

CROWN ETHERS AND ANALOGOUS COMPOUNDS

Edited by
MICHIO HIRAOKA

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Michio Hiraoka

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ANALOGOUS COMPOUNDS**

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Preface

To the memory of

Charles J. Pedersen

1904 - 1989

the discoverer of crown ethers and the founder
of crown ether chemistry, host-guest chemistry
and supramolecular chemistry

Preface

Almost a quarter of a century has passed since the first public announcement by Pedersen in 1967 of the discovery of crown ethers and their unusual characteristics of complexing with alkali and alkaline earth cations.

The discovery of crown ethers had a great impact on many chemists. Since that time, several thousands of crown ethers and analogous compounds have been synthesized. Their specific characteristics have been investigated and a wide variety of applications have been developed. Furthermore, development of the chemistry of crown ethers led to the new fields of chemistry now called "host-guest chemistry" and "supramolecular chemistry" in relation to the clarification of biological processes. Host-guest chemistry, established by Cram, is defined as the field of chemistry consisting of syntheses and applications of highly structural molecular complexes formed by recognition and binding of the matched guest by the host molecule having a designed cavity. Supramolecular chemistry, introduced by Lehn, is the new field of chemistry concerning the higher-order molecular aggregates which are formed by the association resulting from the molecular interaction between two or more molecules. Thus, the new concept of treating a molecular aggregate, formed by weak interactions, as a chemical species has been added to organic chemistry, which so far comprised molecules formed by strong covalent bonds. This is an epoch in the history of chemistry. For their pioneering work, Pedersen, Cram and Lehn were awarded the Nobel Prize in 1987.

This book is intended to present current knowledge of the chemistry of crown ethers and analogous compounds. The first chapter provides an orientation in the new field of chemistry. It covers the discovery of crown ethers in connection with enzymatic reactions and outlines the current topics in the chemistry of crown ethers and analogous compounds. Chapter 2 provides a review of the advances in the synthetic procedures for crown ethers and analogous compounds including azacrown ethers, thiacycrown ethers, functionalized crown ethers, cryptands and others. Chapter 3 focuses on the concept and synthetic strategies for the molecular design of new crown compounds including monocyclic crowns, armed crown compounds, acyclic crown compounds, cryptands and polycyclic crown compounds. It then characterizes guest-binding and structure from the standpoint of host-guest chemistry.

Chapters 4-7 are concerned with noteworthy topics in the applications of crown compounds. Chapter 4 deals with the application to ion-selective electrodes and liquid chromatography, both of which are the most important targets in the analytical application of crown compounds. One major application of crown

ethers is the design and syntheses of artificial molecules which can catalyze a useful synthetic reaction in an enzyme-mimetic reaction manner, through novel non-covalent complexes. Chapter 5 deals with the strategies for enzymatic modeling with crown ethers and the challenging problems which are likely to arise in the future. Chapter 6 presents the principle of amine-selective colour complexation, syntheses of chromogenic acerands and the application to host-guest indicators which have a facility for detecting and determining the target guest species. Chapter 7 reviews switched-on crown ethers that can respond to environmental stimuli. pH-responsive crown ethers, redox-switched crown ethers, crown ethers with electrochemical switches, photoresponsive crown ethers, temperature control of cation binding and their applications are discussed.

Chapter 8 is devoted to a wide-ranging discussion of developments in macrocyclic polyamine chemistry. Unlike crown ethers, macrocyclic polyamines, bearing nitrogen donor atoms which belong to a "soft" base, form complexes with ions of transition metals and heavy metals which are classified as "soft" acids. For the above reason, macrocyclic polyamines are expected to have versatile applications.

It is hoped that this book will stimulate further development of the exciting field of crown ethers chemistry. Deep acknowledgement is expressed to the contributing authors for their painstaking efforts. Thanks are due also to many chemists and biochemists for their aid and encouragement during the preparation of this book.

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Chapter 1

INTRODUCTORY REMARKS

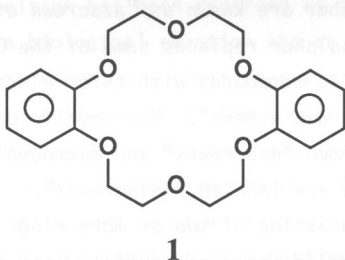
MICHIO HIRAOKA

1.1 CROWN ETHERS AND THE DAWN OF A NEW FIELD OF CHEMISTRY

1.1.1. Discovery of Crown Ethers

The discovery of crown ethers by Pedersen (ref. 1) opened the door to a new field of chemistry.

The first identified crown ether, named "dibenzo-18-crown-6" **1**, was not the target of synthesis in his experiment but a slight amount of unexpected by-product in a 0.4% yield. However, his appreciation of the importance of the discovery followed by energetic research in the area established the foundation for the present status of crown ethers in chemistry.



The first oral announcement of the discovery of crown ethers and their unusual property of complexing alkali and alkaline earth metal salts was made at the Xth International Conference on Coordination Chemistry in Nikko, Japan, on September 15, 1967. Subsequently, the first short communication (ref. 2) followed by the detailed report consists of 20 pages (ref. 3) were published in the Journal of the American Chemical Society before the end of 1967. Furthermore, Pedersen reported the discovery of a series complex crystals and novel crown compounds, including macrocyclic polyether sulphides containing sulphur atoms in the ring structure, by 1971 (refs. 4–7).

Pedersen named these macrocyclic polyethers with specific characteristics "crown ethers", because of their chemical structure as well as the fact that the shape of the complexes resembled a crown on a metal ion. A series of his reports, which covered general synthetic methods and the fundamental characteristics of crown ethers, had a great impact on many chemists throughout the world. Since then, various crown ethers and analogous compounds have been synthesized and many investigations on the analyses of the

structure of the complexes, their specific characteristics as well as applications have been developed rapidly (ref. 8).

Since the publication of Pedersen's reports, a variety of macrocyclic compounds have been synthesized including some with N, S, P, and Se atoms as the electron donors. The review (ref. 9) published in 1974 listed 221 kinds of macrocyclic compounds and the book (ref. 10) on syntheses of macrocyclic compounds published in 1982 contained about 2300 kinds.

1.1.2 Classification of Crown Ethers and Analogous Compounds

Crown compounds have not yet been defined strictly. They are generally described as "macrocyclic compounds with hetero atoms such as O, N, S, P, or Se as the donor atoms in their ring structures and having the property of incorporating cations into their cavities". Crown compounds in a broad sense are sometimes termed "multidentate macrocyclic compounds" or "macroheterocycles".

The macrocyclic polyethers bearing oxygen atoms as the donor atoms are termed "crown ethers". Cyclic amino ethers in which N (NH, NR) replaces some of O donor atoms of a crown ether are known as "azacrown ethers", and cyclic polyether sulphides in which sulphur replaces some of the O donors are called "thiacrown ethers". Macrocyclic compounds with three kinds of donor atoms, O, N, and S, are called "azathiacrown ethers". Macrocyclic polyamines bearing only N atoms as donors are termed "azacrowns" and macrocyclic polysulphides bearing only S atoms as donors are labeled "thiacrowns".

Multicyclic compounds consisting of two or more rings may also be crown compounds. The cage-type bicyclic crown compounds, whose two bridgeheads consist of two N atoms, synthesized and named "cryptands" by Lehn et al. (ref. 11) are the typical example. For a series of polyether compounds, the following classification based on their topology has been proposed by Vögtle (ref. 12): "podand" for open chain polyethers, "coronand" for cyclic polyethers, and "cryptand" for bicyclic and more cyclic polyethers combined by two bridgehead atoms. The name of "crown ethers" still remains for the coronands having only oxygen atoms as the electron donor atoms. According to the above classification, their complexes are named generally by using a suffix, "ate", as "podate", "coronate" and "cryptate" respectively.

1.1.3 Fundamental Characteristics of Crown Ethers

The most striking characteristics of crown ethers is their selective complexation ability. They bind the cationic portion of alkali and alkaline earth metal salts, ammonium salts and ionic or polar organic compounds, such as thiourea, semicarbazide, diazonium salt and acetonitrile (guest), into the

cavity of the crown ring (host). The complex of crown ether with a guest is formed by ion-dipole interaction between the cation and the negatively charged donor atoms in the ring structure of the cyclic polyether.

The selectivity of crown ethers for a given cation is dependent principally on the following points as stated by Pedersen (ref. 3):

- 1) Relative size of the cavity of the crown ring and the diameter of the cation.
- 2) Number of donor atoms in the crown ring and the topological effect.
- 3) The relationship between the "hardness" of the cation and that of the donor atom.
- 4) Charge number of the cation.

1.1.4 A New Field of Chemistry

The formation of molecular complexes caused by the combination of several kinds of the molecular interaction between a host and a guest molecule is known in biological reaction as "molecular recognition". A typical example of such a phenomenon is the initial stage of an enzymatic reaction.

Molecular recognition has been regarded as one of the most fundamental differences between a biological reaction and an artificial chemical reaction. The discovery of crown ethers and their characteristics, particularly the selective binding of a cation to form the complex, can be seen as the moment when the concept of molecular recognition was introduced into the field of non-biological, artificial chemical reactions. In the early 1960s, nearly at the same time as the discovery of crown ethers, the possibility of molecular recognition followed by acceleration of a particular reaction was suggested in studies on the inclusion complexes of cyclodextrins, which are naturally occurring cyclic oligosaccharides consisting of 6~8 molecules of D-glucose (refs. 13, 14).

These exciting research results in that field stimulated the interest of many chemists. There was a burst of development accompanied by the elucidation of many biological reactions.

The development of research on artificially designed host molecules having an ability of molecular recognition led to the birth of "host-guest chemistry" and "biomimetic chemistry" followed by "supramolecular chemistry" which introduced the new field based on a new concept to chemistry (refs. 8f, 15-20).

Cram and his school synthesized a series of chiral crown ethers bearing binaphthyl groups. He developed the systematic research, named "host-guest chemistry", on molecular recognition including optical resolution, optically selective transport and asymmetric reactions by use of the chiral crown ethers

as the host (refs. 21, 22). According to Cram, "host-guest chemistry" is defined as "the field of chemistry consisting of syntheses and applications of highly structural molecular complexes formed by recognition and incorporation of the matched guest by the host molecule having a designed cavity".

In recent years, remarkable progress has taken place in the biological sciences, including biology, biochemistry and biophysics. The fruits of chemical investigations contribute to the biological sciences while the results of biological research boomerang back on chemistry. Thus, the results of the advanced biological science have had a great impact on chemistry and have led to a new field of chemical investigation called "biomimetic chemistry". The term "biomimetic" means to mimic the biological processes. When the term was proposed by Breslow (ref. 23), the image of biomimetic chemistry was limited only to reproduce the excellent stereospecificity of an enzymatic reaction in an artificial chemical reaction. However, the scope of biomimetic chemistry has been expanded to the simulation of vital functions by chemical means at the molecular level. Various areas have been developed rapidly, such as enzyme-mimic reactions, artificial receptors, artificial membranes and vesicles, nitrogen fixation and so on.

Recently, Lehn (refs. 24-26) introduced the term "supramolecular chemistry" as the extension of host-guest chemistry. According to Lehn, supramolecular chemistry is "the structures and functions of supramolecules that result from binding substrates to molecular receptors" or "the new field of chemistry concerning the higher-order molecular aggregates which are formed by the association resulting from the molecular interaction between two or more molecules, that is, chemistry which is beyond the concept of the molecule" in other words. At the present time, the term supramolecular chemistry has not yet been defined strictly. However, it is recognized generally as chemistry relating to the molecular aggregates formed not by covalent bonds but by the combination of weak molecular interactions.

It is well known that the complementarity of enzymes (E) and the substrate (S) is very important in an enzymatic reaction as it is compared to the "lock and key" relation. An enzymatic reaction is represented basically by the equation (1.1). The initial stage consists of the recognition of the



substrate (S) by the enzyme (E) followed by the selective binding of the substrate to form the highly structured enzyme-substrate complex (ES). As a result, only the desired reaction is accelerated remarkably under the

condition in which the mutual relations of the position of the reaction sites as well as the topological relation between the enzyme and the substrate are determined strictly. Thus, only the desired product (P) is formed in the next stage.

For these reasons, the formation process of ES owing to the host-guest interaction is the key-point in the appearance of enzymatic function. The specific effect is exerted by a combination of the following:

- 1) Incorporation and holding of the substrate in the enzyme owing to the combination of interactions such as ionic bond, hydrogen bond, charge transfer, coordinative interaction, hydrophobic interaction and others as schematically depicted in Fig. 1.1.
- 2) Access of the functional group in the substrate to the catalytic functional group in the enzyme.
- 3) The conformation and the overlap of the orbitals which produce the most desirable direction of the orbitals for the reaction of the substrate and the catalytic functional group in the enzyme.
- 4) The steric and electronic strain in E and/or S caused by the formation of the ES complex.

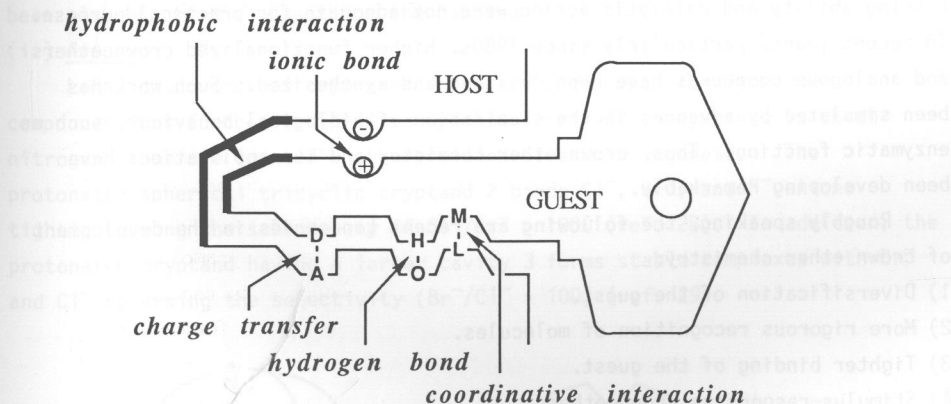


Fig. 1.1 Interactions in the "Lock and Key" Relation (ref. 27)

Therefore, it is not too much exaggeration to say that the specific function of an enzyme, such as the selectivity, the control ability and the acceleration of the desired reaction might be determined by the process in which the ES complex is formed owing to the host-guest interaction. Other than enzymes, many examples of molecular recognition due to host-guest interactions are known in living processes. Antigen-antibody reactions, immune reactions, drugs, and receptors ions and natural ionophores in ion transport, odorous substances and receptors are typical examples.