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What is different about macrocyclic ligand complexes?

1.1 Background

The understanding of the metal-ion chemistry of macrocyclic ligands has important implications for a range of chemical and biochemical areas. Macrocyclic ligands are polydentate ligands containing their donor atoms either incorporated in or, less commonly, attached to a cyclic backbone. As usually defined, macrocyclic ligands contain at least three donor atoms and the macrocyclic ring should consist of a minimum of nine atoms. The metal-ion chemistry of macrocyclic ligands has now become a major subdivision of inorganic chemistry and undoubtedly great interest in this area will continue in the future.

A very large number of synthetic, as well as many natural, macrocycles have now been studied in considerable depth. A major thrust of many of these studies has been to investigate the unusual properties frequently associated with cyclic ligand complexes. In particular, the investigation of spectral, electrochemical, structural, kinetic, and thermodynamic aspects of macrocyclic complex formation have all received considerable attention.

The fact that macrocyclic ligand complexes are involved in a number of fundamental biological systems has long been recognized. The importance of such complexes, for example to the mechanism of photosynthesis, or to the transport of oxygen in mammalian and other respiratory systems, has provided a motivation for investigation of the metal-ion chemistry of these systems as well as of cyclic ligand systems in general. The possibility of using synthetic macrocycles as models for the biological systems has provided an impetus for much of this research.

There are good reasons for nature choosing macrocyclic derivatives for the important complexes just mentioned – enhanced kinetic and thermodynamic stabilities are bestowed on the respective complexes by the

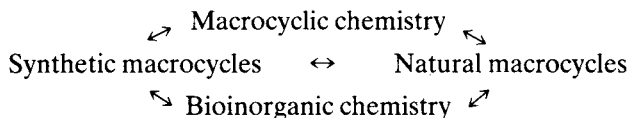
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cyclic ligands. The metal ion is thus firmly held in the cavity of the macrocycle such that the biological function of each is not impaired by, for example, competing demetallation reactions.

The porphyrin ring (1) of the iron-containing haem proteins and the related (partially reduced) chlorin (2) complex of magnesium in chlorophyll, together with the corrin ring (3) of vitamin B₁₂ have all been studied for many years. However, as well as these conjugated systems, there are a number of other quite different cyclic organic ligands found in nature. An example of this latter group is the antibiotic nonactin (4) which binds potassium selectively and acts as a carrier for this ion across such lipid barriers as cell membranes and artificial lipid bilayers.

Prior to 1960, there existed only one well-established category of synthetic cyclic ligands. These were the highly conjugated phthalocyanines. Phthalocyanine (5) and its derivatives bear a strong structural resemblance to the natural porphyrin systems. The extensive metal-ion chemistry of phthalocyanine ligands is both interesting and varied. For example, specific phthalocyanines have been shown to behave as semiconductors, as catalysts for a variety of chemical transformations, and have been involved in model studies for a number of biochemical systems. Moreover phthalocyanines and related derivatives have been the subject of intense research because of their commercial importance as colouring agents. Thus copper phthalocyanine and its substituted derivatives have found widespread use as both blue and blue-green pigments and dyes (the colour is influenced by the particular substituent present). Apart from their intense colours, the complexes also exhibit marked resistance to degradation: they show high thermal stability, fastness to light, and inertness to acids and alkalis. All these properties favour the use of these compounds as pigments and dyes.

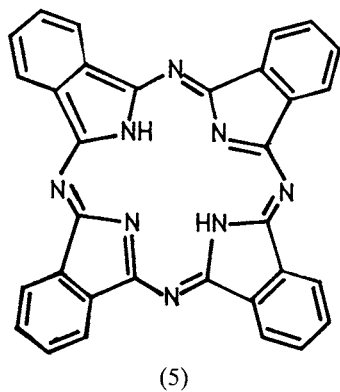
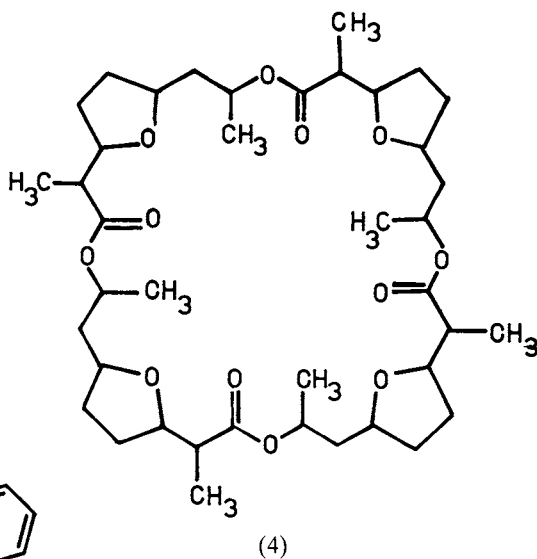
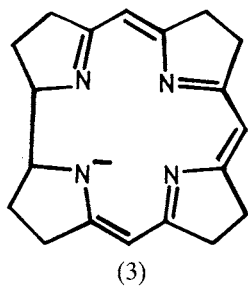
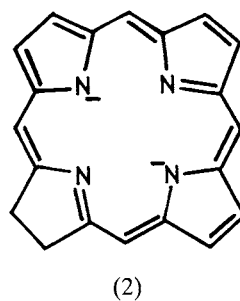
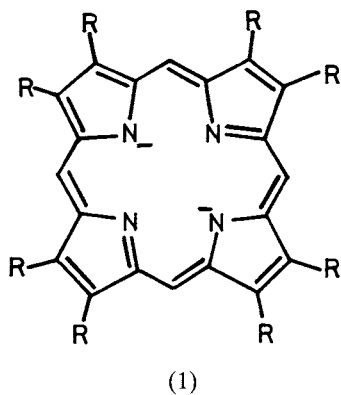
Since 1960, a very large number of other synthetic macrocycles has been prepared and this has resulted in a great increase in interest in all aspects of the chemistry of macrocyclic systems. From about this time there has also been enhanced interest in the role of metal ions in biological systems and many such 'bioinorganic' studies have involved complexes of both natural and synthetic macrocycles. Thus there has been an element of cross-fertilization between these two developing areas, viz:



As mentioned already, a considerable amount of the research involving synthetic macrocycles has been directed towards the preparation of

Background

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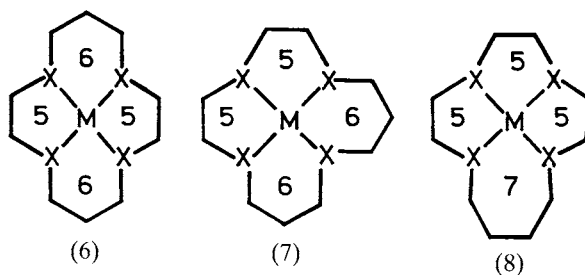
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model compounds for the natural macrocycles. Although these efforts have not always met with spectacular success, the resultant development of new macrocyclic ligand chemistry has provided a valuable background against which the natural systems can often be seen in clearer perspective.

Apart from the biological implications, aspects of the chemistry of macrocyclic ligands are of relevance to a diverse number of other areas. Indeed, there has been a remarkable expansion of research involving these other areas during recent times. Many of the developments impinge on topics such as metal-ion catalysis, organic synthesis, metal-ion discrimination, and analytical methods, as well as on a number of potential industrial, medical and other applications.

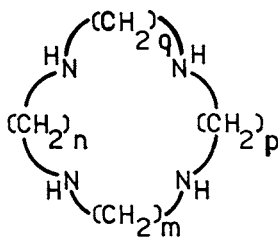
1.2 **Steric and electronic considerations***The macrocyclic cavity*

Macrocyclic rings and chelate rings. As with simple polydentate ligands, the donor atoms in macrocyclic ligands are normally spaced so that on coordination five-, six-, (and occasionally) seven-membered chelate rings are formed with the metal ion. This requirement results in macrocycles incorporating three donor atoms usually containing between nine and 13 atoms in their inner macrocyclic ring. Thus, ring sizes of between 12 and 17 members most commonly occur when the macrocycle contains four donor atoms, 15–21 members when there are five donor atoms, and 18–25 members for six donor atoms. Examples of different chelate ring patterns for metal complexes of 14-membered macrocycles are given by (6)–(8).



Factors influencing the macrocyclic hole size. The hole size of a macrocyclic ligand is a fundamental structural parameter which will usually influence, to a large degree, the properties of resultant metal complexes relative to those of the corresponding non-cyclic ligands. The large number of X-ray diffraction studies now complete for macrocyclic systems makes it possible to define many of the parameters which affect hole size

in such systems. In overall terms, the hole size of a cyclic ligand is very often determined by the number of atoms in the macrocyclic ring. The optimum hole sizes in a series of fully-saturated, tetraaza macrocycles of type (9) in conformations suitable for coordination to a metal ion have



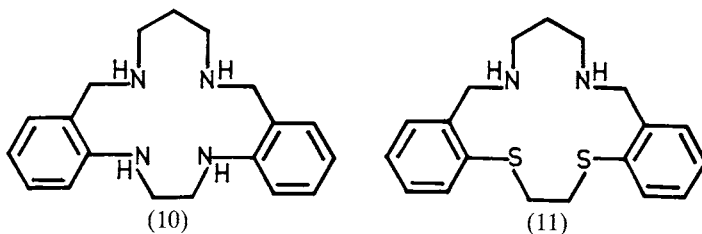
been calculated (Busch, 1978) using the procedures of molecular mechanics. In these calculations the atomic positions corresponding to the minimum strain energies for the respective ligands were derived. The results indicate a regular increment of 0.10–0.15 Å in the mean radius of the central hole for each additional atom in the macrocyclic ring. As calculated, the radii reflect the ‘natural’ variation of the macrocyclic hole size in the uncomplexed ligands. The procedure does not allow for the ring expansions and contractions which are a feature of coordination to metals having radii which are greater or smaller than the ‘natural’ hole size of the free ligand.

A simpler procedure for approximating the hole sizes of macrocyclic ligands for comparison purposes has been used to compare the hole size variations which occur for related coordinated macrocycles as the ring size is systematically varied (Henrick, Tasker & Lindoy, 1985). The procedure gives the expected smaller increase in hole size as the number of atoms in the macrocyclic ring is successively increased. Thus, for the complexes of flexible macrocycles, the moderate differences (of about 0.04–0.05 Å) observed for adjacent rings along a given ligand series reflect expansion of the smaller rings and contraction of the larger rings such that the fit for the metal ion is improved in each complex. Nevertheless, it is to be expected that each ring contraction or expansion will be characterized by a concomitant increase in ligand strain energy which may be reflected in less favourable chelate ring conformations or in distortion of the coordination geometry about the metal ion. Thus for such complexes, the observed macrocyclic hole size will reflect a balance between the dictates of the metal ion and those of the macrocyclic ring involved. When the ligand contains a rigid backbone, the capacity for

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radial expansion or contraction may be severely limited and, under such conditions, metal-donor atom bond distances which are considerably compressed or stretched from their normal values may occur. Thus it has been observed (Hoard, 1975) that the Ni–N bonds in several porphyrin complexes of nickel are longer than occur in related diamagnetic nickel complexes in which a non-constrained N_4 -donor set is presented to the nickel.

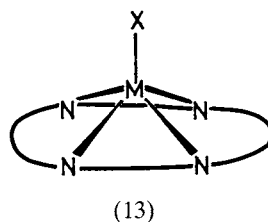
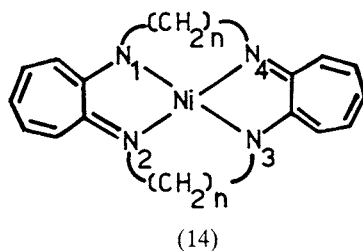
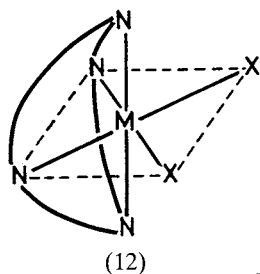
Apart from the number of atoms in the macrocyclic ring, the nature of the donor atoms may also affect the hole size of a macrocyclic ring. Replacement of a small donor atom by a larger one in a given ligand framework is expected to affect (but not necessarily markedly reduce) the cavity size available to the metal ion. For example, on substitution of sulfur for nitrogen, a partial compensation for the effect of the larger sulfur will occur since the carbon-sulfur bonds in the macrocyclic ring will be longer than the corresponding carbon-nitrogen bonds. Thus, although the bonding cavity of the macrocycle tends to be reduced on substitution of larger donor atoms for smaller ones, this effect may be offset to a lesser or greater degree by the corresponding increase in the ‘circumference’ of the macrocyclic ring. Such compensation is well-illustrated by comparison of the structure of the complexes of type *trans*-[NiCl₂L] in which L is the N_4 -donor macrocycle (10) or the S_2N_2 -donor macrocycle (11). Calculations suggest that the bonding cavities in these complexes are very similar in size [and both near ideal for high-spin Ni(II)].



The hybridization of the donor atoms may affect the macrocyclic hole size. Relative to the corresponding ligand containing sp^3 -amine donor atoms, introduction of sp^2 -imine donors into a cyclic ligand normally leads to a reduction of the macrocyclic hole size largely because of decreased ‘bites’ (distances between adjacent donors) for the chelate rings containing the imine groups. However, because of their higher s-orbital character, the sp^2 hybrids are not as diffuse as sp^3 hybrids and hence their overlap with the appropriate metal orbital leads to a decrease in the corresponding metal-nitrogen bond length. In addition, with sp^2 hybridization there is a prospect of metal to ligand π -bond formation in

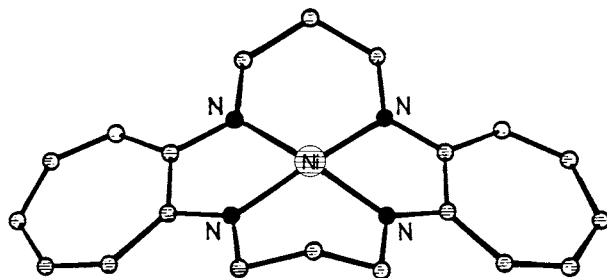
certain cases – this will further shorten the metal-nitrogen bond. Once again, the two effects are in opposition: although the hole size of the imine-containing macrocycle will be reduced, this will tend to be compensated by the smaller effective covalent radius of the sp^2 nitrogens.

Further considerations. Relative to their open-chain analogues, macrocycles have additional stereochemical constraints resulting from their cyclic nature. These constraints, which depend upon several factors such as the overall macrocyclic ring size and the number and nature of the various chelate rings formed on coordination, will influence the positions of the donor atoms both with respect to each other and to the central metal ion. Such constraints are often also further manifested by a limitation of the possible coordination modes and/or conformations of the coordinated macrocycle. For example, when the metal ion is too large to fit into the available macrocyclic hole, then, provided complexation occurs, the macrocycle will either fold or the metal will be displaced from the donor plane of the ring. Structure (12) is an example of a folded system. For sterically rigid rings, such ligand folding will be energetically unfavourable relative to displacement of the metal ion from the donor plane of the ring. In this case the metal is very often also bound to an axial ligand, as illustrated by (13).



Macrocycles may also promote the formation of less common coordination geometries for particular metal ions because of increased macrocyclic ring strain on coordination. Such an effect is illustrated by the variation in the structures of the nickel complexes of the 14-, 16-, 18-, and 20-membered ‘tropocoronand’ macrocycles of type (14) (Imajo, Nakanishi,

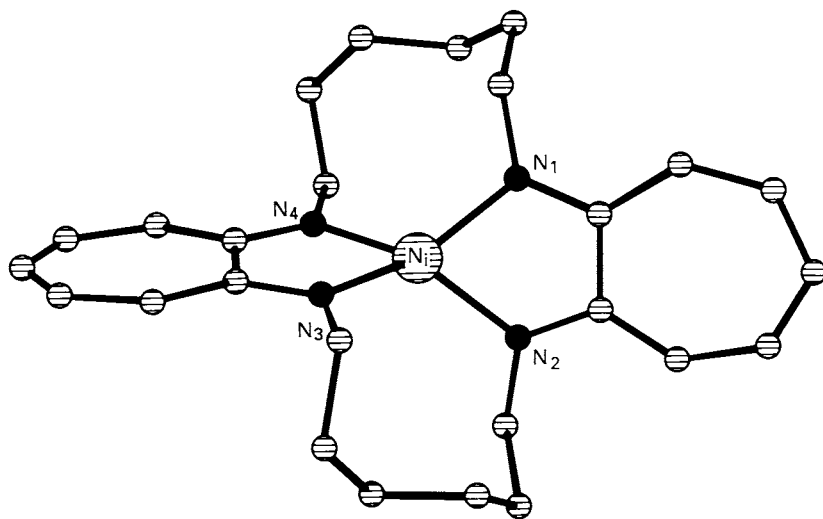
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(15)

Roberts & Lippard, 1983). The coordination geometry for the 14-membered ring complex (15) is approximately planar whereas there is a progressive distortion towards a tetrahedral geometry (less common for nickel) as the ring size is increased. The distortion away from planarity is almost certainly a reflection of the increased steric crowding associated with the progressive introduction of larger chelate rings in the series. For the largest (20-membered) ring species (16) an angle of 85° occurs between the $N_1\text{-Ni-N}_2$ and $N_3\text{-Ni-N}_4$ planes.

Donor atom to metal-ion bond lengths which are shorter or longer than expected as well as unusual angular relationships between such bonds have all been documented in macrocyclic complexes. Such effects can be a prime cause of the unusual properties mentioned previously. Thus the



(16)

properties of a particular complex will reflect the compatibility or otherwise of the central cavity for the steric and electronic requirements of the metal ion involved. When a mismatch between the cavity and the metal ion occurs then unusual properties may be generated. The situation in this case approximates that proposed in the 'entatic state' hypothesis (Vallee & Williams, 1968) which relates the enhanced reactivity of metallo-enzymes to the unusual coordination geometries of the metal ion observed in many such systems. For macrocyclic complexes, such effects tend to be particularly evident in the results from ligand-field spectrophotometric and electrochemical studies and the resultant theoretical implications have provided the motivation for a considerable number of such investigations in the past. Indeed, in a number of cases the macrocyclic complexes contain the metal in a different electronic ground state compared to the corresponding non-cyclic ligand complexes. Likewise, unusual electrochemical behaviour associated with non-ideal metal-donor bond lengths in cyclic complexes has been well documented. There is, for example, a marked tendency for the smaller macrocyclic rings to stabilize the higher oxidation states of a given metal.

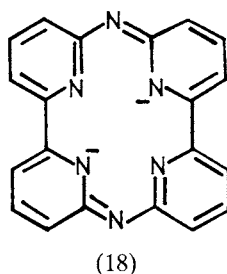
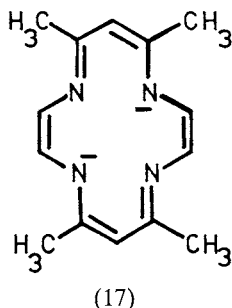
It is important to note that, even when the coordination geometry prescribed by the macrocyclic cavity is ideal for the metal ion involved, unusual kinetic and thermodynamic properties may also be observed (relative to the corresponding open-chain ligand complex). For example, very often the macrocyclic complex will exhibit both enhanced thermodynamic and kinetic stabilities (kinetic stability occurs when there is a reluctance for the ligand to dissociate from its metal ion). These increased stabilities are a manifestation of what has been termed the 'macrocyclic effect' – the multi-faceted origins of which will be discussed in detail in subsequent chapters.

Unsaturation in macrocyclic systems

Consequences of unsaturation. Unsaturation in the macrocyclic ring may have major steric and electronic consequences for the nature of the ring. Extensive unsaturation will result in loss of flexibility with a corresponding restriction of the number of possible modes of coordination. Further, loss of flexibility tends to be reflected in an enhanced 'macrocyclic effect'. For example, if the metal ion is contained in the macrocyclic cavity, the loss of flexibility reduces the possible pathways for ligand dissociation and this tends to increase the kinetic stability of the system. As explained in later chapters, enhanced thermodynamic stabilities will usually also result.

Many macrocycles incorporating high levels of unsaturation have been

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synthesized and, in extreme cases, the system may be completely conjugated to yield annulene-like rings exhibiting various degrees of complexity such as (17) (Truex & Holm, 1972) and (18) (Ogawa & Shiraishi, 1980). As a consequence of the cyclic character of macrocyclic ligands, the possibility also exists that a Hückel aromatic system containing $(4n + 2)\pi$ -electrons will occur – the porphyrins form one such group of ligands. Such aromaticity may thus serve as an additional contribution towards increasing the difference between a particular cyclic ligand and its non-cyclic analogue. Apart from the possible effects of increased rigidity on the complex, the enhanced electron delocalization associated with rings of this type may also markedly affect the nature of the cyclic complex formed. The capacity for such rings to act as electron sinks undoubtedly accounts for the ability of many ligands of this type to stabilize metal ions in unusual oxidation states. For several systems, electron spin resonance and other studies have confirmed that substantial transference of electron density may occur between the metal ion and the macrocyclic ligand. Although the most favourable overlap of the extensive π -cloud will occur when highly-conjugated macrocyclic ligands are planar, a number of structural studies have now amply demonstrated that, for these large ring systems, deviations from planarity can readily occur. For example, the porphyrins yield metal complexes containing the ligand in both planar and ‘ruffled’ non-planar forms. This ‘ruffling’ of the porphyrin core has been discussed (Hoard, 1975) in terms of a concomitant shortening of the metal-nitrogen bond lengths in specific complexes.

Similar distortions from planarity are also observed in a range of conjugated synthetic ring systems. For example, the tetraaza macrocycle (19) adopts a saddle-shaped configuration in its complexes with a number of transition metal ions (Goedken, Pluth, Peng & Bursten, 1976) even though the four donor atoms remain essentially planar. In this case, the non-planarity of the remainder of the ligand appears to result largely from steric clashes between the methyl substituents and the aromatic rings.