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A Review on Some Biologically Active Natural Macrocycles

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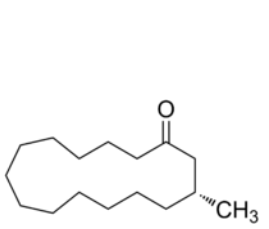
ABSTRACT

Natural product macrocycles and their synthetic derivatives have long been clinically useful and attention is now being focused on the wider use of macrocyclic scaffolds in medicinal chemistry in the search for new drugs for increasingly challenging targets.

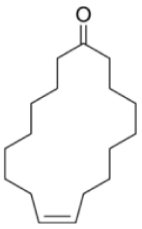
Keywords: Macrocycle, Muscone, Civetone, Macromolecule

INTRODUCTION

A macrocycle is, as defined by IUPAC, "a cyclic macromolecule or a macro-molecular cyclic portion of a molecule"[1]. The chemistry of macrocycles dates back to 1926 when Ruzicka[2] established the large ring structures for the musk ketones, muscone and civetone, prized as perfume components. Muscone was isolated by Walbaum in 1906 from natural musk[3] and civetone in 1912 from civet [civet cat musk][4]. At that time the structures of these compounds were established from their synthesis[2].

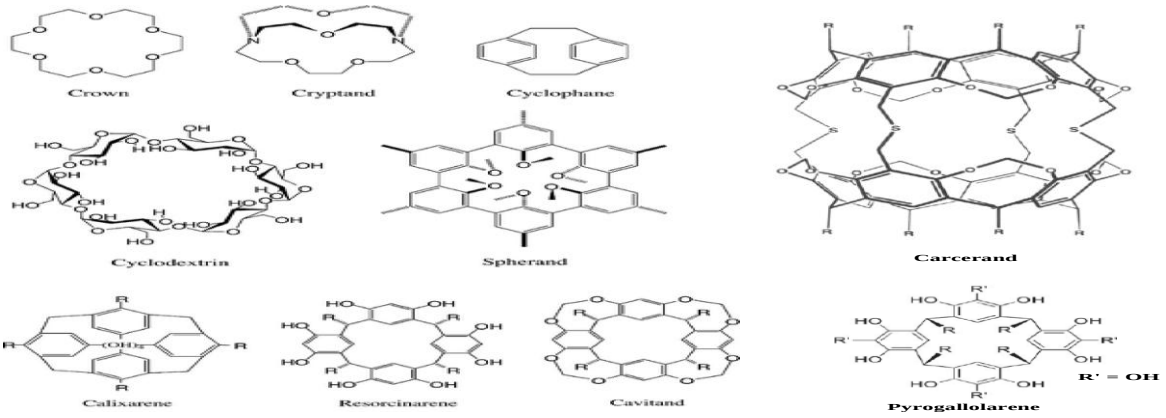


Muscone



Civetone

Macrocyclic compounds may be a single, continuous thread of atoms, as in cyclotetradecane [$(CH_2)_{14}$], or they may incorporate more than one strand or other ring systems (subcyclic units) within the macrocycle or macroring. In addition, macrocycles may be composed of aromatic rings that confer considerable rigidity upon the cyclic system. These aromatic rings may be joined together or coupled by spacer units consisting of one or more carbon atoms. Some compounds which are considered as macrocycles include crown ethers, cryptands, spherands, carcerands, cyclodextrins, cyclophanes, calixarenes, resorcinarenes, pyrogallolarenes, and hybrids of all of them[5].



In the synthesis of macrocyclic ligands, different macrocyclic compounds can be generated from the same ratio of starting materials. For example, starting from a 1:2 ratio of diamine and dihalide (or ditosylate), it is possible to obtain macrocyclic ligands that form with 4-20 or more new bonds[6]. Formation of a particular structure depends on reaction conditions such as template effects, temperature, concentration of starting materials, and other unknown factors.

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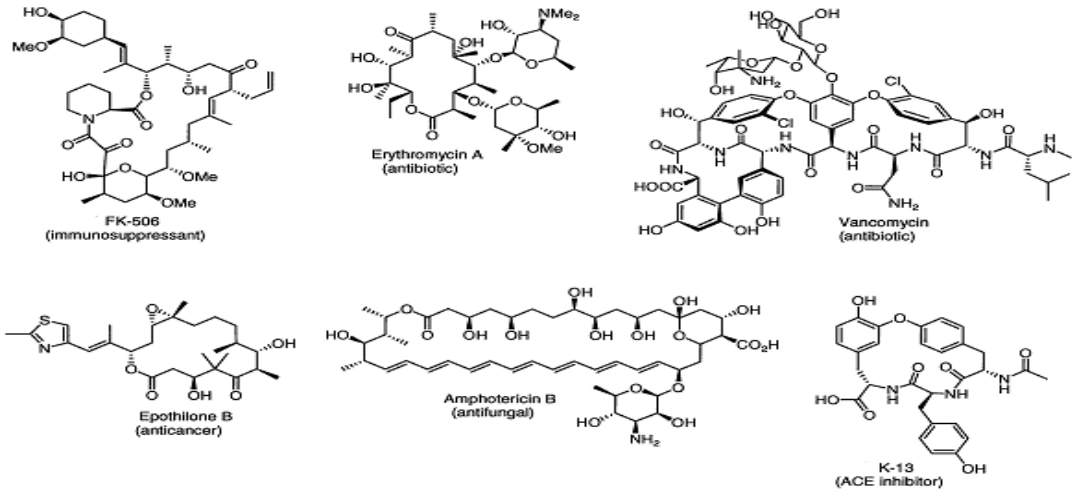


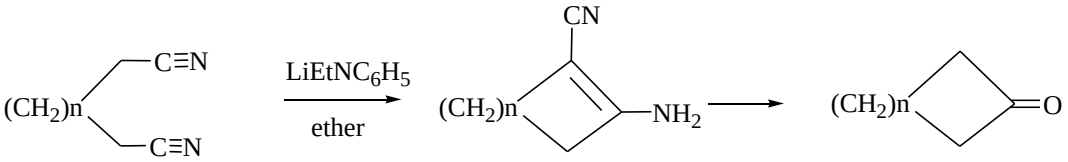
SOME BIOLOGICALLY ACTIVE NATURAL MACROCYCLES

Macrocycles constitute the archetypical components of supramolecular chemistry. Many fundamental aspects of molecular recognition and supramolecular science have been and are being revealed using macrocycles. From the start, both naturally occurring (e.g. cyclodextrins, porphyrins) as well as synthetic macrocycles (such as crown ethers, calixarenes, phthalocyanines) have been employed. Thermodynamic phenomena such as the chelate effect, multivalency and cooperativity, have been and still are topics of thorough investigation.

Macrocycles are applied in ion and molecular sensing, metal ion protection in biomedical imaging, treatment of heavy metal waste streams, drug delivery and increase of drug efficacy, and many, many others. Modern topics of investigation encompass dynamic covalent chemistry with macrocycles to provide evolutionary amplification of optimal receptors, the design of vehicles for drug and gene delivery, and receptor-functionalized platforms as models for cell membrane interactions. These examples suggest that macrocylic chemistry is still and will remain a vibrant area of chemistry for the foreseeable future.

Synthetic polymer chemistry was developed before synthetic macrocyclic chemistry. Organic polymers cannot be synthesized without having macrocyclic compounds as side products and vice versa. The preferential formation of only one product often depends on the conditions of the reaction. During polymerization reactions, thousands of new bonds are formed while cyclization reactions result from only a few formed bonds [7,8].

The first synthesis of macrocyclic compounds (ketones) was achieved by Ruzicka and his students, Stoll, Schinz, and Brugger, in rather low yield through pyrolysis of heavy metal salts of long-chain dicarboxylic acids[2,9], a method previously applied by Zelinsky[10] and by Willstätter[11] to the synthesis of smaller ring systems. Subsequently, Karl Ziegler, applying Ruggli's observation[12] that intramolecular ring closure is favored under conditions of high dilution, used the Thorpe reaction[13] to synthesize muscone and other macrocyclic ketones in high yield[14]. The yields of even-numbered ring ketones were found to be especially high.



The high dilution technique was extended by Hunsdiecker in the synthesis of both muscone and civetone, utilizing *ω*-halo-*β*-keto esters in another carbaionic cyclization reaction[15]. This technique is often used as the most versatile procedure considering the efficiency of the others[16]. On the other hand, Sharghi and others[17-20] have reported the synthesis of macrocycles without the use of high dilution techniques.

Since Pedersen's discovery in 1967 of crown ethers and their ability to bind strongly with metal ions[21,22], the study of crown ethers has grown at an incredible rate. Syntheses of many different types of crown ethers (e.g., crown ether diesters, azacrown ethers, thiacrown ethers, and chiral crown ethers) have been documented in the literature and the binding properties of crown ethers, such as binding strength and selectivity toward a wide range of metal ions, nonmetal ions, and neutral molecules, have been investigated[23]. The incorporation of oxygen, nitrogen, and sulfur donor atoms in these macrocycles also markedly affects the complexing properties because of the hard (O, N) and soft (S) character of the donor atoms and the exodentate tendency of the sulfide linkages[24]. Other changes involve the insertion of aromatic

and/or heterocyclic ring systems into the macrocycles[25]; heterocyclic groups provide rigidity and are able, in some cases, to form complexes through their soft donor atoms[26]. The wide interest in the construction of synthetic macrocyclic compounds containing five and six-membered heterocyclic rings as subunits has led to the preparation of a range of such compounds, which have been shown to possess very interesting properties in a variety of fields[27]. These macrocycles were found to exhibit interesting host–guest complexation characteristics[28] and have shown antibacterial activities,[29] in which the biological activity is highly dependent upon the side-chain substitution pattern.

CONCLUSION:

The brief review presented above shows the importance of some types of biologically active natural macrocycles.

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