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Advancements in Pharmaceutical Science: Synthesis and Application of Molecular Cages Integrating N-Heterocyclic Carbenes for Enhanced Stability and Functionality

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Abstract: ***The synthesis of molecular cages to encapsulate chemical entities, such as metal ions, anions, or small molecules, has emerged as a significant area of research in supramolecular chemistry. This article explores the design and construction of various macrocyclic ligands, particularly crown ethers, cryptands, and multi-branched macrocycles, highlighting their unique structural properties and coordination chemistry with transition metals and alkali ions. We delve into the role of N-Heterocyclic Carbenes (NHCs) in enhancing the stability and functionality of these macrocyclic systems. The integration of NHCs into macrocyclic architectures presents opportunities for novel applications in catalysis, photoluminescence, and biomedical fields. By examining the advancements in macrocycle-NHC chemistry, this article underscores the potential of these systems in developing innovative materials with tailored properties for diverse applications.***

Keywords: Molecular Cages; Supramolecular Chemistry; Macrocyclic Ligands; N-Heterocyclic Carbenes (NHCs); Crown Ethers; Cryptands; Coordination Chemistry; Photoluminescence.

I. INTRODUCTION

The synthesis of molecular cages that can encapsulate chemical entities, such as metal ions, anions, or small molecules, is a highly regarded endeavor in contemporary chemistry [1]. These molecular structures, often referred to as "cages," are defined as arrangements of atoms or molecules that create a space capable of housing another atom or ion [2]. The unique properties of encapsulated compounds can significantly differ from their non-encapsulated counterparts, offering distinct advantages [3].

The creativity and expertise of synthetic chemists in designing polycyclic cage systems enable the inclusion of a diverse range of guest molecules while also evoking aesthetic appreciation. This chapter aims to showcase the significance of residing within a molecular cage and its implications [4].

Research in macrocyclic ligands has gained momentum, particularly due to their intriguing structures and geometries, Which often include heteroatoms that impart interesting conformational and chemical characteristics. Coordination chemistry, rooted in the interactions with transition metals, often involves nitrogen atoms from amines as key σ donors, with ammonia serving as a model ligand. Conversely, for S-block metal ions, SP3 oxygen is the primary donor, with water acting as a typical ligand [5].

While alkali and alkaline earth metal salts dissolve in aqueous environments, forming "aquacomplexes" that are not stable enough for isolation, crystallization leads to salts where metal ions interact directly with anions. Insights from transition metal coordination chemistry have revealed strategies to enhance complex stability, such as utilizing multi-dentate ligands. However, the inherent instability of S-block metal complexes with SP3 oxygen-donating ligands often limits their effectiveness [6].

In contrast, macrocyclic ligands provide geometric advantages that stabilize the oxidation states of central metal ions. These ligands contain multiple electron-donating atoms, facilitating strong coordination with various metal cations. This chapter will first explore different families of macrocycles, followed by an introduction to N-Heterocyclic Carbenes (NHCs) and the synergistic benefits of combining these two families to enhance the properties of metal complexes within molecular cages [7].

A. Different Families of Macrocycles

i. Crown Ethers

Macrocycle chemistry has largely developed within the field of supramolecular chemistry, which emphasizes non-covalent interactions and the associated weak molecular forces, including hydrogen bonds, Van der Waals forces, and electrostatic interactions. Although the principles of intermolecular interactions were well established in biological contexts during the 1960s, there were no known synthesized macrocyclic supramolecular systems at that time. A pivotal breakthrough occurred in 1967 through the pioneering efforts of C. J. Pedersen, an industrial chemist at DuPont. In his attempt to synthesize a multidentate ligand for copper and vanadium, specifically bis[2-(o-hydroxy-phenoxy)-ethyl]ether, Pedersen inadvertently created the first recognized crown ether Diagram1. This discovery marked the beginning of synthetic macrocyclicsupramolecular chemistry [7].

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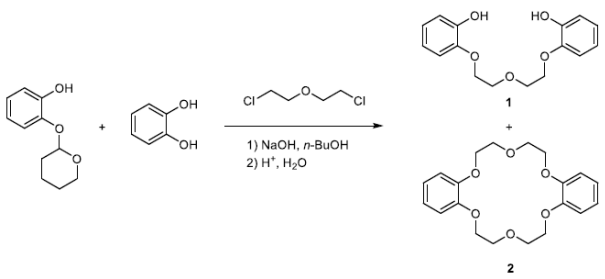
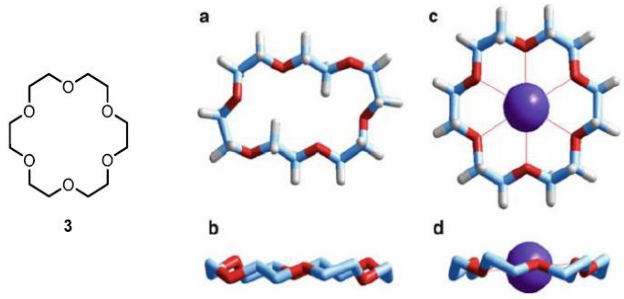


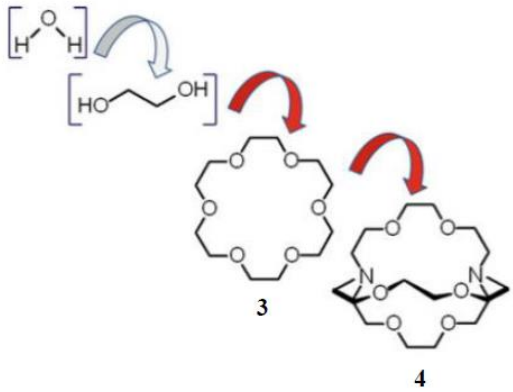
[Diagram 1: Synthesis of the First Aether-Corona 2 Described by Pedersen]

Figure 1 illustrates the structure of the cyclic polyether 18-crown-6, which consists of 18 atoms, including six oxygen atoms. The term "crown" is derived from the pleated arrangement of the sp^3 hybridized carbon and oxygen atoms, as depicted in panels (c) and (d) of Figure 1. When the K^+ ion complexes with the 18-crown-6, it induces a symmetrical reorganization of the molecule, allowing for coordination through six equivalent bonds to the ether oxygen atoms. This configuration is highly suitable for K^+, which fits seamlessly into the crown structure [8].



[Fig.1: Structures of the 18-Crown-6, 3 (a, b) free Cyclic Polyether and its Complex K+ (c, d). The Pleated Arrangement of sp3 Hybridized Carbon and Oxygen Atoms of the Polyether Explains the Trivial Name "Crown"]

The investigation of the interactions in solution between various cavity-sized cyclic polyethers and a uniform class of spherical cations, such as alkali metals, offers valuable insights into the geometric effects on the stability and thermodynamics of the resulting complexes, while also introducing the concept of size selectivity. The optimal development of ligands for an s-block cation that incorporates sp^3 oxygen-donating atoms is illustrated in Figure 2.



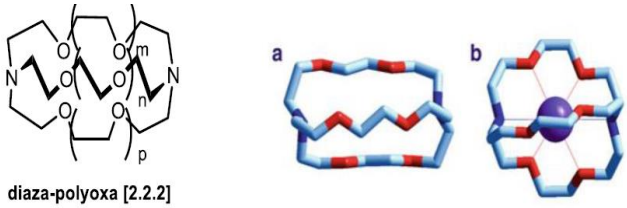
[Fig.2: Evolution of Ligands Containing sp3 Oxygen-Donating Atoms. Only Crown Ethers (e.g. 3, 18-Crown-6) and Cryptands (e.g. 4, 2.2.2 crypt) form Stable Complexes with the Metal Ions of the S-Block]

As depicted in Figure 2, the advancement of ligands has led to the emergence of a new family of macrobicycles known as cryptands. These molecules are formed from an assembly of cyclic or polycyclic ligands that incorporate at least three binding sites for a specific type of cation [9].

II. MACROBICYCLES

A. Has. History and Discovery of the First Cryptands

The synthesis of macrobicyclic compounds containing heteroatoms can exhibit complexation properties similar to those of macrocyclic ligands, while potentially introducing novel characteristics. In 1969, Jean-Marie Lehn, a young professor at Louis Pasteur University in Strasbourg, along with his students Bernard Dietrich and Jean-Pierre Sauvage, reported the synthesis of a family of three-dimensional analogs of crown ethers, which were termed "cryptands"—a name inspired by the secret chambers of a cathedral where valuable artifacts are stored. Lehn and his team were pioneers in the synthesis of macrobicyclic molecules, specifically creating diaza-polyoxa cryptands [2.2.2] that possess a cavity suited for alkaline cations such as sodium and potassium, as shown in Figure 3.

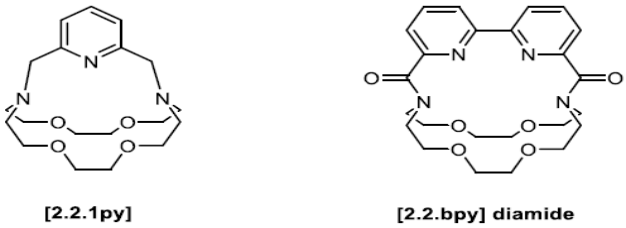


diaza-polyoxa [2.2.2]

i. **m = n = p = 1 ;**
ii. **m = n = 1 ; p = 2 ;**
iii. **m = 1 ; n = p =2 ;**
iv. **m = n = p = 2 ;**

[Fig.3: Structure of Diaza-Polyoxa Cryptand Derivatives [2.2.2] at Different Bond Lengths i, ii, iii, iv. Structure of Diaza-Polyoxa [2.2.2] i. 5(a) and its Potassium(b)6 Complex, as Obtained from x-ray Diffraction Studies on Crystalline Compounds. The Hydrogen Atoms Have Been Omitted for Clarity]

Figure 3a illustrates the structure of diaza-polyoxa [2.2.2] in its crystalline form, featuring an ellipsoidal cavity. When the K^+ ion is included (Figure 3b), the cryptand undergoes a rearrangement, forming a spherical structure around the metal ion. In this cryptate, the metal engages in coordination interactions with six oxygen atoms and two nitrogen atoms. Research continued with the development of amino analogues, and in 1976, Vötgl introduced a heterocyclic motif, such as pyridine, leading to the creation of [2.2.1py] [10]. Shortly thereafter, he described the synthesis of a macrobicycle that incorporates a bipyridine diamide motif, replacing the pyridine motif, as shown in Figure 4.

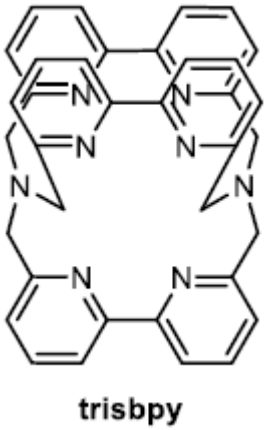


[Fig.4: Structures of the [2.2.1py] and [2.2.bpy] Diamide Macrobicycles]

In the 1990s, research continued in this area, leading to the development of a series of macrobicycles that incorporate bipyridine, phenanthroline, bithiazole, biimidazole, and biisoquinoline. The construction of monotopic macrobisheterocyclic ligands, which contain heterocyclic chelating subunits, is significantly enhanced by the presence of donor heteroatoms such as nitrogen. These subunits are coupled with a π-delocalized electronic system, allowing for a combination of strong complexation properties inherent to heterocycles and the photophysical characteristics that arise from these complexes [11].

B. 2,2'-Bipyridine-Based Cryptand Family

The emergence of cryptands has significantly advanced the field of supramolecular chemistry. Investigations into the complexation properties of cryptands with certain metals, such as the rare earth elements, have demonstrated fluorescence emission with high lifetimes. However, the absorption bands of their ions are typically weak, and the direct excitation of their emissive states is minimal. To enhance the quantum yield of fluorescence, a metal can be complexed with a chromophore that is susceptible to radiation excitation, allowing for energy transfer to the emissive state of the ion. Nitrogenous heterocycles, particularly 2,2'-bipyridine, are commonly employed chromophores in this context. Among this family, the most recognized ligand is the cryptand trisbipyridine (trisbpy), originally described by J.M. Lehn and later developed by Cis Bio International. Due to their three-dimensional structure, complexes of Ln(III) lanthanide ions typically exhibit very high stability constants in aqueous solutions and excellent kinetic stability [12].



[Fig.5: Structure of the Cryptand Trisbipyridine]

In 2019, a study was conducted on the synthesis of luminescent cryptates utilizing trisbispyridine ligands combined with lanthanide ions, specifically Europium(III) and Neodymium(III). The research incorporated 2,2'-bipyridine and 2,2'-bipyridine-N,N'-dioxide units, which have been previously documented in the literature (see Figure 6).

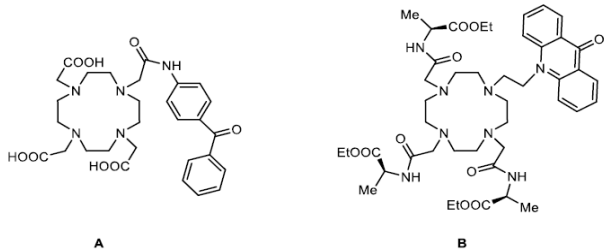
The 2-Ln and 3-Ln species are especially valuable due to their common donor atom types, which include pyridine-N, pyridine-N-oxide, and tertiary amine-N. The primary distinction between them lies in the ratios of these three donor atom types [13].

[Fig.6: Cryptate Structures Developed by Trautnitz et al]

The authors demonstrated the impact of these factors on the radiative lifetimes of Europium(III) complexes and, for the first time, Neodymium(III) complexes. These factors were found to shorten the lifetimes. They identified 2,2'-bipyridine-N,N'-dioxide as a critical component in the synthesis and design of lanthanide complexes with reduced radiative lifetimes, which are advantageous for lanthanide coordination chemistry [14].

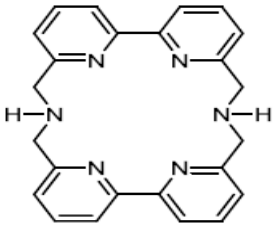
C. "Multi-Branched" Macrocycles - Hemicages

In addition to cryptand chemistry, "multi-branched" macrocycles, also referred to as hemicage-type macrocycles, play an important role. The incorporation of side arms composed of monodentate or polydentate units into these macrocycles facilitates the development of receptors that exhibit both high stability and structural flexibility. The rigid macrocyclic cavity provides overall stability, while the side arms contribute to a three-dimensional architecture. One of the most commonly used macrocyclic structures is cyclene (tetraaza-1,4,7,10-cyclododecane), which features four lateral arms that possess complexing functionalities, such as carboxylic acid, phosphoric acid, and amide groups; one of these arms also contains a chromophore. Some complexes formed with Ln(III) ions demonstrate significant stability in aqueous environments, exhibiting both thermodynamic and kinetic stability. Examples of ligands derived from cyclene are illustrated in Figure 7 (molecules A22 and B23) [15].



[Fig.7: Structures of Cyclene A and B Derivatives]

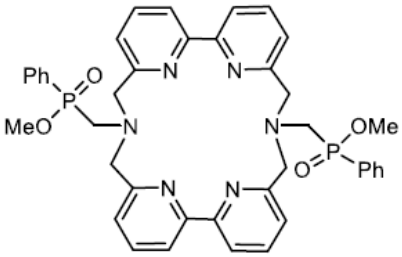
There are additional "multibranched" macrocyclic structures of a bi-heterocyclic nature that closely resemble the cryptand structures previously described. The objective is to attach two bipyridine antennas to a photosensitive macrocycle, such as the [bpy.bpy]14 cage depicted in Figure 8.



[bpy.bpy]

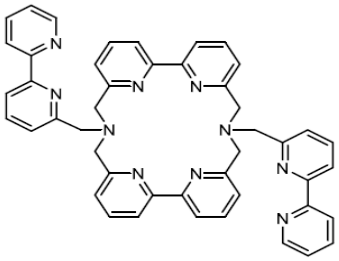
[Fig.8: Structure of the [BPY.BPY]]

The synthesis of a macrocycle featuring two bipyridine units, each functionalized with phosphonate ester groups attached to the two "bridgehead" nitrogen atoms, is described (Figure 9) [15].



[Fig.9: Hemicing Macrocycle Synthesized by Ziessel]

This compound, derived from a mixture of diastereoisomers, was synthesized by reacting the macrocycle [bpy.bpy] with paraformaldehyde and dimethylphenylphosphonite. Its complexes with europium and terbium exhibit high luminescence intensity, despite a low absorption coefficient [16]. The same author also details the synthesis of a macrocycle containing four bi-heterocyclic units (Figure 10). This method involves the preparation of polybipyridine ligands, where two equivalents of bromoethylbipyridine react with one equivalent of [bpy.bpy] in the presence of Na2CO3.



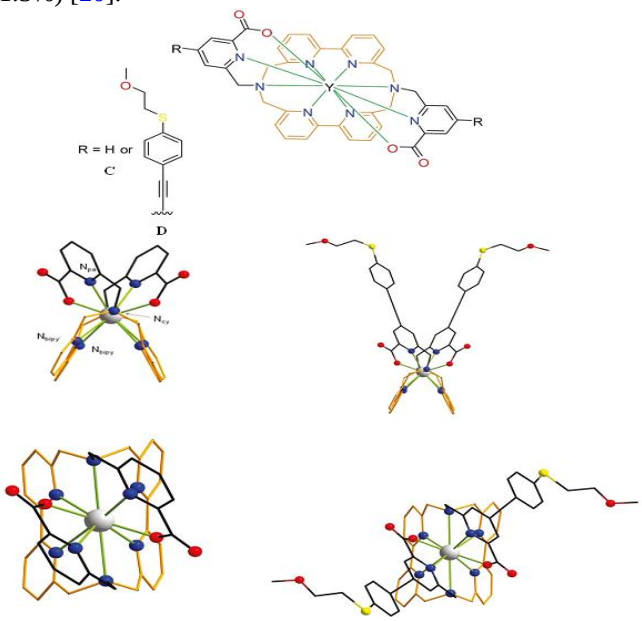
[Fig.10: Structure of the Molecule Synthesized by Ziessel et al]

The significance of this type of molecule lies in its coordination chemistry, which has demonstrated luminescent properties, particularly in hemicage structures linked to two bis-bipyridine arms (Figure 10). These structures exhibit higher extinction coefficients compared to the trisbipyridine cryptate (Figure 6), attributed to the presence of an additional bipyridine unit. Subsequent studies with hemicage ligands based on the [bpy.bpy] molecule have explored their photoluminescence for biomedical applications, including their potential as theranostic agents [17].

For instance, a recent investigation focused on modifying these structures by incorporating other heterocycles, such as pyridines. Two complexes of Europium(III) featuring bis-bipyridine azamacrocyclic ligands based on [bpy.bpy], equipped with flexible arms and with or without π-donor conjugate groups, were synthesized (Figure 11). These new Europium(III) chelating systems were designed to achieve high thermodynamic stability in aqueous environments while exhibiting favorable two-photon absorption (TPA) and luminescence properties [18].

TPA involves the simultaneous absorption of two photons of identical frequencies to excite a molecule to a specific higher energy electronic state. This process can result in excited fluorescence from the absorption of two photons, leading to numerous applications in medical imaging and photochemotherapy. The study outlines promising strategies for designing new bioprobes—biomolecular probes capable of measuring the presence or concentration of biological molecules, structures, or microorganisms by translating biochemical interactions at the probe's surface into quantifiable physical signals [19].

These bioprobes were developed for the treatment of infectious diseases. It was found that the non-functionalized ligand C with L1 (R = H) resulted in a highly stable Europium complex in water, exhibiting strong luminescence properties (Φf = 13%), but demonstrating mediocre two-photon absorption. In contrast, the Europium complex with the ligand featuring an extended conjugate antenna D with L2 (R = π-donor group) displayed a high two-photon absorption cross-section (45 GM; 1 GM = 10^-50 cm^4·s·photons^-1) at 720 nm, although it was less luminescent in water (Φf = 1.3%) [20].

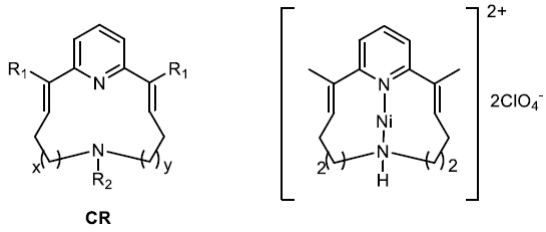


[Fig.11: Structures of Eu(III) Complexes with Ligands L1 with R = H and L2 with R =π-Conjugate Donor Group. DFT-Optimized Structures of [YL1]+(left) and [YL2']+, with the Axis of Symmetry C2 Vertical (top) or Perpendicular to the Figure (Bottom). The ion Eu has been Replaced by the Diamagnetic ion Y (Ytrium) in the Figure for the Computing Facilities. The Nitrogen, Oxygen, and Sulfur Atoms are Drawn in Blue, red, and Yellow Respectively]

III. CYCLOPHANES

Among macrocycles, the cyclophane family has been extensively developed. These compounds are hydrocarbons comprising aromatic units, typically benzene, and aliphatic chains that create bridges between non-adjacent positions of the aromatic ring. More complex derivatives feature multiple aromatic units and bridges, resulting in cage-like structures. Cyclophanes are widely utilized in organic synthesis due to their ability to adopt unusual conformations, which arise from the structural stresses they experience, resulting in a high degree of structural rigidity [21].

Early research in the 1960s led to the development of the first derivatives of a novel CR macrocyclic ligand and its Nickel(II) complexes (Figure 12).



CR

Abréviation	X	y	R1	R2
CR	3	3	CH3	H
N-Me-CR	3	3	CH3	CH3
***des*-diMe-CR**	3	3	H	H

[Fig.12: Different Macrocyclic Derivatives of the CR Ligand and Example of a CR Complex Nickel (II) Developed by Busch]

They demonstrated that the formation of macrocyclic complexes involving CRs and related ligands:

i. requires a minimum cycle size, represented in Figure 12 as x = y = 3;

ii. depends on strong metal complexation at the reaction pH;

iii. proceeds through an intermediate ternary complex [22].

In recent years, cyclophane chemistry has gained attention due to the potential applications of functionalized cyclophanes in supramolecular chemistry, molecular recognition, electronics, and as molecular machines, drug carriers, or catalysts in organic synthesis [23].

Research on cyclophanes and macrocycles functionalized with N-heterocycles has progressed significantly. This has led to various properties and applications, which will be explored further. Indeed, the chemistry of N-heterocyclic carbenes (NHCs) is rapidly evolving [24]. Initially recognized as crucial ancillary ligands in organometallic chemistry, numerous methods for synthesizing metal-NHC complexes are now well-established. The diverse properties associated with these ligands make them excellent candidates for coordination chemistry with transition metals [25].

Let's start by defining N-Heterocyclic carbenes by answering the questions

Following:

How were they discovered? What are their properties and what do they bring to the bond?

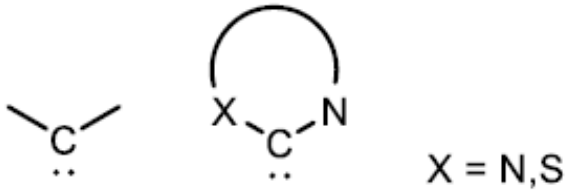
Metal-Ligand?

We will then discuss some interesting examples of macrocycles of the macrocycle type-NHCs [26].

IV. N-HETEROCYCLIC CARBENES (NHCS)

In recent years, there has been significant interest in N-heterocyclic carbenes (NHCs). This enthusiasm is driven by the demand for developing systems in organometallic chemistry, photoluminescence, biomedical applications, and catalysis. NHCs differ from many tetravalent carbon compounds, where all four valence electrons of carbon are involved in bonding. In contrast, "divalent" species have only two electrons engaged in covalent bonds, with two unbound electrons remaining at the carbon atom. Examples of these divalent carbon derivatives include carbon monoxide, isocyanides, and carbenes [25].

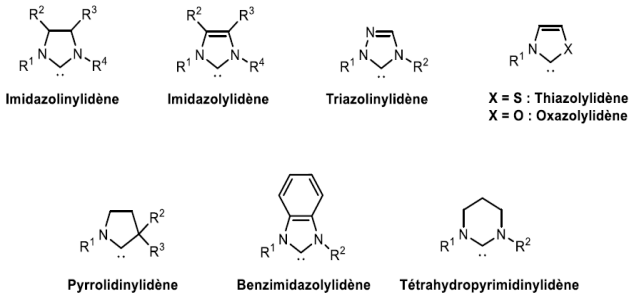
NHCs are notably stable compounds that consist of a carbon atom with six valence electrons in a divalent state, along with at least one nitrogen atom (Figure 13).



[Fig.13: General Structures of a Carbene (left) and an NHC (Right)]

A. Different Families of NHCs

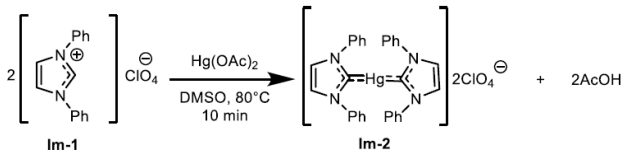
N-heterocyclic carbenes (NHCs) can be classified into seven primary families based on the heteroatoms and unsaturations present, as illustrated in Figure 14. These compounds are heterocycles that typically contain two or three heteroatoms. Generally, imidazolinylidenes and imidazolylidenes are the most frequently employed as ligands in organometallic catalysis and coordination/complexation chemistry with various transition metals, whereas triazolinylidenes and thiazolinylidenes are primarily utilized in organic catalysis [27].



[Fig.14: The Main Families of NHC]

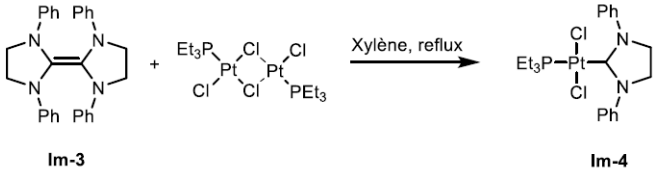
B. History and Discovery

In a historical context, Wanzlick proposed the synthesis of an imidazolidin-2-ylidene through the α-elimination of chloroform from an imidazoline derivative; however, it could only be isolated as the enetramine dimer. In 1968, were the first to synthesize N-heterocycles [28]. They achieved this by reacting the imidazolium salt Im-1 with mercury acetate, resulting in the formation of the Im-2 complex, where the NHC is coordinated to Hg (Diagram 2).



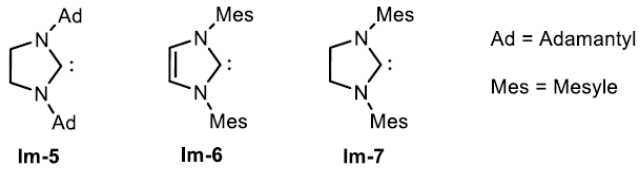
[Diagram 2: Reaction Diagram of the Development of the first N-Heterocyclic Carbene]

Stable complexes have also been observed during this period, primarily focusing on the synthesis of platinum complexes with NHC ligands. The first trans-PtCl2 complex, [C(NPhCH2)2]PEt3 (Im-4), was successfully synthesized from the enetetramine Im-3 (Diagram 3). Following this, a series of complexes with various metals were subsequently synthesized [29].



[Diagram 3: Reaction Diagram of the first Platinum Complex from N- Carbene Heterocyclic]

Three years later, Arduengo and colleagues successfully isolated and characterized 1,3-bis-(adamantyl)-imidazol-2-ylidene (Im-5), marking the first example of an N-heterocyclic carbene (NHC), followed by its analogues Im-6 and Im-7 (Figure 15). Since the isolation of this NHC, the study of this new class has significantly progressed. Intensive research on these compounds and their metal complexes has continued for over 25 years [30].



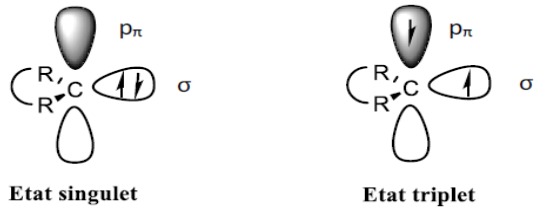
[Fig.15: Structure of the First NHCs Isolated by Arduengo]

Since then, a variety of carbenic diaminoheterocyclic derivatives, ranging from small to complex structures, have been synthesized. As research advanced, carbenes garnered increasing interest among chemists. This group of ligands has become significant and diverse in their ability to donate carbon, attracting considerable attention from researchers. Consequently, this interest has enhanced the understanding of NHC properties through observations made in various studies. Generally, all ligands are characterized by two key parameters—electronic properties and sterics—which profoundly influence their behavior and reactivity; NHCs are no exception [31].

C. Properties of free NHCs

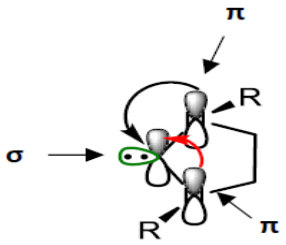
i. has. Electronic Properties

From a general perspective, it is essential to understand the electronic behavior of N-heterocyclic carbenes (NHCs). As previously mentioned, NHCs are neutral species featuring a divalent carbon atom with six valence electrons. The two non-bonding electrons of the carbene can be distributed in two distinct ways [32]. In the singlet state, the electrons are paired within the same orbital, while in the triplet state, they occupy two different orbitals (Figure 16).



[Fig.16: Electronic Configurations of a Carbene in the Singlet and Triplet States]

N-heterocyclic carbenes feature a σ orbital in the plane of the heterocycle and an empty pπ orbital perpendicular to this plane. They are electronically stabilized through the donation of filled orbitals from the two adjacent nitrogen atoms into the empty pπ orbital of the carbene carbon (Figure 17). This interaction destabilizes the π orbital and increases its separation from the filled σ orbital of the carbene, rendering the carbene in a singlet state [33].

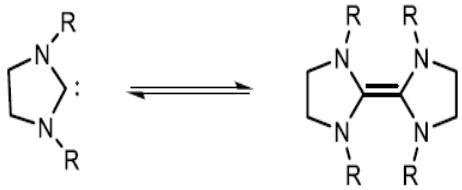


[Fig.17: Representation of the Orbital Interaction of a free NHC]

Furthermore, unlike "traditional" carbenes, which are often considered electron-poor, NHCs represent a family of electronically rich carbenes and nucleophiles [34].

ii. Steric Properties

The steric hindrance created by the substituent groups on the two nitrogen atoms provides kinetic stabilization to the carbene. These carbenes have a tendency to dimerize, forming a tetra-structure in accordance with the Wanzlick equilibrium (Diagram 4). This phenomenon is commonly observed in carbene chemistry, where the introduction of a steric "shield" around the carbene center enhances its stability. The incorporation of bulky groups around the nitrogen atoms protects them kinetically from dimerization reactions, thereby increasing their lifetime in solution. However, this protective effect is not a decisive factor, as carbenes with minimal steric congestion have also been successfully isolated [35].



[Diagram 4: Wanzlick Equilibrium]

D. Properties of the Metal-Ligand Bond

i.has. Electronic Properties

The electronic properties of free carbenes dictate the characteristics of the metal-NHC.

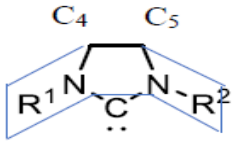
[Fig.18: Representation of the Orbital Interaction of the M-L Bond]

These ligands are rich in electrons and are highly effective σ donors, forming very stable complexes with transition metals (Figure 18). As singlet carbenes, they are classified as L ligands in Green's formalism. In this context, L-type ligands correspond to neutral ligands that donate two electrons through a lone pair involved in complex formation. Their π-acceptor character is influenced by factors such as the nature of the metal, co-ligands, and the architecture and orientation of the carbene [36].

Historically, N-heterocyclic carbenes (NHCs) were considered weak π-acceptor ligands due to the π donation from nitrogen into the empty orbital of the carbene. However, it is now established that the retro-donation from the metal to the ligand can account for up to 30% of the total orbital interaction energy in the complex, significantly contributing to metal center stabilization. The electronic properties of an NHC ligand, particularly its σ-donor strength, can be experimentally quantified using infrared spectroscopy. By comparing the CO vibration bands in complexes such as RhL(CO)2Cl, IrL(CO)2Cl, NiL(CO)3, or LCr(CO)5 (where L represents either NHC or PR3), these experiments demonstrate that NHCs are more effective ligands than the most basic alkyl phosphines. However, the donor properties of NHCs are only weakly affected by the nature of the R substituents on the nitrogen atoms. Since these R groups are not directly associated with the donor atom and are positioned far from the carbene center, they have limited influence on the electronic properties of the ligand [37].

ii.Steric properties

From a geometric perspective, the steric hindrance around the metal center is primarily influenced by the substituents attached to the nitrogen atoms of the heterocyclic ligand. The plane of the heterocycle containing the carbene is relatively unobstructed, and substituents at the C4 or C5 positions are located far from the metal's coordination sphere (Figure 19). In contrast, substituents on the nitrogen atoms exert the greatest steric influence, as they are directed toward the metal, creating a "pocket" around it. These nitrogen-driven substituents belong to the class of "enveloping" ligands, which contribute significant steric bulk around the metal. As a result, the steric strain imposed by the N-heterocyclic carbene (NHC) ligand can be so pronounced that it may displace more labile ligands from the coordination sphere. The identity of the substituent significantly affects both the overall shape of the ligand and the steric pressure exerted on the metal's coordination environment [38].



[Fig.19: Three-Dimensional Arrangement of an N-Heterocyclic Carbene]

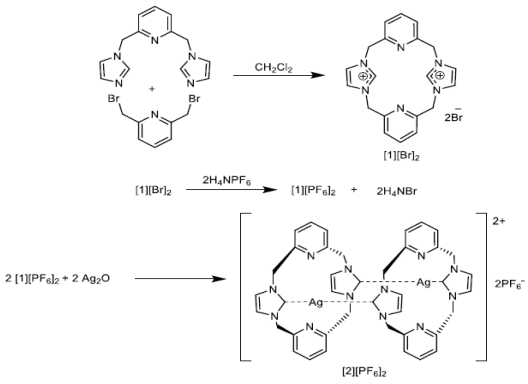
To modulate the electronic and steric properties of N-heterocyclic carbenes (NHCs), modifications can be made to the R groups attached to the nitrogen atoms. Additionally, replacing one of the nitrogen atoms with a sulfur or oxygen atom within the heterocycle can further adjust the electronic characteristics of the NHCs. In recent years, the combination of NHCs with macrocycles has gained significant attention. In this context, we will explore several examples of NHC-macrocycle complexes and their respective properties. Furthermore, we will examine the various applications of these complexes, particularly in relation to the type of transition metal incorporated into the macrocycle [39].

V. MACROCYCLES-NHCS

A. Early Examples of Cyclophane-Type and Complex Macrocycle-diNHCs

i. Associated Silver(I)

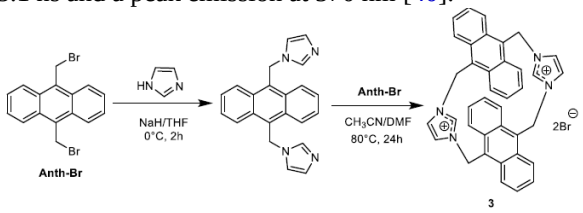
Initial studies, conducted in 1999, explored the combination of cyclophanes with imidazolium cores. It was in 2001 that J.C. Garrison and colleagues first reported the synthesis of N-heterocyclic carbene (NHC)-linked compounds. Carbenes impart both electronic and steric properties to macrocycles, thereby broadening their range of applications. The chemistry of these compounds is of significant importance, as carbenes can coordinate to transition metals, facilitating the creation of new host-guest chemical systems with potential for molecular recognition. As part of this research, they focused on the development of cyclophanes containing two pyridine rings linked to two imidazolium units [40]. In their work, they also described the first synthesis and characterization of a dimeric N-carbenene silver complex derived from this compound (Diagram 5) [41].



[Diagram 5: Schematics of Synthesis of Cyclophane-NHC Complexes with Ag(I)]

In 2008, researchers focused on the development of cyclophanes and their role in biomolecular recognition. As part of this work, they designed two novel cyclophane derivatives

incorporating anthracene and imidazolium groups, and investigated their photophysical and optoelectronic properties both in the presence and absence of DNA, micelles, and proteins [42]. One of the synthesized cyclophanes, the symmetrical cyclophane 3 (Diagram 6), exhibited particularly notable characteristics. In the presence of DNA, this cyclophane formed a new sandwich-type excimer, which showed a bathochromic shift in emission to longer wavelengths, as well as significantly increased fluorescence lifetimes. This study represents the first report demonstrating how DNA can facilitate the formation of an excimer with an exceptionally long fluorescence lifetime of 143.1 ns and a peak emission at 570 nm [40].



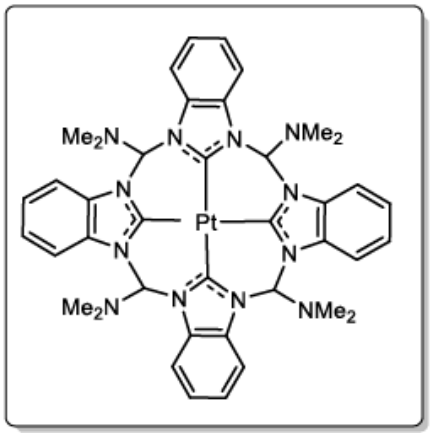
[Diagram 6: Schematic Synthesis of the Cyclophane-Anthracene-di-NHC Ligand]

Cyclophane 3 is notable for two key features: it demonstrates both solubility and stability in aqueous environments, and it selectively interacts with DNA in a buffered medium. These interactions occur through an excimer emission mechanism [42].

B. Examples of Cyclophanous-Type Tetra-NHC Macrocycles and Various

i. Transition Metals Developed: Towards Different Applications

During this period, tetracarbene macrocyclic ligands, constructed from four NHC units, also gained significant attention, particularly following the synthesis of the first tetracarbenene platinum(II) complex. This complex was created through a controlled reaction based on a model developed for this purpose (Figure 20).

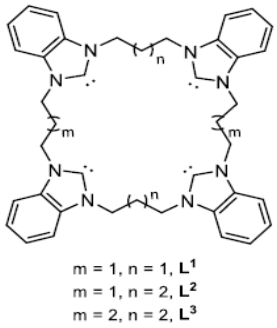


[Fig.20: First tetra-NHC Complex of Pt(II) Synthesized by Hahn]

Over the past decade, the development of macrocyclic NHC ligands and their complexes has seen significant progress, revealing unique structural properties and novel reactivities. This has led to the emergence of several interesting applications. As a result, numerous metal complexes featuring various tetracarbenene macrocyclic ligands have been reported. Below are some examples of complexes derived from tetracarbene macrocyclic structures [43].

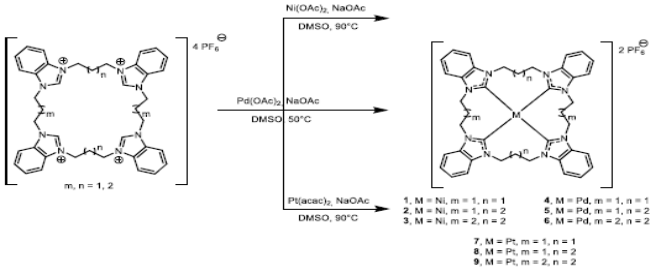
ii. has. Macrocyclic tetrabenzimidazolium salts at different bond lengths flexible and complex Ni(II), Pt(II) and Pd(II) associated

The synthesis of a series of tetrabenzimidazolium salts, including [H4L1][PF6]4, [H4L2][PF6]4, and [H4L3][PF6]4 (Figure 21), has been reported. These compounds, with varying flexible bond lengths, were designed as supramolecular receptors for anions [44].



[Fig.21: Macrocyclic Ligand Structures From Tetrabenzylimidazolium Rings]

In 2017, the synthesis and characterization of fourteen new metal complexes (Ag, Au, Ni, Pd, and Pt) featuring macrocyclic tetra-NHC ligands (L1, L3) with varying bond lengths were reported (Figure 21). This includes a series of synthesized complexes of Nickel(II), Platinum(II), and Palladium(II) (Diagram 7).



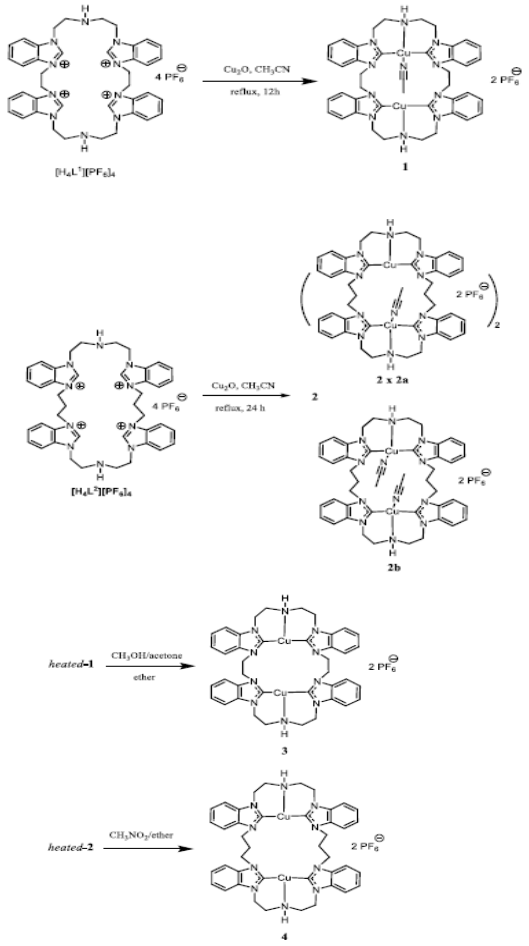
[Diagram 7: Preparation of tetra-NHC Complexes of Pt(II), Ni(II) and Pd(II)]

For the metal ions Ni, Pd, and Pt, the highly flexible tetra-NHC ligand wraps around the metal center, resulting in a square planar geometry. As the size of the ligand increases, the metal–Ccarbene bond distance also increases. The π-π stacking interactions, which arise from the benzimidazole rings, play a key role in determining the stacking arrangement within the crystal lattice. Additionally, the size of the ligand influences the strength of these π-π interactions. Binuclear complexes of Ag(I) and Au(I) formed with this tetra-NHC macrocyclic ligand have demonstrated photoluminescence [45]. This photoluminescent behavior has also been observed in complexes involving other metals, such as copper (Cu(I)).

iii. Cu(I)-tetra-NHC complexes: towards photoluminescence properties

Cu(I) complexes containing N-heterocyclic carbene (NHC) ligands have been extensively studied for their catalytic properties. In

recent years, luminescent Cu(I)-NHC complexes have garnered significant interest. Since the first report of a luminescent dinuclear Cu(I) complex with a bis-(NHC) ligand in 2009, a variety of luminescent Cu(I)-NHC complexes, including mono-, di-, and trinuclear species with two, three, or four Cu(I) ions coordinated, have been described. Recently, a research team designed two tetra-NHC macrocyclic precursors, [H4L1][PF6]4 and [H4L2][PF6]4, which contain four benzimidazolium units and two secondary amines with varying alkyl bridging groups between the benzimidazolium units [46]. These precursors were used to synthesize Ag(I), Au(I), Ni(I), Pd(II), and Ir(I) complexes. To explore the luminescent properties of the resulting Cu(I) complexes, they conducted complexation studies with copper oxide (Cu2O) [47]. The team reported detailed studies on the luminescent behavior of a series of dinuclear Cu(I) complexes (1-4) (Diagram 8).



[Diagram 8: Preparation of Cu(I)-Tetra-NHC Complexes 1-4]

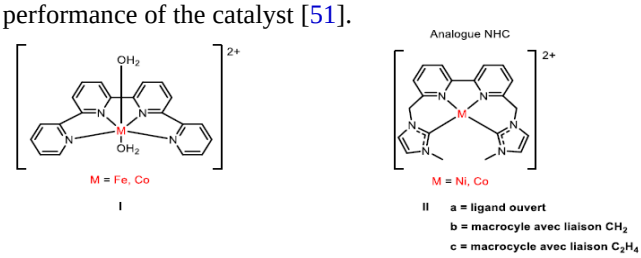
Among these, Compound 3, which exhibits the shortest Cu-Cu distance, demonstrates strong emission with the highest quantum luminescence efficiency, achieving a value of 0.93. In addition to the photoluminescent properties observed in Cu(I), Ag(I), and Au(I) complexes, metal complexes with N-heterocyclic carbene ligands have proven to be valuable in various applications, including catalysis, as exemplified by their use with Iron(II) complexes [48].

iv. Iron(II)-tetra-NHC complexes: towards catalysis applications

Tetra-NHC macrocyclic complexes of Fe(II) have gained significant attention for their potential in catalysis, particularly in electrocatalytic CO2 reduction. This process is crucial for addressing global challenges such as climate change and the depletion of fossil resources. By facilitating the conversion of CO2 into carbon-based materials or fuels, it offers a method for recycling CO2, turning it into an abundant and inexpensive carbon source. This, in turn, could mitigate the impact of anthropogenic CO2 emissions, which contribute to the greenhouse effect, while also reducing reliance on finite fossil fuel resources [49].

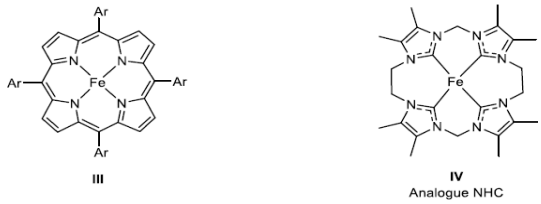
Transition metal complexes, especially those of Iron(II), Cobalt(II), and Nickel(II), have shown promise as electrocatalysts for CO2 reduction. Among the various molecular electrocatalysts studied, Fe-heme-type porphyrins have been particularly prominent. Modifications to the porphyrin ligands have provided insights into the influence of the ligand environment on CO2 electroreduction and have enabled better control over proton transfer mechanisms. Many of these transition metal electrocatalysts incorporate N-donor ligands, which play a key role in enhancing catalytic activity [50].

Recent studies have also explored Nickel(II) and Cobalt(II) complexes with both macrocyclic and non-macrocyclic NHC (N-heterocyclic carbene) ligands. A comparative analysis of the Co-qpy I complex (where qpy refers to quaterpyridine, a tetrapyridine ligand) and the best-performing bpy-NHC complexes (IIb and IIc), in which the NHC units are linked to form a macrocycle, has revealed notable differences in Faradaic efficiency (FE). The Faradaic efficiency, defined as the ratio of the actual electrical charge used in an electrochemical process to the theoretical charge, varies with different complex structures, affecting the overall performance of the catalyst [51].



[Diagram 9: Structures of Qpy I and Bpy-NHC II Ligands]

These investigations have prompted further exploration of the structural similarities between porphyrins and NHCs. A recent study (ref. 72) has focused on the development of a purely organometallic analogue (IV) of the traditional Fe-porphyrin complex (III) (Diagram 10), which shows promise as an electrocatalyst for CO2 reduction [52].



[Diagram 10: Structures of the Fe-Porphyrin III Complex and the Tetra-NHC IV Macrocycle]

In recent years, Iron(II) complexes with tetra-NHC macrocyclic ligands have

been extensively studied, primarily

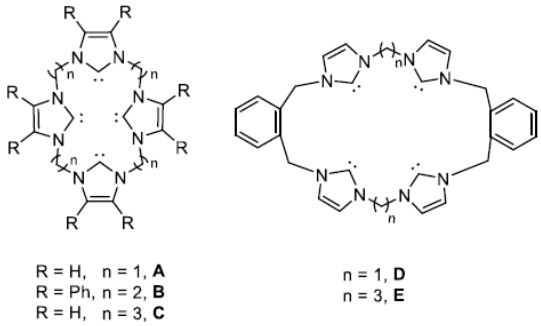
for their roles in redox reactions. However, this study shifts focus to the reductive chemistry of these "organometallic analogues of heme," which has not been as widely explored. The authors report the synthesis of a tetra-NHC iron complex as a pre-catalyst for the electrochemical conversion of CO2 to CO. Tetra-NHC ligands, such as the one in compound IV, have a structure similar to porphyrins, but unlike porphyrins, they lack intrinsic redox properties, relying entirely on the central metal ion for redox activity. Furthermore, the macrocyclic tetra-NHC ligand platform offers considerable flexibility, particularly through modifications to the cycle size and the peripheral substituents on the NHC units [53]. These complexes have been shown to be more stable under catalytic conditions compared to heme-based systems, even though their catalytic rates are fast due to their favorable electronic structures. Despite their relatively recent development, these tetra-NHC iron complexes represent the first known examples of NHC-linked iron complexes capable of electrocatalytically reducing CO2 to CO.

Although most studies on NHCs have concentrated on their catalytic applications, recent research has increasingly explored their potential in biomedical applications. NHC ligands exhibit strong σ-donor and weak π-acceptor properties, which can be easily tuned by modifying the substituents at the NHC ends to adjust solubility, steric hindrance, and electronic properties. These ligands are also effective at stabilizing metal ions in various oxidation states and coordination geometries, making them promising candidates for the development of metal-based anticancer drugs. Several studies have highlighted the potential of NHC-metal complexes, particularly those involving Pd(I), Cu(I), Au(I), and Ag(I) ions, for use in chemotherapy due to their cytotoxic effects against various cancer cell lines. Biological studies of Au(I)-NHC complexes, in particular, have sparked increasing interest in designing and synthesizing biologically active compounds. The following discussion will focus on a study of Ag(I)-NHC complexes and their biological properties within the biomedical field [54].

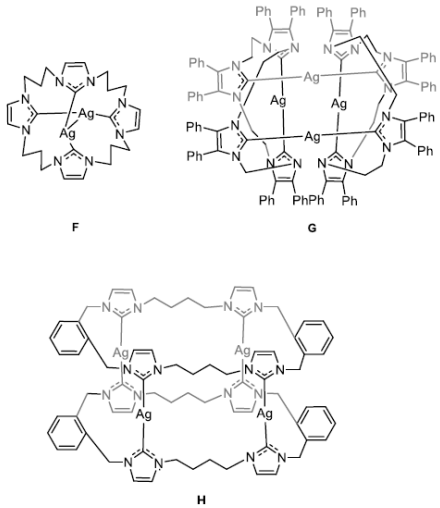
v. Silver(I) di- and tetra-NHC complexes: towards applications in the field biomedical

i. Examples of original macrocyclic tetra-NHC complexes of Ag(I)

Several studies have explored tetraimidazolium salts derived from cyclophane-type structures, which can be used to synthesize mononuclear and dinuclear Ag(I) carbene complexes with macrocyclic polycarbene ligands. These macrocyclic tetra-NHC Ag(I) complexes exhibit complex architectures, with three distinct structures identified (Figure 23). The first structure features a binuclear unit containing two silver ions encapsulated within the complex (molecule F derived from ligand C, Figure 22). The second type of complex adopts a cage-like or box-like geometry, consisting of four Ag(I) ions and two tetracarbenic ligands. In this structure, two Ag(I) ions serve as a bridge between the two NHC units, while the remaining two silver ions coordinate with the intramolecular carbenes (G). This complex adopts a "twisted" configuration and was synthesized using ligand B (Figure 22). The third structure is characterized by a "sandwich" arrangement (H), which has been observed in silver complexes of ligands A or E (Figures 22 and 23).



[Fig.22: Tetracarbenene Macrocyclic Structures Known From the Literature]



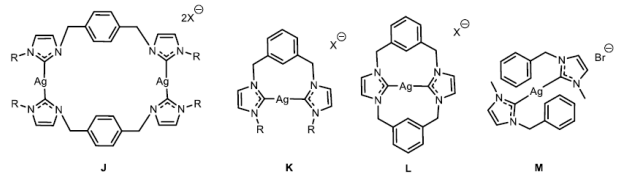
[Fig.23: Structures of the Ag(I) Complexes of the F, G and H Ligands]

In addition to the tetracarbene complexes mentioned previously, other macrocyclic complexes featuring bidentate and polydentate NHCs have also been investigated. These compounds typically contain an imidazolylidene core, which imparts NHC-like characteristics, with the exception of the tetra(benzimidazolylidene)-Pt(I) macrocyclic complex synthesized by Hahn et al. (Figure 20). The NHC-Ag(I) complexes have emerged as promising candidates for antimicrobial agents, offering potential advantages over conventional antibiotics, such as reduced risk of rapid loss of efficacy, resistance, or argyrism. The relatively low toxicity of silver has facilitated its consideration for widespread use in this context. It has been proposed that the enhanced stability of NHC-Ag(I) complexes results in a slower release of the silver ion, thereby prolonging the antimicrobial activity compared to traditional silver-based compounds. A biological study examining the antimicrobial properties of silver(I)-NHC complexes will be discussed in the following section [55].

ii. Examples of Argent(I) di-NHC complexes: towards applications in the Biomedical field

This study focused on the synthesis of a new series of macrocyclic precursors featuring bis-imidazolium units, as well as their

coordination behavior in the presence of silver oxide (Ag_2O). The cytotoxicity of the resulting silver complexes was evaluated against two cancer cell lines: MCF-7 (breast cancer) and DLD-1 (colon cancer), to investigate the impact of bidentate ligands on their activity. Modifications were made to the nitrogen substituents (R groups), the position (meta or para) of these substituents, and the counterion (X-) in order to establish and analyze structure-activity relationships. In parallel, a monodentate derivative was synthesized and tested to compare the efficacy of bidentate ligands with their monodentate counterparts. The results showed no significant activity when silver salts or ligands alone were tested, underscoring the importance of complex formation in enhancing the bioactivity of the silver complexes [56].



[Fig.24: Ag(I)-bis(NHC) Complexes J-M. a: R = Me, X = Br-; b: R = nPr, X = Br-; c :R = tBu, X = Br-, d : R = Me, X = BF4]

The in vitro cytotoxicity of bis-NHC-Ag(I) complexes (J-M compounds) (Figure 24) was assessed using MTT assays, a colorimetric method that allows for rapid quantification of viable cells. The ratio of live to dead cells was then calculated, making this method particularly useful in toxicity evaluations of new compounds. The assay involved a 6-day exposure period to the drug. In addition to the bidentate bis-NHC-Ag(I) complexes (J-L), a monodentate complex (M) as well as imidazolium salts (AgBr and $AgBF_4$) were also tested for comparison. These compounds were initially investigated as potential alternatives to cisplatin (cis-diaminedichloridoplatinum(II)), a widely used inorganic anticancer drug.

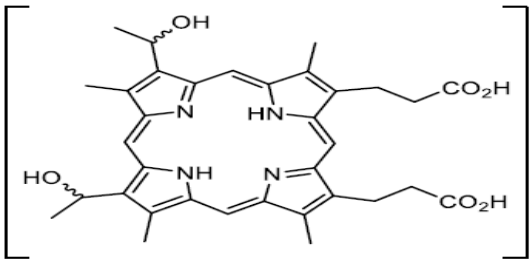
The monodentate M complex exhibited significantly lower cytotoxicity against MCF-7 cells compared to the bidentate bis-NHC-Ag(I) complexes. This can be attributed to the increased stability of the bidentate complexes, which are likely more effective due to their enhanced structural rigidity. Similar to their antibacterial counterparts, the greater stability of these complexes may lead to a more controlled and prolonged release of silver ions, potentially contributing to sustained bioactivity. The macrocyclic nature of the complexes also plays a crucial role, providing additional stability due to the rigid coordination environment. However, if a complex is too stable, it may fail to release enough silver ions, which can reduce its efficacy over time. This phenomenon was observed with complex L, which was less cytotoxic than some of the bidentate complexes (J and K, Figure 24).

The stability of the complex seems to influence its activity, although the rate of silver ion release appears to be the most critical factor. The activities of these complexes were found to be comparable to that of cisplatin, with a favorable toxicity profile. These molecules hold promise as potential therapeutic agents. However, a major challenge for the continued development of these compounds is the lack of a defined mechanism of action or a specific cancer target [56].

The tetra-NHC macrocyclic systems discussed above, with their varied potential applications, are structurally similar to porphyrin-based systems, particularly in terms of their square planar coordination geometry. Porphyrins and analogous macrocycles possess valuable biological, photochemical, catalytic, and luminescent properties, making them strong candidates for use in phototherapy and other disease treatments [57]. The diverse coordination chemistry of these systems, along with their high light absorption and emission properties, has led to the development of numerous porphyrin-based analogues for a wide range of functional applications. Thus, these structures correspond to potential photosensitizers (PS) [58].

VI. PHOTOSENSITIZERS

A photosensitizer is a molecule that can absorb a photon and transfer its energy to an acceptor compound, initiating a chemical or biological reaction. The concept of photosensitization was first discovered in 1898 by Oscar Raab, who observed the death of *Paramecium* when exposed to light in the presence of a non-toxic dye, acridine. In 1903, photodynamic therapy (PDT) was used to treat skin cancer, when researchers Jesionek and von Tappeiner applied eosin topically to tumors and irradiated the area with white light. This treatment highlighted the role of oxygen in the process. PDT, which involves the activation of a photosensitizer by monochromatic or polychromatic light in the presence of oxygen, is now primarily utilized in medical applications, particularly for tissue destruction. In 1909, the phototoxic properties of hematoporphyrin (Hp) (Figure 25) were identified by Hasselbach. This molecule, found in the blood, became a key photosensitizer in PDT due to its ability to localize preferentially in tumor tissues and its sensitizing properties, making it crucial for the development of PDT as a therapeutic approach.



[Fig.25: Structure of Hp Hematoorphyrin]

Commercial hematoporphyrin was initially impure, leading many researchers to work on its purification, resulting in the development of "Hematoporphyrin Derivative" (HpD). In 1985, the first hematoporphyrin derivative, HpD, was marketed under the name Photofrin II® (Figure 26) for the treatment of lung cancers (primarily in the bronchi) and esophageal cancer. Since then, ongoing research has focused on improving the properties of photosensitizers. The design and synthesis of new photosensitizing molecules must meet several key criteria to be effective:

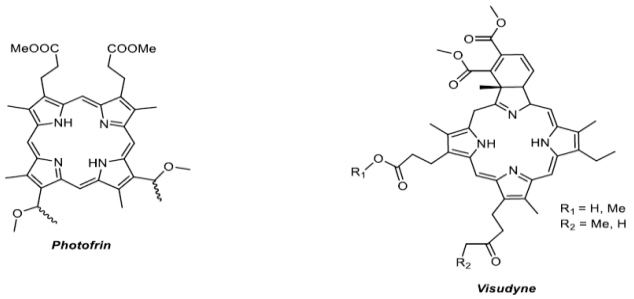
1. **Defined Structure**: The molecule should have a well-defined structure that is easy to synthesize

reproducibly on both small and large scales, with minimal cost.

2. **Non-Cytotoxic in the Dark**: It should be non-toxic in the absence of light, preferentially accumulate in tumor cells, and be rapidly cleared from healthy tissue to minimize unwanted side effects.
3. **Effective Excitation**: The molecule must be sufficiently excited by light and have a long enough excited-state lifetime to facilitate energy transfer to reactive species, resulting in high singlet oxygen quantum yield.
4. **Red Light Absorption**: It should absorb strongly in the red light region, allowing for deeper tissue penetration and maximizing the therapeutic effect of PDT.
5. **Amphiphilicity**: The molecule should have amphiphilic characteristics to enhance its transport through the bloodstream and delivery to the target site.
6. **Fluorescence**: The compound should exhibit fluorescence for easy tracking after accumulation in the target tissue.

If a molecule meets these criteria, it can be classified as a photosensitizer (PS) and capable of transferring its excitation energy to another compound. Photosensitizers can be broadly classified into natural or synthetic types, based on their chemical nature—either tetrapyrolic or non-tetrapyrolic. Non-tetrapyrolic photosensitizers are typically derived from plants, such as hypericin or psoralens, which are primarily used in the treatment of psoriasis. Unlike tetrapyrolic photosensitizers, these molecules act directly on DNA and RNA by intercalating between strands.

Tetrapyrrolic photosensitizers are further categorized into three generations, which will not be discussed in detail here. The majority of photosensitizers used in PDT belong to the porphyrin family. Two examples of commonly used and commercially authorized photosensitizers in PDT are shown in Figure 26.



[Fig.26: Structures of the Main Photosensitizers (PSs) with MA]

VII. CONCLUSION

The synthesis of molecular cages and the incorporation of chemical entities within them represent a remarkable advancement in supramolecular chemistry. This article has highlighted the diverse families of macrocyclic ligands, including crown ethers, cryptands, and multi-branched macrocycles, emphasizing their unique structural properties and coordination capabilities. The integration of N-Heterocyclic Carbenes (NHCs) into these systems not only enhances their stability and functionality but also opens up new avenues for applications in catalysis, photoluminescence, and biomedicine.

As we continue to explore the intricacies of macrocycle-NHC chemistry, it is evident that these molecular architectures possess significant potential for the development of innovative materials tailored to specific applications. The ability to encapsulate metal ions, anions, and small molecules within these cages enhances their chemical properties, providing a distinct advantage over non-caged counterparts.

Ultimately, the ongoing research in this field promises to yield exciting new materials and methodologies that could have far-reaching implications across various scientific domains, from advanced materials science to biomedical applications. The ingenuity of synthetic chemists in designing these molecular systems exemplifies the creativity and innovation that drive progress in supramolecular chemistry.

DECLARATION STATEMENT

I must verify the accuracy of the following information as the article's author.

- **Conflicts of Interest/ Competing Interests:** Based on my understanding, this article has no conflicts of interest.
- **Funding Support:** This article has not been funded by any organizations or agencies. This independence ensures that the research is conducted with objectivity and without any external influence.
- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Authors Contributions:** The authorship of this article is contributed solely.

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