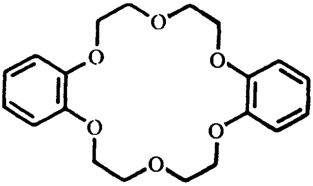
Transition Metal Complexes of Synthetic Macrocyclic Ligands

By L. F. Lindoy
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY, JAMES COOK UNIVERSITY OF NORTH QUEENSLAND, QUEENSLAND, 4811, AUSTRALIA

1 Introduction

Naturally occurring macrocyclic-ligand transition metal complexes such as complexes of the porphyrin or corrin ring systems and the industrially important metal phthalocyanine complexes have been studied for many years. More recently, a large number of other macrocyclic ligands have been synthesized and their metal complexes have been extensively studied. The present review gives an outline of the transition-metal chemistry of this latter group of cyclic ligands with an emphasis being placed on the more recent work.

The chemistry of synthetic macrocyclic ligands can be divided into two broad divisions. Firstly there are the cyclic polyethers of the 'crown' type of which (1) is a typical example.[1] Ligands of this general category have received much recent attention because of their unusual behaviour towards a range of non-transition metal ions.[2] Few studies involving transition metal ions have been reported[3] and it is evident that the majority of such polyether ligands show a limited tendency to form stable complexes with these ions.[4]



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The second category of macrocyclic ligands incorporates the synthetic ring systems containing donor atoms other than oxygen. The majority of such ligands contain nitrogen donor atoms although ligands incorporating sulphur

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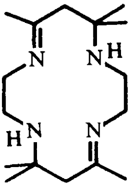
[1] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017; C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.

[2] *Structure and Bonding*, ed. J. D. Dunitz, P. Hemmerich, J. A. Ibers, C. K. Jorgensen, J. B. Neilands, D. Reinen, and R. J. P. Williams, Vol. 16, 1973.

[3] J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74**, 351.

[4] A. C. L. Su and J. F. Weiher, *Inorg. Chem.*, 1968, **7**, 176.

donors as well as phosphorus donors are also known. Typically such ligands form strong complexes with transition metal ions; structures (2),[5] (3),[6] and (4)[7] illustrate early examples of this category. Ligand (2)[5,8] was reported by Curtis in 1960 in its nickel complex and was isolated as one product from the reaction of tris(ethylenediamine)nickel(II) ion with acetone; the corresponding isomer containing *cis*-imine groups was also formed in the reaction.



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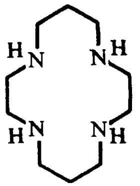

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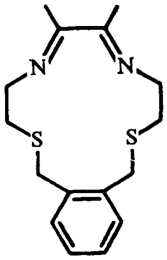

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A large number of other synthetic macrocycles have been investigated subsequently and aspects of the transition-metal chemistry of such macrocyclic systems have been discussed.[3,8–11]

2 General Considerations

The majority of all nitrogen-donor macrocycles that have been studied are quadridentate, *e.g.* ligands (2) and (3). To fully encircle a first-row transition metal ion a macrocyclic-ring size of between 13 and 16 members is required provided that the nitrogen donors are spaced such that five-, six-, or seven-membered chelate rings are produced on co-ordination.[9,10] Smaller great rings can be accommodated if the macrocycle folds and does not completely encircle the metal ion on co-ordination. For ligands incorporating sulphur donors, or for metals of larger ionic radii, there is evidence that ring sizes greater than 13 members are required to surround the metal ion.[11]

A number of larger ring macrocycles containing more than four donor atoms

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[5] N. F. Curtis, *J. Chem. Soc.*, 1960, 4409.

[6] B. Bosnich, C. K. Poon, and M. L. Tobe, *Inorg. Chem.*, 1965, **4**, 1102; C. K. Poon and M. L. Tobe, *J. Chem. Soc.* (*A*), 1967, 2069; 1968, 1549.

[7] M. C. Thompson and D. H. Busch, *J. Amer. Chem. Soc.*, 1964, **86**, 3651.

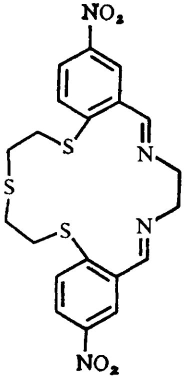
[8] N. F. Curtis, *Co-ordination Chem. Rev.*, 1968, **3**, 3; *J. C. S. Dalton*, 1974, 347 and references therein.

[9] D. H. Busch, *Helv. Chim. Acta, Fasciculus Extraordinarius Alfred Werner*, 1967, 1974; L. Y. Martin, L. J. DeHayes, L. J. Zompa, and D. H. Busch, *J. Amer. Chem. Soc.*, 1974, **96**, 4046.

[10] L. F. Lindoy and D. H. Busch, *Prep. Inorg. Reactions*, 1971, **6**, 1.

[11] D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melnyk, C. R. Sperati, and N. Tokel, in 'Bioinorganic Chemistry', Advances in Chemistry Series No. 100, American Chemical Society, New York, 1971, p. 44.

have also been prepared;[3] (5)[12] and (6)[13] illustrate ligands of this type. For co-ordination to a transition-metal ion, these large ring macrocycles generally (but not always[14]) must be capable of twisting so that favourable co-ordination geometries are achieved about the central ion. Isolated examples of related large-ring ligands incorporating more than one transition metal ion are also known; (7) is one such example.[15] However complexes of this type have been observed more frequently with polyether macrocycles and non-transition metal ions.[1–3]



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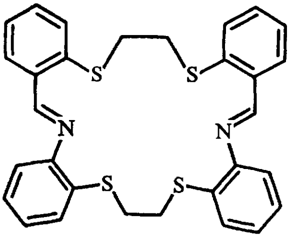

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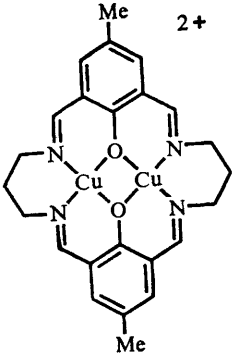

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[12] D. St. C. Black and I. A. McLean, *Inorg. Nuclear Chem. Letters*, 1970, **6**, 675.

[13] L. F. Lindoy and D. H. Busch, *Chem. Comm.*, 1968, 1589; *J. Amer. Chem. Soc.*, 1969, **91**, 4690.

[14] L. F. Lindoy, D. H. Busch, and V. Goedken, *J.C.S. Chem. Comm.*, 1972, 683; L. F. Lindoy and D. H. Busch, *Inorg. Chem.*, 1974, **13**, 2495; N. W. Alcock, D. C. Liles, M. McPartlin, and P. A. Tasker, *J.C.S. Chem. Comm.*, 1974, 727.

[15] N. H. Pilkington and R. Robson, *Austral. J. Chem.*, 1970 **23**, 2225.

Another category of polydentate macrocycles includes the polycyclic 'cages' which completely encapsulate the metal ion on co-ordination; these are discussed in a later section. A number of such complexes having unusual co-ordination geometries have now been synthesized.

It is pertinent, at this point, to consider why macrocyclic ligands often yield complexes which show unusual properties (compared with similar complexes of related open-chain ligands). There are three main considerations. Firstly, on complex formation, it is apparent that geometrical factors arising from the cyclic nature of the ligands often impose additional constraints on the positions of the donor atoms. As a reflection of these constraints, macrocyclic ligand complexes containing unusual metal–donor atom bond distances, unusual bond angles, or grossly strained chelate-ring conformations are all known. Indeed, a few examples of constraints of the latter type leading to complexes which have unusual co-ordination geometries have also been reported.[10,14]

Secondly, if the cyclic ligand is fully conjugated and incorporates $(4n+2)$ π electrons then enhanced electron delocalization and ligand stability are characteristic of the resulting Hückel aromatic system.

Thirdly, cyclic-ligand complexes are almost always found to be considerably more stable thermodynamically and kinetically (with respect to dissociation of the ligand from the metal ion) than their corresponding open-chain analogues. Such properties seem to be an intrinsic feature related to the cyclic nature of the ligands and have been collectively referred to as the macrocyclic effect.[16] Studies are still underway concerning the nature of this effect.[16,17] However, it seems clear that the enhanced thermodynamic stability does not reflect solely an increased 'chelate' effect owing to the presence of an additional chelate ring in the cyclic-ligand complex (*cf.* the analogous open-chain complex). Recent studies[17] on a series of nickel open-chain and macrocyclic amine complexes suggest that the enhanced thermodynamic stability associated with the macrocyclic effect results largely from a more favourable ΔH° term. This is so even though the donor–metal bond strengths do not appear to differ greatly between similar open-chain and macrocyclic complexes. Rather the enthalpic differences are attributed to decreased ligand solvation in the macrocycle which thus has less associated (hydrogen-bonded) water to be displaced on complex formation. Hence ΔH° for complexation of the macrocycle will be more negative than that for complexation of the linear-chain ligand which, because of its open structure, is postulated to be more highly solvated in its uncomplexed form. On the other hand although there will be a greater loss of configurational entropy on co-ordination of the linear-chain ligand, this will tend to be compensated by the more favourable ΔS° component arising from the release of a greater number of solvent molecules in this case.

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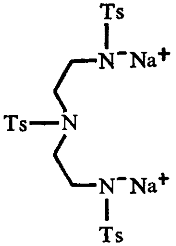
[16] D. K. Cabbiness and D. W. Margerum, *J. Amer. Chem. Soc.*, 1969, **91**, 6540; P. Paoletti, L. Fabbrizzi, and R. Barbucci, *Inorg. Chem.*, 1973, **12**, 1961.

[17] F. P. Hinz and D. W. Margerum, *J. Amer. Chem. Soc.*, 1974, **96**, 4993; *Inorg. Chem.*, 1974, **13**, 2941.

3 Typical Synthesis

Cyclic ligands have been prepared both directly, by conventional organic synthesis, and by *in situ* procedures involving cyclization in the presence of a metal ion. The 'crown' polyethers are examples of macrocycles which have been prepared mainly by direct syntheses.[1] Typically, in these preparations, the cyclization reaction is performed under conditions of moderate to high dilution in order to minimize competing linear polymerization reactions. Similarly the quadridentate amine (3; 'cyclam') can be obtained in small yield by condensation of 1,3-bis-(2′-aminoethylamino)propane and 1,3-dibromopropane in alcoholic potassium hydroxide under high dilution conditions;[6] however a recent report gives an improved procedure involving an *in situ* condensation for obtaining this cyclic amine.[18,19]

New direct synthetic procedures for obtaining related cyclic amines (and amine-ethers) in excellent yields have been developed recently.[20] A typical reaction involved the condensation of the tosylated reactants (8; Ts = tosyl) and (9) by heating in DMF at 100 °C for 1 h. The tetratosyl derivative (10) was obtained in 80% yield; the tosyl groups of (10) were readily removed by heating this product in concentrated sulphuric acid.



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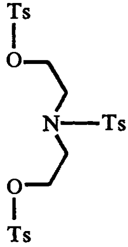

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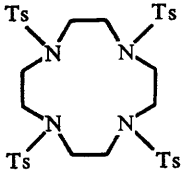

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Although a number of macrocyclic ligands can be synthesized both by direct as well as by *in situ* procedures, it is nevertheless true that a large proportion of other cyclic ligands can only be obtained *via in situ* techniques. Such cyclization reactions, in some instances, may be aided by metal-ion induced reactivity of one of the condensing functional groups as well as by steric factors involving the appropriate positioning around the co-ordination sphere of the reacting moieties in the ring-closing step. Some representative examples of such metal-ion template reactions will now be discussed.

The Schiff-base condensation between a carbonyl compound and an organic amine to yield an imine linkage has formed the basis of many successful macrocyclic-ligand syntheses;[21,22] *e.g.*, condensation of 2,6-diacetylpyridine with the

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[18] E. K. Barefield, *Inorg. Chem.*, 1972, **11**, 2273.

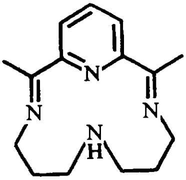
[19] E. K. Barefield and F. Wagner, *Inorg. Chem.*, 1973, **12**, 2435.

[20] J. E. Richman and T. J. Atkins, *J. Amer. Chem. Soc.*, 1974, **96**, 2268.

[21] L. F. Lindoy, *Quart. Rev.*, 1971, **25**, 379.

[22] D. St. C. Black and A. J. Hartshorn, *Co-ordination Chem. Rev.*, 1972, **9**, 219.

appropriate triamine in the presence of several transition-metal ions yields corresponding complexes of the 14-membered macrocycle (11) in high yield.[23] This approach has been adopted subsequently to the synthesis of a number of related Schiff base macrocycles based on 2,6-diacetylpyridine;[24–28] several of these latter ligands incorporate more than four donor atoms.



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The *in situ* condensation of a di-(or poly-)amine with a dicarbonyl moiety has been a common procedure for the preparation of complexes of new macrocyclic ligands. Such condensations are usually quite facile when, as in the reactions just discussed, the dicarbonyl moiety incorporates one or more donor atoms between the two carbonyl groups. Lewis acids are known to catalyse nucleophilic reactions at carbonyl-carbon atoms[29] and it has been suggested[10] that the presence of additional, appropriately spaced, donor atoms between the carbonyl groups will result in the carbonyl-containing moiety bonding more strongly to the metal ion (Lewis acid). With respect to this enhanced bonding, the ability of the dicarbonyl moiety to form a number of chelate rings is undoubtedly important. In such a situation, the activation of a carbonyl group bound to the metal ion has been ascribed to increased polarization of the carbonyl group so that attack by the amine nucleophile on the carbonyl-carbon is facilitated. Nevertheless the situation can be more complex than the simple polarization argument suggests and caution is needed when rationalizing an observed rate enhancement solely in terms of polarization effects.[30] Indeed, for a number of related reactions involving nucleophilic attack at bound carbonyl centres, the observed rate enhancements result largely, in fact, from favourable

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[23] J. D. Curry and D. H. Busch, *J. Amer. Chem. Soc.*, 1964, **86**, 592; L. F. Lindoy, N. E. Tokel, L. B. Anderson, and D. H. Busch, *J. Co-ordination Chem.*, 1971, **1**, 7 and references therein.

[24] S. M. Nelson, P. Bryan, and D. H. Busch, *Chem. Comm.*, 1966, 641.

[25] E. Fleischer and S. W. Hawkinson, *J. Amer. Chem. Soc.*, 1967, **89**, 720.

[26] R. H. Prince, D. A. Stotter, and P. R. Woolley, *Inorg. Chim. Acta*, 1974, 9, 51.

[27] R. W. Stotz and R. C. Stoufer, *Chem. Comm.*, 1970, 1682.

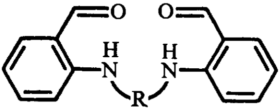
[28] J. Rikernap and D. W. Meek, *J.C.S. Chem. Comm.*, 1974, 442.

[29] R. W. Alder, R. Baker, and J. Brown, 'Mechanism in Organic Chemistry', Wiley-Interscience, London, 1971, p. 314.

[30] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Cornell University Press, Ithaca, 1953, pp. 49—52.

entropies of activation and not from favourable enthalpic terms as would be expected to occur as a consequence of polarization effects.[31]

Another related series of *in situ* cyclizations involving a moiety which contains two terminal aldehyde functions as well as other suitably-spaced donor atoms in the backbone is illustrated by the reaction of simple diamines with dialdehydes of type (12).[32] The reaction can be performed in the presence of the metal acetate so that the corresponding neutral complex, of which (13) is a typical example, is produced. Alternatively, for some of the cyclic ligands derived from (12), the free macrocycle can be prepared directly. This is in contrast with the four-nitrogen macrocycle (11) which has not been isolated free of its metal ion. Complexes of the macrocyclic ligands (14) containing two sulphur[33] or two oxygen[34] donors have also been prepared; in both cases the *in situ* cyclizations proceed smoothly, and some of the oxygen ligands have also been isolated in the absence of a metal ion. These latter macrocycles are of interest since they are intermediate in structure between the 'crown' polyethers and the macrocycles which incorporate four nitrogen donor atoms. A limited number of other related intermediate macrocycle types have been reported recently[3,20] and there



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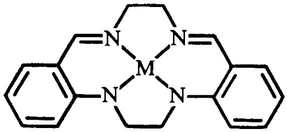

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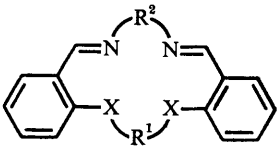

X □ S,O

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[31] D. A. Buckingham, J. MacB. Harrowfield, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1974, **96**, 1726 and references therein; D. A. Buckingham, J. Dekkers, A. M. Sargeson, and M. Wein, *J. Amer. Chem. Soc.*, 1972, **94**, 4032.

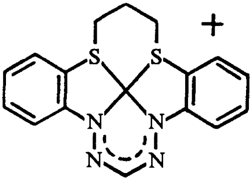
[32] M. Green and P. A. Tasker, *Chem. Comm.*, 1968, 518; M. Green, J. Smith, and P. A. Tasker, *Inorg. Chim. Acta*, 1971, **5**, 17; D. St. C. Black and P. W. Kortt; *Austral. J. Chem.*, 1972, **25**, 281; E. N. Maslen, L. M. Engelhardt, and A. H. White, *J.C.S. Dalton*, 1974, 1799.

[33] L. F. Lindoy and D. H. Busch, *Inorg. Nuclear Chem. Letters*, 1969, **5**, 525.

[34] L. G. Armstrong and L. F. Lindoy, *Inorg. Nuclear Chem. Letters*, 1974, **10**, 349; *Inorg. Chem.*, 1975, **14**, in the press.

is evidence that such ligands may show an enhanced specificity towards a number of metal-ions, relative to related ligands containing only oxygen or only nitrogen donor atoms.[3,34]

Salts of the diamagnetic complex ion (15) have been isolated from the reaction, in THF, of the dihydrazine (16) with formaldehyde in the presence of nickel ion.[35] Inherent in the synthetic strategy for this template reaction is the thought that the use of a dihydrazine moiety such as (16) may well overcome the masking of the nucleophilic character of amines which is usually observed when amines are co-ordinated to metal ions.[21] Unlike a co-ordinated amine, a co-ordinated hydrazine still contains a nitrogen with an unshared electron-pair which may participate in nucleophilic condensation reactions. For co-ordinated amines [*e.g.* (17)[36]] such reactions are usually inhibited unless the amine first dissociates from the metal ion.[21] The preparation of (15) is typical of a number of other recent *in situ* syntheses in which hydrazine (or hydrazone) precursors are involved.[37–39]



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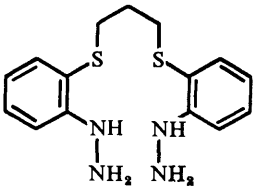

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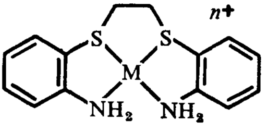

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6,6′-Dihydrazino-2,2′-bipyridyl has recently been demonstrated[39] to be a highly reactive precursor for the formation of macrocyclic ligands. On complexation this dihydrazine chelates strongly through the α-di-imine nitrogens of the bipyridyl residue but steric influences allow only weak interaction between the metal and the terminal amines of the hydrazine groups. Such groups are

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[35] N. W. Alcock and P. A. Tasker, *J.C.S. Chem. Comm.*, 1972, 1239.

[36] L. F. Lindoy, unpublished work.

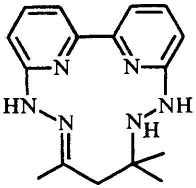
[37] V. L. Goedken and S. Peng, *J.C.S. Chem. Comm.*, 1973, 62.

[38] C. M. Kerwin and G. A. Melson, *Inorg. Chem.*, 1973, **12**, 2410; 1972, **11**, 726; G. A. Melson, *Inorg. Chem.*, 1974, **13**, 994; V. L. Goedken, Y. Park, S. Peng, and J. M. Norris, *J. Amer. Chem. Soc.*, 1974, **96**, 7693.

[39] J. Lewis and K. P. Wainwright, *J.C.S. Chem. Comm.*, 1974, 169.

thus in a state of unusually high lability and nucleophilicity. Indeed the nickel(II) complex reacts with refluxing aqueous acetone in a few minutes with the formation, in near-quantitative yield, of the nickel complex of the Curtis type macrocycle (18). These conditions are the mildest yet observed for ring-closing reactions of the Curtis type.

The synthesis of a quadridentate macrocycle derived from another 'classical' chelating ligand (namely, 1,10-phenanthroline) has also been achieved recently.[40] From the reaction of 2,9-dichloro-1,10-phenanthroline with 2,9-diamino-1,10-phenanthroline in nitrobenzene in the presence of potassium carbonate, the macrocycle (19) can be isolated in high yield. This reaction provides an example of another category of macrocycle direct synthesis. Unlike the previously discussed examples, the present cyclization involves sites which are remote from the donor atoms. Reaction of (19) with copper chloride in nitrobenzene leads to the loss of two protons with the formation of the neutral metal complex.



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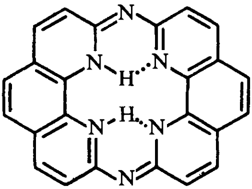

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4 Reactions Involving Co-ordinated Macrocyclic Ligands

A number of macrocyclic-ligand complexes have been chemically modified to produce new cyclic-ligand complexes. The relative kinetic inertness of most macrocyclic-ligand complexes (even when they contain normally labile metal ions) makes such systems ideal for the study of metal-ion-influenced ligand reactions since the prospect of ligand dissociation during the course of the reaction is much reduced.

Redox reactions involving chemical, electrochemical, and catalytic procedures are collectively the most studied group of cyclic ligand reactions. Oxidative dehydrogenations of a range of cyclic-ligand complexes have been reported using a variety of chemical oxidizing agents. In most instances the reaction has involved the conversion of co-ordinated secondary amines to imine functions. The reverse process, *viz.* hydrogenation of an imine to an amine, is also facile for many cyclic ligand complexes. Hydrogenations of this type have frequently been achieved catalytically (H_2 in the presence of Raney nickel or a precious metal catalyst) or chemically, using reagents such as sodium borohydride. Both reactions have also been performed electrochemically.[41]

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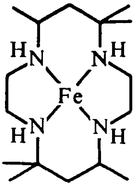
[40] S. Ogawa, T. Yamaguchi, and N. Gotoh, *J.C.S. Chem. Comm.*, 1972, 577.

[41] F. V. Lovecchio, E. S. Gore, and D. H. Busch, *J. Amer. Chem. Soc.*, 1974, **96**, 3109 and references therein.

Starting from the nickel complex of (11), it has been possible, by a combination of selective hydrogenations and chemical oxidations, to produce a range of derivatives containing from zero to three imine linkages, respectively.[42,43] The nickel complexes of a range of Curtis macrocycle derivatives containing from zero to four imine groups have also been isolated as the products of a similar series of redox reactions.[8]

There is evidence that redox reactions of the type just described are metal-ion dependent both in the ease with which a reaction takes place as well as in the nature of the product formed. These points are well illustrated by comparison of the oxidation of the Curtis iron(II) complex (20) with that of its nickel(II) analogue. In acetonitrile, the former undergoes a stepwise reaction with molecular oxygen to yield (21) as the final product;[44] whereas, for the nickel complex, oxidation leads to the tetra-imine species (22).[8] As in this case, it is generally true that iron(II) complexes undergo more facile oxidative dehydrogenations than do their nickel(II) analogues.[44] Furthermore if the diene complex (23) is used as the starting complex then on reaction with oxygen in acetonitrile, an intermediate of type (24) initially forms but this spontaneously tautomerizes to (25).



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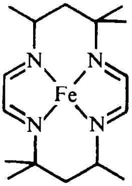

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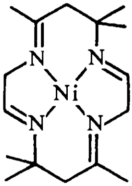

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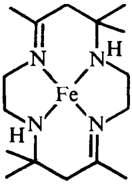
Compared with the behaviour of the corresponding nickel system,[8] the above



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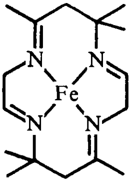

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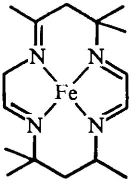

(25)

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[42] E. K. Barefield, F. V. Lovecchio, N. E. Tokel, E. Ochiai, and D. H. Busch, *Inorg. Chem.* 1972, **11**, 283.

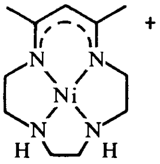
[43] J. L. Karn and D. H. Busch, *Inorg. Chem.*, 1969, **8**, 1149.

[44] J. C. Dabrowiak, F. V. Lovecchio, V. L. Goedken, and D. H. Busch, *J. Amer. Chem. Soc.*, 1972, **94**, 5502; V. L. Goedken and D. H. Busch, *ibid*, 1972, **94**, 7355.

reactions clearly indicate the well-known preference[45] of iron(II) for ligands containing an α-di-imine linkage.

The ligand oxidative dehydrogenations so far discussed have all involved the introduction of unsaturation adjacent to nitrogen donor atoms. Examples of unsaturation being introduced between adjacent carbons in the backbone of a chelate ring are also known although such reactions have been observed less frequently. An example of this class of reaction involves the nickel complex (26) which incorporates a negatively charged electron-delocalized chelate ring derived from acetylacetone.[46] On reaction with bromine in acetonitrile, this complex yields (27) in which a localized C=C linkage has been introduced into the six-membered chelate ring; conjugation has also been extended into an adjacent chelate ring.

Oxidations in which unsaturation is introduced between carbon atoms in five-membered chelate rings have also been reported recently.[47] Such reactions involve nickel(II) and copper(II) complexes of type (28). Treatment of these complexes with three equivalents of trityl tetrafluoroborate in acetonitrile leads to oxidative dehydrogenation such that 15π-electron species of type (29) are produced. Reduction of (29) with sodium borohydride in ethanol yields the uncharged 16π-electron species (30). Voltammetric studies indicate that (29), (30), and (31) are interconvertible by means of a series of one-electron (reversible) redox steps; the terminal member of this series (31) contains a stable (4n+2) π-electron ring system.



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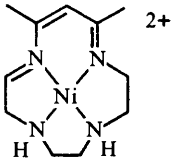

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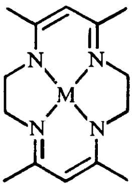

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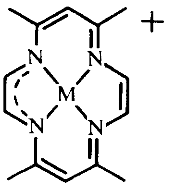

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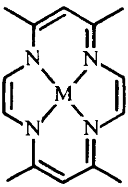

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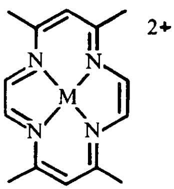


(31)

[45] L. F. Lindoy and S. E. Livingstone, *Co-ordination Chem. Rev.*, 1967, **2**, 173.

[46] C. J. Hipp, L. F. Lindoy, and D. H. Busch, *Inorg. Chem.*, 1972, **11**, 1988.

[47] T. J. Truex and R. H. Holm, *J. Amer. Chem. Soc.*, 1972, **94**, 4529.

There is considerable evidence that higher oxidation states of the central metal are involved in the mechanisms of many ligand oxidative dehydrogenations of the type so far described;[41,44,46-48] *e.g.*, oxidation of nickel(II) and iron(II) complexes may proceed *via* generation of the respective tervalent states followed by intramolecular redox processes in which the ligand is oxidized. Indeed, examples have been reported of iron(III) macrocyclic-ligand complexes spontaneously generating new imine linkages *via* oxidative dehydrogenations under certain conditions.[44] In addition, it has been possible to isolate a number of macrocyclic-ligand nickel(III) complexes as products from oxidation reactions on selected corresponding nickel(II) species.[49,50] Typically, chemical oxidizing agents such as concentrated nitric acid, ammonium persulphate, or nitrosyl tetrafluoroborate in acetonitrile have been used in these syntheses.

Electrochemical studies have amply demonstrated the ability of certain macrocyclic ligands to stabilize a wide range of oxidation states of co-ordinated metal ions.[41,51-53] The relative stabilities of the bi- and tervalent oxidation states of iron depend on the degree and nature of the unsaturation in the attached cyclic ligand.[44] Cyclic voltammetry indicates that each of the iron(II) complexes (20), (21), (23), and (25) can be reversibly oxidized in acetonitrile to its iron(III) analogue. Such complexes of tervalent iron have also been prepared directly and shown to reduce at the expected half-wave potentials. Whereas the $E_{\frac{1}{2}}$ value for the Fe^{II}/Fe^{III} couple becomes slightly more positive for each additional isolated double bond introduced into the ligand, the presence of an α-di-imine linkage has a much more dramatic effect and leads to considerably greater positive shifts of $E_{\frac{1}{2}}$.

Nickel(II) complexes of a range of neutral (*e.g.*, cyclam) and dianionic macrocyclic ligands have also been demonstrated to undergo one-electron electrochemical oxidations to yield stable six-co-ordinate and square-planar nickel(III) species,[41] respectively. The authenticity of the nickel(III) state (d^7 configuration) in these compounds cannot be established unambiguously from magnetic moment measurements alone since the technique is unable to rule out the alternative possibility that the compounds are nickel(II) species containing stabilized cation radical ligands. However e.p.r. studies clearly indicate that the unpaired electron is localized on the nickel ion in each case; the compounds are therefore correctly formulated as nickel(III) species.

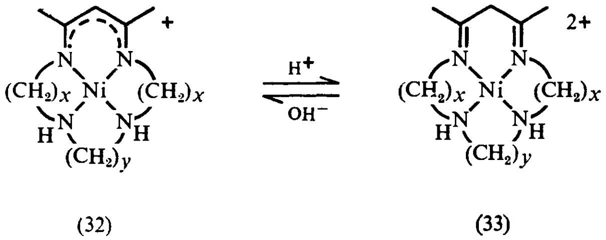
The complementary one-electron reduction products of the above complexes have also been studied.[41] In the case of the uncharged-ligand complexes the e.p.r. spectra fall into two categories. For the complexes of saturated ligands or for those containing isolated imine groups, axial symmetric spectra are observed with $g_{\perp} < g_{\parallel}$. Such spectra are consistent with the presence of nickel(I) (d^9) species.

[48] D. F. Mahoney and J. K. Beattie, *Inorg. Chem.*, 1973, **12**, 2561 and references therein.
[49] E. K. Barefield and D. H. Busch, *Chem. Comm.*, 1970, 522.
[50] E. Gore and D. H. Busch, *Inorg. Chem.*, 1973, **12**, 1.
[51] D. C. Olson and J. Vasilevskis, *Inorg. Chem.*, 1969, **8**, 1611.
[52] D. C. Olson and J. Vasilevskis, *Inorg. Chem.*, 1971, **10**, 463.
[53] D. P. Rillema, J. F. Endicott, and E. Papaconstantinou, *Inorg. Chem.*, 1971, **10**, 1739.

However, for complexes containing α-di-imine groupings, an isotropic e.p.r. spectrum (containing no hyperfine splitting) is observed with a g value close to that of the free electron. Clearly the unpaired electron in these systems is delocalized on the ligand and such complexes are best formulated as containing nickel(II) co-ordinated to a stabilized anion-radical ligand. Hence, as with the iron complexes discussed above, the presence of an α-di-imine group stabilizes the bivalent state of nickel relative to the tervalent state.

These results form part of a recent extensive study[41] of the influence of structural and electronic parameters on the electrochemical redox behaviour of a range of four-nitrogen macrocyclic complexes of nickel(II). The redox behaviour of such complexes in a given solvent is a composite function of a range of factors such as ring size, ring substituents, degree and type of unsaturation, charge type, and co-ordination number. It has been possible to document, in a semi-quantitative manner, the effects of such factors and a concept of additivity of structural contributions to redox behaviour has been proposed.

A second category of the reactions of co-ordinated macrocycles involves the acid–base properties of certain ligands of this type. The reversible protonation of the charge-delocalized six-membered chelate ring in nickel(II) and copper(II) complexes of type (32) to yield species of type (33) has recently been investigated.[54,55] The pK_a for the dissociation is markedly metal-ion dependent; *e.g.*, for 14-membered macrocycles the pK_a of the nickel complex is 6.45 while for the copper analogue a pK_a of 9.3 was observed. The values obtained for the 13-membered macrocyclic complexes are of the same order of magnitude as above but there is a considerable decrease in acidity for the 15-membered macrocyclic complexes. Although the reasons for these differences are somewhat obscure, an explanation based on different degrees of steric crowding has been proposed. Other examples of related reversible protonations have also been documented.[11,56,57]



Ligand-substitution reactions provide a further category of reactions involving co-ordinated macrocyclic ligands, and a number of such substitution reactions have been studied. An example is the alkylation of co-ordinated

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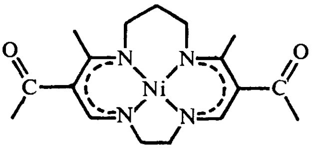
[54] J. G. Martin and S. C. Cummings, *Inorg. Chem.*, 1973, **12**, 1477.
[55] J. G. Martin, R. M C. Wei, and S. C. Cummings, *Inorg. Chem.*, 1972, **11**, 475.
[56] C. J. Hipp and D. H. Busch, *J.C.S. Chem. Comm.*, 1972, 737.
[57] E. Jäger, *Z. Chem.*, 1968, **8**, 30.

(secondary) amines of bound macrocyclic ligands. Such co-ordinated amines normally do not show nucleophilic properties; however, an amide nucleophile is generated on deprotonation. The conditions for performing such *N*-deprotonations and *N*-alkylations have been well established previously[58] and the reaction has been extended to a number of fully saturated cyclic-ligand complexes such as the nickel complex of cyclam (3).[59] In this case the nickel complex of tetra-methylated cyclam is produced and this is a typical product of such reactions.[59]

Tetra-methylated cyclam can also be prepared by direct[19,60] organic synthesis and interestingly, when it is treated with nickel ion, a kinetically labile complex is produced.[19] In contrast, the similar complex resulting from ligand alkylation *in situ* is remarkably kinetically inert.[59] The different kinetic stabilities of these two products reflect different configurations of the four *N*-methyl groups. Apparently the product from the synthesis involving pre-formed ligand has the four methyl groups arranged on the same side of the co-ordination plane defined by the four donor nitrogen atoms.[19] In contrast, a crystal structure determination on the product from the *in situ* reaction indicates that this complex contains two of the methyl groups above and two below the co-ordination plane of the four nitrogen donors.[59]

The reactions of various reagents (particularly electrophiles) towards a range of macrocyclic complexes containing acetyl-substituted charge-delocalized chelate rings has recently been reported.[56,61] The neutral complex (34) is typical of the compounds used in these studies and in several instances the reactivity patterns observed resemble those of transition-metal corrole complexes. The acetyl groups of (34) are displaced by protonation of the carbons to which they are attached. Subsequent studies have indicated that a range of nitrogen electrophiles also effect electrophilic displacement reactions so that the corresponding dinitro-species, *e.g.* (35), are produced. Sodium nitrite and trifluoroacetic acid in acetonitrile, nitric oxide in the presence of air, nitrosyl tetrafluoroborate in dichloromethane (under oxidizing conditions) and concentrated nitric acid have all been used for reactions of this type. Hence the dinitro-species can be produced either by nitrosation under oxidizing conditions or by direct nitration. The



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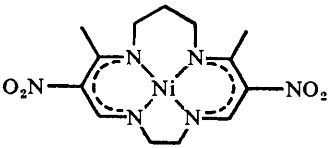

(35)

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[58] G. W. Watt and P. W. Alexander, *Inorg. Chem.*, 1968, **7**, 537 and references therein.

[59] F. Wagner, M. T. Mocella, M. J. D'Aniello, A. H. J. Wang, and E. K. Barefield, *J. Amer. Chem. Soc.*, 1974, **96**, 2625.

[60] R. Buxtorf and T. A. Kaden, *Helv. Chim. Acta* (*A*), 1974, **57**, 1035.

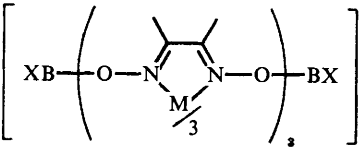
[61] C. J. Hipp and D. H. Busch, *Inorg. Chem.*, 1973, **12**, 894.

success of these reactions thus confirms the considerable nucleophilic character of the reaction sites of the precursor complexes.

5 The Cage Macrocycles

Over the past few years complexes of a number of novel three-dimensional 'cage-like' macrocyclic ligands (clathrochelates) have been synthesized. These ligands encapsulate the central metal ions and the resulting complexes often exhibit unusual properties. For complexes of this type investigations pertaining to stereochemistry, metal-ion redox behaviour, and metal-ion transport across membranes are of special interest. Examples of cage-ligand complexes are (36)[62] and (37).[63,64]

The synthesis of (36; X = F) was based on the previously reported procedure[65] involving reaction of boron trifluoride etherate with bis(dimethylglyoximato)-nickel(II). The product of this reaction is the very stable complex (38; M = Ni^{II})



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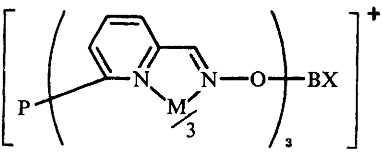

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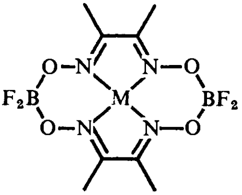

(38)

in which —BF_2— linkages have bridged adjacent oxime groups. In a related fashion, the reaction of the tris(dimethylglyoximato)cobalt(III) anion and boron trifluoride yields the cage (36; M = Co^{III}, X = F, n = 1).[62] Apart from the boron halides, a number of other Lewis acids such as $SnCl_4$, $SiCl_4$, and H_3BO_3

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[62] D. R. Boston and N. J. Rose, *J. Amer. Chem. Soc.*, 1968, **90**, 6859.

[63] J. E. Parks, B. E. Wagner, and R. H. Holm, *J. Amer. Chem. Soc.*, 1970, **92**, 3500; *Inorg. Chem.*, 1971, **10**, 2472.

[64] E. Larsen, G. N. La Mar, B. E. Wagner, J. E. Parks, and R. H. Holm, *Inorg. Chem.*, 1972, **11**, 2652.

[65] G. N. Schrauzer, *Chem. Ber.*, 1962, **95**, 1438; D. Thierig and F. Umland, *Angew. Chem.*, 1962, **74**, 1438.

have been used for similar capping reactions.[66] More recently it has been shown that there is no need to isolate the intermediate tris-dioxime complex but that the required clathrochelate can be isolated directly from a mixture of all reactants.[67] This latter *in situ* procedure has been used to obtain iron(II) clathrochelates of type (36) with X = F, OH, OMe, OEt, OPr^i, or OBu^n and $n = 0$.

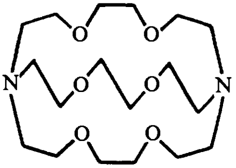
A similar capping procedure has also been used to prepare clathrochelates of type (37; M = Fe^{II}, Co^{II}, Ni^{II}, or Zn^{II}) from the complexes of the corresponding trigonally symmetric sexadentate ligand containing a phosphorus bridgehead and three terminal oxime groups.[63,64] Both boron trifluoride and the tetrafluoroborate ion were used as capping reagents in this case.

It is clear from a number of *X*-ray structural studies[68,69] that both the cage types above show a tendency to promote a trigonal prismatic co-ordination geometry about the central metal ion; examples of such complexes which are almost exactly trigonal prismatic as well as structures showing various degrees of distortion from this basic geometry are known.

The *in situ* preparations of metal complexes of a new cage derived from three molecules of the bis-hydrazone of biacetyl (and capped by reaction with formaldehyde) have been reported.[37] Although the synthetic procedure falls into the category previously discussed involving condensation at terminal hydrazine or hydrazone moieties little can be said, in the absence of further studies, about the generality of such a capping procedure for the preparation of other cages.

A number of polyether-amine cages related to the 'crown' macrocycles have now been prepared and their behaviour towards an extensive range of non-transition ions has been studied in considerable detail.[2,3] Such ligands are usually synthesized directly; (39) and (40) are two typical examples having different cavity sizes. A feature of such ligands is that they are flexible enough to allow entry of suitably sized cations without ligand rupture.

The complexation of (40) with cobalt(II) has recently been reported.[70] The structure of the resulting cation indicates that the cobalt is completely enclosed within the cavity and is bonded to each of the seven donor atoms in a distorted



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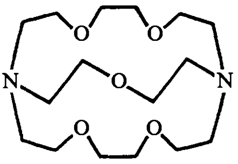

(40)

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[66] D. R. Boston and M. J. Rose, *J. Amer. Chem. Soc.*, 1973, **95**, 4163.

[67] S. C. Jackels and N. J. Rose, *Inorg. Chem.*, 1973, **12**, 1232; S. C. Jackels, D. S. Dierdorf, N. J. Rose, and J. Zektzer, *J.C.S. Chem. Comm.*, 1972, 1291.

[68] G. A. Zakrzewski, C. Chilardi, and E. C. Lingafelter, *J. Amer. Chem. Soc.*, 1971, **93**, 4411.

[69] M. R. Churchill and A. H. Reis, *Chem. Comm.*, 1970, 879; 1971, 1307; *Inorg. Chem.*, 1972, **11**, 1811, 2299; 1973, **12**, 2280; *J.C.S. Dalton*, 1973, 1570.

[70] F. Mathieu and R. Weiss, *J.C.S. Chem. Comm.*, 1973, 816.

pentagonal bipyramid co-ordination geometry. One of the factors that appears to influence the formation of this unusual geometry is the small size of the cobalt(II) ion with respect to the ligand cavity. The situation appears to parallel that which obtains in a number of metallo-enzymes in which constraints in the immediate vicinity of the metal ion are also known to result in unusual co-ordination geometries.[71]

6 Macrocyclic Ligand Complexes Related to the Biological Macrocyclic Systems

Synthetic ring complexes which copy aspects of the behaviour of the more complicated natural macrocyclic-ring systems (such as those containing porphyrin or corrin rings) are known and at present the study of such compounds is receiving much attention. Although the results obtained so far do not always closely parallel those in nature, a knowledge of the chemistry is being built up and the biochemical role of metal ions in the natural systems is beginning to be better understood. In this section selected examples of the use of synthetic macrocyclic complexes for model studies are briefly discussed.

Since the discovery that the natural product, coenzyme B_{12}, is a cobalt(III) corrinoid complex containing a σ-bonded alkyl ligand (occupying an axial position),[72] there has been much interest in the preparation and study of synthetic analogues of vitamin B_{12} and its coenzymes. A large number of model compounds containing stable cobalt-alkyl moieties have now been reported, and much interest has centred on the factors influencing stabilization of the cobalt–carbon bond.[11,73–75] The majority of the model compounds so far prepared have contained unsaturated nitrogen-donor ligands (not necessarily macrocyclic) in the equatorial plane. For example, bis(dimethylglyoximato)cobalt derivatives[73] (the cobaltoximes) show many of the reactions of the B_{12}-systems; so do the corresponding cyclic derivatives of type (38). Other cobalt-containing macrocycles such as (11) have also been used for similar studies.[11] For such unsaturated ligands, synthesis of the respective cobalt–alkyl species has very often involved the reaction of a corresponding cobalt(I) or cobalt(II) precursor with alkyl halide although other synthetic procedures have also been successfully employed.[76] It has generally been assumed that unsaturated ligands in the equatorial plane are a prerequisite for the formation of stable cobalt(III)–alkyl bonds. However a recent photochemical procedure has enabled the isolation of stable cobalt(III)-alkyl complexes of saturated macrocycles such as cyclam.[77] Thus it seems clear

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[71] D. D. Ulmer and B. L. Vallee, in ref. 11, p. 187.

[72] P. G. Lenhert and D. C. Hodgkin, *Nature*, 1961, **192**, 937.

[73] G. Schrauzer, *Accounts Chem. Res.*, 1968, **1**, 97; H. A. O. Hill, J. M. Pratt, and R. J. P. Williams, *Discuss. Faraday Soc.*, 1969, **47**, 165; J. Lewis, R. H. Prince, and D. A. Stotter, *J. Inorg. Nuclear Chem.*, 1973, **35**, 341; D. G. Brown, *Progr. Inorg. Chem.*, 1973, **18**, 177.

[74] J. M. Pratt, 'Inorganic Chemistry of Vitamin B_{12}', Academic Press, New York, 1972; J. M. Pratt and P. J. Craig, *Adv. Organometallic Chem.*, 1973, **11**, 331.

[75] M. Green, J. Smith, and P. A. Tasker, *Discuss. Faraday Soc.*, 1969, **47**, 172; L. M. Engelhardt and M. Green, *J.C.S. Dalton*, 1972, 724.

[76] V. L. Goedken, S. M. Peng, and Y. Park, *J. Amer. Chem. Soc.*, 1974, **96**, 284 and references therein.

[77] T. S. Roche and J. F. Endicott, *Inorg. Chem.*, 1974, **13**, 1575.

from the model studies that neither highly unsaturated nor macrocyclic ligands are essential for the stabilization of cobalt–alkyl bonds of the type found in the B_{12} series. Nevertheless the special properties (*e.g.* unusual redox properties[78]) that result from incorporation of the highly unsaturated corrin ring in vitamin B_{12} and related coenzymes are no doubt of major importance to other aspects of the biological function of this important group of compounds.

A common feature of the cobalt in vitamin B_{12} as well as the iron in such species as cytochrome *c*, haemoglobin, and myoglobin is that one of the axial co-ordination positions is occupied by a heterocyclic base (*viz.* an imidazole derivative). Synthetic planar quadridentate macrocycles containing flexible side-chains incorporating appropriately positioned nitrogen donor groups (mainly heterocyclic) have been reported recently.[79,80] In these the side-chains are of sufficient length to permit the attached nitrogen donors to occupy a position axial with respect to the plane of the macrocycle. The iron(II) complex (41) of one such ligand has been used as a model for the myoglobin active site.[80] This complex binds oxygen reversibly both in solution (in methylene chloride at −45 °C) and in the solid state and, like myoglobin and haemoglobin, binds carbon monoxide more strongly than it binds oxygen.

It has been known for a considerable time that a variety of cobalt(II) complexes of both cyclic and non-cyclic ligands will reversibly bind molecular oxygen at room temperature.[81] However, previous solution studies involving corresponding iron(II) complexes have characteristically resulted in oxygen-uptake followed by autoxidation during which the iron(II) is converted into the tervalent state.[11,82] Oxygen-uptake is thus irreversible in such cases.

Recent studies,[83–86] all at low temperature, have shown that the covalent attachment of an imidazole derivative to the haem group such as occurs in (41) is not essential for reversible oxygenation but that, under controlled conditions in solution, oxygenation will also occur in the presence of non-attached amines. Nevertheless, although not essential for reversible oxygenation, covalent attachment of the imidazole to the haem group does still appear to aid the reaction.[84]

It has been suggested[87] that one mechanism for autoxidation of iron(II) complexes involves the initial 1:1 binding of molecular oxygen by the iron(II)

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[78] N. S. Hush and I. S. Woolsey, *J. Amer. Chem. Soc.*, 1972, **94**, 4107.

[79] K. B. Sharpless and H. P. Jensen, *Inorg. Chem.*, 1974, **13**, 2617; V. Katovic, L. T. Taylor, and D. H. Busch, *J. Amer. Chem. Soc.*, 1969, **91**, 2122.

[80] C. K. Chang and T. G. Traylor, *Proc. Nat. Acad. Sci. U.S.A.*, 1973, **70**, 2647; *J. Amer. Chem. Soc.*, 1973, **95**, 5810, 8475, 8477.

[81] R. G. Wilkins, in ref. 11, p. 111; M. J. Carter, D. P. Rillema, and F. Basolo, *J. Amer. Chem. Soc.*, 1974, **96**, 392 and references therein.

[82] J. H. Wang, A. Nakahara, and E. B. Fleischer, *J. Amer. Chem. Soc.*, 1958, **80**, 1109; J. P. Collman and C. A. Reed, *ibid.*, 1973, **95**, 2048.

[83] G. C. Wagner and R. J. Kassner, *J. Amer. Chem. Soc.*, 1974, **96**, 5593.

[84] W. S. Brinigar and C. K. Chang, *J. Amer. Chem. Soc.*, 1974, **96**, 5595.

[85] D. L. Anderson, C. J. Weschler, and F. Basolo, *J. Amer. Chem. Soc.*, 1974, **96**, 5599.

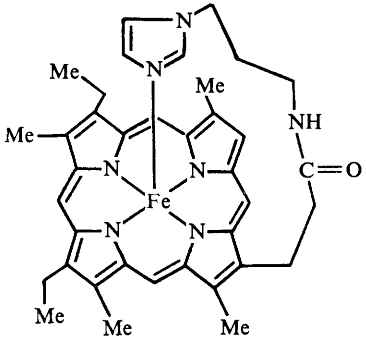
[86] J. Almog, J. E. Baldwin, R. L. Dyer, J. Huff, and C. J. Wilkerson, *J. Amer. Chem. Soc.*, 1974, **96**, 5600.

[87] J. E. Baldwin and J. Huff, *J. Amer. Chem. Soc.*, 1973, **95**, 5757 and references therein.

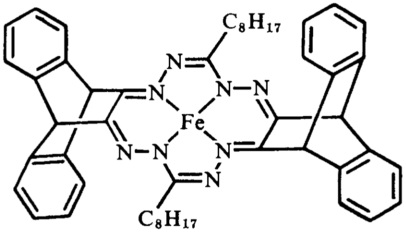
followed by a rapid bimolecular redox process which eventually leads irreversibly to an iron(III) complex:

$$Fe^{II} + O_2 \rightleftharpoons Fe^{II}O_2 + Fe^{II} \rightarrow Fe^{II}O{-}OFe^{II} \rightarrow Fe^{III}$$

If such is the case then autoxidation should be suppressed by constructing a bulky organic ligand which would effectively sterically prevent the formation of the intermediate iron(II) oxygen-bridged species;[87] the situation might then be similar to that in haemoglobin in which the haem groups occupy molecular cavities in the globin portion of the molecule.[88] The syntheses of iron complexes of ligands which are able to enclose a bound O_2 molecule in a cavity of organic material have been achieved recently.[87,89,90] Following the initial synthesis of (42)[87], which reversibly binds oxygen at low temperatures and which contains a cavity (with two open sides), the iron(II) complex of the 'picket fence' ligand (43) was prepared.[89] This synthetic porphyrin derivative undergoes reversible oxygenation *at room temperature* in the presence of various bases; moreover the molecular oxygen adduct (with *N*-methylimidazole as the axial ligand) has been characterized by an *X*-ray structural analysis.[91] Like oxyhaemoglobin this complex is diamagnetic. The iron(II) lies in the plane of the porphyrin ring and the iron–oxygen bond is bent in a manner previously predicted for oxyhaemoglobin.[92] There also appears to be substantial double-bond character in the iron–oxygen bond.[91,93]



(41)



(42)

Based in part on the results of the studies discussed above, a second iron(II)

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[92] L. Pauling, *Stanford Med. Bull.*, 1948, **6**, 215; *Nature*, 1964, **203**, 182.

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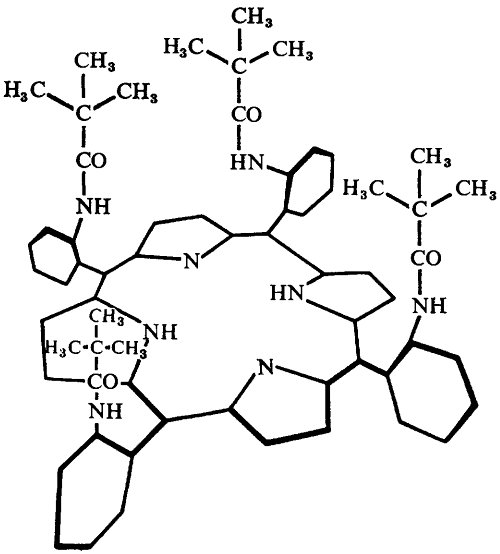
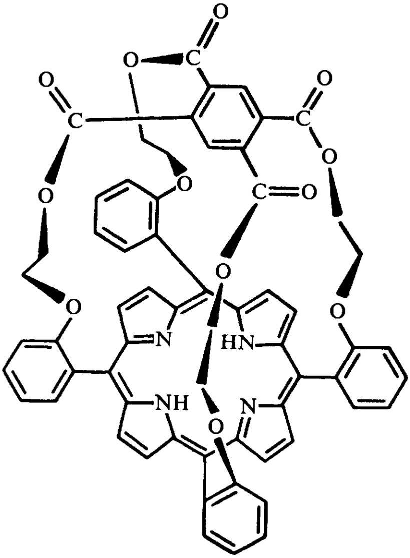


(43)

complex has been synthesized[90] which also binds molecular oxygen at room temperature. This new complex contains the synthetic 'capped' porphyrin (44)



(44)

and is so designed that the organic cavity above the porphyrin plane is large enough to admit molecular oxygen but will not allow entry of other small molecules such as those of the solvent. In the presence of heterocyclic base, an oxygen adduct is readily formed. The stability towards oxidation of the oxy-complex depends markedly on the type and concentration of the heterocyclic base present. The rate of autoxidation is reduced under conditions which favour co-ordination of base in the axial site opposite the 'capped' side of the molecule. It appears that when this axial site is unoccupied, attack by molecular oxygen can also occur at this then unprotected position. Indeed, if no base is present in the reaction solution then autoxidation occurs rapidly on exposure to oxygen.

Clearly, if the axial base could be held in position by a covalent linkage of the type found in (41) then the resulting complex should be a very efficient oxygen carrier and one that, in essence, contains all the basic structural attributes of the haemoglobin active site.