increase the hydrogen content or decrease the oxygen, nitrogen, or halogen content of a molecule.

Hydrogenation is simply the addition reaction of molecular hydrogen to a π-bond. Like all addition reactions, the product incorporates all the atoms of the starting materials. Hydrogenation is efficient because hydrogen is low cost. These factors make hydrogenation the predominant process for reduction on the industrial scale. Under laboratory conditions nonpolar π-bonds in alkenes are also reduced by catalytic hydrogenation, but for reduction of polar π-bonds a variety of different reduction techniques exist, many utilizing expensive reagents. For example, laboratory reduction of aldehydes, acid chloride, ketones, and carboxylic acids are accomplished with expensive and often hazardous reagents such as sodium borohydride ($NaBH_4$) or lithium aluminum hydride ($LiAlH_4$). Furthermore, these reactions are done in solution, often with anhydrous solvents.

All commercially important hydrogenation reactions are carried out in the presence of solid catalysts. The majority are carried out heterogeneously, with the substrate in the gas phase. A broad range of catalysts, mostly metal oxides and metal salts such as nickel, palladium, platinum, copper oxide-chromium oxide and molybdenum and tungsten sulfides, catalyze industrial hydrogenation reactions by alternating between two oxidation states. One of the proven hydrogenation mechanisms for reduction of alkenes to alkanes (developed and used in small-scale laboratory reactions) is shown for a homogeneous catalyst in Figure 8. $RhCl(PPh_3)_3$ is converted into the catalyst, a weakly coordinated complex of Rh(I), after the ligand dissociates in the first step.[80] The reactants, hydrogen and an alkene, enter the cycle by binding to the complex. In the final step the alkane product dissociates with regeneration of the catalyst, and the cycle continues. Complexes of platinum and palladium are most popular for their activity as hydrogenation catalysts, but they are also very expensive. There is usually a tradeoff in hydrogenation processes between catalyst activity and cost. Since cheaper catalysts are typically less active, more vigorous reaction conditions are needed.

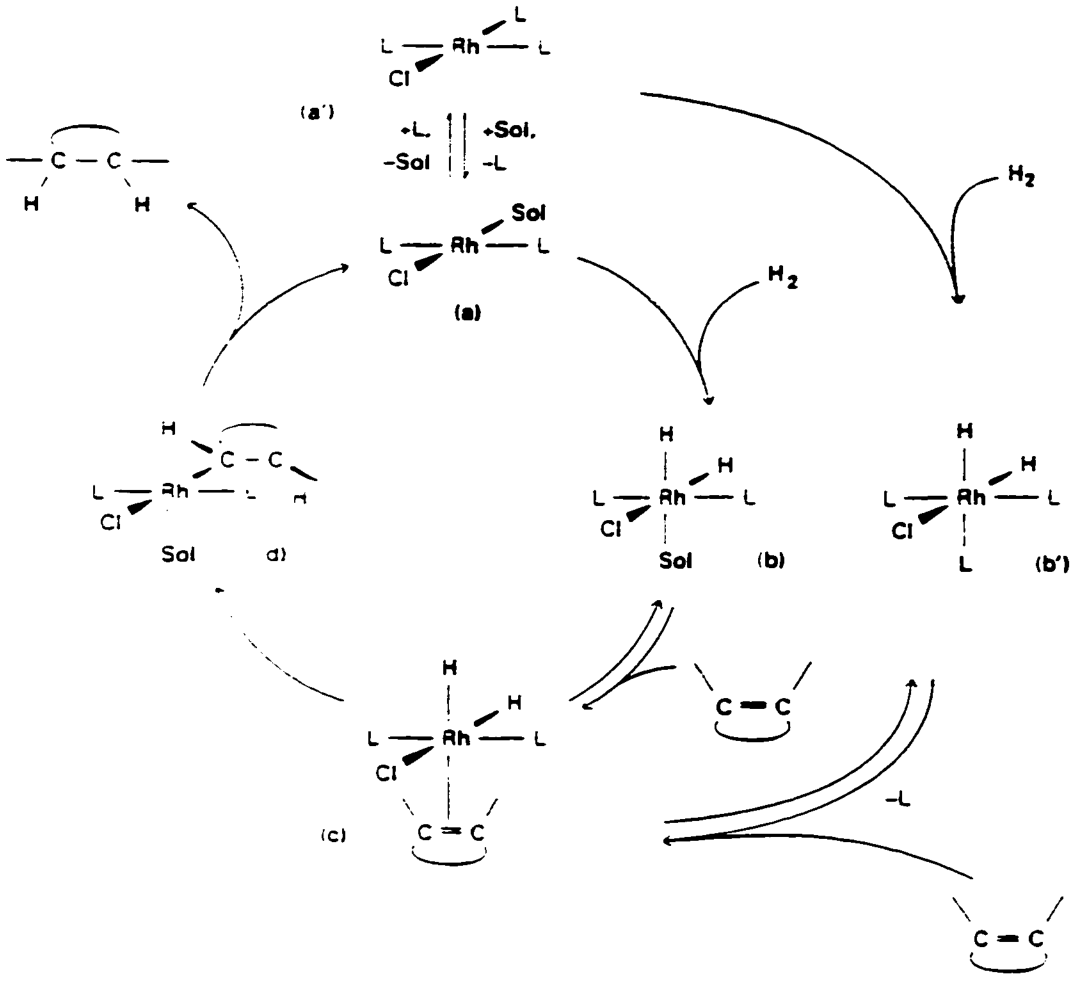


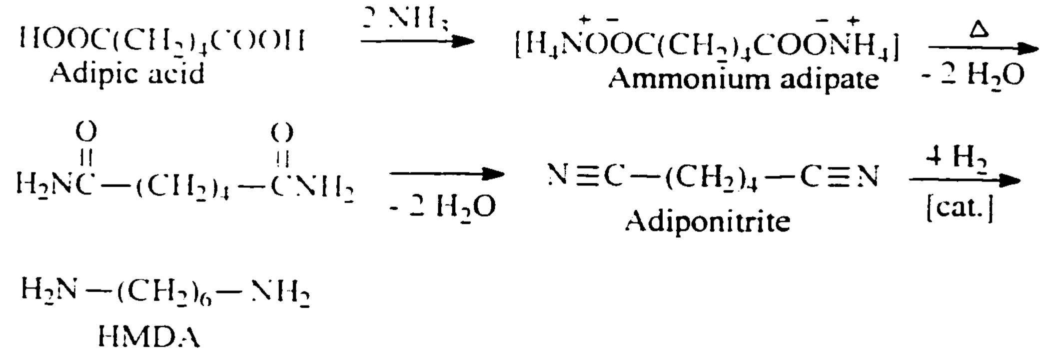
Figure 8. Mechanism of reduction of alkenes to alkanes with homogeneous catalysts. Reprinted from ref. 16. Copyright 1994 Shriver.

Hexamethylene Diamine (HMDA)

Already discussed was a commercial synthetic route to adipic acid, one of the monomers of Nylon 6.6. The other monomer, hexamethylenediamine, is produced by hydrogenation of adiponitrile. The reaction is carried out in the presence of a supported nickel or cobalt catalyst in the temperature range of 120-170 °C and 270-400 atm pressure (Eq 43). Side reactions lead to formation of hexamethyleneimine and polyamines. HMDA can be obtained in 95% yield.[81]

$$\underset{\text{Adiponitrite}}{NC(CH_2)_4CN} + 4\,H_2 \xrightarrow{[\text{cat.}]} \underset{\text{HMDA}}{H_2NCH_2(CH_2)_4CH_2NH_2} \qquad (43)$$

It's interesting to follow the industrial history of adiponitrile synthesis to show once again the example of developing of what is called "a laboratory reaction" into an economical industrial process. The old adiponitrile synthesis involved a reaction between adipic acid and ammonia to produce ammonium adipate. The vapor-phase reaction took place at 275 °C in the presence of a a dehydrating agent, a mixture of boric and phosphoric acids. Ammonium adipate was dehydrated first to the amide, then the nitrile. Finally, HMDA was formed by catalytic reduction (Eq 45).[81] Today adiponitrile is synthesized much more economically from the addition of hydrogen cyanide to butadiene (Eq 46). The mechanism involves a shift, similar to the addition reaction in the adipic acid synthesis from butadiene (Eq 17, p. 59) discussed above. The catalyst, nickel with triaryl phosphite ligands $Ni(P(OAr)_3)_4$, assists in maintaining the double bond in a terminal position in the first step and facilitates the anti-Markovnikov addition of hydrogen cyanide to the terminal bond in the second step, via formation of a sigma-bond with the terminal carbon (Scheme 13).[82] The second step is more thermodynamically favored than the first, since the stabilizing resonance structure of butadiene is given up in the first step.

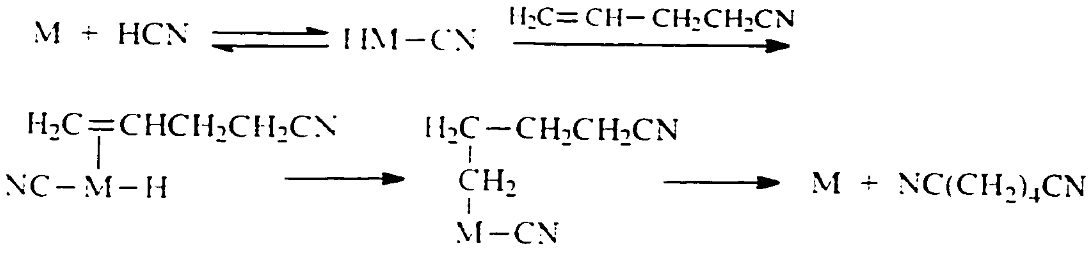


$$\underset{\text{Adipic acid}}{\mathrm{HOOC(CH_2)_4COOH}} \xrightarrow{2\,\mathrm{NH_3}} \underset{\text{Ammonium adipate}}{[\mathrm{H_4\overset{+}{N}\overset{-}{O}OC(CH_2)_4COO\overset{-}{}\overset{+}{N}H_4}]} \xrightarrow[-\,2\,\mathrm{H_2O}]{\Delta} \mathrm{H_2N\overset{O}{\overset{\|}{C}}-(CH_2)_4-\overset{O}{\overset{\|}{C}}NH_2} \xrightarrow[-\,2\,\mathrm{H_2O}]{} \underset{\text{Adiponitrite}}{\mathrm{N{\equiv}C-(CH_2)_4-C{\equiv}N}} \xrightarrow[\text{[cat.]}]{4\,\mathrm{H_2}} \underset{\text{HMDA}}{\mathrm{H_2N-(CH_2)_6-NH_2}}$$

(45)

$$\mathrm{CH_2{=}CH-CH{=}CH_2} \xrightarrow[\text{[cat.]}]{\mathrm{HCN}} \mathrm{CH_2{=}CH(CH_2)_2-CN} \xrightarrow[\text{[cat.]}]{\mathrm{HCN}} \mathrm{NC(CH_2)_4CN} \qquad (46)$$

Scheme 13*



* $M = Ni[P(OAr_3)_4]$

Another modern synthetic route to adiponitrile is electrodimerization of acrylonitrile, the only important industrial electrochemical process used in the manufacturing of an organic chemical (Eq 47).[83]

$$2\,CH_2{=}CHCN + 2\,H^+ + 2\,e^- \longrightarrow NC(CH_2)_4CN \qquad (47)$$

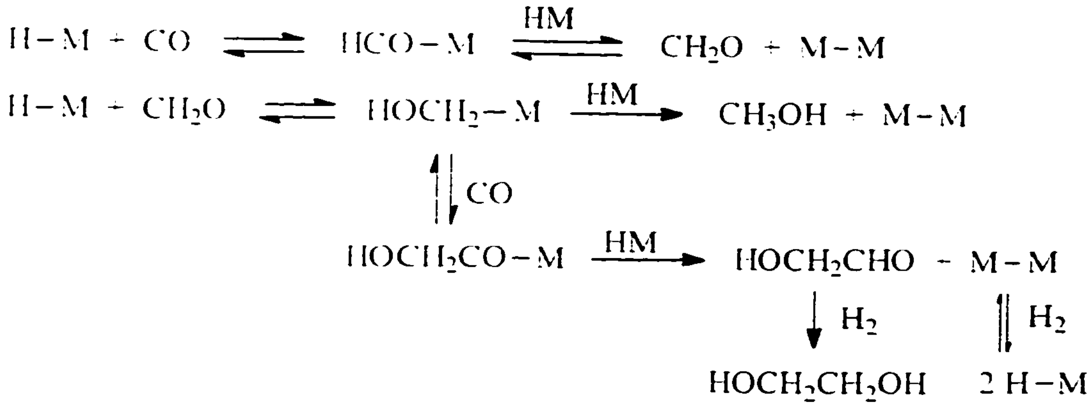
Catalytic hydrogenation of nitriles and imines (reductive amination) to amines is also used under laboratory conditions whenever possible. The laboratory reduction from nitriles to amines is often carried out by catalytic hydrogenation, but more frequently lithium aluminum hydride $LiAlH_4$ is used as a reagent. This process is too costly (cost of $LiAlH_4$ is \$251/lb) and too dangerous to be used industrially. Also, like all processes utilizing hydride reagents, it is accompanied by significant byproduct waste.

Glycols

Oxidation of ethylene to ethylene glycol in the presence of acetic acid has already been described in the oxidation section of this thesis. New processes for ethylene glycol synthesis are being developed with a goal of utilizing synthesis gas and natural gas rather than limited petrochemical feedstock as the raw material.

A process for ethylene glycol based on direct combination of carbon monoxide and hydrogen was developed by Union Carbide.[84] The reaction is catalyzed by the five-coordinate neutral rhodium complex $HRh(CO)_3L$, where the ligand is bulky trialkylphospine. The formation of formaldehyde from CO and H_2 is the rate-determining step. The phosphine ligand stabilizes the catalyst, hydride-metal complex, and facilitates the CO insertion into the metal hydride to accelerate the formation of formaldehyde. The subsequent reaction proceeds via an hydroxymethylated rhodium complex to give glycolaldehyde (Scheme 14). The glycolaldehyde is then reduced to ethylene glycol.

Scheme 14*

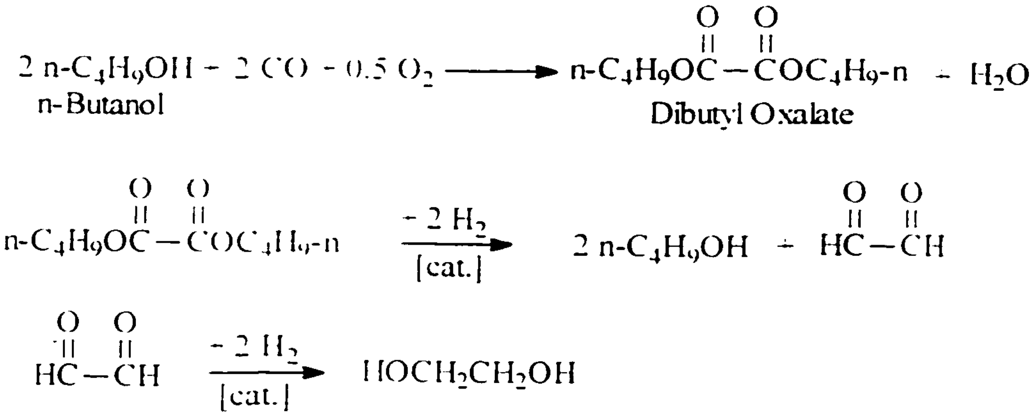


* M = $Rh(CO)_3L$ or $Rh(CO)_4$

In addition, indirect methods based on synthesis gas-dependent intermediates like methanol, methyl formate or formaldehyde have been developed.[85] One catalyst is a rhodium carbonyl cluster that requires temperatures of 240 °C and pressures of 1000-3000 atm. Another is a ruthenium carbonyl complex with trimethylethoxysilane that operates at 400 °C and 1000 atm.[86] Usually reactions under such extreme conditions tend to have poor selectivities, and in this process selectivity for ethylene glycol is only 60%.

In order to improve selectivities, a new process based on the hydrogenation of oxalate esters has been recently developed by Union Carbide, together with Ube Industries in Japan (Scheme 15).[87] Much higher selectivities are achieved when the reaction is carried out in two steps. The first carbonylation step gives di-n-butyl oxalate. In the second operational step, the hydrogenation of the carbonyls yields two n-butanols and is followed by the final hydrogenation of the two aldehydes. n-Butanol is then recycled. Both steps take place under relatively mild conditions. The carbonylation is run at 200 °C and 100 atm and the hydrogenation at 20 C and 30 atm. High selectivity is achieved. Further improvements in the catalysts have the potential to make this process competitive with the current oxidation route to ethylene glycol (if coal-based synthesis gas becomes a major feedstock).

Scheme 15



$$2\,n\text{-}C_4H_9OH + 2\,CO + 0.5\,O_2 \longrightarrow n\text{-}C_4H_9O\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}OC_4H_9\text{-}n + H_2O$$

n-Butanol

Dibutyl Oxalate

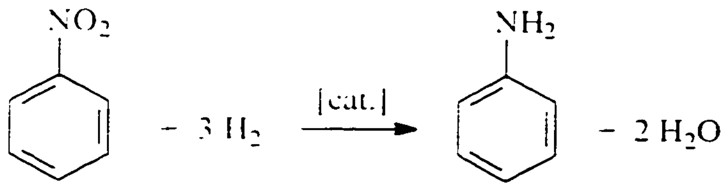
$$n\text{-}C_4H_9O\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}OC_4H_9\text{-}n \xrightarrow[\text{[cat.]}]{+2\,H_2} 2\,n\text{-}C_4H_9OH + H\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}H$$

$$H\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}H \xrightarrow[\text{[cat.]}]{+2\,H_2} HOCH_2CH_2OH$$

Hydrogenation of Aromatic Compounds

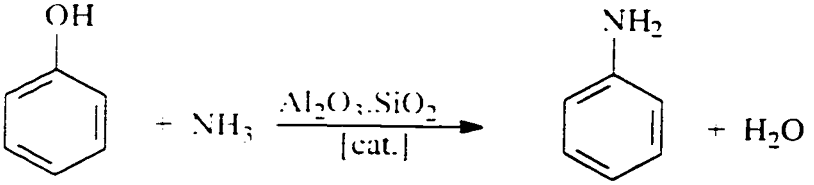
Aniline

An industrial hydrogenation process familiar to the reader from undergraduate organic chemistry textbooks is hydrogenation of nitrobenzene to aniline (Eq 48). Aniline is one of the most important compounds in aromatic chemistry, since many aromatic commodity chemicals are manufactured from it. This reaction is carried out in the vapor or liquid phase, usually with a copper-on-silica catalyst at 270 °C and at atmospheric pressure.[88] A continuous process with its small reactor volume is preferred because the reduction reaction of nitroaromatics with hydrogen is so strongly exothermic that efficient cooling would be difficult in large reactors. Smaller scale reactors are needed to keep the reduction under control at all times. Recent advances for this process are the extended lifetime (over seven years) achieved for the solid catalyst support (Lewis acid type alumina, titania or zirconia-alumina with additional promoters) and the development of an efficient distillation column for the separation of phenol from aniline in the reaction product.[64] Recent progress in catalyst design allows nearly quantitative yields.



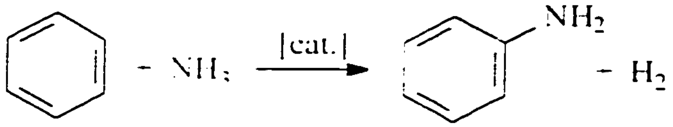
(48)

The newest process for aniline preparation involves treatment of phenol with ammonia (Eq 49).[49] This process is not a reduction reaction, but we'll discuss it here in order to compare with the traditional aniline process. This reaction is reversible and is driven to the right by a high ammonia/phenol ratio, which also retards formation of diphenylamine. The reaction takes place at 425 °C and 200 atm with magnesium, aluminum, and tungsten oxides along with the proprietary catalyst. Aniline selectivity is lower (90%) than in the nitrobenzene process. However, recently selectivities to anilines in this process were shown to improve significantly (up to 99%) by using zeolite ZCM-5 as the catalyst under pressure at 400-500 °C. The phenol route has a lower capital cost than the nitrobenzene process. This is offset by the high raw material cost of phenol relative to nitrobenzene. A clear advantage of the ammonolysis process is the elimination of the ecological problems associated with the sulfuric and nitric acids used for the preparation of nitrobenzene.



(49)

The lowest possible material cost can be envisioned for the direct amination of benzene via intermolecular dehydrogenation (Eq 50). In this reaction benzene and ammonia are allowed to react over a NiO/Ni catalyst containing promoters such as zirconium oxide at 350 °C and 300 atm to give a 97% selectivity to aniline with a benzene conversion of 13%.[89] A major issue with this process is the required catalyst regeneration, since hydrogen formed in the reaction reduces the NiO part of the catalyst. Because the catalyst regeneration has not yet been achieved and because of low benzene conversion, this reaction has not yet been commercialized.

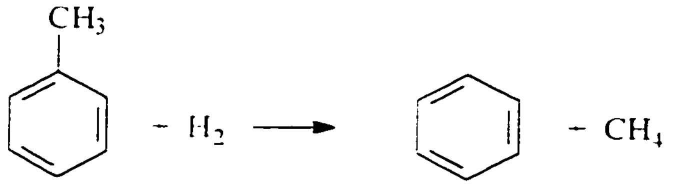


(50)

Benzene

The proportions of benzene, toluene and xylenes produced by catalytic reforming are not in line with requirements for these materials in chemical applications, with the amounts of toluene and xylenes usually being far higher than required. Hydrogenation of toluene to benzene called hydrodealkylation assists in balancing out the toluene/benzene ratio from the natural sources and accounts for 25-30% of world's benzene production.[90] This is an interesting example in which the process operations are dictated by economic factors. Hydrodealkylation plants are in operation when amount of toluene obtained from gasoline is significantly higher than that of benzene.

Hydrodealkylation is carried out both catalytically with a rhodium-alumina catalyst at 600 °C and thermally without a catalyst, with 99% yields from both processes (Eq 51).[89] Note that for this process (as well as for many others used in industry) high temperatures are required. Even though the reaction is thermodynamically favored (e.g. $\Delta H < 0$), it might not proceed at lower temperatures in a reasonable amount of time, since the rates are very slow. Temperatures above 600 °C are necessary for the hydrodealkylation reaction to overcome the activation energy barrier and achieve acceptable rates.



(51)

Dehydrogenation

With cracking and reforming processes (see pp. 47-48) being dehydrogenation reactions (which they technically are), dehydrogenation can be considered the most important reaction carried out industrially. Dehydrogenation reactions are normally designed to proceed in the vapor phase over solid catalysts.

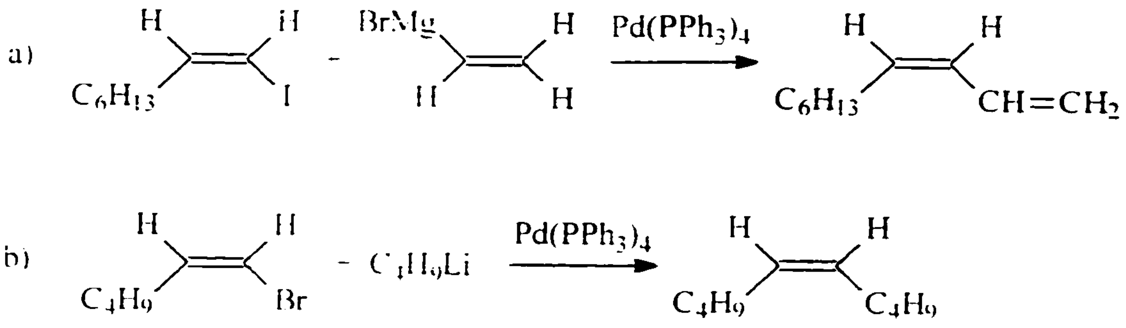
The major factors usually considered before designing any commercial hydrogenation process are the cost of hydrogen and the location of hydrogen feedstock. Considering low density, low critical temperature of -240 °C, and high critical pressure of hydrogen, its transporting can be very expensive. Therefore, hydrogenation plants must be built next to a hydrogen source, either a steam reforming plant (since hydrogen is generated from steam reforming of hydrocarbons) or a plant that produces hydrogen as a byproduct. We note that these types of considerations are never an issue in conducting a small-scale synthesis, but they are always a major concern in commercial-scale manufacturing.

Dienes

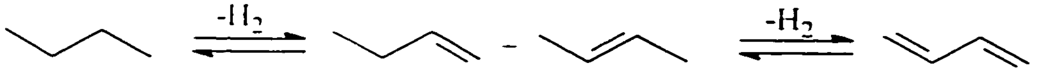
In the laboratory, 1,3 butadiene can be synthesized from allyl bromide (3-bromopropene) in a Wittig reaction with triphenylphosphine followed by an addition of formaldehyde. Alternatively, 1,3 butadiene can be obtained by oxidative coupling of alkenes with Grignard or lithiumcopper reagents in high yield.[91] As expected, the cost of the reagents is fairly high. Slightly modified, the latter process can be converted to a catalytic reaction. For example, in the case of highly functionalized molecules, coupling of alkenyl halides with Grignard or organolithium reagents can be catalyzed by tetrakis (triphenylphosphine) palladium. Still, the starting materials make this process uneconomical on an industrial scale (Scheme 16). In industry the Grignard reagent cannot be used because of cost and safety issues. In general, the economics of the laboratory reactions is not comparable with that of the industrial process. Butadiene is currently sold for \$.15/lb.

Butadiene, the highest volume material among all dienes, is used in large quantities for synthetic rubber manufacture. The annual production of butadiene in the U.S. was 4.1 billion pounds in 1997.[8] Butadiene is produced in small quantities from petroleum cracking. However, this limited amount of butadiene is not enough to satisfy the demand in the U.S. Modern butadiene production is based on dehydrogenation of n-butane or n-butenes obtained from petroleum cracking (Eq 52).[92] The more ethylene is produced

Scheme 16



annually, the more butadiene is produced as a co-product of the petroleum cracking. As a result, less is required from the dehydrogenation route.



(52)

The butane/butene dehydrogenation process is carried out at 480-600 C at reduced pressure over a heterogeneous catalyst. Current catalysts are based on iron oxide and give selectivity to butadiene of up to 93%.[92,93] Similar to most dehydrogenation reactions, this process proceeds in equilibrium and is endothermic. Endothermic reactions are driven toward completion at higher temperatures. Since dehydrogenation involves an increase in the number of moles of gas, the reduced pressure shifts the equilibrium toward formation the final product. The low pressure reactor design requires an addition of steam as a diluent to help to achieve the low partial pressure of butane. In addition to its role as a diluent, steam assists in transferring the heat and prevents rapid catalyst deactivation from deposition of carbon on the catalyst, by reacting with carbon to produce carbon monoxide.

The temperature of this process is quite critical. The enthalpy change for the conversion of butenes to butadiene is positive (ΔH = 109 kJ/mol).[92] Since free energy of reaction is defined as $\Delta G = \Delta H - T\Delta S$, at low temperatures ΔG is also positive, e.g. free energy of the products is higher than free energy of the reactants. This makes the reaction thermodynamically unfavorable at low temperatures. An increase in temperature can make the reaction favorable ($\Delta G < 0$), if the change in entropy (ΔS) from reactants to products is positive. In the butene dehydrogenation reaction entropy is positive, since the number of product molecules is greater than the number of reactant molecules. In order to make the butadiene process favorable (spontaneous), the process temperature has to be maintained above 450 °C.

Several different processes for the manufacture of butadiene are still in use around the world, including those utilizing two-carbon raw materials such as acetylene or ethanol. However, the majority of modern industrial processes for butadiene synthesis are based on petrochemicals.[92] The butane/butene dehydrogenation process has the lowest raw materials cost.

Styrene

Surpassed only by ethylene and vinyl chloride, styrene is the third most important monomer for the manufacture of thermoplastic materials, in particular, block copolymers, due to its ability to polymerize easily with itself and many other monomers. Thermoplastics, one of the two large groups of plastics (the second group is thermosets), are defined by their ability to soften repeatedly when heated and become rigid again upon cooling. Thermoplastic elastomers are usually block copolymers, where blocks of a "soft" flexible polymer alternate with blocks of a more rigid "hard" polymer. A block of polymerized styrene fulfills the role of the rigid polymer in the styrene-butadiene resin (SBR) used in cups, trays, containers, toothbrush handles, knobs and switches.

The styrene process is an excellent example of industrial dehydrogenation of alkylated aromatics. The main commercial route to styrene is the catalytic dehydrogenation of ethylbenzene (Eq 9, p. 38). The latter is produced in the same plant by the Friedel-Crafts alkylation of benzene with ethylene in the presence of Lewis-acid catalysts, or, more recently, as a continuous flow alkylation over ZCM-5 zeolite catalyst.[64]

The most economical process for this endothermic dehydrogenation is carried out in the gas phase in a continuous flow reactor over a solid long-lived catalyst. The dehydrogenation of ethylbenzene proceeds at 550 °C, the temperature above which ΔG

for the reaction becomes favorable. In order to limit side reactions, the partial pressure of ethylbenzene is reduced, and steam is used as diluent.[94] The decrease in pressure shifts the equilibrium toward the formation of the products, styrene and hydrogen. Similar to the butadiene process, steam serves several purposes in the synthesis of styrene. It transfers the heat necessary for this endothermic reaction, acts as a diluent, and limits deposition of carbon from hydrocarbon decomposition on the catalyst. This is a good example of an efficient industrial process, when the same substance performs several roles in the same reaction.

The best catalyst for this process in terms of selectivity and stability to vapor is iron oxide promoted with chromic oxide and potassium carbonate. This is the same catalyst mixture that is used for dehydrogenation of butenes to butadiene. The selectivity for styrene needs to be improved, to reduce formation of benzene, toluene, and other byproducts. The selectivity of styrene is only 93% at 40% conversion.[94]

The oxidative dehydrogenation to styrene was never considered practical because both ethylbenzene and styrene are oxygen sensitive. The dehydrogenation process is made more successful if any O_2 is removed by a reaction with H_2. In 1986, a new catalyst was discovered for this reaction. It is comprised of platinum, tin, and lithium on alumina.[95] The catalyst preferentially oxidizes the hydrogen to water vapor in a separate step, driving the equilibrium toward styrene production. The formation of water during this dehydrogenation process eliminates the need to add steam. The catalyst is used in combination with present dehydrogenation catalysts.

There is no single-step process to produce styrene. All routes involve the formation of the intermediate, ethylbenzene. This is rather unusual, since one of the goals of industrial process development is minimizing the number of process steps. The reason is the mature technology and a highest selectivity of the ethylbenzene process compared to all other processes.

Formaldehyde

Formaldehyde has been manufactured by the dehydrogenation of methanol since 1888. A mixture of methanol vapor reacts with a limited amount of air over a silver or copper catalyst at 700 C. Today a fixed bed silver catalyst is used.[96] The endothermic dehydrogenation of methanol and the exothermic air oxidation of hydrogen occur simultaneously in the same reactor (Scheme 17). The very clever exploitation of the thermodynamics of this dual set of reactions makes the process more economical. The methanol/air ratio can be adjusted so that the heats of reaction balance out. Then no external heating is required to maintain the reaction temperature. Selectivities of 85 to 95% are achieved at 65% conversion.[97] Since the cost of methanol represents over 60% of the production cost of formaldehyde, fluctuations in the commercial price of formaldehyde fairly accurately reflect fluctuations in the price of methanol.

Scheme 17

$$CH_3OH \rightleftharpoons H_2CO + H_2$$

$$H_2 + 0.5\,O_2 \longrightarrow H_2O$$

Aromatic Substitution

Aromatic substitution reactions are of major importance in industrial chemistry. Aromatic hydrocarbons, available from catalytic reforming and other sources, may be converted into a large number of useful products.

Electrophilic aromatic substitution reactions involve the addition of an electrophile to the aromatic ring to give a cationic intermediate (not isolated). Loss of a proton regenerates the aromatic ring. Electrophilic aromatic substitution reactions of major commercial importance are nitration, sulfonation, Friedel-Crafts and related reactions, and chlorination. Nitration of benzene produces nitrobenzene, the starting material for aniline manufacture. Sulfonation of benzene produces benzenesulfonic acid, a starting material for one of the phenol syntheses. The reactions are described well in undergraduate organic chemistry textbooks.

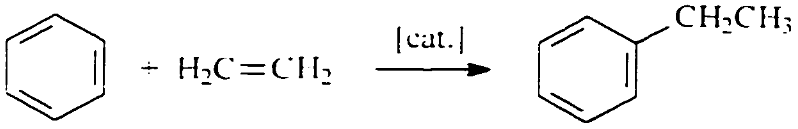
Friedel-Crafts reactions are amongst the most familiar to organic chemistry students. The original Friedel-Crafts reaction used an alkyl or acyl halide as the electrophile and $AlCl_3$ as a catalyst. The modern process of Friedel-Crafts alkylation is similar, with the exception that alkenes have replaced alkyl halides as starting materials, eliminating a necessity for the two-step process.

Alkylation is one of the least important Friedel-Crafts reactions in the laboratory, since the alkylated product is more reactive than the starting material leading to polyalkylation. On the contrary, alkylation is the most important of all Friedel-Crafts reactions in industry and is used in the production of such top U.S. chemicals as cumene and ethylbenzene. The preparation of ethylbenzene is of major importance as a step in the manufacture of styrene. The selectivity of the industrial process to the monoalkylated product is increased by limiting the benzene conversion to approximately 50%.[98] High benzene/alkene molar ratio is maintained throughout the reaction, since an alkene deficiency prevents further alkylation to higher alkylbenzenes.

Another very important application of Friedel-Crafts alkylation is the reduction of benzene levels in gasoline. Gasoline originally contains between 2 and 5 volume % of benzene, which is a known carcinogen. However, neither benzene separation nor gasoline hydrogenation to reduce the benzene level proved practical. Only alkylation of benzene by a mixture of C_2-C_4 alkenes effectively removes benzene from gasoline, thereby decreasing the level of environmental hazard.[98]

Ethylbenzene

Some ethylbenzene is produced during catalytic reforming and can be removed from the C_8 fraction by so-called superfractionation. However, most ethylbenzene is synthesized by alkylation in a Friedel-Crafts reaction between benzene and ethylene.[99] As already mentioned, this reaction is a first step in the major process for styrene manufacture and is produced in the same plant in the presence of Lewis-acid catalysts (Eq 53). The Friedel-Crafts alkylation was historically carried out at 90 °C at atmospheric pressure in the liquid phase with aluminum chloride.

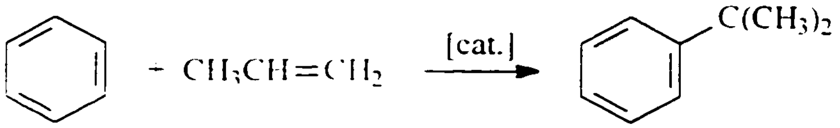


(53)

Because the aluminum chloride catalyst is corrosive and has to be frequently regenerated, gas-phase Friedel-Crafts processes were developed. The gas-phase ethylation is usually carried out with phosphoric acid on a solid support as a catalyst at about 300 °C and 40 atm pressure.[100] The reaction proceeds via protonation of the ethylene on the catalyst surface to give an adsorbed ethyl cation, which then attacks the benzene. Ethylene is a limiting reagent to suppress further alkylation. The development of more selective zeolite ZCM-5 catalysts for continuous gas-phase reactions was a significant improvement. The improved process gives ethylbenzene with 99.5% selectivity at 98% ethylene conversion.[100]

Cumene

Cumene is an intermediate in the most important process for the manufacture of phenol and is made by acid-catalyzed gas-phase alkylation of benzene with propylene (Eq 54). This process is similar to ethylbenzene gas-phase production and typically proceeds at 200-300 C and 20-40 atm pressure.[101] Note that milder conditions are used than in alkylation with ethylene, since propylene is more readily protonated. Protonation of propylene leads to formation of an adsorbed secondary carbocation, which is more stable than the primary carbocation formed by protonation of ethylene.



(54)

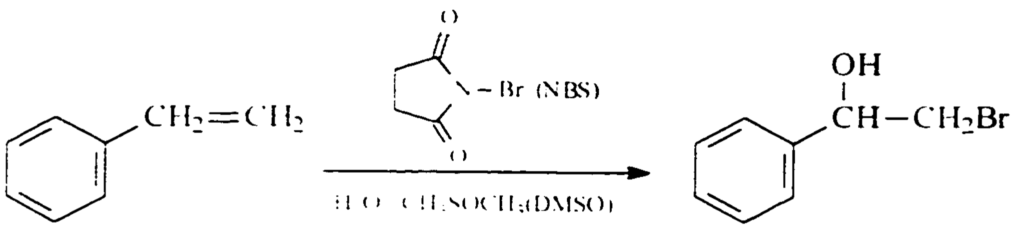
The most recently developed cumene processes are based on zeolite catalysts and offer economic and environmental advantages over conventional supported phosphoric acid technology. Yields are nearly quantitative. Newly developed zeolite catalysts called MCM-22 and MCM-56 (Mobil-raytheon) are believed to have activity tailored to minimize propylene oligomerization and coke formation, the biggest complications in such processes. These catalysts have an unusual pore structure, consisting of two independent two-dimensional pore systems. They have an exceptionally high activity for benzene alkylation and may prove to be the next generation of alkylation catalysts. New cumene processes based on zeolite catalysts will allow existing cumene plants to increase capacity by 30 - 40% which is a significant economic breakthrough, considering that a volume of six billion pounds of cumene is produced annually.[102]

Finally, catalytic distillation (CD) processes for manufacture of cumene have been developed.[71] Catalytic distillation is a process in which both the chemical reaction and separation of products occur simultaneously within the same distillation column. In the alkylation CD reactor, propylene (gas) flows upward and benzene (liquid) flows downward in what is called a countercurrent operation. Cumene is continuously removed from the reactor in the benzene flow. This helps drive the reaction to completion and limits byproduct formation. A significant advantage of the CD process is an ability to control the highly exothermic reaction. The heterogeneous catalyst in the CD process acts as distillation packing as well as a catalyst and is at any time surrounded by boiling liquid. Therefore, the temperature of the catalyst particles is very close to the boiling point of the liquid. This provides an accurate isothermal control in the CD reactor compared to the standard exothermic process in which temperature gradients exist. Twenty-five percent lower capital costs is a very important advantage over conventional cumene production techniques. CD cumene technology is currently being commercialized.

The Friedel-Crafts alkylation to cumene is a good illustration of the significance of raw materials cost in the economics of industrial synthesis. The cost of the raw materials. benzene and propylene. account for as much as 90% of total process cost for cumene manufacture.

Halogenation

The variety of halogenated compounds used in laboratory scale synthetic applications is well known to all students of organic chemistry. These compounds are often used as synthetic precursors on the path to some other final product. Halogenation is a very convenient and direct method for laboratory purposes. For example. halogens may be added to alkenes to obtain halohydrins. and common alkyl halides can be easily synthesized from alkenes. alcohols. and carboxylic acids. Bromine and iodine are preferred in laboratory scale reactions. since these halogens have a higher reactivity than chlorine. However. these halogens are also more expensive but easier to handle than chlorine. Besides elemental bromine and iodine. halogen reagents with the ability to donate electrophilic halogen atom are frequently used in laboratory. An example is the use of N-bromosuccinimide in DMSO to form bromohydrins.[103] NBS is very expensive and DMSO is a hazardous solvent (Eq 55). The cost of this process would exceed $36 per 1 pound of the product generated.



Styrene

2-Bromo-1-phenylethanol (Bromohydrin) (55)

The prime issue with halogen reagents in industry in substitution or elimination reactions is that halogens often cannot be recovered for a future use. Since cost is normally a major factor in choosing a commercial route, the use of halogen compounds on the large industrial scale tends to be avoided where possible. On the small scale, e.g. in pharmaceutical production, where the cost of the halogen raw material is a smaller proportion of the total production cost, chlorine is usually chosen since it is the cheapest of the halogens.[27]

A drawback of using low cost chlorine in industrial electrophilic substitution processes is the formation of hydrogen chloride as a byproduct. This means additional waste disposal costs. Even when there is another use for hydrogen chloride, such as the production of hydrochloric acid by dissolving the hydrogen chloride in water, it is not possible to utilize the very large quantities generated as a byproduct, since the demand for hydrochloric acid is limited. All the above factors tremendously limit the use of halogen compounds in industrial processes.

Among the few halogen compounds produced on a large industrial scale is methyl chloride, a precursor for methylene chloride. Methyl chloride is made by the direct chlorination of methane.[27] Subsequent chlorination of methyl chloride produces methylene chloride, which finds a wide use as a very powerful solvent. Another common solvent, carbon terachloride, is made by the chlorination of carbon disulfide (Eq 56).

$$CS_2 + 2\,Cl_2 \xrightarrow[30^{\circ}C]{Fe} CCl_4 + 2\,S \qquad (56)$$

The manufacture of vinyl chloride is the largest-scale operation in organo-chlorine chemistry. Fifteen billion pounds of vinyl chloride are produced annually worldwide. This process consumes about 20% of all the chlorine produced in the U.S.[104] Vinyl chloride is the only starting material in the polymerization to form polyvinyl chloride (PVC) and is an important monomer in the synthesis of various vinyl chloride copolymers.

There have been major changes in processes used for the manufacture of vinyl chloride during the last several decades. For thirty years vinyl chlorine was manufactured from acetylene (Eq 57).[105] Synthesis of vinyl chloride via addition of hydrogen chloride to acetylene had several advantages. The reaction is exothermic (no heat needs to be applied) and proceeds in one step. In addition. it is atom-economical. since all the raw materials get incorporated into the product. However. the high price of acetylene compared to other hydrocarbons overrides all the process advantages.

$$CH{\equiv}CH - HCl \longrightarrow H_2C{=}CHCl \qquad (57)$$

Vinyl chloride switched from an acetylene-based to ethylene-based process after ethylene became available from petroleum and natural gas cracking in the 1950s (Eq 8. p. 38). Ethylene chlorination generally takes place in the liquid phase in a bubble-column reactor. The addition of chlorine to ethylene results in formation of 1.2-dichloroethane which gives vinyl chloride by elimination of hydrogen chloride. The elimination is endothermic and entropically favored. This thermolytic cleavage is carried out at 500-600 °C and 25-35 atm pressure and proceeds by a radical chain mechanism.

The disposal of the hydrogen chloride byproduct presented a problem for a long time. until the oxychlorination process for ethylene was developed. The formation of vinyl chloride from ethylene and hydrogen chloride in the presence of oxygen is known as oxychlorination. This reaction proceeds in the gas phase at 240 °C (Eq 58). The process effectively adds Cl_2 from hydrogen chloride oxidation then eliminates HCl to achieve the net substitution of chlorine for hydrogen. A supported mixture of cupric chloride and potassium chloride is used as a catalyst in this continuous process. Selectivities of over 90% at about 95% conversion are achieved. Cupric chloride is regenerated from cuprous chloride by the reaction of oxygen and hydrogen chloride.[105]

$$CH_2{=}CH_2 + 2\,HCl + 0.5\,O_2 \longrightarrow ClCH_2CH_2Cl \longrightarrow HCl + H_2C{=}CHCl \qquad (58)$$

Since the manufacture of dichloroethane by the oxychlorination process requires a supply of hydrogen chloride, the chlorination route to vinyl chloride and the oxychlorination route are often carried out in parallel.[106] The HCl byproduct of the chlorination process is used in the oxychlorinaton as a starting material. Presently, a half of our vinyl chloride is made by the chlorination process, and the other half by oxychlorination. This is a very clever solution to the waste disposal problem. Certain disadvantages of oxychlorination as compared to direct chlorination - higher capital investment, higher operating costs, and slightly lower purity product - are outweighed by the major advantage, the ability to consume hydrogen chloride generated in the direct chlorination process. The latter eliminates the cost of hydrogen chloride disposal.

New developments in vinyl chloride manufacture have focused on eliminating the multiple stages of combined processes (chlorination, oxychlorination, and thermolysis) which add considerably to the capital and process costs. A basic simplification of the process would be achieved by direct chlorine substitution with Cl_2 or oxychlorination of ethylene to vinyl chloride, without isolation of the ethylene dichloride intermediate. These pathways to vinyl chloride have been investigated but have not yet led to commercial processes due to the high temperatures required and the consequent side reactions.[107]

As mentioned earlier, an objective of the chemical industry has been to replace alkene raw materials with alkanes. Likewise, there has been extensive research aimed at developing a route to vinyl chloride from ethane rather ethylene. In the vapor-phase oxychlorination of ethane developed by ICI Corporation, ethane is fully converted to ethylene which then undergoes the oxychlorination reaction. The catalyst, metallic silver with salts of manganese or lanthanum impregnated on zeolite, gives a selectivity for vinyl chloride up to 51%.[108] More development is needed to improve selectivity before the process becomes commercialized.

Hydrolysis and Hydration

Since hydrolysis reactions are wasteful of raw materials, almost no chemical on the industrial scale is produced by hydrolysis. The only exceptions are those situations where no alternative route is available. This differs substantially from the laboratory synthesis where hydrolysis is widely used. For example, a classical route to carboxylic acids includes the hydrolysis of nitriles.

Unlike hydrolysis, which necessarily yields unwanted byproducts, hydration is an addition reaction with no other products. Thus hydration reactions are of substantial commercial importance. Hydration of alkenes, for instance, provides one of the major routes to alcohols. In the laboratory alkenes are commonly hydrated by either oxymecuration (treatment with mercuric acetate following reduction by sodium borohydride) or hydroboration (addition of borane followed by treatment with basic hydrogen peroxide).[1] Both procedures not only involve costly reagents, but also are two-step processes. This is highly uneconomical on a large scale.

The hydration of ethylene to ethanol is the most important process for the industrial synthesis of ethanol. With the availability of cheap ethylene from steam cracking since the 1950s, the petrochemical route to ethanol became more economical than the fermentation route used previously. The original ethylene hydration process was a sulfuric acid mediated process. Ethylene was mixed with concentrated sulfuric acid to form a mixture of ethyl hydrogen sulfate and diethyl sulfate, which was then hydrolyzed to ethanol (Eq 1).[109] This process is still operated in some countries, but in the U.S., to avoid the use of sulfuric acid, it has been replaced by a direct hydration reaction.

The direct hydration process continuously combines water and ethylene over a silica or celite-supported phosphoric acid catalyst in the vapor phase at 300 °C and 70 atm. The selectivity for ethanol is as high as 98%.[110] By protonating the ethylene substrate, catalysts lead to formation of an ethyl carbocation-like intermediate, activating ethylene toward nucleophilic attack of water (Eq 59). The reaction proceeds at equilibrium.

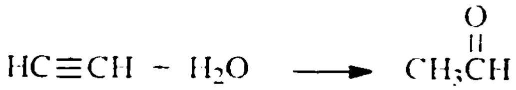
$$H_2C{=}CH_2 + H_3O^+ \rightleftharpoons CH_3CH_2^+ \xrightleftharpoons[-\,H_2O]{+\,H_2O}$$

$$CH_3CH_2{-}OH_2^+ \xrightleftharpoons[-\,H_2O]{-\,H_2O} CH_3CH_2OH + H_3O^+ \qquad (59)$$

The ethanol process by direct hydration is an excellent example illustrating the importance of selectivity over yield or conversion in industry. Recall that in the laboratory, yield is the major factor. Industrially, the conversion of ethylene by the direct hydration process is as low as 4% per pass. The reaction conditions, 300 °C and 70 atm pressure, are chosen to optimize selectivity.[110] The conversion is high enough to provide acceptable yields, but low enough to limit the formation of byproducts such as diethyl ether and ethylene oligomers. An increase in pressure shifts the equilibrium toward the formation of fewer moles of gas, e.g. toward ethanol production. Although conversions higher than 4% could be achieved by a further increase in pressure, this is uneconomical, since polymer formation tends to increase at higher pressure. In addition, the pressure can't be raised without extra capital and operating costs. Because of the low conversion, large amounts of ethylene must be recycled.

Many catalysts, other than "solid phosphoric acid", have been suggested for the direct hydration process, including metal oxides and metal salt catalysts. Although the search for a more active catalyst and increasing ethanol conversion are important issues in direct ethylene hydration, the cost of ethylene (and its sources, crude petroleum and natural gas) is the major factor in future process development. Synthesis gas, the use of which was discussed in the last section, may eventually serve as the raw material for ethanol synthesis.[31]

Hydration of acetylene leads to the formation of acetaldehyde (Eq 60). This reaction is not of major significance in industry, since acetylene is a much more expensive two-carbon raw material than ethylene. As shown in the previous discussion, acetaldehyde is now manufactured almost exclusively by oxidation of ethylene in Wacker Chemie process.



$$HC{\equiv}CH + H_2O \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}H$$

(60)

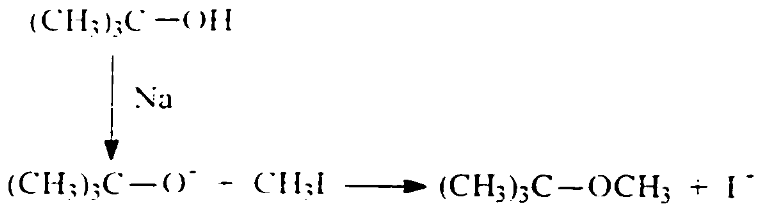
Etherification: MTBE

As discussed above, aromatic compounds have high octane numbers, which is very important for gasoline. However, since the Clean Air Act demanded a drastic reduction in the aromatic content of gasoline, other components with high octane numbers were needed and were found in oxygenates, particularly in methyl tert-butyl ether (MTBE). Oxygenates increase resistance to knocking by slowing down the radical reactions that cause autoignition in the automobile engine.[98] In addition, MTBE is used to prevent air pollution, by oxidizing carbon monoxide to carbon dioxide and thereby reducing carbon monoxide emissions. The content of MTBE in gasoline required now by the Clean Air Act is as high as 11 to 17% (by volume) depending on gasoline type and the required oxygen content in gasoline. As a result, the demand for MTBE has grown tremendously in recent years. (Very recently, there has been an evidence of MTBE contamination of underground water. Therefore, the use of MTBE in gasoline might be reduced and eventually eliminated.[111])

MTBE is synthesized from the reaction of isobutene with methanol over an acid catalyst, usually an acidic ion exchange resin (Eq 61). The reaction proceeds via nucleophilic attack of methanol at the initially formed tertiary carbocation. MTBE is successfully produced by catalytic distillation. This was the first commercialized CD process. In the CD process isobutylene conversion is as high as 99% which is higher than in the conventional S_N1 process due to the ability of the CD process to increase conversions beyond the equilibrium limit. Nearly pure MTBE is removed upon formation at the bottom of the CD column.[98]

$$CH_3OH + CH_2{=}C(CH_3)_2 \rightleftharpoons \underset{\text{MTBE}}{CH_3OC(CH_3)_3} \qquad (61)$$

The MTBE process gives us an example of ether synthesis in industry, which is interesting to compare with the classical S_N2 Williamson ether synthesis pathway used in the laboratory. MTBE can be synthesized in the laboratory by an S_N2 displacement reaction, using tert-butyl alcohol and methyl halide as raw materials (Eq 62).[51] Note that in the industrial reaction methyl group comes from the nucleophile (methanol), while in the laboratory reaction the electrophile (methyl iodide) is a source for methyl group. The reason is that methyl iodide is more reactive than a tertiary halide as an electrophile for S_N2 displacements. On the contrary, for the industrial reaction a tertiary electrophile is needed, since it proceeds via a carbocation intermediate. As is known, tertiary carbocations are more stable than secondary or primary carbocations due to hyperconjugation.



$$(CH_3)_3C-OH \xrightarrow{Na} (CH_3)_3C-O^- + CH_3I \longrightarrow (CH_3)_3C-OCH_3 + I^-$$

(62)

Unlike the industrial synthesis, the laboratory reaction is a two-step process in which the alkoxide ion first has to be prepared from the reaction of alcohol with a strong base or sodium metal. The total raw materials cost to prepare 1 pound of MTBE by this method is about \$68. Compare this cost to the \$0.60 cost for raw materials for the industrial synthesis of 1 pound of MTBE.

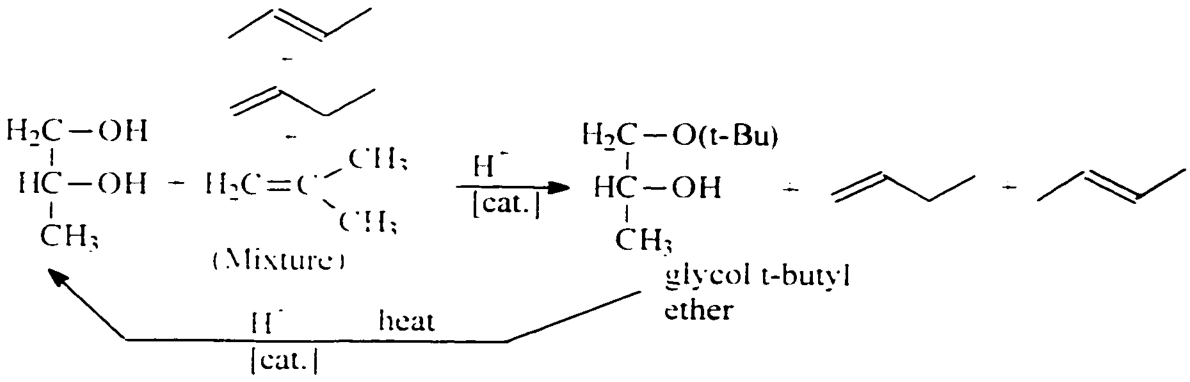
Formation of Isobutene for MTBE Synthesis

Since the development of MTBE as a gasoline oxygenate, isobutene available from the refinery suddenly became an important chemical. This is a good example of how a cheap byproduct can become an important starting material for a key process. MTBE production in the US was 17.6 billion pounds in 1995, up from 13.6 billion pounds in 1994, and only 31 million pounds in 1982.[98] Obviously, the existing supply of isobutene was not nearly sufficient for this increased demand. A separate process was needed.

Isobutylene can be produced by isomerization of n-butane to isobutane followed by dehydrogenation.[31] These processes are now in use, but they are costly. It would be commercially beneficial to convert n-butene directly to isobutene instead of performing a two-step process. The major problem with a one-step process has been the formation of dimers, which could only be prevented at temperatures above 450 °C, the temperatures at which the catalyst is rapidly deactivated.

Recently Shell and Lyondell developed a catalytic isomerization process, which directly converts n-butene to isobutene, without catalyst deactivation.[112,113] This breakthrough became possible because of the development of a new catalyst - a medium-pore zeolite called FER. With this catalyst thermodynamic equilibrium in the isomerization amongst the butene isomers is reached at a temperature of 350 °C. The catalyst remains active and selective at this temperature. In addition, Engelhard Corporation has designed a new family of refinery cracking catalysts that will dramatically increase yields of isobutene from existing refinery equipment.[114]

An interesting synthetic method of capturing isobutene from the C_4 refinery stream takes advantage of the fact that isobutene is the only butene isomer capable of forming a tertiary carbocation on protonation. The process involves the preparation of a glycol ether intermediate using solid acid catalysts (Eq 63).[115] Initially isobutene is captured from the mixture of C_4 alkenes by etherification with a suitable aliphatic diol. With 1,2-propylene glycol the high boiling glycol mono-t-butyl ether is formed. The low boiling point alkenes are easily separated and used in other applications. Deetherification of the monoether at higher temperatures yields pure isobutene and regenerates the glycol. The principal acid-catalyzed reaction is deetherification of the glycol t-butyl ether to isobutene. This reaction occurs due to the fact that E1 elimination is only possible at the tertiary site. It was shown that solid inorganic acid catalysts such as heteropolyacids (HPA) and acidified montmorillonite clays provide improved performance because of their much higher thermal stability. The economic advantages of this process are high reaction rates, catalytic stability, the lack of byproducts disposal, and the lack of strong acid corrosion problems.[59]



(63)

IV. Future of Industrial Organic Chemistry: New Development in Industrial Synthesis

Economic activity and the needs of society ultimately drive the current and future development of industrial organic chemistry. It is beneficial for future industrial chemists to be aware of these trends. The current and expected demands are summarized from the current literature. They include a demand for a lower cost raw materials for existing products. demand for new processes to generate larger quantities of an existing product. demand for environmentally compliant procedures. and demand for higher product yield. In addition. there is a demand for fundamentally new industrial processes utilizing more abundant natural resources. Some of the recently developed processes have been already mentioned in Section III. Here some of the most important developments are summarized and classified by their purpose.

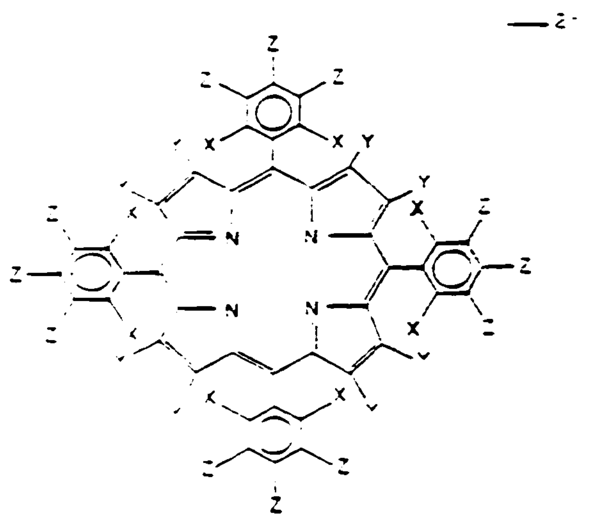
The Need for Lower Cost Raw Materials

For most chemical processes. raw material costs constitute approximately 70% of the total manufacturing cost and are. therefore. the most important factor to attack when a large financial impact is needed.[9] By far the strongest current research toward lower cost feedstock is the effort to use alkanes in several processes. Major research efforts are directed toward the substitution of alkanes. such as ethane. propane. and butane. for the corresponding alkenes. In addition. several current research projects aim to convert methane to alkenes or aromatics.[73] The task is challenging. due to the low reactivity of alkanes which leads to poor selectivity. Remember that C-H bonds are nonpolar. since electronegativities of carbon and hydrogen are very similar. In addition. the C-H bond energy is high enough for the bond to be stable and unreactive. On the other hand. when polar heteroatoms such as oxygen or nitrogen are present. the carbon atom becomes electron-deficient and is prone to an attack of an electron-rich species following protonation of the heteroatoms.

Obviously. in organic reactions functional groups are necessary to provide a good reactivity and selectivity toward a particular product (some bonds may be broken much more easily than others are). However. even alkanes are not entirely unreactive. since primary. secondary. and tertiary C-H bonds are slightly different in their bond dissociation energies. The economic driving force for developing selective alkane activation catalysts is the difference in price between these alkanes and the corresponding alkenes which can frequently cost as much as $0.10/lb more. Therefore. this research is being actively pursued.

For example. a process for the direct one-step ammoxidation of propane to acrylonitrile was developed to potentially replace an existing acrylonitrile process based on propylene ammoxidation.[74] The Monsanto process for making acetic acid via methanol carbonylation involved a change in raw materials. Methanol replaced ethylene, which had been used in the previously dominant Wacker process.[7] An increased difference between prices for methanol and ethylene in recent years have made the cost advantage of the methanol carbonylation route even more significant. Currently, the price of ethylene is three times higher than the price of methanol ($0.18 versus $0.06 per pound).

The challenge of alkane oxidation reactions is poor selectivity, which results in complex and costly separation and purification requirements that lead to highly capital-intensive processes. One of the most important developments in alkane functionalization is selective air oxidation of alkanes to alcohols in the liquid phase over a halogenated porphyrin complex, tetraphenylporphyrinatoiron(II) azide, which acts as a catalyst (Figure 9). It was found that halogen content directly affects activity of the catalyst. When perfluorophenyl substituents are present on the ortho and para positions of the phenyl groups, catalytic activity is so greatly enhanced that even propane can be selectively air-oxidized under mild conditions.[116] Highly electron-withdrawing fluoro-substituents in the ortho and para positions cause high electron-deficiency in the iron-porphyrin complex. This activates the metal and increases its reactivity toward hydrocarbons. The mechanism of the alkane hydroxylation possibly involves formation of an iron (IV) oxo complex, which abstracts a hydrogen atom from the alkane, subsequently donating a hydroxyl group to the alkyl radical.[116] This finding might allow industry to use alkanes instead of alkenes as a feedstock, provided the cost of porphyrin or porphyrin-related substance is relatively low.



LIGAND	X	Y	Z
(TPP)	8H	8H	12H
(TPPβ-Br$_4$)	8H	4H,4Br	2H
(TPPCl$_8$)	8Cl	8H	2-
(TPPCl$_8$$\beta$-Br$_4$)	8Cl	4H,4Br	2H
(TPPF$_{20}$)	8F	8H	12F

Figure 9. Halogenated porphyrinato ligand system for iron (III) complexes. Reprinted from ref. 116.

Other demands for more economical raw materials include the need for alternative sources of ethylene. Ethylene is the chemical industry's most important raw material. 40% of all organic chemicals are derived from ethylene. Thus. there is a strong incentive to find a lower cost route to ethylene. such as selective catalytic dehydrogenation (to replace the current capital intensive thermal cracking process) or. preferably. selective oxidative coupling of methane. An extensive worldwide effort is now underway to develop the oxidative coupling of methane to ethylene and to aromatics.[71,117]

Currently the synthesis of alkenes from a C1 source can be practically achieved only through the traditional Fisher-Tropsch synthesis of hydrocarbons from synthesis gas (molecular hydrogen and carbon monoxide) obtained from coal (Scheme 18). Carbon from coal is oxidized by molecular oxygen to carbon monoxide. Hydrogen. another component of synthesis gas. is obtained by treatment of carbon monoxide with water. Reactions of carbon monoxide with hydrogen produce a mixture of alkanes and alkenes with a broad range of molecular weight by growth of carbon chains on an iron-based catalyst. without any size restrictions. Products are mostly C_5-C_{11} straight chain hydrocarbons. with small amounts of methane. ethylene. and propylene produced. The alkenes are formed first and may be reduced to alkanes. The Fisher-Tropsch process is costly and unreliable in operation. Expensive. mechanically complex reactors are needed to process solid coke. This process is currently operated only in South Africa.[118]

Scheme 18

$$\begin{aligned} n\,CO + 2n\,H_2 &\longrightarrow C_nH_{2n} + n\,H_2O \\ 2n\,CO + n\,H_2 &\longrightarrow C_nH_{2n} + n\,CO_2 \end{aligned}$$

Natural gas, in areas of abundance, can also be used as a source of synthesis gas for potential production of hydrocarbons (Eq 64). However, commercialization of this process will require better catalysts. Catalysts with high selectivity for methane are needed, since methane is less reactive than the products of its conversion, CO and H_2O. The preferred ruthenium catalyst gives good results in the lab but will probably never be used in the commercial process because of its great expense.[119] The recent success was due to the development of highly selective molecular sieve catalysts which could handle multiple regenerations. The new catalyst has been commercially produced and is currently used in pilot plant scale.[119]

$$CH_4 + H_2O \longrightarrow H_2 + CO \longrightarrow C_nH_m + H_2O \qquad (64)$$

Methane has been increasingly used as a source for higher hydrocarbons, because it is cheaper and more abundant than petrochemical feedstock. At the same time, utilizing this hydrocarbon resource with minimum environmental impact has become a major challenge to catalytic chemistry. Especially since the oil embargo in 1973, there has been an extensive worldwide effort to pursue the chemistry of methane. This has resulted in a number of research breaktroughs. For example, carbonylation of methanol (produced from methane) to acetic acid over homogeneous rhodium-based catalysts allows selectivities approaching 99%. Furthermore, the process may be run at much lower pressures than required for prior catalysts.[43] Ethylene glycol (antifreeze) can also be produced via the oxidative coupling of methanol. In addition to acetaldehyde, ethanol, and ethylene glycol, other large-volume chemicals currently made from ethylene or propylene may become attractive candidates for manufacture by one-carbon chemistry.

The Need for Larger Quantities of Product

The demand for most commodity chemicals doesn't vary dramatically from one year to the next. A counterexample is MTBE. The demand for this gasoline additive has grown tremendously.[120] As discussed above, the high demand for MTBE is in turn creating a large demand for isobutylene feedstock produced via catalytic dehydrogenation of isobutane, and, recently, by isomerization of butenes at the refinery. Recent research is attempting to develop oxidative dehydrogenation of lower alkanes - ethanes, propane and isobutane - to their corresponding olefins utilizing new catalysts.

The Need for Environmentally Compliant Procedures

As mentioned above, major environmental hazards in industrial reactions are caused by corrosive liquid acid catalysts. This section will summarize the results of recent development on solid acid and superacid catalysts that have the potential to solve this environmental challenge.

Development of Solid Acid Catalysts

An attempt to replace liquid acid catalysts with solid acids is currently one of the major R&D efforts in industrial chemistry. Solid acids have many advantages over the homogeneous acid catalysts traditionally used. They are environmentally benign and present fewer waste disposal problems. They are noncorrosive and do not require special equipment. Finally, they can be tailored to give increased selectivity and longer catalyst life by surface modification and other improvement methods practiced with heterogeneous catalysts.

Several improved processes based on solid acids have been commercialized in the past several years, and emerging solid acid technology shows a potential for further improvements.[24] The first successful solid acid process for chemical production was the Mobil-Badger ethylbenzene process, first commercialized in 1980. Since then, solid acid catalysts have been introduced in many synthetic processes such as aromatic alkylation, acylation, hydration, and condensation.

New types of solid-acid catalysts may potentially replace zeolite catalysts in the synthesis of cumene by benzene alkylation. The Nafion-silica nanocomposites, a novel ion-exchange polymer material developed at DuPont, show high activity for the reaction of benzene with propylene in the liquid phase under very mild conditions (60 °C).[101] Nafion is a polytetrafluoroethylene-based polymer that contains small proportions of sulfonic or carboxylic ionic functional groups. This polymer used by itself has a low activity for reactions involving nonpolar reactants, because these reactants are not able to access the acid sites in the interior of the beads. Because nanometer-size Nafion particles are entrapped in a porous silica network in the new catalyst, most of the acid sites are made accessible. The nanocomposite catalysts are already being used commercially for some applications.

Development of Superacid Catalysts

The term 'superacid' is usually defined as an acid stronger than 100% H_2SO_4. The role of superacids catalysts in industrial organic chemistry deserves some discussion.

A superacid has an ability to protonate almost all functional groups. This unique acidic strength is caused by combination of a Lewis acid and a strong Bronsted acid in the same molecule. For example, protonated fluorosulfuric acid can be produced if Lewis acid SbF_5 is dissolved in a mixture of HSO_3F and SO_3.[16] Solid superacids would be more attractive candidates than liquid superacids which are corrosive, hazardous, unstable, and, therefore, unsuitable for industrial catalysis.

All solid superacid research is focused on making stable solids that are extremely strong proton donors. Newly developed solid superacid catalysts, $AlCl_3$/sulfonic acid resin, and heteropolyacids such as 12-tungstophosphoric acid, $H_3PW_{12}O_{40}$, are so strong that they react with such weak bases as alkanes by hydride abstraction, converting, for example, n-butane into isobutane. The most active of known superacidic solid catalysts is sulfated zirconia (SO_4^{2-}/ZrO_2) with iron and manganese as promoters.[121] Sulfated zirconia-based catalysts appear to have the greatest potential for use in industrial isomerization processes, because the catalyst is stable and highly active for alkane interconversions. The conversion of n-butane into isobutane can proceed at room temperature. Similarly, sulfated zirconia is able to catalyze an n-pentane isomerization to isopentane even at such low temperatures as -25 °C.[121] Such low temperature conversions are very advantageous, because the equilibrium favors the valuable branched products to an even greater extent at low temperatures (although at these temperatures the reactions are very slow). Branched molecules are more thermodynamically stable, with more negative enthalpies of formation, compared with their linear isomers. For example, $\Delta H°_f$ for liquid isopentane is -178.5 kJ/mol versus -173.5 kJ/mol for liquid n-pentane.

Currently n-butane isomerization is the biggest potential application for the superacid catalysts based on sulfated zirconia, because the product isobutane is in demand as a precursor of isobutene and methyl-t-butyl ether (MTBE), a component of high octane gasoline. Other branched alkanes are required for use in alkylation reactions and as additives to gasoline to increase its octane number.

Sulfated zirconia is more strongly acidic than zeolites, since it is very active for light paraffin conversion at temperatures of about 200 °C, much lower than those at which zeolites are usually used.[121] The drawback of very strong acids used as catalysts is their selectivity: these catalysts are so active than they tend to have high selectivities only for light alkanes such as isobutane and propane. Interconversion of medium range alkanes result in formation of a mixture of branched isomers formed by miltiple hydride shift on the carbocation. However, because multi-branched products have higher octane numbers, they are more desirable than their less branched isomers. Therefore, catalysts with higher selectivity for the formation highly branched molecules are required for isomerization of C_6 and higher alkanes.

Modern catalytic alkylation at refineries still uses a process from the early 1940's in which a mixture of liquid acid (either sulfuric or hydrofluoric acid) and aluminum chloride/boron trifluoride act as catalysts. Both liquid acid alkylation processes have strong potential environmental and health hazards associated with them. The byproduct of sulfuric acid alkylation, so-called red oil, is toxic, and HF, which is a gas under standard conditions, is violently reactive even with such normally inert materials as glass.

Solutions of HF will penetrate through skin and destroy bone and other tissue. California is currently considering a ban on hydrofluoric acid storage that would affect several refineries using HF. New environmental requirements were a driving force for the development of a silica and zirconia supported H_3PO_4-BF_3-H_2SO_4 catalyst introduced as an HF replacement. This catalyst shows good alkylation selectivity, and therefore is a potential solution to both environmental and economic issues.[122]

Solid superacid catalysts are also promising as replacements for the homogeneous $AlCl_3$ and BF_3 Friedel-Crafts catalysts in aromatic acylation processes. Heteropolyacids (HPAs) appear to be especially active as acylation catalysts, probably because the large HPA anion can stabilize the cationic intermediates in such reactions. Partially exchanged alkali metal salts of HPA are soluble in reaction media and have high surface areas. They are more active than such popular active and selective catalysts as zeolite-Y and Nafion. The high surface area of these catalysts is a result of their microporous (pore width up to 2nm) and mesoporous structure (pore width from 2 to 50 nm). Sulfated zirconia catalysts have also proved to be acidic enough to catalyze acylation by carboxylic acids and acid anhydrides as well as acyl chlorides. These catalysts are now being tested for commercial applications.[101]

Even though the new catalytic systems are not yet as effective as sulfuric and hydrofluoric acid, there is a good reason to believe that further research will eventually yield economically viable, environmentally friendly catalysts.

The Need for Higher Yield

An increase in a product yield in current processes can bring economic advantage and reduce environmental hazards. One breakthrough is a dramatic improvement in the recovery of fuel oil, a product of crude oil distillation.

One of six fractions obtained by fractionation is the residue fraction containing fuel oil, valuable material whose boiling point is slightly above 340 °C. Usually, maximum operating temperatures of crude oil distillations do not exceed 340 °C, since at higher temperatures significant amount of coke is formed, blocking up the distillation tower. Therefore, fuel oil can not be distilled as a separate fraction and has to be obtained from catalytic cracking of the residue. The residue is difficult to process because of the deposited carbon, which acts as a catalytic poison and causes fast catalyst deactivation and reduced selectivity.[18] Now, due to an increase in marketplace competition, the inability to process the residue fraction (or resid) leads to economic failure for many refineries. An intensive research program resulted in the identification of catalysts with higher selectivity for fuel oil and greater resistance to poisoning and contamination.[37]

Typically crude oil is cracked as it is distilled at refineries. A catalyst for the fluid catalytic cracker (FCC) consists of zeolite and a matrix. The major function of the matrix is to allow large molecules with high boiling points to reach the zeolite crystals, since the pores in the latter are too small to accept these molecules directly. The matrix materials are usually binders and metal traps which provides functionalities needed to trap contaminants. Several modifications of FCC catalysts leading to improved residue processsing were introduced within the past 5 years. Zeolites were made more selective by hydrothermal treatment to remove aluminum from the zeolite crystals.[123] The catalyst retained high activity and good stability.

New Lower Cost Technique: Catalytic Distillation

Catalytic distillation (CD) is one of the new techniques in synthetic industrial chemistry with which future industrial chemists should be familiar. This is a process in which both the chemical reaction and separation of products occur simultaneously within the same distillation column.[98] The CD method is classified as countercurrent, because the liquid and gas flow in opposite directions inside the distillation column. The desired product is collected from the bottom of the reactor, and the co-products and unreacted starting materials are distilled. The CD process has fewer steps, requires less equipment, and therefore has a much lower capital cost than a conventional process. It is interesting to note that in catalytic distillation the heterogeneous catalyst acts as distillation packing as well as a catalyst for the reaction. The reactions that benefit the most from the application of CD are equilibrium-limited reactions. such as hydrolysis. etherification. esterification. and alkylation. Le Chatelier's Principle limits the conversion in a one-step. but not multistep CD process. Since first applied to the synthesis of MTBE. catalytic distillation is increasingly considered as a general reaction technique.[71]

Several important advantages of CD processes allow process cost to be reduced tremendously. In particular. conducting two-unit operations in one apparatus offers significant capital savings over a conventional reactor-distillation column scheme. Another important feature of the catalytic distillation method is an ability to improve both selectivity and conversion. an extremely desirable outcome. CD processes are operated so that the reaction product is selectively removed from the reaction zone. causing more product to form. according to Le Chatelier's principle. Other higher boiling products are removed by distillation.

CD increases the conversion of an equilibrium-limited reaction beyond the thermodynamic limit for an isolated reaction system. In addition. CD offers a solution to the problem of corrosion and hazard associated with most catalysts. In CD columns. the heterogeneous catalyst does not contact the walls of the column. Therefore. expensive and corrosion-resistant construction materials are not necessary.

Along with its advantages. the CD technology has certain limitations. which exclude many chemical reactions. For the CD method to be considered, distillation must be a practical method of separating the reagents and products. Additionally, the reaction must take place in the liquid phase because the catalyst pellets must be constantly wet and at a temperature equivalent to the boiling point of the liquid in the column. Also, because it is very expensive and labor intensive to change the catalyst in CD column, heterogeneous catalysts with a long life span (one or two years) must be available.[98]

Summary

Top organic chemicals form the backbone of the heavy chemical industry. Large volume commodity chemicals such as ethylene, propylene, or vinyl chloride are used extensively as monomers for the synthesis of widely used polymers such as polyethylene and polyvinyl chloride. Simple alkanes and alkenes are produced by petroleum refinery processes. For example, ethylene is produced by thermal cracking. Other top organic chemicals are manufactured by oxidation, hydrogenation, hydration, aromatic substitution, and halogenation.

Industrial and laboratory processes have different objectives. In commercial processes, the goal is to manufacture a product at a minimum total cost. The main consideration that determines whether an industrial project will be worth pursuing is its return on investment defined as the average annual profit divided by total capital investment. In the small scale laboratory, the objective is usually to synthesize a compound in the most convenient and timely fashion in the highest yield possible. For industry achieving a high selectivity for a desired product (usually by developing selective catalysts) is a major task. The second component of yield, conversion, is of less importance, because unreacted starting materials can usually be recycled.

Industrial synthesis is driven primarily by economic and environmental considerations.

Industrial oxidation processes use gaseous oxygen or air as the oxidant. and reduction processes use molecular hydrogen as the reducing agent. The use of expensive laboratory reagents is avoided. Since the cost of waste disposal. often fairly high. is a part of the total cost. it affects the profitability of the process. Therefore. the environmental concern of industrial synthesis is closely related to the economic concern and leads to minimizing air and water pollution from gases and process waste streams.

Modern industrial chemistry for the most part is designed and driven by catalyst development. Industrial processes. unlike laboratory reactions. utilize selective heterogeneous and less common homogeneous catalysts. Many industrial processes were commercialized only after catalysts with suitable selectivity (at least 70-80%) for a desired product were developed. Catalysts are generally used in industry in place of laboratory reagents to reduce raw material cost and avoid waste stream generation and disposal issues. The most important type of industrial catalysts are acid catalysts. among which new zeolite catalysts are most effective. The high selectivity of zeolites results from their three-dimensional channels that orient reactive intermediates toward formation of specific products. Another very important group of catalysts are transition metal catalysts that catalyze reactions by forming coordination complexes with alkene π-bonds. The Wacker oxidation of ethylene to acetaldehyde or vinyl acetate is the most well-known example. Transition metal catalysts allow more economical addition reactions to be used instead of substitution reactions.

Of all bulk industrial organic synthetic processes oxidation and hydrogenation are the most widely used. Oxidation processes give cyclohexanol and cyclohexanone for the synthesis of the nylon precursors adipic acid and caprolactam. Phenol. ethylene oxide. propylene oxide. ethylene glycol. acrylonitrile. acetaldehyde. and acetic anhydride are also produced by industrial oxidation. Carboxylic acids such as acetic. adipic. acrylic. and terephthalic acids have been traditionally manufactured by oxidation. New. lower cost processes for carboxylic acid synthesis are based on carbonylation. a direct insertion of carbon monoxide in a C-H bond.

Most hydrogenation processes are carried out with heterogeneous metal oxide or metal salt catalysts. Reduction in the laboratory is carried out with reducing reagents such as sodium borohydride. Hexamethylediamine (for Nylon 6.6 production). aniline and benzene are produced in industry by hydrogenation.

Industrial dehydrogenation processes are normally run in the vapor phase over solid catalysts. Butadiene. styrene. and formaldehyde are produced by dehydrogenation. Vinyl chloride is synthesized by an oxychlorination process. and ethanol is manufactured by hydration. Ethylbenzene and cumene are synthesized by Friedel-Crafts substitution in a new catalytic distillation process. Catalytic distillation is a method that simultaneously performs a chemical reaction and separates the reagents and products.

An example of a large-scale etherification is the methyl t-butyl ether process. The demand for MTBE has increased dramatically in recent years. New processes for formation of isobutylene, a starting material for MTBE synthesis, have been developed.

Future development in industrial organic chemistry will attempt to satisfy societal demands to eliminate waste disposal problems, corrosion issues, and protect the environment. Therefore, major avenues of development in industrial chemistry are directed toward a search for a lower cost raw materials, new atom-economical processes generating larger quantities of product, environmentally complaint procedures, and higher product yield. Development of superacid and solid acid catalysts to replace corrosive liquid acids is one of the major avenues of current and future development in industrial chemistry. Solid acid catalysts such as zeolite catalysts or nafion-silica nanocomposites have been already developed. Future work will focus on superacid catalysts usually formed by a combination of a Lewic acid and a strong Bronsted acid in the same molecule. Sulfated zirconia is the most active of currently developed superacid catalysts. Another important path for future development is substitution of alkanes raw materials for the corresponding higher cost alkenes.

References

1. McMurry. J.: *Organic Chemistry*. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000; Chapter 7.

2. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991: Vol. 9.

3. Chenier. P. J. *Survey of Industrial Organic Chemistry*. 2nd ed.: VCH: New York. 1992: p 469.

4. McMurry. J.: *Organic Chemistry*. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000: Chapter 17.

5. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991: Vol. 1. p 101.

6. Humphreys K.: Wellman P. *Basic Cost Engineering*, 3d ed.: Marcel Dekker: New York. 1996: Chapter 9.

7. Ray. P. *European Chemical News* **1994**. 9. 7.

8. *C&EN* **1998**. 76 (26). 43.

9. Clausen III. C.A.: Mattson. G. *Principles of Industrial Chemistry*: J.Wiley & Sons: New York. 1978: Chapter 12.

10. Clausen III. C.A.: Mattson. G. *Principles of Industrial Chemistry*: J.Wiley & Sons: New York. 1978: Chapter 6.

11. Thoenes. D. *Chemical Reactor Development*: Kluwer Academic: Dordrecht/Boston. 1994: Chapter 2.

12. Trost. B. M. *Angew. Chem. (Int. Ed.)* **1995**. 34 (3). 259.

13. Thoenes. D. *Chemical Reactor Development*; Kluwer Academic: Dordrecht/Boston. 1994; Chapter 1.

14. Thoenes. D. *Chemical Reactor Development*: Kluwer Academic: Dordrecht/Boston. 1994: Chapter 10.

15. Clausen III. C.A.: Mattson. G. *Principles of Industrial Chemistry*: J.Wiley & Sons: New York. 1978: Chapter 10.

16. Shriver. D.: Atkins. P.: Langford C. *Inorganic Chemistry*. 2nd ed: Freeman: New York. 1994.

17. Foster. D. *J. Am. Chem. Soc.* **1976**. 98. 846.

18. Lerner. B. A. *Chem & Ind* **1997**. 1. 16.

19. Tundo. P. *Continious Flow Methods in Organic Synthesis*: Ellis Horwood: New York. 1991: Chapter 3.

20. Naworski. J.S.: Velez. E. S. in *Applied Industrial Catalysis*: Leach. B.E.. Ed.: Academic Press: New York. 1983: Vol. 1.

21. Shriver. D.: Atkins. P.: Langford C. *Inorganic Chemistry*. 2nd ed: Freeman: New York. 1994: Chapter 17.

22. Plank. J. *Chemtech* **1984**. 14 (4). 243.

23. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991: Vol. 9. p 821.

24. Tundo. P. *Continious Flow Methods in Organic Synthesis*: Ellis Horwood: New York. 1991: Chapter 12.

25. Witcoff. H.: Reuben. B. *Industrial Organic Chemicals*: Wiley-Interscience: New York. 1996: Chapter 5.

26. *C&EN* **1996**. 74 (15). 16.

27. Wiseman. P. *Introduction to Industrial Organic Chemistry*. 2nd Ed.: Applied Science: London. 1979: Chapter 6.

28. Sedriks. W. *Chemtech* **1995**. 25 (11), 56.

29. Benson. J. *Chemtech* **1976**. 6 (1). 16.

30. Wiseman, P. *J. Chem. Educ.* **1977**, 54, 154.

31. Witcoff, H.; Reuben, B. *Industrial Organic Chemicals*; Wiley-Interscience: New York, 1996; Chapter 2.

32. Sterba, M.; Haensel, V. *Ind. Eng. Chem. Res. Dev.* **1976**, 15, 2.

33. Witcoff, H. *J. Chem. Ed.* **1987**, 64, 773.

34. Witcoff, H.; Reuben, B. *Industrial Organic Chemicals*; Wiley-Interscience: New York, 1996; Chapter 7.

35. Dodjson, J. et al *Chem & Ind* **1989**, 24, 830.

36. Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 3d ed.; VCH: New York, 1997; Chapter 10.

37. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Ed.; Wiley-Interscience: New York, 1991; Vol. 1, p 481.

38. *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Gerhartz, W., Ed.; VCH: Weinheim, 1985; Vol. A1.

39. McMurry, J.; *Organic Chemistry*, 5th ed.; Brooks/Cole: Pacific Grove CA, 2000; Chapter 19.

40. *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; 2nd ed.; Pergamon: New York, 1993; Vol. 3, Chapter 8.

41. Witcoff, H.; Reuben, B. *Industrial Organic Chemicals*; Wiley-Interscience: New York, 1996; Chapter 9.

42. *Chemical Week* **1996**, 158 (26), 22.

43. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Ed.; Wiley-Interscience: New York, 1991; Vol. 1, p 129.

44. Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 3d ed.; VCH: New York, 1997; Chapter 7.

45. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Ed.; Wiley-Interscience: New York, 1991; Vol. 4, p 830.

46. De Rooij. A. H.: Dijkhuis. G.: Van Goolen. J. T. J. *Chemtech* **1977**. 7(5). 309.

47. Morgan. M. L. *Chem & Ind* **1998**. 3. 90.

48. Pujado. P. et al *Hydrocarbon Processing* **1978**. 57 (3). 91.

49. Witcoff. H.: Reuben. B. *Industrial Organic Chemicals*: Wiley-Interscience: New York. 1996: Chapter 7.

50. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 13.

51. McMurry. J.: Organic Chemistry. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000; Chapter 18.

52. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991: Vol. 9. p 923.

53. Ozero. B. I.: Procelli. J. V. *Hydrocarbon processing* **1984**. 63 (3). 55.

54. *Chemtech* **1995**. 25(8). 37.

55. *Handbook of Chemical Production Processes*; Meyers. R.. Ed.: McGraw-Hill: New York. 1986: Chapter 1.

56. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991: Vol. 20. p 277.

57. Gusevskaya. E. V.: Karandin. A. V.: Likholobov. V. A.: Kondratiev. A. V. *Applied Catalysis A*: General **1993**. 97. 1-15.

58. Bobulev B. et al U.S. Patent 3. 957. 7. 690. 1986.

59. McMurry. J.: *Organic Chemistry*. 5th ed.; Brooks/Cole: Pacific Grove CA. 2000; Chapter 7. Chapter 17. Chapter 21.

60. Crabtree. R. H.: *The Organometallic Chemistry of the Transition Metals*; Wiley: New York. 1988: p 173.

61. Jira. R.: Blau. W: Grimm. D. *Hydrocarbon Processing* **1976**. 55 (3). 97.

62. *Ullmann's Encyclopedia of Industrial Chemistry*. 5th ed.: Gerhartz. W.. Ed.: VCH: Weinheim. 1985: Vol. A27.

63. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 9.

64. Tundo. P. *Continious Flow Methods in Organic Synthesis*: Ellis Horwood: New York. 1991: Chapter 3.

65. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991: Vol. 12. p 700.

66. McMurry. J.: *Organic Chemistry*. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000: Chapter 7. Chapter 17. Chapter 7.

67. March. J. *Advanced Organic Chemistry*. 3ed.: Wiley-Interscience: New York. 1985: p 933.

68. McMurry. J.: *Organic Chemistry*. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000; Chapter 21.

69. Grasselli. R.K. *J. Chem. Ed.* **1986**. 63. 216.

70. *Chemtech* **1978**. 8(4). 235.

71. *Hydrocarbon Processing* **1994**. 73 (11). 85.

72. Centi. G: Marchi. F: Perathoner. S *J. Chem. Soc.*. Faraday Trans. **1997**. 92. 13.

73. *C&EN* **1997**. 75(23). 15.

74. *C&EN* **1997**. 75(40). 15.

75. *Chem. Eng. Progress* **1997**. 93 (12). 20.

76. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 7.

77. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991; Vol. 1. p 146.

78. *Applied Catalysis A: General* **1992**. 85. 1-4.

79. Seuillet. B.: Castanet. Y.: Mortreux. A.: Petit. F. *Applied Catalysis A: General*. **1993**. 93. 219-229.

80. Shriver. D.: Atkins. P.: Langford C. *Inorganic Chemistry*. 2nd ed: Freeman: New York. 1994: Chapter 17.

81. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 10.

82. Luedeke. V. D. in *Encyclopedia of Chemical Processing and Design*; McKetta. J., Cuningham R.. Eds.: Dekker: New York. 1977: Vol. 2. p 146.

83. Danly. D. E. *Hydrocarbon Processing* **1981**. 60 (4). 161.

84. Kaplan. L.: Bergman. R. G. US Patent 4 360 600. 1982.

85. Dombek. B. D. *J.Chem. Educ.* **1986**. 63. 210.

86. Ishimo. M.: Tamura. M.: Deguchi. T.: Nakamura. S. *Journal of Catalysis* **1992**. 133. 325-331.

87. Nishimura. K.: Uchimi. S.: Fujii. K.; Nishihira. K: Yamashita. M.: Etatani. H. US patent 4 229 589. **1980**.

88. Gans. M. *Hydrocarbon Processing* **1976**. 55 (11). 145.

89. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 13.

90. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991; Vol. 4. p 83.

91. *Comprehensive Organic Synthesis*; Trost. B.M.. Ed.; 2nd ed.: Pergamon: New York. 1993; Vol. 3. Chapter 3.

92. Yoshioka. A.: Hakari. H.: Sato. R.: Yamamoto. H.: Okumura. K. *Hydrocarbon Processing* **1984**. 63 (11). 118.

93. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.: Kroschwitz. J. I.. Ed.; Wiley-Interscience: New York. 1991; Vol. 4. p 676.

94. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991: Vol. 22. p 969.

95. O'Hara J. et al US Patent 4. 565. 898. 1986.

96. Witcoff. H.: Reuben. B. *Industrial Organic Chemicals*: Wiley-Interscience: New York. 1996: Chapter 10.

97. Diem. H. *Chem. Eng.* **1978**. 85 (5). 83.

98. Podrebarac. G. G.: Ng. F. T. T.: Rempel. G. L. *Chemtech* **1997**. 27 (5). 37-45.

99. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I., Ed.; Wiley-Interscience: New York. 1991: Vol. 22. p 957.

100. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 13.

101. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991: Vol. 7. p 730.

102. Horsley. J. A. *Chemtech* **1997**. 27 (10). 45-49.

103. McMurry. J.: *Organic Chemistry*. 5th ed.: Brooks/Cole: Pacific Grove CA. 2000: Chapter 7.

104. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 9.

105. Witcoff. H.: Reuben. B. *Industrial Organic Chemicals*: Wiley-Interscience: New York. 1996: Chapter 3.

106. McPherson. W.: Starks. C. M.: Fryar. G. I. *Hydrocarbon Processing* **1979**. 58 (3). 75.

107. Hofen R. et al British Patent Applications 2. 095. 242A and 2. 095. 245A. 1982.

108. *Kirk-Othmer's Encyclopedia of Chemical Technology*. 4th ed.: Kroschwitz. J. I.. Ed.: Wiley-Interscience: New York. 1991: Vol. 9, p 817.

109. Weissermel. K.: Arpe. H.-J. *Industrial Organic Chemistry*. 3d ed.: VCH: New York. 1997: Chapter 8.

110. *Kirk-Othmer's Encyclopedia of Chemical Technology*, 4th ed.: Kroschwitz, J. I., Ed.; Wiley-Interscience: New York, 1991; Vol. 1, p 103.

111. U.S.Senator Dianne Feinstein Press Release, http://www.senate.gov/~feinstein/releases/mtbe4.html, March 29, 1999.

112. *Chem. Eng. Progress* **1994**, 90 (1), 25.

113. Haggin, J. *C&EN* **1993**, 71 (43), 30-32.

114. Haggin, J. *C&EN* **1992**, 70 (6), 5.

115. Knifton, J. F. *Chemtech* **1994**, 24 (5), 43-48.

116. Ellis, P. E.; Lyons, J. E. *Catal. Lett.* **1989**, 3, 389.

117. Roth, J. F. *Chemtech* **1991**, 21 (6), 357.

118. Witcoff, H.; Reuben, B. *Industrial Organic Chemicals*; Wiley-Interscience: New York, 1996; Chapter 12.

119. Haggin, J. *C&EN* **1991**, 69 (17), 22.

120. Weirauch, W. *Hydrocarbon Processing* **1995**, 74 (8), 23.

121. Cheung, T-K; Gates, B. C. *Chemtech* **1997**, 27 (9), 28-37.

122. Vora, B.; Pujado, P., Imai, T.; Fritsch, T. *Chemistry & Industry* **1990**, 6, 187-191.

123. Shelley, S. *Chem. Eng.* **1994**, 101, 67-69.