

CHAPTER II

THEORY

Most hydrocarbons derived from crude oil are unfortunately burned to carbon dioxide and water. In the near future, three or four decades from now, saturated hydrocarbons should mainly be used as raw material for the manufacturing of chemicals.⁵ However, the direct activation of saturated hydrocarbons by classical methods usually requires drastic conditions, affording mixtures of products derived from overoxidation. Therefore, the oxidation under mild conditions of the most abundant and cheapest class of organic compounds is an intellectually stimulating and industrially important aim of current relevance.

Literature Review on the Activation of Saturated C-H Bonds

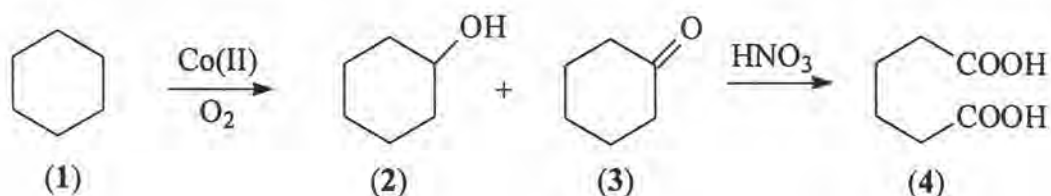
- Industrial Process for the Homogeneous, Metal-catalyzed Oxidation of Saturated Hydrocarbons

The three most important homogeneous procedures of industrial hydrocarbon activation are:⁶

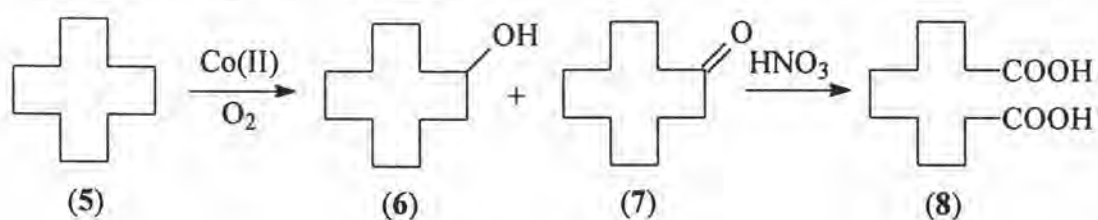
1. oxidation of cyclohexane to cyclohexanol and cyclohexanone, leading to adipic acid, an intermediate for nylon-6 production,
2. oxidation of cyclododecane to cyclododecanol and cyclododecanone, leading to the production of intermediates for polyamide production, and
3. butane oxidation into acetic acid, a solvent and starting material of extensive use in the chemical industry (vinyl acetate, cellulose acetate, *etc.*)⁷

1. Cyclohexane oxidation represents the biggest scale of these operations. It is produced in $> 10^9$ lb/year quantities by duPont.⁵ In this procedure, cyclohexane (1) is converted to cyclohexanol (2) and cyclohexanone (3) catalyzed by cobalt (II)

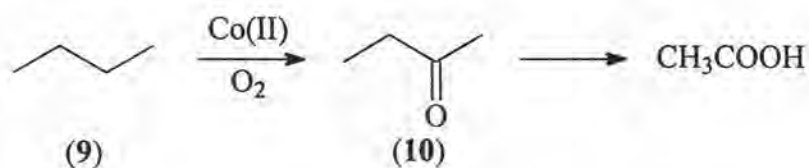
carboxylates. The reaction is driven to a 4% conversion at 180-250⁰C and 8-10 bar air pressure, where it gives a 70% selectivity in the formation of the desired product.² The mixture of cyclohexanol and cyclohexanone is then converted into adipic acid (4) by nitric acid oxidation :



2. The oxidation of cyclododecane (5) is done by a process very similar to that of cyclohexane: cobalt (II) carboxylates are used as catalysts, at 160-180⁰C temperature and 1-3 atm air pressure.⁶



3. Butane (9) is oxidized by air, in an acidic solution, catalyzed by cobalt (II) acetate. Reaction conditions are 160-200⁰C temperature and 60-80 atm air pressure. At 30% conversion acetic acid is obtained with 45% selectivity. The by products are propionic acid and butyric acid and 2-butanone (10), which are used for the production of other compounds. More recent procedures use milder condition and convert practically all by-products into acetic acid: a 75% yield of acetic acid is attainable at 85% conversion.⁸



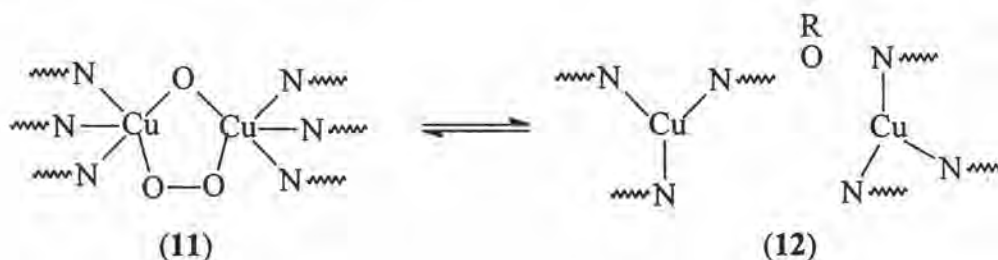
The easy interconversion of Co(II) and Co(III) oxidation states facilitates these processes by providing an electron source for the electron steps of the autoxidation of hydrocarbons and the decomposition of alkyl hydroperoxides formed in the reaction.⁹

- Biological Systems for the Functionalization of Unactivated C-H Bonds

There have been a large number of biological systems capable of hydroxylation of saturated hydrocarbons reported. Particularly the enzymatic systems in mammals can functionalize or convert saturated hydrocarbons to other organic compounds under mild conditions, *i.e.*, ambient temperature and atmospheric pressure. Oxygenation of organic substrates catalyzed by Cytochrome P-450, oxidation by peroxidases, oxidative halogenation by chloroperoxidases, and hydrogen peroxide dismutation by catalase are among examples of those fascinating enzymes.

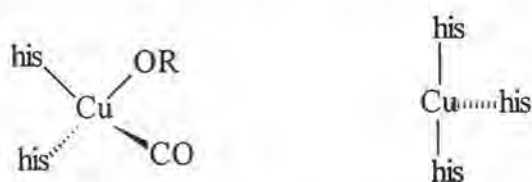
Copper-containing non-heme oxygenases

Hemocyanin Despite its name, hemocyanin does not contain either a heme moiety or a cyano group. It binds one dioxygen molecule by two Cu atoms at its active site. The ligands of the coppers are proposed to be all N-atoms of histidine residues of the enzyme,¹⁰ with an additional bridging oxo-group between the two Cu atoms in the oxidized form (11).¹¹ This bridge is missing and the Cu atoms are separated in the deoxy-form (12):



The oxo-bridge was suggested to be a tyrosine oxygen, which moves only slightly away from the dicopper center in the deoxy form. The possibility for asymmetry

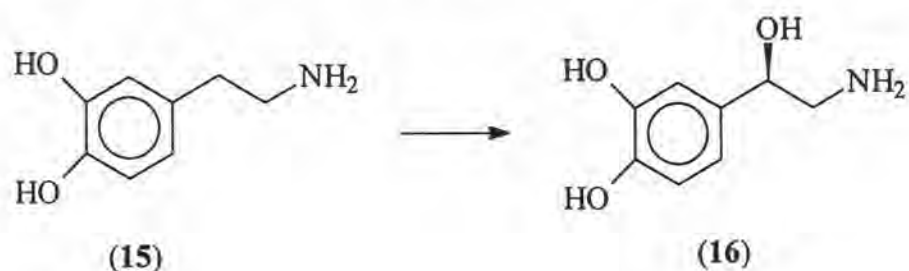
between the two Cu atoms was suggested because the reaction of the complex with carbon monoxide only one CO molecule is bound to only one of the Cu atoms:¹²



However, these are only speculation based on model compounds, *e.g.* methemerythrin azide, whose X-ray crystal structure is available, and EXAFS and resonance Raman spectroscopic observations. The exact nature of O₂-binding in hemocyanin is still a subject of much debate, with two possible modes, the *cis*- μ -1,2 (13) and the μ - η^2 - η^2 conformation (14) proposed.¹³



Dopamine β -hydroxylase Dopamine β -hydroxylase is one of the few copper containing oxygenase enzymes capable of the activation of dioxygen and saturated C-H bonds. It hydroxylates dopamine (15) to norepinephrine (16):¹¹

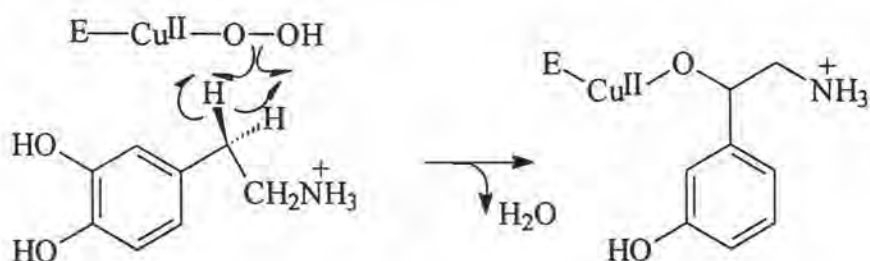


The substrate specificity of the enzyme is quite broad, and similarly to methane monooxygenase. It has two major appearances: soluble and membrane bound, although the structure of the two forms appear to be very similar.¹⁵ It usually requires ascorbate or a similar reducing agent to get from the resting Cu^{II}-state to the active

Cu^I-state. It has been demonstrated that the enzyme has two Cu atoms at the active site, both of which are needed for optimal in oxygen activation and the hydroxylation of dopamine. The ligand environment of the Cu atoms, however, is not unambiguously defined, although studies based on comparison between the CO complex of reduced dopamine β -hydroxylase and the CO complex of deoxyhemocyanin,¹⁶ and EXAFS measurement¹⁷ are being conducted. At least three histidine nitrogens were believed to complex to each Cu ion, with no agreement on the additional ligands.

The two Cu atoms are not antiferromagnetically coupled by a bridging ligand, as seen from their ESR- active behavior,¹⁸ but the enzyme is still referred to as one containing a binuclear Cu-site because the two Cu atoms act together in the hydroxylation of dopamine.¹⁹

The chemical mechanism of the hydroxylation process postulates the formation of a benzylic radical from dopamine after H-abstraction by a copper-oxygen intermediate,²⁰ although the exact nature of this oxidized active copper species is not established yet. The existence of higher oxidation state Cu (*e.g.* Cu^{III}) under the conditions of biochemical process is still debated in the literature.²¹ The steps of H-abstraction and O-transfer are proposed to be different from the "rebound" mechanism seen in P-450 oxidations, in that the H-abstraction species is supposed to be Cu^{II}-OOH, and the mechanism is concerted:¹⁵



Another enzyme where copper plays a catalytic role in the hydroxylation of a saturated C-H bonds has recently been described. This enzyme is called a peptidylglycine α -hydroxylating monooxygenase and it is responsible for the

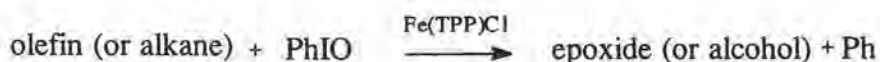
conversion of peptide bound glycine residue (17) into α -hydroxylating residues (18):²²



Mechanism studies are currently underway of elucidating the pathway of this transformation.²³

- Model Systems for Mimicking Non-heme Oxygenase Activity

Much attention has been focused on the imitation of several biological systems which have the ability to hydroxylate unactivated carbon-hydrogen bonds under mild conditions. Among those catalyzed by transition metals, iron has been recognized as an important metal for activation of various oxygen species. A great number of model studies based on iron ions or complexes has therefore been introduced and developed. For instance, in 1979, the first article on the use of iodosylbenzene as simple oxygen atom donor in olefin epoxidation and alkane hydroxylation, catalyzed by iron *meso*-tetrakis-(phenyl)porphyrin chloride [Fe(TPP)Cl] was published.²⁴



Cyclohexene preferentially gives cyclohexene oxide; the allylic oxidation product, cyclohexenol, is also detected.

Later, many investigators found that metal salts or metal complexes that were simply prepared could be used as a catalyst. Those developed systems could provide a good and efficient catalytic system for oxidizing cyclohexane. For example, D.H.R. Barton *et al.*²⁵ have developed a family of chemical systems which allow the oxidation and functionalization of saturated hydrocarbons under mild conditions. All of them involved a pyridine-acetic acid (or other carboxylic acids) solution of the

hydrocarbon being oxidized, an Fe-based catalyst, an oxidant, and an electron source. These Fe-based models were able to activate saturated hydrocarbons in almost quantitative yields at 10-25% conversions.²⁶ Ketones were the major product of the reaction.

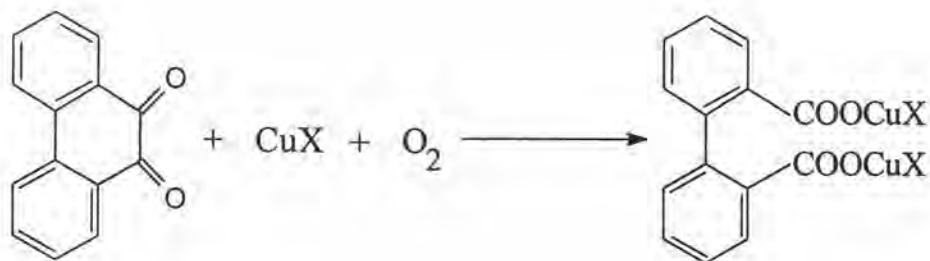
D.T. Sawyer *et al.* presented many catalytic systems for the functionalization of saturated hydrocarbons. The iron-catalyzed ketonization of cyclohexane by hydrogen peroxide (H_2O_2) in various solvents was disclosed.^{27,28} For example, $\text{Fe}(\text{PA})_2$ in pyridine, pyridine/acetic acid (various ratios), acetonitrile (CH_3CN), and acetonitrile/ acetic acid (3.6:1 molar ratio), $\text{Fe}(\text{PA})(\text{ClO}_4)$ or $\text{Fe}(\text{DPA})$ in pyridine/acetic acid (2:1 molar ratio).

Besides iron, several transition metals have recently also been shown to be capable of catalyzing the oxidation of saturated hydrocarbons. For instance, P. Battioni *et al.*²⁹ found that meso-tetrakis-(dichlorophenyl)porphyrin chloride [$\text{Mn}(\text{TDCPP})\text{Cl}$] and imidazole could be used as a catalyst for the oxidation of cyclohexane. The cyclohexanol to cyclohexanone ratio was 3:1. D.T. Sawyer *et al.*³⁰ later reported $\text{Co}^{\text{II}}(\text{bpy})_2^{2+}$ in acetonitrile/pyridine (4:1 molar ratio) as a catalyst in the oxidation of saturated hydrocarbons with hydrogen peroxide.

Copper

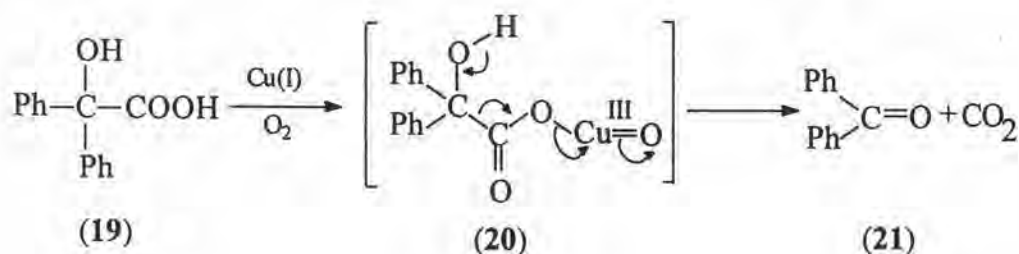
Even though a variety of organic substrates have been oxidized with the help of copper catalysts with hydrogen peroxide (*e.g.* ethanol, diphenylacetic acid, triphenylphosphine and toluene),³¹ with *tert*-butyl hydroperoxide (*e.g.* cyclohexene and styrene),³² or with trimethylamine *N*-oxide (ligand oxidation of alcoholates, carboxylates and aromatics),³³ reports about oxidation with dioxygen and reports of alkane oxidation are scarce.

Speier and Tyeklar described a Cu^{I} -catalyzed oxidation of 9,10-phenanthrenequinone with dioxygen into Cu^{II} -carboxylates.³⁴



X = Cl, Br

Capdevielle and Maumy observed the Cu^{I} -catalyzed oxygenation of diphenylhydroxyacetic acid (**19**) into benzophenone (**21**) and CO_2 .³⁵



where they proposed the participation of a transient Cu^{III} -carboxylate (**20**). Later a similar proposal for the participation of a transient trivalent copper intermediate in the Cu^{I} -mediated hydroxylation of *N*-salicyloyl glycine (**22**) was proposed.³⁶



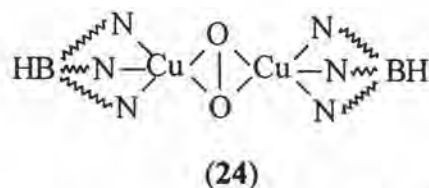
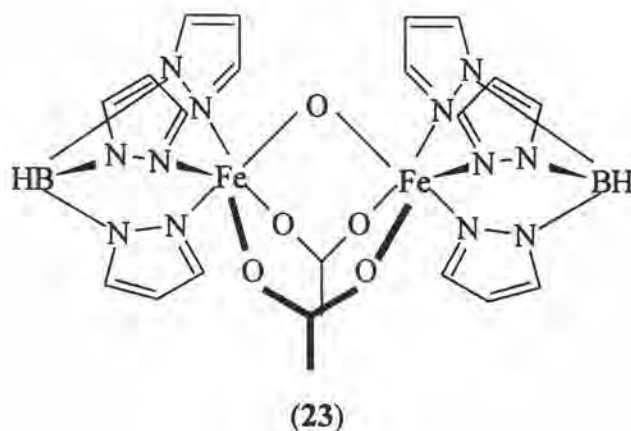
This process was suggested to be a model reaction for the action of the peptidyl-glycine α -hydroxylating monooxygenase.²²

The oxidation of hydrocarbons by copper(II) perchlorate and hydrogen peroxide was reported by Lubimova *et al.*³⁷ This oxygenation of cyclohexane in pyridine yielded mainly cyclohexanone with cyclohexanol, and 2-methylbutane gave mostly 3-methyl-2-butanone. The true oxidizing agent was believed to be pyridine *N*-oxide radical cation.

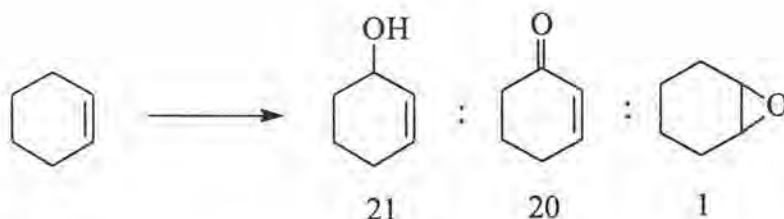
Murahashi *et al.*³⁸ presented copper-catalyzed oxidation of alkanes and alkenes with molecular oxygen in the presence of aldehydes. $\text{Cu}(\text{OH})_2$ and acetaldehyde were used as a catalyst and as a co-oxidant, respectively. In this system, the oxidation of cyclohexane in dichloromethane yielded cyclohexanone and cyclohexanol (1.5:1) while cyclohexene gave mainly epoxycyclohexane.

Parallel to the investigation of these oxidation systems, much research has been focused on the preparation and characterization of Cu-complexes capable of dioxygen activation which could serve as potential models for hemocyanin and perhaps be able to perform hydrocarbon functionalization.

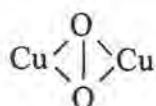
Kitajima and Moro-oka synthesized a peroxy binuclear copper complex from the borate ligand of (23), where the peroxy bridge between the two coppers was shown by X-ray crystallography to be of the $\mu\text{-}\eta^2\text{-}\eta^2$ type (24)³⁹ as opposed to the cis- $\mu\text{-}1,2\text{-peroxy}$ bridge previously suggested as the binding mode of oxygen in hemocyanin.



This raised questions about the possibility of a similar $\mu\text{-}\eta^2\text{-}\eta^2$ in hemocyanin.⁴⁰ This complex was later shown to be in the oxidation of cyclohexene in the presence of dioxygen.



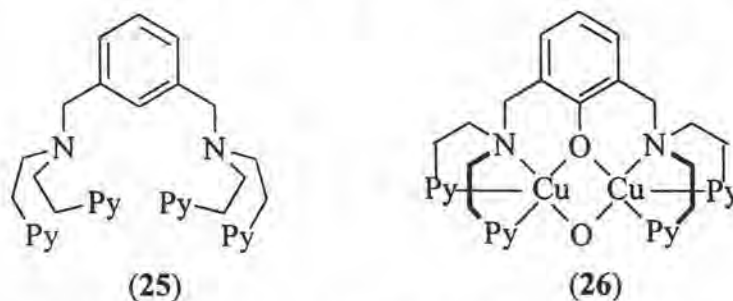
It also oxidized phenols and catechols.⁴¹ Nonempirical calculations on $(\text{Cu}^+)_2\text{-O}_2$ structures also suggest that the most stable conformation for these kind of systems is



the structure, with no additional bridging ligands needed.⁴²

Aerobic oxidation of alkanes in the presence of acetaldehyde catalyzed by copper-crown ether was described by Murahashi *et al.*⁴³ Cyclohexanone (61% based on acetaldehyde) and cyclohexanol (10%) were the products of the oxidation of cyclohexane. Copper-crown ether complexes proceeded as efficiently as the combined use of CuCl_2 with 18-crown-6 under the same conditions.

Karin and his colleagues assembled a series of binuclear ligands and tested the ability of binuclear Cu complexes, held together by μ -oxo bridges in these ligands, for the reversible binding and activation of dioxygen.⁴⁴ These complexes were also intended to emulate hemocyanin behavior, and possibly the action of tyrosinase, a tyrosine hydroxylating protein with a μ -oxo bridged dicopper active sites. The binucleating are of the type (25), which after oxygenation in the presence of Cu(I) ions gives a μ -phenoxo- μ -oxo structure (26) (confirmed by X-ray crystallography).



This complex yields the phenol ligand which can then be reassembled with Cu(I) ions to give a μ -phenoxo bridge complex. The monobridged Cu(I) binuclear

molecule has the ability to bind and release dioxygen and CO at low temperatures ($<-60^{\circ}\text{C}$).⁴⁵ Later Karlin and Blackburn reported that a Cu(I) complex with simple imidazole ligand is also capable of O_2 -binding and the formation of a $[(\text{L}_3\text{Cu})_2\text{O}_2]^{2+}$ peroxo complex (L = 1,2-dimethylimidazole) at -90°C .⁴⁶

Other O_2 -binding Cu complexes of binucleating ligands have also been described.⁴⁷ However, no Cu-dioxygen complex has been reported as yet, where the binding of oxygen occurs asymmetrically, at one Cu atom only, as proposed in the mechanism of dopamine β -hydroxylase. There was also a report from Thompson of a possible monomeric Cu(II)-superoxide on the tetrahedral copper,⁴⁸ but further spectroscopic studies have not confirmed the arrangement yet. Thompson also observed hydroxylation of a $-\text{CH}_2-$ group on an ethyl group a N,N,N',N' -tetraethylethylenediamine ligand after its Cu(I)-dioxygen complex has been exposed to oxygen.⁴⁹