CHAPTER II

THEORY

2.1 Ferrocene

In 1951, P. Pauson and S. A. Miller independently discovered ferrocene, $(\eta^5\text{-}C_5H_5)_2Fe$, and approximately a year later G. Wilkinson[1] reported its structure as shown in Figure 2.1.

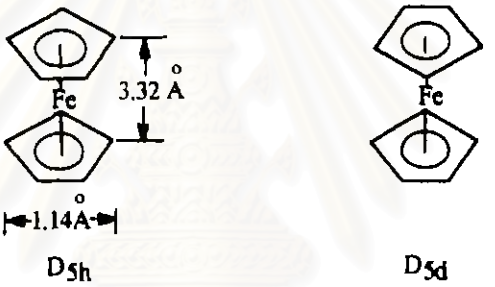


Figure 2.1 Structures of ferrocene

Ferrocene at room temperature crystallizes in a monoclinic form. In this form, the eclipsed conformation (D_{5h}) is more stable than the staggered (D_{5d}).[2] Ferrocene is the main focus of research primarily due to its remarkable stability and ease of preparation. It has a greater reactivity in the electrophilic substitution than does benzene. For example, it is acetylated with acetyl chloride and anhydrous aluminium chloride 10^6 times faster than benzene. Ferrocene is a starting material for the preparation of numerous derivatives used in many areas of chemistry. It is derivatised mostly by electrophilic substitution or by lithiation as a first step.[3]

Monolithioferrocene[4] can be made by the following methods:

a) lithiation of ferrocene by excess of *n*-butyllithium in diethyl ether at room temperature to give monolithioferrocene (25% yield)

b) metal-halogen exchange reaction between bromoferrocene and *n*-butyl lithium in diethyl ether (60-65% yield).

c) transmetallation reaction between chloromercuriferrocene and *n*-butyl lithium in diethyl ether (excellent yield).

Dilithioferrocene is obtained in good yields by direct metallation of ferrocene with *n*-butyllithium/TMEDA in hexane or with *tert*-butylithium in diethyl ether.

2.2 Cyclodextrins

Cyclodextrins, also known as Schardinger dextrins, cycloamyloses, and cycloglucoamyloses, comprise a family of cyclic oligosaccharides obtained from starch by enzymatic degradation. They were discovered in 1981 by Villers, but the first detailed description of the preparation and isolation was made in 1903 by Schardinger. In the preparation process, the starch is treated with a group of amylases called glycosyltransferases or cyclodextrinases (Figure 2.2). The starch helix is hydrolyzed off, and its ends are joined together through α-1, 4 linkages. Since these enzymes are not very specific as to the site of hydrolysis, the product contains α-, β- and γ-cyclodextrins together with small amounts of higher analogues consisting of up to 13 glucose units. Up to now, α-, β-, γ- and δ-cyclodextrins, which are comprised of six, seven, eight and nine glucose units respectively, have been isolated by selective precipitation with appropriate organic compounds. Cyclodextrin with 10-13 glucose units were also identified by chromatographic methods. Cyclodextrins composed of less than six glucose units are not known to exist due to steric hindrance and the 6-fold character of the starch helix.[5]

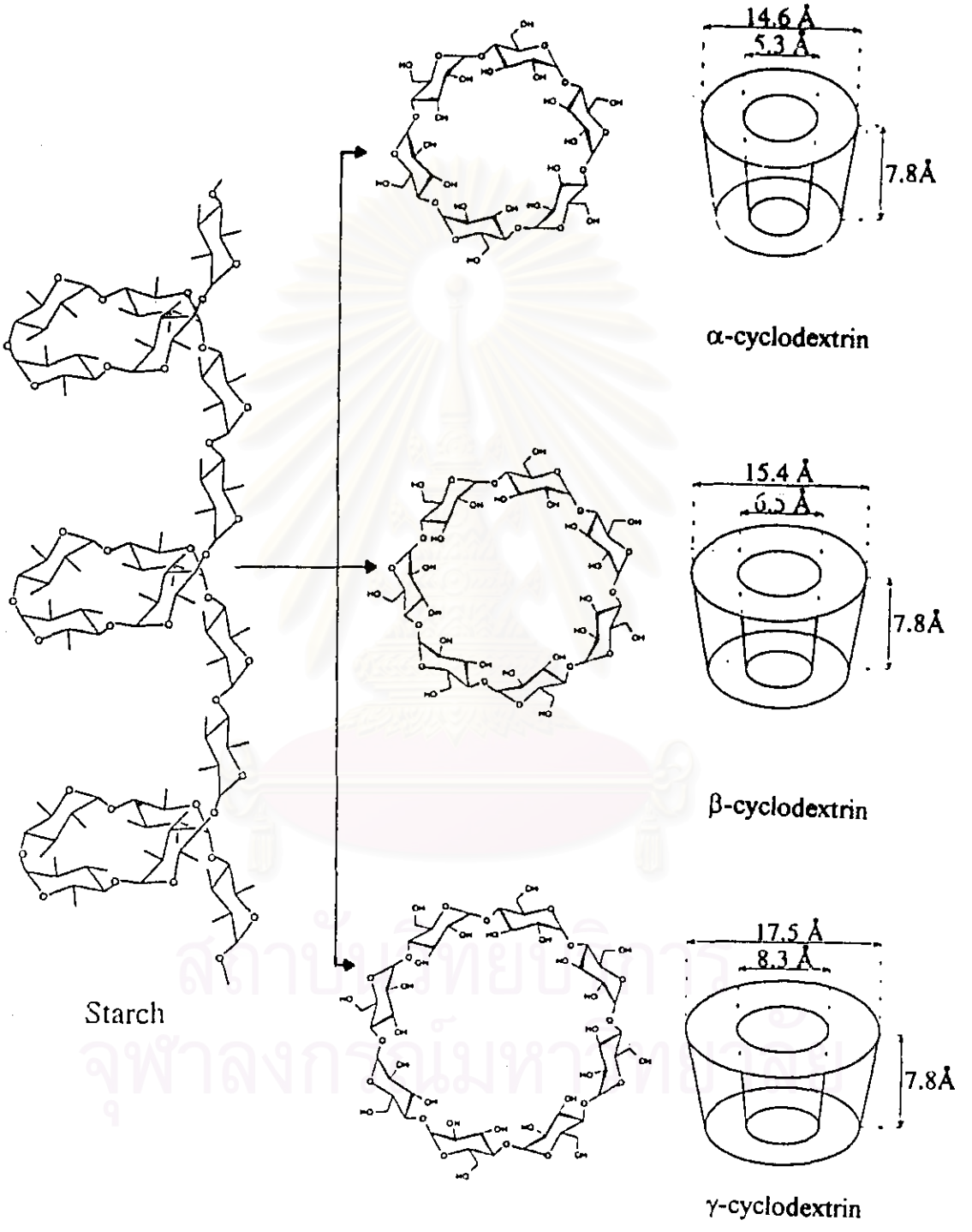


Figure 2.2 Structures of α-, β- and γ-cyclodextrins

Cyclodextrins consist of glucose unit building blocks which form the macrocycle and which are generally in the $^4C_1$ chair conformation. The structures of native cyclodextrins are fairly rigid due to intramolecular hydrogen bonds between the OH(2) and the OH(3) of adjacent glucose units (Figure 2.3).

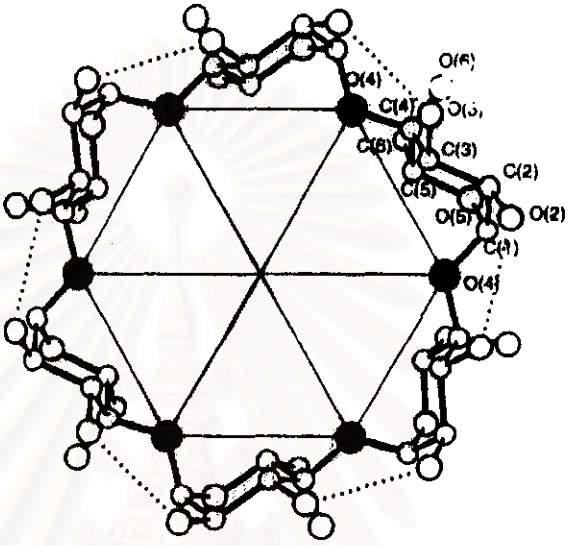


Figure 2.3 X-ray structure of α-cyclodextrin. The hexagon composed of the six glycosidic oxygen atoms is shown with thin lines. Dotted lines denote possible hydrogen bonds between the OH(2) and OH(3) of adjacent glucose units. Oxygen atoms are shaded.

The cavity width of the macrocyclic structure is defined by a polygon composed of glycosidic O(4) atom. The average radii of the O(4) polygons, which are the average values of the distances from the center of the polygons to each O(4), are 4.2, 5.0, and 5.9 Å in α-, β- and γ-cyclodextrins respectively, while the side lengths fall in the range 4.2-4.6 Å (Table 2.1). The macrocyclic ring is distorted from ideal *n*-fold symmetry in the crystalline state. The deviations from perfect symmetry are most easily seen as differences in inclinations of each glucose unit. To evaluate the relative inclination, the tilt-angle is defined as the angle made by the O(4) plane and the plane through the C(1), C(4), O(4) and O(4′). The average tilt angle tends to increase as the number of glucose units increases.[6]

Table 2.1 Some parameters describing the macrocyclic conformation of cyclodextrins

Parameters	α	β	γ
Radius of the O(4) polygon (Å)	4.2 (0.1)	5.0 (0.2)	5.9 (0.1)
O(4)...O(4')distance (Å)	4.2 (0.1)	4.3 (0.1)	4.5 (0.1)
O(2)...O(3') distance (Å)	3.0 (0.1)	2.9 (0.1)	2.8 (0.1)
O(4) angle (°)	119 (1)	118 (1)	117 (1)
Planarity of the O(4) polygon (Å)	0.10	0.16	0.11

The cyclodextrin cavity has a hydrophobic character because the inside wall of the cavity is composed of many hydrogen atoms from the H(3) and H(5) methine groups and the H(6) methylene groups. The cyclodextrin molecule is often described as a shallow truncated cone, the primary hydroxyl rim of the cavity opening having a reduced diameter compared with the secondary hydroxyl rim[5] as shown in Figure 2.4.

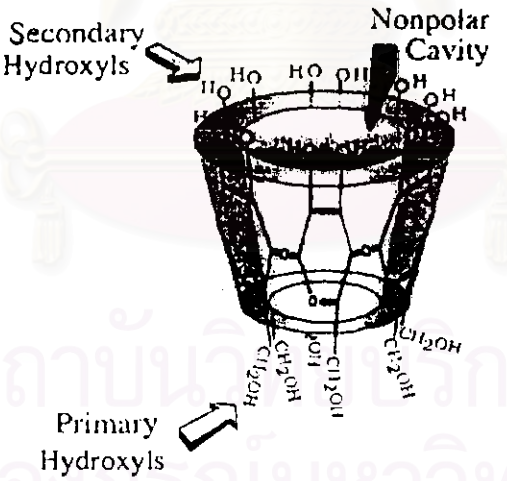


Figure 2.4 Characteristic structural features of cyclodextrin

Cyclodextrins have some unique physical and chemical properties. Some of important properties and characteristics are listed in Table 2.2

Table 2.2 Some physical properties and characteristics of various cyclodextrins

Characteristics	α	β	γ
Molecular weight	972	1135	1297
Glucose monomers	6	7	8
Internal cavity diameter (Å)	5.3	6.5	8.3
Water solubility (g/100ml : 25 °C)	14.2	1.85	23.2
Melting range (° C)	255-260	255-265	240-245
Water molecules in cavity	6	12	17

2.3 Inclusion Compounds

The inclusion process is a result of the ability of one compound, owing to its suitable steric properties and partially also polarity, to enclose spatially another compound. The terms host and guest were used to clarify their functions. An important characteristic property of the host is its ability to form a structure with free cavities with dimensions that permit the enclosure of a guest molecule. The formation of inclusion compounds is not dependent on the chemical affinity or the presence of certain groups, but rather on the spatial arrangement and interactions, where primarily van der Waals forces and oriented dipole interactions are important.[7]

In conclusion, the following conditions are decisive for the formation of inclusion compounds:

1. The host structure must contain free cavities of molecule dimensions which need not be present originally, they are frequently formed in the presence of the guest substance.

2. The spatial arrangement (dimension) of the guest molecule must correspond to the dimension of the free cavity in the host substance.

Generation of the knowledge on inclusion compounds[8] leads to the following characteristics:

1. Inclusion compounds are formed by combination of host and guest molecules.

2. The information cannot be explained by common chemical reactions.

3. The interaction between the host and guest at the level of van der Waals forces corresponds to the energetically most suitable mutual arrangement.

4. Inclusion compounds are stable as solid substances at the normal pressure and temperature, the guest substance cannot leave its position in the host structure.

5. Formation and decomposition depend on a suitable solvent.

6. Some types of host substances are able to interact stereospecifically with the guest molecules in the gaseous phase under certain conditions.

The possession of the cavity makes the cyclodextrin attractive for study. The cyclodextrin exterior, bristling with hydroxyl groups, is fairly polar, whereas the interior of the cavity is nonpolar relative to the exterior and relative to the usual external environments, water in particular. These compounds have therefore been studied as "hosts" for "guest" molecules capable of entering (in whole or in part) the cavity and forming noncovalent host-guest inclusion compound.[8]

Cyclodextrins form a number of crystalline complexes by including a variety of guests. Usually, the shape and size of the included guests are limited by the accommodation space in the crystal and/or intramolecular cavity of the host. The physiochemical property of the host cavity also affects the mode of inclusion. The interior wall of the host cavity consists of H(5) and H(3) methine groups, H(6) methylene groups, and O(4) oxygen atoms. As a result, the host cavity has a rather positively charged character. In contrast to this, hydroxyl groups are found in the circle at both ends of the cavity. There are twice as many secondary hydroxyl groups as primary hydroxyl groups and such an asymmetry in charge distribution causes a strong dipole moment parallel to the pseudo symmetry axis of cyclodextrins. The positively charged cavity favorably includes neutral molecules and anions. Complexes with cations are rarely found.[9]

It has been generally accepted that the binding forces involved in the complex formation are:

1. Van der Waals interactions (or hydrophobic interactions) between the hydrophobic moiety of the guest molecules and the cyclodextrin cavity.

2. Hydrogen bonding between the polar functional groups of guest molecules and the hydroxyl groups of cyclodextrin.

3. Release of high-energy water molecule from the cavity in the complex formation process.

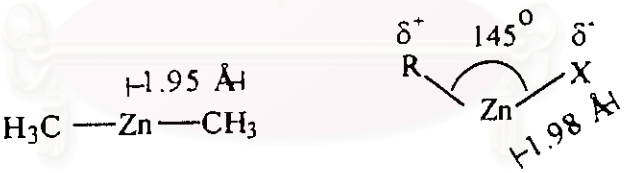
4. Release of strain energy in the ring system of the cyclodextrin.

The geometric capability and the polarity of guest molecules, the medium, and temperature are the most important factors for determining the kind of guest molecule that can penetrate into the cavity. If the guest is too small, it will easily pass in and out the cavity with little or no bonding at all. Inclusion compound with guest molecules significantly larger than the cavity may also be possible, but the complex is formed in such a way that only certain groups or side chains penetrate into the cyclodextrin cavity. Only substrates that are less polar than water can form inclusion compounds with cyclodextrins. The stability of an inclusion compound is proportional to the hydrophobic character of the guest molecule. Highly hydrophilic molecules form complex very weakly or not at all.[5]

In principle, inclusion compound can be formed either in solution or in the crystalline state. However, inclusion is usually performed in the presence of water. The stability strongly depends on the nature of the medium used for inclusion. A commonly accepted model for complex formation suggests that the complex forms when a suitable hydrophobic molecule displaces water from the cavity. Such models for inclusion are supported by solution NMR studies, many crystal structures reported illustrate the interaction between the apolar cavity and the hydrophilic portion of guest molecules.[10]

2.4 Organozinc Chemistry

Organozinc chemistry provides an opportunity to examine the catalytic alkylation of benzaldehyde. Although dialkylzincs are inert to ordinary carbonyl substrates in hydrocarbon or ethereal solvents, their reactivity may be enhanced by additives.[11] Dimethylzinc has a linear structure with a 1.95 Å bond length between the zinc and carbon atoms and does not add to aldehyde. Addition of certain donor ligand can generate coordinatively unsaturated, bent structures possessing higher reactivity. Particularly, replacement of the alkyl group by an electronegative substituent increases polarity of the alkyl-Zn bond to a great extent and, consequently, enhancement of the donor property of the alkyl group and the acceptor character of the Zn atom is resulted. X-ray analysis of the complex revealed that the coordination chemistry of the zinc atom changes to the tetrahedral with a 145° carbon-zinc-carbon bond angle as shown in Figure 2.5. It should be noted that the bond length between zinc and carbon atoms becomes longer. This means that the bond energy of the zinc and carbon bond decreases and that the nucleophilicity of the methyl group of dimethylzinc increases.[12]



Unreactive Reactive

X = alkyl, N, O, halogen, etc.

Figure 2.5 Geometries of dimethylzinc

2.5 Enantioselectivity[13]

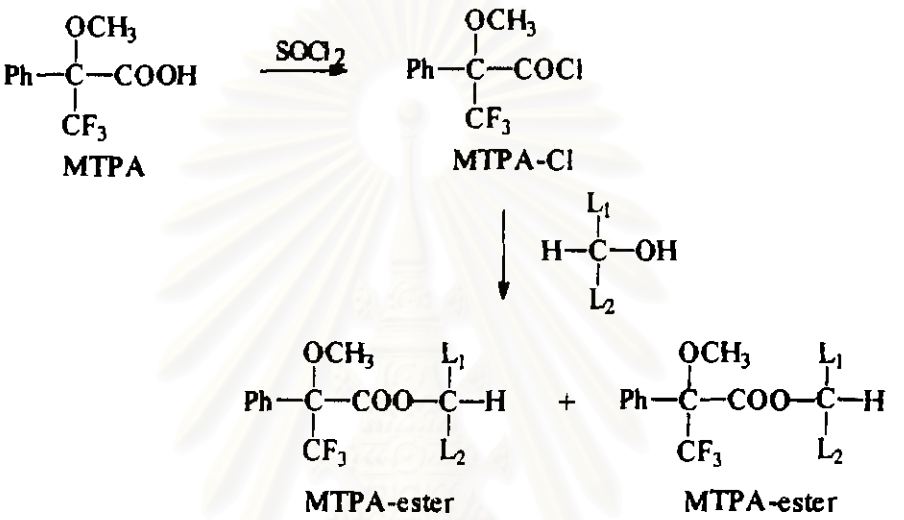
The most commonly used measure of the degree of enantioselectivity achieved is the **enantiomeric excess (e.e.)**. This is defined as the proportion of the major enantiomer less that of the minor enantiomer and is commonly expressed as a percentage. For example, if the reduction of benzaldehyde is carried out asymmetrically to give the enantiomeric alcohols (R-configuration and S-configuration) in a ratio of 90:10, then the e.e. of the process is 80 %. Similarly an e.e. of 90 % would correspond to an enantiomer ratio of 95:5. The reason for using the enantiomeric excess rather than the enantiomer ratio is that in almost all cases it corresponds directly with the optical purity. Thus in the example above R-configuration has an optical rotation of -120° and S-configuration of $+120^{\circ}$. A sample of 80 % e.e. which contains 90 % of R-configuration and 10 % of S-configuration will have a net optical rotation of $(0.9\times-120^{\circ}) + (0.1\times 120^{\circ}) = -96^{\circ}$ which is 80 % of the value for the pure major enantiomer. Thus for any samples of a compound for which the optical rotation of the pure emantiomer is known, the e.e. can be determined directly from the observed rotation.

2.6 Determination of Optical Purity

There are many methods to determine the optical purity of a mixture of enantiomers.

1. Physical separation of the enantiomers with chiral column of high performance liquid chromatography and gas chromatography
2. Inversion the mixture of enantiomers into a mixture of diastereomers by reaction with asymmetric reagent
3. Polarimetry as well as optical rotatory dispersion and circular dichroism
4. Nuclear magnetic resonance

The determination of absolute configuration by NMR[14-17] is based on the derivatization of the compound to be investigated with the two enantiomers of chiral reagent, such as α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, Mosher's reagent) and comparison of the chemical shift of resulting diasteromers as shown in Scheme 2.1



Scheme 2.1 Esterification of chiral alcohol with MTPA-Cl

The influence of phenyl ring lead to the difference of NMR signals of L_1 and L_2 in the MTPA-ester. The difference of chemical shift can be used to infer the absolute configuration at the chiral center to which L_1 and L_2 are attached.[15]

The advantages of Mosher's reagent[14] for the determination of enantiomeric composition of the chiral alcohol are the following:

1. Its versatility, it may be used for determination of enantiomeric composition of primary and secondary amines as well as carbinols.

2. The generally excellent separation of both proton and fluorine NMR signals of the diastereomers.

3. Its marked stability toward racemization even under severe conditions of acidity, basicity and temperature.

4. Its inherent volatility, which allows lower molecular weight derivatives to be purified, as well as analyzed, by gas chromatography.