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Synthesis and coordination chemistry of topologically constrained azamacrocycles

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Contents

Abstract

Bridging superstructures added to small azamacrocycles, through the accompanying additional topological constraint, enhance the characteristic that makes azamacrocycles indispensable ligands for transition metal coordination including biomimetic chemistry: high complex stability. This review begins by briefly revisiting the coordination chemistry concepts leading to this advantage over less topologically complex ligands. Then, it details the approaches used to synthesize such bridged azamacrocycles, including direct organic synthesis, the use of templates, protection/deprotection chemistry, and various condensation reactions. The example of a specific ligand type and its transition metal complexes, which are useful for biomimetic applications, illustrates the potential of the field and lead to some general conclusions.

Keywords: Bridged macrocycle; Macrobicycle; Azamacrocycle; Topoligical constraint

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1. Factors for strong binding: molecular organization

Macrocycles are important and powerful ligands, ubiquitous in transition metal coordination chemistry for the following reasons: (1) they mimic important biological ligands developed long ago by nature, for example the porphyrin prosthetic group of many metalloproteins [1]. (2) They impart thermodynamic and kinetic stabilities to their metal complexes uncommon or non-existent with ligands of less complex topology. For the purposes of this review, a macrocycle is defined as a cyclic compound with nine or more members including at least three donor atoms [2]. In this review, topologically constrained azamacrocycles, defined as macrocycles having additional bridges besides the basic parent ring between nitrogen atom donors, will be discussed. Special attention will be paid to a unique class of macrocycles consisting of cross-bridged macrocyclic ligands having added components of topological and rigidity constraints. These impart exceptional kinetic and thermal stabilities to the complexes, dramatically accentuating the advantages of macrocyclic ligands, both (1) and (2) above.

The characteristics present in macrocycles leading to their uncommonly stable metal complexes are now fairly well understood, and can be grouped together under the term 'molecular organization' [3]. It will be useful to review these factors with simple systems in order to illustrate their utilization in the topologically constrained azamacrocycle complexes that are the subject of this review.

The two major areas of molecular organization, as related to coordination chemistry, are complementarity and constraint factors. To construct the ultimately stable metal–ligand complex, both of these factors should be maximized. Complementarity, the sum of size, geometry, and electronics matching between the metal ion and the ligand is conceptually the simplest of these two to understand and to manipulate. For a given metal ion, selection of the electronic properties, number, geometrical arrangement, and bond distance of donor atoms to maximize complex stability, either using predictive theory or by iterative experimentation or a combination of the two, results in the best pairing from the range of possibilities. Much of the theory and experimentation necessary to make an advantageous selection is well established and constitutes the vast database of coordination chemistry knowledge.

Since there are a finite number of metal ions, donor types, geometries, and useful ligand sizes, it is apparent that for a given metal ion, the complementarity of a ligand can be maximized. But, maximizing complementarity is only the first step in maximizing metal–ligand complex stability [3]. It is only through the exploitation of the constraint factors that metal–ligand binding can be increased further. Constraint is concerned with the number and flexibility of the connections between those donor atoms. Complementarity may be described as a 'first-order' factor for complex stability; it is a requirement of stable complexes, but can only be improved to a finite level. Constraint, on the other hand, might be described as a 'second-order' factor.

As will be seen below, constraint is concerned with ligand rigidity and complexity, factors of seemingly infinite variability. These parameters can be manipulated to produce large jumps in complex stability compared with ligand systems that lack them, if care is taken to maintain the difficultly achieved complementarity relationships.

The components of constraint are *topology*, here meaning the interconnectedness of ligand donor atoms, and *rigidity*, how fixed in space those donor atoms are with respect to each other [3]. Among the two, topology is the most well studied, variously described in the chelate, macrocyclic, and cryptate effects, which will be considered in turn below. Rigidity, although intimately involved in the three effects just mentioned, has been less well treated both theoretically and experimentally.

The linking of two donor atoms together results in a chelate. Surprisingly, such a linkage results in a large increase in the binding constants with metal ions as compared with the separate donor groups. Various causes for this phenomenon have been described, [4–6] and though not exhaustively, some will be delineated here using amine donors as examples. The common thermodynamic rationalization for the chelate effect points out the increase in entropy associated with chelate binding as compared with the binding of separate monodentate donors. This arises because there is an increase in the total number of particles in the former (Fig. 1). A second explanation of the chelate effect is the increased effective concentration [4,7] of the second donor, because its distance from the metal ion is fixed by the link to the bound first donor. This distance is short compared with an unlinked second donor, whose average distance from the metal ion will depend primarily on its concentration (Fig. 2). A variation of this rationalization of the chelate effect is that the formation of the second M–N bond is abnormally fast, compared with an unlinked second donor. The dissociation of the individual donors, in a flexible chelate, is as fast as that for a corresponding monodentate ligand. Experiments with $Ni(trien)^{2+}$ (trien = triethylenetetraamine) show the individual Ni–N bond

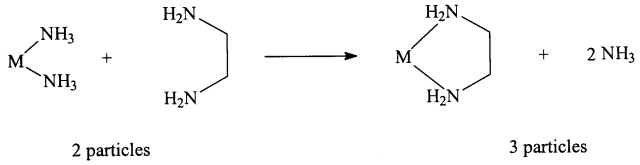

Fig. 1. Entropy in the chelate effect.

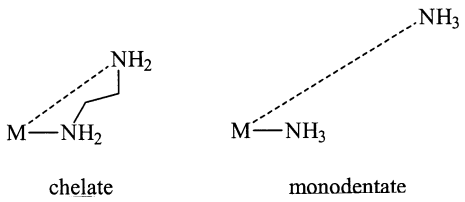

Fig. 2. Effective concentration in the chelate effect.

cleavages occur at similar rates to those for monodentate ammonia (on the order of 1–20 s^{-1}) [8]. Thus, in order to explain the increased stability of chelates, the kinetic effect must be an associative one; the second donor must exhibit abnormally fast re-binding or the chelate would be lost at a similar rate to that of a monodentate ligand.

As might be expected, tying successive donor atoms together produces tri- or tetradentate chelates and further increases the metal complex stability as a function of the number of chelate rings [3]. But, an impressively large additional stabilization occurs from linking the terminal donor atoms into a ring; this phenomenon was termed the macrocyclic effect [9]. The stabilization is much larger than can be explained by the simple addition of one more chelate ring. An accepted explanation for the macrocyclic effect is the difficulty in dissociation of the first donor atom from the metal ion in what is expected to be a stepwise dissociation of the polydentate ligand. A polydentate chelate can dissociate from a metal ion through successive S_N1 replacement steps, beginning with a terminal donor. The macrocyclic ligand cannot dissociate through a similarly simple mechanism because there is no end group. Some type of ligand rearrangement must occur to weaken one metal–donor atom bond prior to its dissociation. Only then, can the rest of the ligand dissociate (Fig. 3). This rearrangement exacts a cost in energy making the dissociation slow. Although similar problems might be expected to slow the formation reaction as well, experiments have shown that the macrocyclic effect arises primarily from the dissociation step, indicating that dissociation is more hindered than is binding [3]. This primarily dissociative effect is in addition to the highly associative chelate effect, which is still in effect for macrocycles. Compounding these effects results in the large increase in stabilization for macrocyclic complexes.

A further extension of topological constraint is the cryptate effect, in which the addition of a second ring to a macrocycle (resulting in a macrobicyclic ligand), further enhances the stability of its metal complexes [10]. As for the change observed in transition from chelate to macrocyclic effects, the cryptate effect is often even higher than would be expected for simple addition of a second fused macrocycle. This phenomenon has been variously attributed to entropic and enthalpic causes, but its exact origin is not yet agreed upon. However, the trend is clear: increased topological constraint increases binding affinity with the caveat that high complementarity must be maintained [3].

Busch has attributed this enhanced stability to multiple juxtapositional fixedness (MJF), [11,12] the fact that stepwise donor atom dissociations from metal ions are much slower due to the above mentioned lack of end groups in topologically complex ligands. But MJF also addressed, for the first time, the rigidity of the overall ligand structure, i.e. donor fixedness as an important parameter. A similar concept called preorganization [13] was developed to describe the observation that ligands preformed in a size and geometry complementary to the targeted metal ion, had higher stabilities with those ions than other ligands. It was proposed that entropic costs associated with complexation are prepaid, because the preorganized ligand does not have to reorganize itself around the metal ion during complexation. This cost is already paid in the ligand synthesis. This prepayment of the entropic costs of complexation would explain why topologically more complex ligands form more stable complexes, if complementarity were maintained.

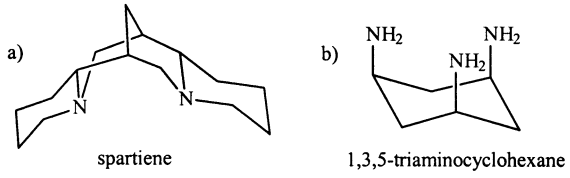

Fig. 4. Rigid non-macrocycle ligands.

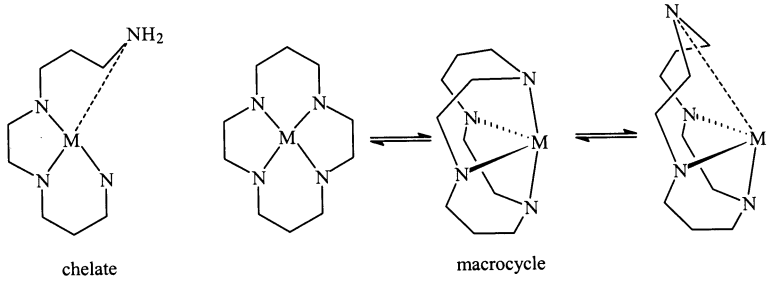

Fig. 3. First donor dissociation in chelate vs. macrocycle.

Ligand rigidity is both part and parcel of MJF and preorganization. Both invoke rigidity as a parameter to be increased for the formation of more stable complexes, and a few experiments can further illustrate this idea. For example, the rigid bidentate chelate spartiene forms remarkably inert complexes with labile [14,15] Cu^{2+} (Fig. 4a). Although more intricate than the usual bidentate chelate, topologically the ligand is not a macrocycle (vide supra). Yet, it is much more rigid than the simple chelate ethylenediamine because of the ligand superstructure. Stepwise donor dissociation is much more difficult for spartiene than for more flexible ligands, since the deformations needed to remove the first nitrogen donor from a metal ion are inhibited by the rigid backbone. Even though not a macrocycle, spartiene's rigidity influences the donor dissociation rate, the hallmark of the macrocyclic and cryptate effects. It is easy to imagine how increasing the rigidity of a macrocycle would similarly enhance this inhibition of dissociation. A second example is provided by the 1,3,5-triaminocyclohexane Ni^{2+} complex [16]. It is much more inert to acidic dissociation ($t_{1/2} = 7$ min in 5 M HNO_3) as compared with linear tridentate ligands ($t_{1/2}$ = fractions of seconds in 5 M HNO_3 under similar conditions) [8] (Fig. 4b). Clearly, the exploitation of rigidity factors, especially combined with the complex topologies of macrocycles or macropolycycles, would provide an excellent means to increase complex stability in the cases where complementarity can be maintained. This is the approach used in choosing bridged azamacrocycles as ligands for the production of extremely stable coordination complexes.

2. Methods for bridged azamacrocycle synthesis

2.1. Defining the field

What follows is a brief review of nitrogen-bridged azamacrocycles and their syntheses. Throughout the discussion, references will be made to what are believed to be the most effective iteration of this family for making stable complexes, the short cross-bridged variety. Rationalizations of why this group should have special properties even within the domain of bridged azamacrocycles will be given. After an overview of other types of polycyclic ligands, the focus will turn to this subclass of nitrogen cross-bridged tetra- and pentaazamacropolycycles. The success of this ligand type in producing stable transition metal complexes for biomimetic applications is viewed through the lense of the other bridged ligand types explored in this section.

Macrocyclic ligands have been modified through the addition of bridging 'superstructures' [3,17,18] for many years and for many purposes. Probably the most famous are the cryptands (Fig. 5a), which were synthesized [19,20] by a high dilution bridging reaction soon after the discovery of the monocyclic crown ethers [21,22] to improve the binding ability of these polyether ligands for alkali and alkaline earth metal ions. The clathrochelates, [23] or sepulchrates, [24] though usually synthesized by template methods involving acyclic precursors, produce macrobicycle ligands which may be viewed as tetraazamacrocycles spanned by a bis-donor bridge connected to carbon bridgehead atoms of the ring (Fig. 5b). These ligands provide unprecedented stability [25] for some metal ions of good secondary amine complementarity by filling all coordination sites and providing the topology necessary for the cryptate effect.

Various strapped porphyrins use bridging superstructures to fix axial bases into position [26] or to provide a binding site for oxidizable substrates [27]. Finally, in an exemplary biomimetic example, various bridges join the bridgehead carbon atoms of a tetraazamacrocycle to provide a protected area for the binding of dioxygen to metal complexes of the resulting macrobicycles (Fig. 5c) [28].

These, and other interesting examples are too numerous to treat fully here. But, the less abundant and most recently synthesized examples of tetra- or pentaazamacrocycles bridged between nitrogen donors will be discussed. An effort will be made to focus the discussion

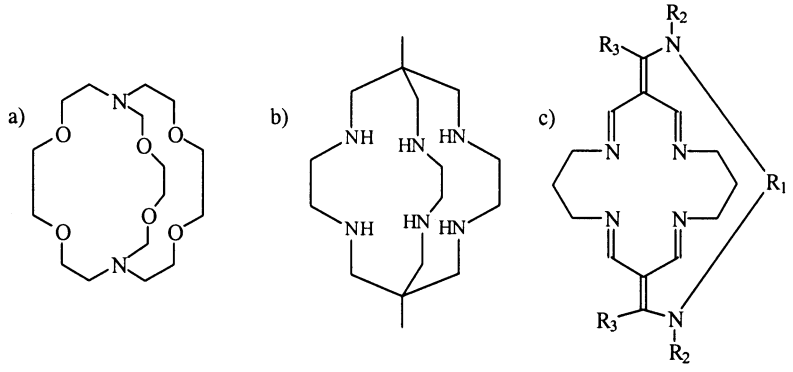

Fig. 5. Classical bridged ligands.

on the smaller macropolycycles most likely to strongly bind only one transition metal ion. Clearly, the rigidity benefits of ligand bridging, a key point of this review, are lost in extremely large linkages. Finally, special attention will be given to ligands shown to be complementary for transition metal ion binding, rather than main group or lanthanide binding.

There are, essentially, four synthetic routes described in the literature for making nitrogen bridged tetra- or pentaazamacrocycles: direct organic synthesis, the use of templates, protection/deprotection chemistry, and condensation reactions. Below is an extensive, but not exhaustive, review of these techniques and the ligand structures they have produced. Occasionally, an example of a particular synthetic type will be discussed in an adjacent section. This has been done to keep together similar structural types, or related work from the same group, and should be obvious.

2.2. Direct organic synthesis

Wainwright introduced two-carbon bridges between adjacent nitrogen atoms of cyclam and cyclen by simply reacting the macrocycle with dibromoethane. Both mono- and di-bridged 'structurally reinforced macrocycles' resulted (Fig. 6) [29,30].

These ligands lived up to their name, producing Ni^{2+} complexes of very high ligand field strengths (as demonstrated by their electronic spectra), evidence of rigid square-planar geometries. The single observed absorption of the low spin Ni^{2+} complex of the singly side-bridged cyclen, is found at 23 980 cm^{-1}, one of the highest such energies known, and is taken directly as the in-plane ligand field strength. Hancock et al. studied the thermodynamic stabilities of various metal complexes of the same cyclen analogue and found that the extra structural reinforcement made the ligand more metal ion selective; it binds the small ions Cu^{2+} and Ni^{2+} more strongly than cyclen due to increased rigidity in the presence of similar complementarity, but larger ions Pb^{2+} and Cd^{2+} less well. In the latter cases, complementarity is defeated by rigidity; the ligand cannot as easily fold to accommodate the large ions, as does cyclen [31].

Hancock et al. later adapted this synthesis for the production of larger, 'side-bridged' tetraazamacrocycles.

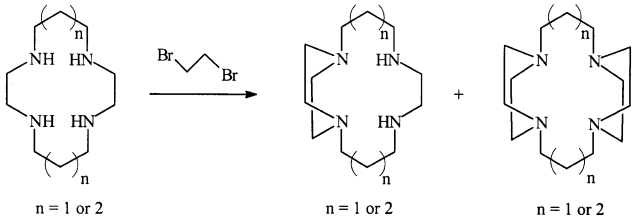

Fig. 6. The first 'structurally reinforced' tetraazamacrocycles.

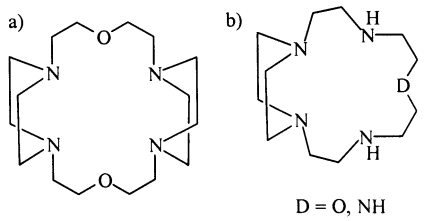

Fig. 7. Large structurally reinforced macrocycles.

They aimed to make larger rings more size selective (e.g. for Pb^{2+}) by prevention of ligand folding through structural reinforcement; with small ions, folding occurs in complexes of large macrocycle ligands and defeats size selectivity [32].

One ligand so synthesized (Fig. 7a) indeed was selective for Pb^{2+} complexation ($\log K = 4.73$), binding no other metal ions to a measurable extent [33]. Hancock has also used conventional (protection/deprotection) macrocyclization methods [34] to make other structurally reinforced macrocycles (Fig. 7b). The ditosylate of *N*,*N*′-bis(2-aminoethyl)-piperazine was condensed with the tosylates of diethanolamine and diethylenetriamine to give side-bridged ligands. Again, selectivity for Pb^{2+} is observed due to size match and prevention of folding [35].

Use of a different bridging agent, diethyloxalate, produced bis-amide side-bridged ligands that can be reduced to give ligands similar to those described immediately above [36,37]. (Fig. 8). Kaden et al. selectively mono- and di-acylated the remaining secondary amines, reduced the amides, and then studied the Cu^{2+} and Ni^{2+} complexes of the side-bridged ligands, having only tertiary nitrogen donors [38]. They found that while the Cu^{2+} complexes of these ligands could either be four or five coordinate, the Ni^{2+} complexes did not bind fifth ligands, but were always four coordinate. This observation was explained by the hypothesis that Ni^{2+} must become high spin for

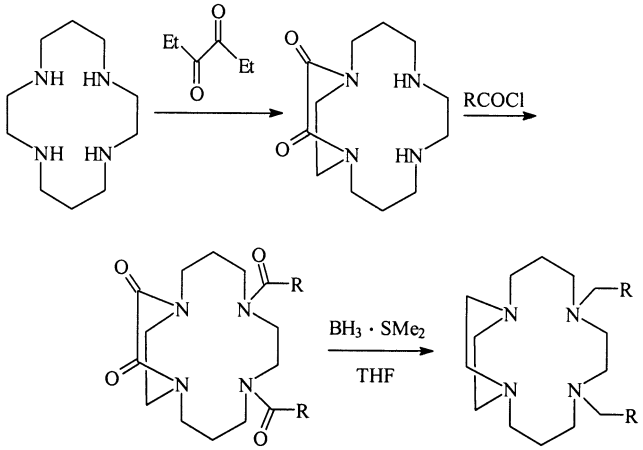

Fig. 8. Substituted structurally reinforced tetraazamacrocycles.

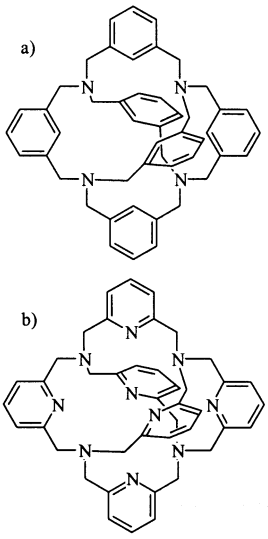

Fig. 9. Aromatic, doubly cross-bridged macrocycles.

pentacoordination, and that the ligands were too rigid to accommodate this larger ion.

Finally, the surprising formation of a macrotricyclic compound (Fig. 9) from 1,3-bis(aminomethyl)benzene and 1,3-bis(bromomethyl)benzene is a direct synthesis. This molecule is similar to Lehns' 'spherical cryptands' (vide infra), having all nitrogen atom lone pairs directed into the cavity [39].

Unfortunately, the cavity is too small to bind anything but a proton because of the six aromatic protons projecting into the cavity. Replacement of some, or all, of the benzene groups by pyridine [40] produces an octaamine cryptate that is a strong K^+ binder [41]. More recent studies have found that one Cu^+ or two Ag^+ ions can be complexed inside the electron rich cavity [42].

2.3. Template directed synthesis

Template directed synthesis is the organization of an assembly of atoms with respect to one or more geometric loci to achieve a particular linking of atoms [43,44]. The seminal [45,46] template macrocycle synthesis, as well as many more exotic examples, [47] utilize metal ions as the 'anchor' of the template complex. Lawrence et al., extending a technology previously developed for simple macrocycle synthesis, [48] used a Cu^{2+} template to produce ethylene side-bridged 15-membered macrobicycles from piperazine derivatives (Fig. 10) [49]. The advantages of this synthesis are the ease and high yield of the reaction, as well as the addition of a pendant donor through reduction of the nitro group to an amine. The initial Cu^{2+} complex (NO_2 arm) is very similar electronically and structurally to the unbridged version. The reduced ligand (NH_2 arm) is a pentadentate donor [49,50] when bound to Co^{3+}, having the primary amine pendant arm bound as well as the ring nitrogen donors. The ligand cannot fold, however, as the unbridged version does in a related complex [51]. This rigidifying effect is common (vide supra) for structurally reinforced macrocycles. An analogous ligand with a pendant-COOH group has more recently been prepared using an ester in place of the nitro-starting material. The Ni^{2+} complex does coordinate the pendant carboxylate [52]. High spin Ni^{2+} can now be accommodated by the 15-membered macrocycle, without folding, which is prevented by the bridge. Pentacoordination was not observed in smaller side-bridged ligands (vide supra), which also cannot fold, but are too small to accommodate high spin Ni^{2+}.

In 1989, a fascinating side-bridged ligand having a sulfur donor was described [53]. The macrobicycle was formed by a template synthesis of the corresponding [9]aneSN_2 bis-pendant arm ligand and glyoxal, followed by hydrogenation, and is notable because it is the first successful glyoxal cyclization using Cu^{2+} as the anchor (Fig. 11). (Ni^{2+} serves this function in the classic synthesis of cyclam [54].) The five-coordinate Cu^{2+}, and six coordinate Ni^{2+} complexes were synthesized and structurally characterized. The cyclam ring is bound in its usual *trans* conformation with the sulfur bound to M^+ at an axial position. The long side-bridge does not exert a large influence on the macrocycle rigidity compared with the shorter bridged 'structurally reinforced macrocycles.'

Ligands similar to those of Lawrence et al. were produced by template reactions involving *N*,*N*′-bis($(CH_2)_n$–NH_2)-1,4-diazacycloheptanes as the starting materials in place of the piperazine starting materials of Lawrence et al. Ni^{2+} templated reactions of these tetraamines have produced several side bridged ligands which might be best described as ethylene bridged, this time across trimethylene-separated adjacent nitrogens of various macrocycles (Fig. 12) [55,56]. Again, Ni^{2+} and Cu^{2+} complexes were investigated to study the effect of

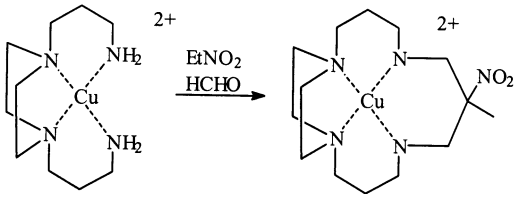

Fig. 10. Template closure of a side-bridged macrocycle.

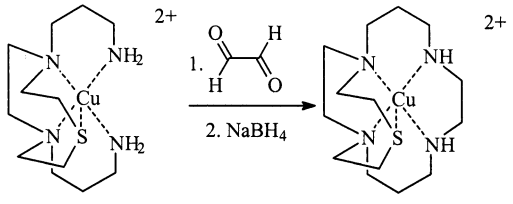

Fig. 11. Cu^{2+} templated closure of a sulfur-containing macrobicycle.

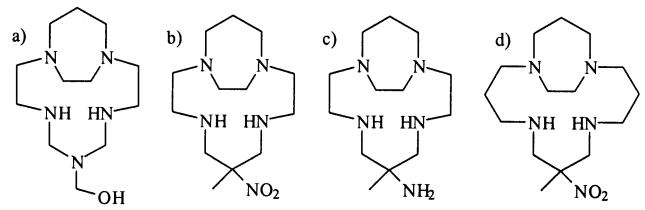

Fig. 12. 1,4-Diazacycloheptane containing macrobicycles.

added rigidity on ligand field strength. The ligand in Fig. 12c has a slightly higher ligand field strength than the singly ethylene side-bridged cyclen, the previous champion (vide supra). The authors explained that Ni^{2+} in the cyclen-derived ligand, which has a high ligand field strength due to Ni–N bond compression, is slightly out of the plane, (N–Ni–N angles are about 169°) while in their ligand, Ni^{2+} is planar, creating a better overlap for Ni–N bonding.

In summary, it is apparent that direct and template syntheses work best for bridging adjacent nitrogens in polycyclic azamacrocycles. Few cross-bridged ligands have been made by these methods. These 'simple' syntheses produce what are in terms of rigidity, less effective ligands than the cross-bridged tetraazamacrocycles to be described below. When the bridgehead nitrogen atoms are already linked to each other by di- or trimethylene chains (adjacent bridging) the effect on overall rigidity of the ligand is not maximized. The adjacent donor atoms are very rigidly separated, but the rest of the macrocycle, a quite lengthy unbridged portion, is little affected. The majority of the macrobicycle is still quite flexible, and the full advantages of rigidification through bridging are not realized.

2.4. Protection/deprotection synthesis

Where the more facile direct syntheses or template directed methods failed or were not feasible, protection/deprotection of functional groups, a more sophisticated, synthetically challenging synthesis of small bridged azamacrocycles has been applied. Cryptands and spherical cryptands can be described as once and twice bridged azamacrocycles (Fig. 13). The simplest cryptands, however, generally have only two nitrogen atoms, albeit they are bridgeheads. The rest of the donors are usually ether oxygen atoms in what are essentially bicyclic crown ethers where nitrogen provides only the necessary three points of attachment. These ligands, (Fig. 5a) like the crown ethers, [21,22] are used almost exclusively for alkali and alkaline earth metal ion complexation, and as such, are not discussed fully here [19,20,57–59].

Spherical cryptands, on the other hand, have the 'required' four nitrogen atoms, all of which are of the bridgehead variety. These macrotricycles take the topology of the cryptands one step further by providing two

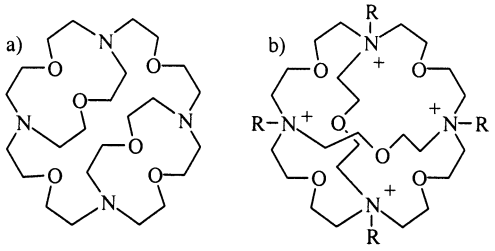

Fig. 14. Cylindrical macrotricycles and quaternized spherical cryptands.

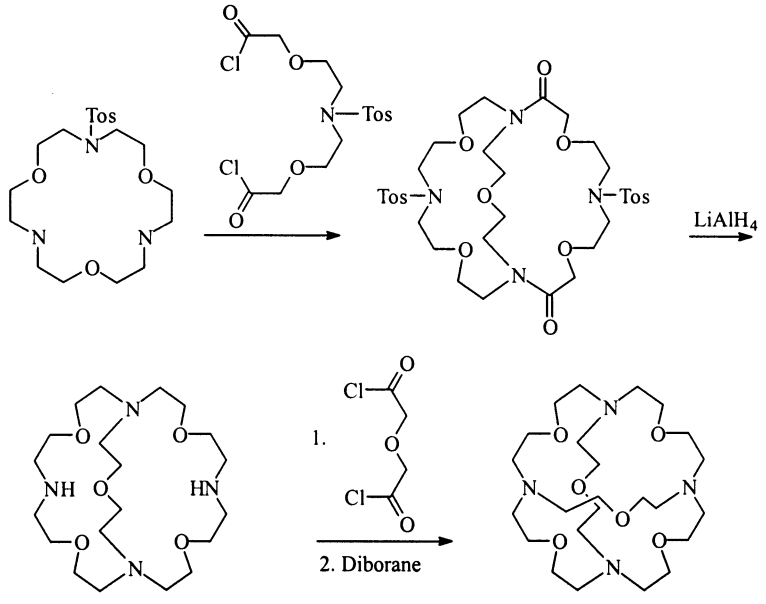

Fig. 13. Synthesis of spherical cryptands.

more nitrogen atoms for points of attachment of a second bridging group [60–62]. The synthesis of spherical cryptands, and many other cross-bridged azapolycycles (vide infra) is dependent on (1) protection/deprotection reactions and (2) high dilution techniques, which are required to limit oligomerization in reactions involving difunctional reagents.

Side-bridged analogues, described as 'cylindrical macrotricycles' (Fig. 14a) have been synthesized similarly and used for the same purposes [63,64]. These ligands, like the crowns and simple cryptands, have been used mostly for the complexation of alkali and alkaline earth metals, [61] but have also been applied to complexation of the NH_4^+ cation [62]. The spherical cryptands, while topologically complex enough to exhibit a 'spherical cryptand effect' even greater than the cryptate effect, generally have bridges long enough to limit their effect on overall rigidity. One result is that they are not proton sponges [61] a property commonly associated with the more rigid, smaller, bridged azamacrocycles (vide infra). Their cavity sizes, and the predominance of ether oxygen donors also makes them noncomplementary for the first row transition metal ions that are the focus of this review.

The use of spherical cryptands having quaternized nitrogens, as ligands for the binding of anions, should briefly be mentioned. Researchers in the growing area of anion binding [65] have utilized these multiply-bridged macrocycles, in some cases making considerably larger analogues to accommodate the larger anions (Fig. 14b) [66–68]. It is anticipated that the same principles discussed here for cation binding will be valid for the coordination of anions as well.

A smaller series of bridged azamacrocycles requiring protection/deprotection synthesis has been extensively exploited by a large contingent of Italian chemists. The ligands are always based on *trans* dimethylated cyclen (Fig. 15) [69] which is prepared by classical macrocyclization methods [34] from the disodium salt of *N′*-methyl-*N,N″*-bis(toluene-*p*-sulphonyl)diethylenetriamine and bis(2-chloroethyl)methylamine. The tosyl groups can be removed after cyclization to give the *trans*-methylated (protected) starting material. The

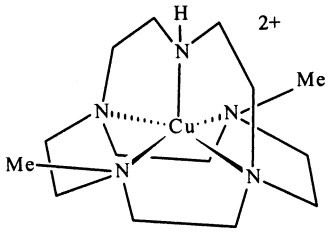

Fig. 16. Copper coordination of a pentadentate cross-bridged cyclen.

variety of bridging moieties used to span this macrocycle is considerable (Fig. 15) and ranges from $-CH_2CH_2-$ [70] to $-CH_2CH_2OCH_2CH_2-$ or $-(CH_2)_3-NR-(CH_2)_3-$ [71] to $-CH_2-S-(CH_2)_2-$ [72,73]. Nearly all of these macrobicycles are proton sponges and strong lithium binders, and most are capable of strong Cu^{2+} binding as well [74]. The small cyclen parent ring was reported to prevent binding by most other, larger cations for the shortest, most rigidifying cross-bridge ($-CH_2CH_2-$), [70] an observation disproven in our own work (vide infra). The ligands having longer bridges, at least five atoms, usually including a central donor such as N or S, 'open up' the cage enough to bind some transition metal ions, including Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} (Fig. 16). Under strongly acidic conditions, the Cu^{2+} and Zn^{2+} complexes have remarkable stabilities, with no measurable decomposition over months (Cu^{2+}), or decomposing over the course of days or weeks (Zn^{2+}) [72,73,75,76]. In one case (bridge = $-CH_2CH_2-SCH_2CH_2-$), it was possible to measure the thermodynamic binding constant for Cu^{2+} to the ligand. This value ($\log K = 18.2$) is not larger than that for many monocyclic ligands. It was concluded from this data that the kinetic inertness of the complex must arise from the relative rigidity of the ligands, which prevents stepwise

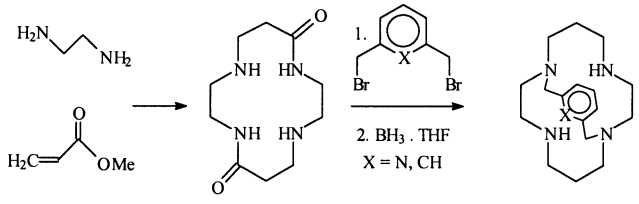

Fig. 17. Cross-bridging *trans*-dioxocyclam.

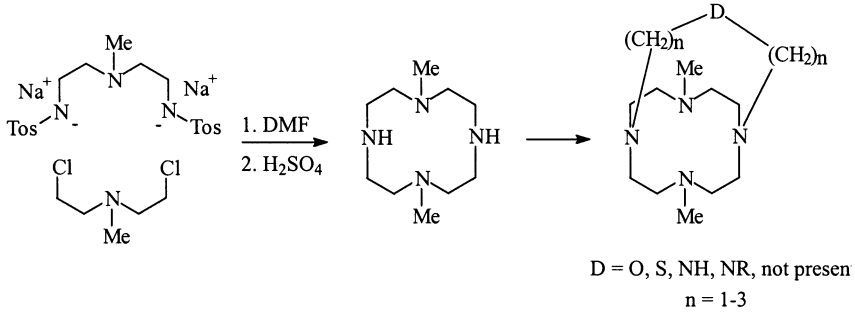

Fig. 15. Cross-bridged cyclen macrobicycles.

donor dissociation. It is exactly this property we hoped to duplicate or surpass in the work that is the subject of our own recent efforts. We also sought to produce metal complexes that are less completely engulfed by the ligand, to enhance their possible use as oxidation catalysts (vide infra).

Another protection/deprotection bridging synthesis uses amides as protecting groups to cross-bridge cyclam [77,78]. The *trans* dioxocyclam starting material, 1,4,8,11-tetraazacyclotetradecane-5,12-dione, [79] is the product of a Michael addition involving ethylenediamine and methyl acrylate (Fig. 17). Two aromatic groups, 1,3-bis(bromomethyl)benzene and 2,6-bis(bromomethyl)pyridine, have been used to cross-bridge the *trans* protected macrocycle under high dilution conditions. Reduction by BH_3 in THF results in 'deprotection' by conversion of the two amides to amines. Neither the amides nor their reduced derivatives have yet been characterized with respect to coordination behavior.

Collinson et al. [80]have used the pyridine ring and the methyl group of the macrocycle 7-methyl-3,7,11,17-tetraazabicyclo[11.3.1] heptadecane-1(17),13,15-triene as protective groups in another cross-bridging reaction (Fig. 18). A second pyridine donor was introduced via bridging with *O*,*O*′-bis(methanesulfonate)-2,6-pyridine dimethanol in yet another high dilution reaction. This ligand forms acid stable complexes with Mn^{2+} and Fe^{2+}.

Many other nitrogen-bridged bicyclic ligands have been prepared, but most contain bipyridine or phenanthroline bridges and are larger and contain more nitrogen donors than the four or five that are the focus of this review (Fig. 19). Their synthesis generally parallels that of the cryptands, replacing the polyether chains with bipy or phen groups. The large ligands that result have mostly been used for alkali and alkaline earth metal complexation, but interesting complexes can also be formed with the lanthanides in some cases [81].

Finally, protection/deprotection chemistry has produced an intriguing family of bridged tetraazamacrocycles in the laboratories of the Springborg group. Regioselective, stoichiometric, *trans* bis-tosylation of cyclen (82% yield) allows the macrocycle to be cross bridged by 1,3-ditosyl propane [82]. Deprotection,

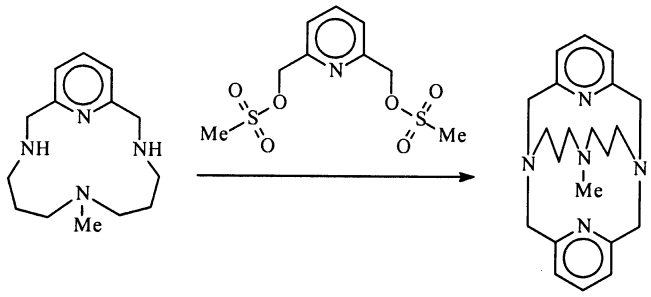

Fig. 18. Collinson's pyridine-donor macrobicycle.

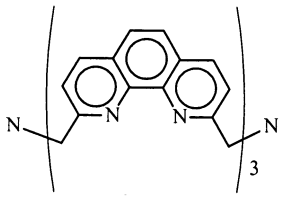

Fig. 19. A large aromatic cross-bridged azamacrocycle.

followed by a second bridging step, results in the spherical cryptand-type doubly cross-bridged product (Fig. 20) [83]. Both the singly and doubly bridged ligands behave as proton sponges due to the rigid arrangement of nitrogen atom lone pairs directed into the cavity. Only the less complex macrobicycle has been shown to complex a metal ion, Cu^{2+}, resulting in a relatively stable complex ($t_{1/2}$ in 5 M HCl > 5 days) [84,85]. Though impressive, this stability is only a fraction of that reported by the Italian group for their longer cross-bridged pentadentate ligands (vide supra). No report of other metal ion complexation with these small proton sponges has yet been made. Miyahara et al. have only recently completed the synthesis of the smaller, *T*-symmetric, all-ethylene doubly bridged macrotricycle, which they call 'hexaethylenetetraamine', and is yet another proton sponge [86].

A direct synthesis between a triazamacrocycle and a trifunctional bridging group produces the larger, similarly symmetric tricyclic analogue having all trimethylene bridges (Fig. 21) [87]. Oxidative cleavage using NaI in H_2SO_4 removes one bridge to produce the macrobicycle [88]. This larger macrobicycle, though still a proton sponge, has been reported to be a more useful transition metal complexing agent for Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+} [89].

In conclusion, the protection/deprotection methods appear to be more effective in terms of the range of bridges they can produce, as well as in their ability to cross-bridge the macrocycles. The latter characteristic is vital for synthesizing the most rigid ligands.

2.5. Condensation synthesis

This synthetic route to bridged azamacrocycles is at once the most mechanistically complex and the easiest in terms of number of steps, physical labor, and yields. And, as the route followed for the syntheses of the ligands in the biomimetic example below, will be discussed in detail there.

Condensation of an aldehyde with two amines to form aminal functional groups is well known, for example, the condensation of formaldehyde with ammonia to form hexamethylenetetramine (Fig. 22a) [90]. Similar reactions of formaldehyde with tetraazamacrocycles has yielded compounds with single carbon atom bridges between adjacent nitrogen atoms (Fig. 22a) [90–

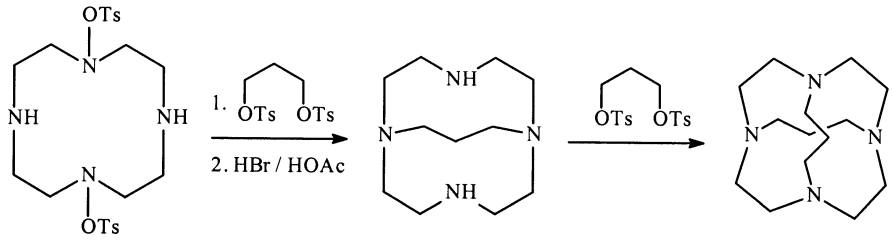

Fig. 20. Springborg's propylene cross-bridged cyclens.

95]. These macropolycycles have not been exploited for transition metal coordination, since it is believed the one-carbon bridges would prevent both aminal groups from binding the same ion [91].

Condensation of the bisaldehyde glyoxal with tetraazamacrocycles has been more widely utilized to produce tetracyclic tetraamines varying in size and substitution pattern (Fig. 23). These interesting organic molecules are formed when each aldehyde functional group reacts with two secondary amines of the macrocycle, completing an aminal group and closing a tetracyclic, panel-like molecule [91,96–101]. While receiving a fair share of attention from heterocyclic chemists, these compounds have been ignored as transition metal ligands, since the two-carbon central bridge occupies the position of the metal ion in most tetraazamacroycle complexes [91]. However, the extremely complex topology (each nitrogen is connected to every other nitrogen by three chains, much like Springborg's small spherical cryptands, except the two cross-bridges have in common the same two carbon atoms) and associated rigidity prompted us to explore their coordination chemistry [102–104].

Facile transition metal coordination with these tetracycles as ligands has only been achieved for Pd^{2+}, [102] Cu^{+}, [103,104] Cu^{2+} [103]. In all cases of the former and latter metal ions, the ligands have coordinated as *cis* bidentate chelates, usually through non-adjacent nitrogen donors, which direct their lone pairs into a common cleft of the folded ligand (Fig. 24). The Pd^{2+} complexes have been structurally characterized as having square-planar geometries around the metal ion, with the other two *cis* coordination sites occupied with chloride ligands (Fig. 24) [102]. One Cu^{+} complex was unique in having two of the tetracyclic ligands bound, but only through one nitrogen atom each (Fig. 25) [104]. The linear coordination geometry is common to Cu^{+} and appears to result from the steric crowding of the bulky ligands that would be required of bidentate coordination. This intriguing structure led us to explore the oxygen binding and reduction chemistry of the Cu^{+} and Cu^{2+} complexes of these rigid bidentate chelates [103].

Hard to characterize Cu^{+} complexes clearly demonstrate dioxygen binding and bond rupture, producing bis-μ-hydroxo bridged bimetallic complexes as characterized by X-ray crystallography (Fig. 26), [103] the common product of similar complexes upon exposure to dioxygen. Details of the reaction mechanism and characterization of the potential high valent intermediates will require further study. The desired property of azamacrocycle bridging, complex stability, is not likely to be fully realized since these ligands act as only bidentate donors.

Unexpectedly, these tetracyclic organic curiosities have been used as precursors to the intriguing, and more coordinatively functional, ethylene cross-bridged tetraazamacrocycles (Fig. 27) [105–107]. The coordination chemistry of these ligands was completely unknown until very recently, and will be discussed in detail below. In a variation of this synthesis, if the reduction step uses diisobutylaluminum hydride, side-bridged ligands previously prepared by direct routes can also be prepared [108].

Condensation of glyoxal with two equivalents of a diamine, followed by further formaldehyde condensation, can give smaller tetracyclic macrocycles having what amounts to four included aminal groups (Fig. 28) [109].

Another interesting 'tetraaminal', this time a pentacyclic hexamine ligand, is a [2+2] condensation product of glyoxal and diethylenetriamine (Fig. 29) and has been

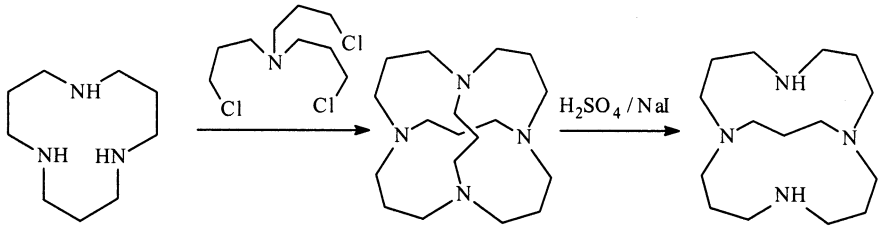

Fig. 21. Springborg's propylene cross-bridged [16]aneN4's.

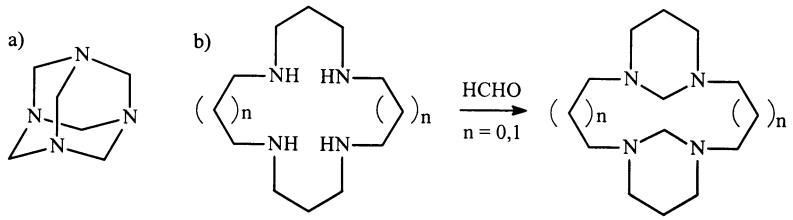

Fig. 22. Formaldehyde condensates with (a) ammonia and (b) macrocycles.

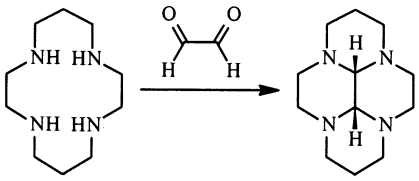

Fig. 23. Tetracyclic cyclam–glyoxal condensate.

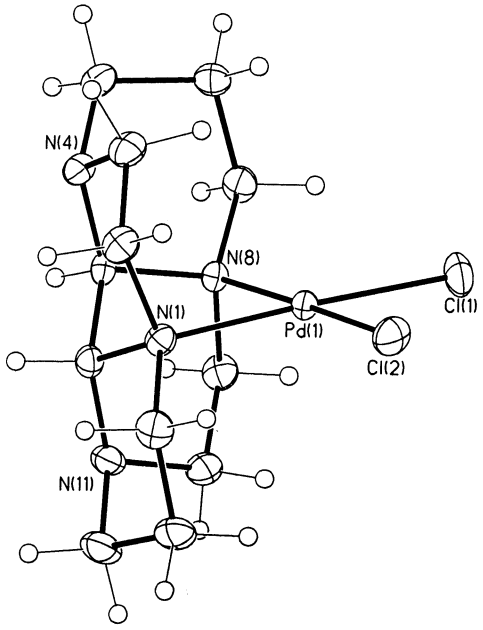

Fig. 24. X-ray crystal structure of the Pd^{2+} complex with the cyclam–glyoxal condensate.

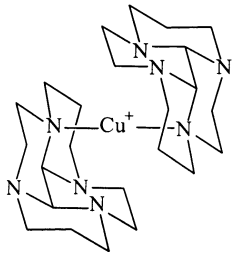

Fig. 25. A schematic of the Cu^{+} bis ligand complex of the cyclam–glyoxal condensate.

found to coordinate to Cd^{2+} and Mn^{2+} in a tetradentate fashion [110–112].

Synthesized from two linear triamines, this pentacycle is much more elongated than the tetracyclic ligands made from tetraazamacrocycle–glyoxal condensations. This characteristic, along with the presence of six potential nitrogen donors, four of which direct their lone pairs into the much wider and deeper cleft formed in the coordinated ligand (and allowing tetracoordination reminiscent of 2,5-diaminopiperazine), demonstrate the greater flexibility of this ligand as compared with the more constrained, more rigid tetracycles.

Condensation of butanedione, the first ketone thus employed, with linear tetraamines has also been used for simple tetraazamacrocycle synthesis, proceeding through a tetracyclic intermediate (Fig. 30) [113]. The initial tricyclic intermediate, an 'organic template complex', (vide supra) having a two-carbon anchor, is bridged by a difunctional reagent before the butanedione 'anchor' is removed to yield the desired macrocycle. Glyoxal derived central bridges are much more stable than this butanedione derivative, requiring quaternization of at least one of the nitrogen atoms before any of the aminal C–N bonds can be broken [105].

A similar preparation of cyclen condenses dmfdma (the dimethyl acetal of dmf) with triethylenetetraamine in the first step, then bridges the resulting bisimidazole with dibromoethane to form the bromine salt of the monoimine tetracycle (Fig. 31).

Refluxing in 10% H_2O_2 removes the interior bridge [114]. Application of the same reagent to cyclam forms different products depending on the solvent used. In ethanol, an alkene bridged tetracycle is formed that can undergo air oxidation to the bis-urea derivative of cyclam (Fig. 32) [115]. However, in chloroform, the same reaction yields a *cis*-bridged (diprotected) cyclam that is useful for the preparation of *cis* disubstituted cyclams [116].

The last group of tetracyclic azamacrocycles to be considered here are the 2,2′-bisimidazole derivatives which can be bridged by various dihalo reagents to produce highly charged aromatic tetracycles (Fig. 33) [117]. These compounds have not been studied as ligands, but as fascinating heterocycles with interesting electrochemical and reactive properties.

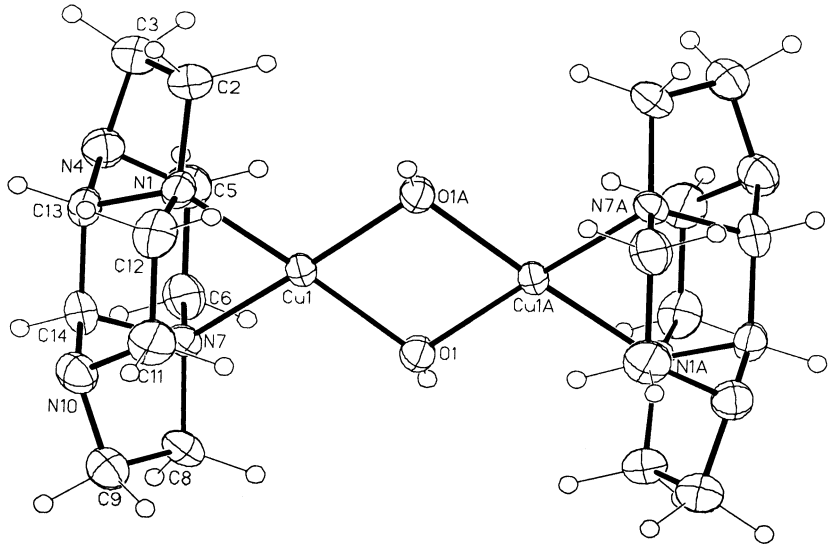

Fig. 26. A typical bis-μ-hydroxo copper(II) complex.

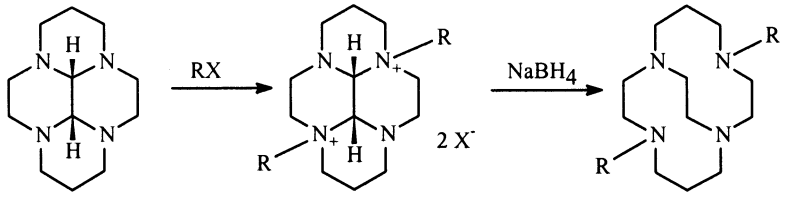

Fig. 27. Synthesis of ethylene cross-bridged cyclams.

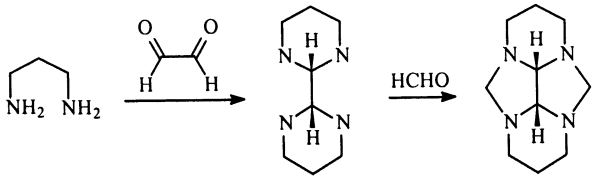

Fig. 28. Tetracycle from successive aldehyde condensation with a diamine.

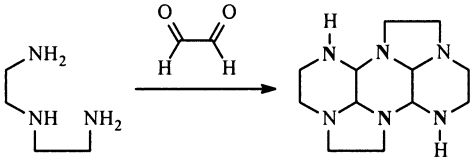

Fig. 29. Tetraaminal from a triamine and glyoxal.

2.6. Conclusions

As can be seen, their are many examples of nitrogen-bridged tetra- and pentaazamacropolycycles resulting from the application of a very few general synthetic strategies. First, the simplest strategies, direct synthesis and template synthesis, generally only introduce bridging between adjacent nitrogen donors. The resulting ligands, though topologically complex, do not maximize rigidity constraint factors in their complexes. To achieve that result, the more sophisticated protection/deprotection strategy has been invoked in order to place the bridging superstructures between nonadjacent nitrogen donors. This method has been quite successful, producing the prototypical cryptands and spherical cryptands, as well as several additional small azamacropolycycles that are complementary to transition metal ions. These ligands are invariably proton sponges, an indication of their rigidity. Directing and holding fixed multiple nitrogen lone pairs into a bi- or tricyclic cavity is responsible for this behavior, one that is seemingly indicative of strong binding for complementary metal ions as well. Finally, the condensation reactions appear to simplify azamacrocycle bridging, although through rather complex mechanisms. This technique has thus far been limited to producing one- or two-carbon bridges between adjacent, nonadjacent, or sometimes both sets of nitrogen donors. But as these reactions become better understood, it is likely that their benefits will be retained while the range of macropolycycles they produce will expand.

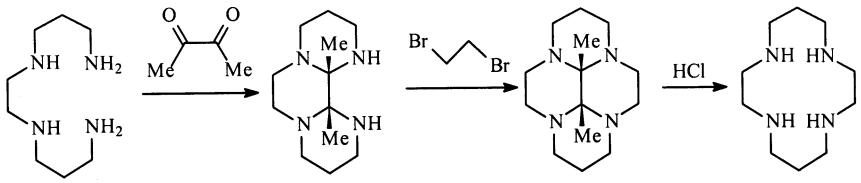

Fig. 30. Tetraamine–diketone condensation leads to cyclam.

3. A successful example

3.1. Choosing metal ions and topologically constrained ligands for biomimicry

Historically, a primary use of macrocycles has been to generate metal complexes having some properties of those found in biological systems. The similarity of synthetic macrocycles to the naturally occurring porphyrins, corrins, and chlorophylls is obvious. These aromatically rigidified prosthetic groups, especially when coupled with large protein carriers, provide uniquely stable complexes of certain metal ions. Most notably, manganese, iron, and copper are so stabilized that they can carry out extensive organic transformations on substrate molecules by the activation of dioxygen, or its reduction products under relatively mild biological conditions [118].

Similar reactions utilizing small molecule metal catalysts, sometimes under much different reaction conditions, are much desired in chemical synthesis, process industry, and other fields.

One such application, and the motivation for our recent work, is the use of metal catalysts to activate O_2 or H_2O_2 towards the bleaching of undesirable colored organic molecules, such as stains or dyes, in the industrial or consumer cleaning of fabric or hard surfaces, or in the bleaching of lignin in wood pulp processing. Unfortunately, these processes are generally carried out under aqueous conditions at extreme pH's that are inhospitable to most complexes of the metal ions known to have such activation abilities: manganese, iron, and copper. Labile Cu^{2+} easily loses most simple ligands in acidic aqueous media, as can iron and manganese, which are also relatively labile. These latter metal ions are also easily converted to insoluble oxides under oxidative aqueous conditions to give rust (Fe_2O_3) or MnO_2, respectively. This transformation not only destroys the catalyst, but also creates other undesirable effects, such as staining or surface oxidations caused by the insoluble metal oxides [119]. The knowledge of modern coordination chemistry (vide supra) indicates a potential solution to these problems. In order to produce complexes of these ions that would be stable under harsh conditions, we should maximize complementarity and use topological and rigidity constraints to further enhance the binding affinity of the ligand for the metal ion.

Of course, when designing potential oxidation catalysts, there are other factors to consider besides complex stability: (1) the catalysts should have at least one labile coordination site for binding/activation of substrate/oxidant. (2) The ligand itself should be resistant to oxidation to prevent auto-deactivation. (3) The ligand should stabilize several oxidation states of the metal ion, but not any one too much, or activation/substrate oxidation will be unfavorable. (4) The ligand should be amenable to iterative structural changes in order to maximize activity. (5) The complex should have adequate solubility in both aqueous and organic phases (stains/dyes on surfaces behave this way).

To fulfill these criteria, as well as that of predictable high stability under harsh aqueous conditions, the cross-bridged tetraazamacrocycles (Fig. 34) were selected for study. This ligand family was chosen because of several characteristics. First, is the known complementarity of tetraazamacrocycles for the late first row divalent metal ions. Nitrogen donors provide the donor types favored for these metal ions and 12–14 membered macrocycle rings appear to provide some of the highest complementary structures for several of these ions [2,120]. Second is the complex topology of these ligands. They are bicyclic, like the classic cryptands, the namesake of the cryptate effect, and should therefore have complex stabilities much greater than the simple macrocycles. Finally, the uniquely short cross-bridge should provide additional rigidity constraint to the ligands' complexes

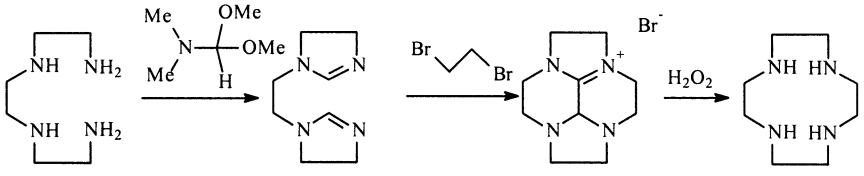

Fig. 31. Cyclen synthesis from tetraamine–dmfdma condensation.

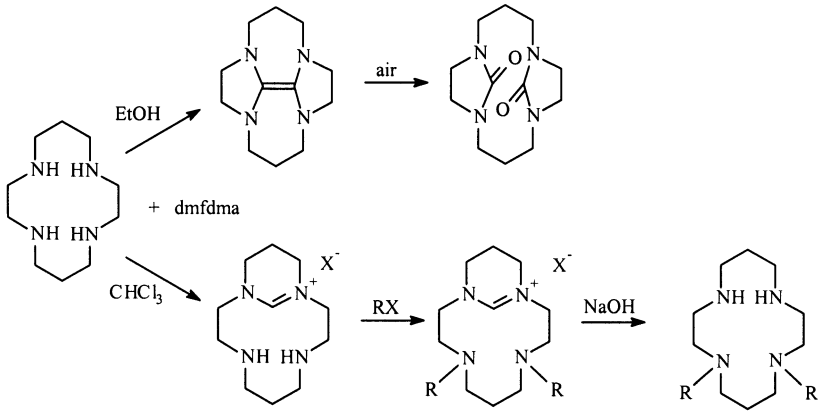

Fig. 32. Solvent-dependent cyclam–dmfdma condensations.

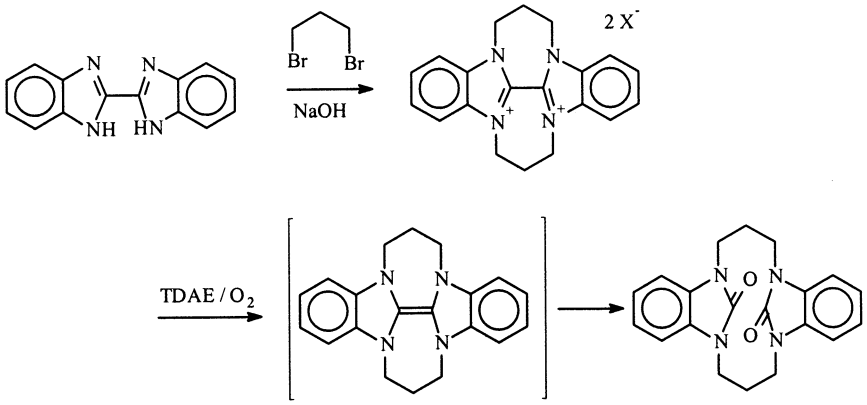

Fig. 33. Tetracycles from 2,2′-biimidazole bridging.

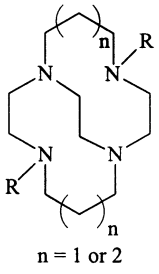

Fig. 34. Ethylene cross-bridged tetraazamacrocycles.

that are not maximized in more common, longer-bridged macrobicycles (vide supra).

The nature of these bicyclic ligands differs from many others, such as the clathrochelates, [23,25] in that the bridgehead atoms are also donor atoms. This characteristic imparts an extra component of rigidity to the ligands, especially for small macrobicycles, and especially in the metal-bound form, which provides an additional reduction of freedom of motion for the donor atoms. The cryptands also utilize bridgehead donor atoms (N), but they are polyethers and often quite large ligands, used mostly for complexation of alkali and alkaline earth metal ions, where the nitrogen donors are not necessarily involved in coordination. The 'strap', non-bridgehead ether oxygens are more complementary for these ions and provide the bulk of the coordination. This lack of complementarity for transition metals causes us to reject the classic cryptands in favor of the cross-bridged tetraazamacrocycles.

In the typical hexaaza-clathrochelate (Fig. 35a), the topology is complex, but each component donor atom is still a secondary nitrogen tethered in only two directions to the rest of the ligand. However, in the cross-bridged tetraazamacrocycles (Fig. 35b), the two bridgedhead nitrogen donors are tethered to the rest of the ligand through three straps, all of which are only two or three carbons long. These bridgehead nitrogen atoms are quite constrained in their potential movements even prior to complexation. Moreover, metal complexation provides an additional 'bridge' between all of the ligand donor atoms, essentially fixing them in place upon complexation. The coordinatively saturated bridgehead nitrogen atoms have no bonds that are not part of the multicyclic (chelate rings included) network, once metal complexations occurs. Since the macrocyclic and cryptate effects are largely dissociative in nature, this is the species of primary interest. Finally, the cross-bridged

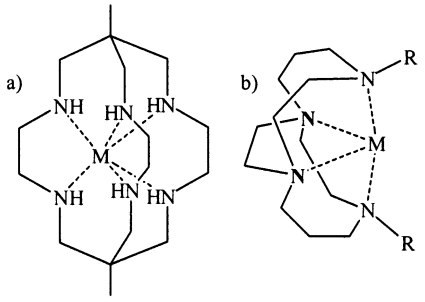

Fig. 35. Metal coordination: clathrochelate vs. cross-bridged tetraazamacrocycle.

tetraazamacrocycles do not coordinatively saturate most metal ions, as do the clathrochelates, increasing the likelihood of meaningful reactivity at the metal center.

In addition to the complementarity, topological constraint, and rigidity constraint exhibited by these ligands, the cross-bridged tetraazamacrocycles have further traits believed to be desirable for transition metal oxidation catalysts: (1) in their octahedral complexes, two labile coordination sites are available for reaction with terminal oxidant or substrate. (2) They are tunable with respect to parent ring size and substituents (R groups in Figs. 34 and 35). (3) As tertiary, saturated amines, their donors are relatively resistant to oxidation [12]. (4) Various metal oxidation states should be stable as is commonplace for tetraazamacrocyclic derivatives. (5) As neutral ligands, they should form cationic, water soluble, metal complexes, yet anion coordination would neutralize this charge, perhaps generating organic solubility.

A synthetic methodology with reported high yields was already known for their synthesis, at least for one ring size, at the start of this work [105]. Researchers at the University of New Hampshire, led by Weisman and Wong developed the condensation synthesis outlined previously in Section 2.5. They have recently produced several transition metal complexes of the ligands, mostly utilizing Cu^{2+} [121]. They have also capitalized on the complexes' stability for in vivo applications such as radiopharmaceuticals [122]. Gd^{3+} complexes of cross-bridged tetraazamacrocycles have also been synthesized and appear to be promising MRI contrast agents due to high complex stability notwithstanding multiple open coordination sites for interaction with tissue water [123].

3.2. Cross-bridged tetraazamacrocycle complexes for biomimicry

3.2.1. Ligand solution behavior

The four cross-bridged ligands shown in Fig. 36 having *N*-methyl groups and differing in ring size or ring substitution, represent the majority of our studies in this area. The literature [70,105] and our own prior studies [124] informed us of the proton–sponge behavior of ethylene cross-bridged tetraazamacrocycles. For example the potentiometric titration of **1** revealed it to be a dibasic ligand with $pK_{a1} = 9.58(3)$ and $pK_{a2} > 13$ [125]. Ligand **2** behaves similarly to **1** under aqueous conditions, exhibiting a single observable deprotonation of $pK_{a2} = 6.71(2)$ [124]. However, the elemental analysis and the stoichiometry of the titration point to the presence of two additional protons whose pK_a's cannot be determined under normal aqueous conditions. From this result, it is clear that the first proton dissociates with $pK_{a1} < 2$ and that the third proton dissociates with $pK_{a3} > 13$. Thus, in addition to having the proton–sponge character associated with **1**, **2** is also able to bind a third proton, but very weakly.

Ligand **3** behaves as a tribasic ligand as well [124]. Our potentiometric titrations confirmed that the first deprotonation occurs below the pH region normally studied in aqueous solutions. However, we were able to observe both pK_{a2} and pK_{a3} under our conditions. According to our fit, $pK_{a2} = 5.77(2)$ and $pK_{a3} = 11.3(2)$. The fact that all three deprotonations occur in a normal range indicates that ligand **3** is not a true proton sponge and that it behaves much more like an unbridged tetraazamacrocycle [126]. This difference from ligands **1** and **2** must arise from the smaller ring size of the 12-membered parent macrocycle, producing a shallower cavity which binds more protons than **1**, but binds them less strongly. Crystal structures of triprotonated **3** [70] and diprotonated **4** [127] have been published and demonstrate exactly this structural relationship (Fig. 37).

The potentiometric titration of **4** [124] reveals it to behave like **1** rather than like **3**. Ligand **4** is stoichiometrically diprotonated in aqueous solution, but like **1** and **2**, exhibits only one observable pK_a under normal aqueous conditions (Fig. 2c). Our experiment assigned $pK_{a1} = 11.45(3)$, which is the highest first deprotonation of all four ligands studied. Again, pK_{a2} was not observed indicating that it is greater than 13 in water.

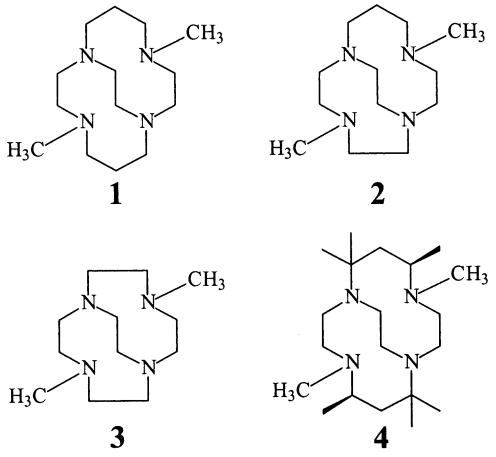

Fig. 36. Structures of cross-bridged ligands discussed below.

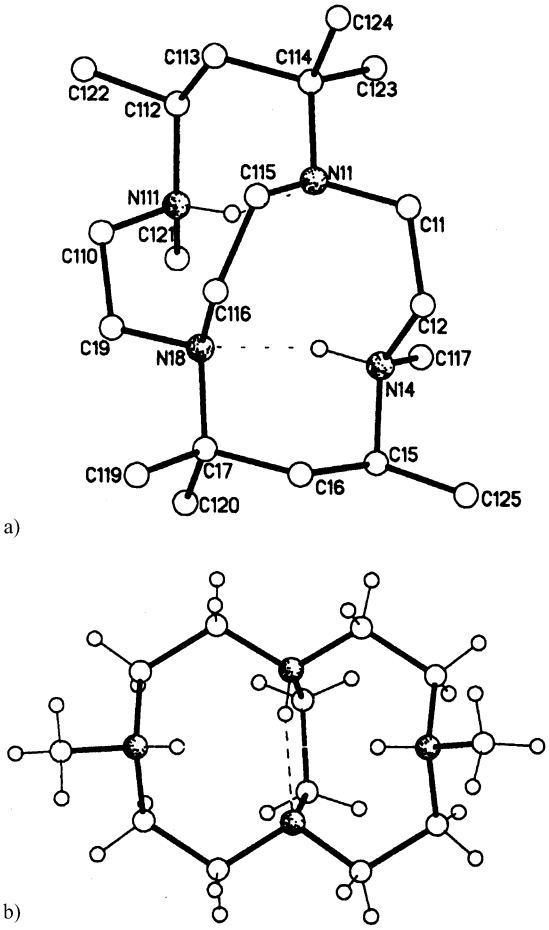

Fig. 37. Molecular structure of (a) $H_2(\mathbf{1})^{2+}$ and (b) $H_3(\mathbf{3})^{3+}$.

The increase in basicity of **4** versus **1** is possibly due to the increase in rigidity associated with the presence of six methyl substituents on carbon atoms of the ring. Crystal structures of diprotonated **1** [105] and **4** [127] show that their bicyclic skeletons have virtually identical conformations (see Fig. 37a).

3.2.2. Preparation of metal complexes

Due to the extreme basicity outlined above, only Cu^{2+} and Ni^{2+}, the thermodynamically strongest binding (first row, divalent) transition metal ions, [128] had been complexed to ethylene cross-bridged tetraazamacrocycles prior to our work [105,106]. Our attempts at the complexation of **1** and **2** with Fe^{2+} and Mn^{2+} salts in protic solvents or in aprotic solvents using hydrated metal salts were entirely unsuccessful. We therefore soon concluded that Cu^{2+} and Ni^{2+} are much better at competing with protons for the binding cavity in protic solvents than most divalent transition metal ions. This is especially true of the ions of primary interest for biomimicry, the relatively 'hard' oxyphilic ions of manganese and iron.

We have overcome this obstacle through the reaction of anhydrous metal salts with strictly deprotonated ligands (distillation from KOH after extraction from $pH \geq 14$ water) in rigorously dry aprotic solvents under a dry, inert atmosphere [107]. With routinely high yields, complexes of Mn^{2+}, Mn^{3+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Co^{3+}, Ni^{2+}, Cu^{+}, Cu^{2+}, Zn^{2+} and other metals have been obtained. In many cases, elimination of any source of protons is crucial for complexation. X-ray crystal structures have been obtained on ca. 30 complexes [129] with ligands having 12- and 14-membered rings, and a variety of R groups. In all cases, the ligand is folded, and in most cases it occupies two axial and two *cis* equatorial sites of distorted octahedra.

3.2.3. Kinetic stability in acidic solution

The behavior of the Cu^{2+} complexes with ligands **1**–**4** has been reported previously, [107,127] and illuminates the relationships between complementarity and the enhanced stability associated with the short cross-bridge. Cu^{2+} is known for forming the most thermodynamically stable yet most kinetically labile divalent transition metal complexes [128]. Consequently, it provides a fascinating window through which to view the stabilities of the metal complexes of these rigid ligands. The UV–vis spectrum of a 0.1 mM solution of $Cu(\mathbf{1})^{2+}$ in 1 M $HClO_4$ remains essentially unchanged over 1000 h at 40 °C; from estimated errors, the lower limit of the half-life for ligand dissociation is >6 years (pseudo first order rate constant of dissociation $= 3.5 \times 10^{-9}\ s^{-1}$) [107]. This is to be compared with the classic experiments [130] with $Cu(tetA)^{2+}$ (tetA, *meso*-5,5,7-12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane). A blue isomer is believed to contain tetA in the folded form, a structural feature closely related to that forced by our cross-bridged ligands. This blue isomer was converted to the hydrated metal ion and protonated ligand in 6.1 M HCl with a half-life of about 3 min. Replacing the six C-methyls in tetA by two *N*-methyl groups and the short two-carbon cross-bridge in Me_2(B14N4) increased the kinetic stability of the corresponding complex by something like six orders of magnitude, or more. Even the square-planar red isomer of $Cu(tetA)^{2+}$ is much more labile than the folded bridged cyclam complex, showing a half-life of 22 days in 6.1 M HCl, making it at least 100 times more labile than $Cu(\mathbf{1})^{2+}$.

Another appropriate comparison to illustrate the kinetic stabilization imparted by the cross-bridge is that of $Cu(\mathbf{1})^{2+}$ with $Cu(tmc)^{2+}$ (tmc, 1,4,8,11-tetramethylcyclam) whose unbridged ligand is most similar to **1** (14-membered tetraazamacrocycle, all the nitrogens in both ligands are tertiary). The half-life of this configuration I complex (all methyl groups on the same side of the ring) at 25 °C in 1 M HNO_3 (calculated from the experimentally determined rate law [131]) is only 2 s, or eight orders of magnitude smaller than that of $Cu(\mathbf{1})^{2+}$. Further, it must be emphasized that 6 years

is the lower limit of the half-life for the loss of ligand from $Cu(\mathbf{1})^{2+}$ in 1 M $HClO_4$; the actual half-life is almost certainly substantially longer. Parallel experiment carried out on the $Cu(\mathbf{4})^{2+}$ and $Cu(\mathbf{3})^{2+}$ complexes under the same conditions [127,132] demonstrated a similar stability for the complex of **4**, with a half-life of >8 years (pseudo first order rate constant of dissociation $= 2.6 \times 10^{-9}$ s^{-1}). Despite the absence of exhaustive experiments, we conclude that the half-lives of these compounds, in media that would instantly destroy most typical Cu^{2+} complexes, is of the order of years. But the complex of ligand **3** is much less stable kinetically, having a half-life of only 30 h (pseudo first order rate constant of dissociation $= 6.4 \times 10^{-6}$ s^{-1}).[127] This ligand is somewhat smaller than **1** and **4**, and these results confirm the conclusion that it is less complementary to Cu^{2+}.

The kinetic stability of a Mn^{2+} complex under severe conditions is also enlightening. The dissociation of Mn^{2+} from **1** in 1 M DCl was monitored by ^{1}H-NMR by measuring the integrated intensity of the NMR spectrum of free ligand as a function of time [125]. The protons on the metal complex are too paramagnetically broadened to be observed, but upon decomplexation the protons of the free ligand are observable, albeit broadened. In this way, the pseudo first-order rate of dissociation in 1 M DCl was found to be 1.4×10^{-5} s^{-1} ($t_{1/2} = 13.8$ h) at 298 K [125]. Remarkably, this ligand dissociates from Mn^{2+} at a rate that is 12 orders of magnitude slower than the rate of water exchange from the hydrated Mn^{2+} ion [126]. Other ligands, such as tetra-(3-*N*-methylpyridyl)porphyrin, [133] dissociate with a half-life of 74 μs in 1 M HCl. Likewise, the addition of HCl or $HClO_4$ to an ethanol solution of the Mn^{2+} complex of tetA causes the instant precipitation of a white solid identified as the protonated ligand [134]. This complex does indeed enjoy, in relative terms, an immense increase in kinetic stability.

A further pair of comparisons from the literature are useful. The Springborg group has produced kinetically inert Cu^{2+} complexes of a trimethylene cross-bridged cyclen (see Fig. 20) [84,85]. The crystal structure shows a coordination geometry similar to that of the present complexes, a macrobicycle engulfed copper ion with a labile fifth ligand and a geometry intermediate between trigonal bipyramidal and square pyramidal. Kinetic studies in 5 M HCl reveal a first-order dissociation constant for the macrobicycle in $CuLCl^+$ of 1.48×10^{-6} s^{-1} (or a half-life of over 5 days).

Though an impressive number, it is still some three orders of magnitude less stable than the dimethylene cross-bridged cyclam complex, but somewhat better than the copper complex of ligand **3**. The likely reasons for the improved stability for $Cu(\mathbf{1})^{2+}$ are better size complementarity for the Cu^{2+} ion by the larger parent macrocycles and greatly improved rigidity of the bound ligand, apparently due to decreasing the length of the cross-bridge by one carbon atom, from trimethylene to dimethylene. Yet, making the macrobicycle too small, as in the case for **3**, sacrifices some complementarity and, consequently, weakens its ability to hold onto the metal ion. Inescapably, size does matter; the addition or removal of a single methylene group causes vast stability differences.

Extensive studies have been reported on bridged cyclen derivatives in which the bridge is a chain that contains a fifth donor atom (see Fig. 15). The corresponding five coordinate Cu^{2+} complexes also exhibit exceptional stabilities under strongly acidic conditions, although dissociation rates have not been quantified [70–76]. Even though the bridging group is longer (providing less rigidification) in these examples, addition of a fifth donor, and the associated extra chelate rings, could explain why these complexes are so stable. The exceptional kinetic stability is due to the difficulty of stepwise donor dissociation of the topologically constrained cross-bridged ligands. The above comparisons elucidates the principles for strong metal–ligand complexation outlined in Section 1 above: appropriate complementarity enhanced by topological and rigidity constraints through ligand superstructures.

3.2.4. Solution behavior of a biomimetic complex

The titration data for $Mn(\mathbf{1})Cl_2$ has been fit very well by treating the compound as a weak monoprotic acid [125]. While conductance measurements showed that both chlorides are replaced by water in aqueous solution, [125] only one appears to have a pK_a in the accessible pH region. The pK_a for this bound water is 10.87(4), which agrees very well with that found for $Mn(H_2O)_6^{2+}$, (10.9) [126] and indicates that ligand **1** does not significantly alter the electron density of Mn^{2+} from that of the hexaquo complex. Since the combination of the tetradentate cross-bridged macrocycle and two water molecules leave the electron density on the metal ion about the same as in the hydrated ion, it follows that the great stability of the complex arises from topological and rigidity effects, not from electronic effects. With the electron density little changed from that of the hydrated metal ion, the complex might be expected to exchange its two water molecules at similar rate to that of hydrated Mn^{2+}.

Electrochemical studies further confirm the promise of this manganese complex for homogeneous oxidative catalysis in aqueous media [125]. The cyclic voltammogram of the $Mn(\mathbf{1})Cl_2$ complex in acetonitrile is shown in Fig. 38. The rigid ligand stabilizes a range of oxidation states for manganese, from Mn^{2+} to Mn^{4+} as shown by the two reversible oxidations. From this perspective the manganese complex is very likely to

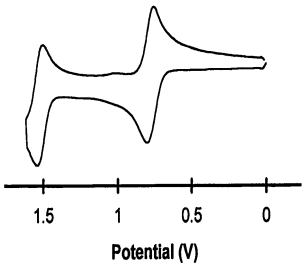

Fig. 38. Cyclic voltammogram for Mn(**1**)Cl_2.

function as an oxidation catalyst with a variety of terminal oxidants.

3.2.5. Catalytic oxidation studies

The catalytic ability of the $Mn(\mathbf{1})^{2+}$ complex in aqueous solution has been assessed in epoxidation and hydrogen abstraction reactions [125]. Carbamazepine (CBZ) is a moderately water soluble substrate suitable for epoxidation studies. Oxidation reactions on CBZ in aqueous solution with several oxidants at various pH values have been reported [125]. Maximum CBZ conversion was found to be 76% using $KHSO_5$ as oxidant. The most selective oxidants were H_2O_2 and *t*-BuOOH, which produced CBZ-epoxide as the exclusive product, even at pH 10, using H_2O_2 as the oxidizing agent. Mechanistic investigations of this system continue.

A variety of industrial and biochemical processes involve oxidation reactions that proceed via hydrogen atom transfer. The well-known biological processes are assumed to proceed by means of high-valent 'M=O' intermediates. A convenient substrate model for studies of this type of reaction is 1,4-cyclohexadiene (CHD). The catalytic oxidation of CHD in the mixed solvent system, MeOH/H_2O (1:1 v/v) with H_2O_2 as the terminal oxidant shows quantitative formation of benzene [125]. Kinetic measurements of CHD disappearance and benzene formation show first-order curves, with the observed rate constants 4.0×10^{-4} and 3.8×10^{-4} s^{-1}, respectively. Under experimental conditions comparable to those used for the CBZ epoxidation the conversion of CHD was 63.2 and 23.8% with H_2O_2 and *t*-BuOOH, respectively. This amounts to ca. ten times the yield for the oxidation of CBZ, demonstrating the selectivity of the oxidation catalyst [119].

3.2.6. Conclusions

In conclusion, the concepts of the introduction should be revisited in light of the data presented in this final section. Complementarity, preorganization and/or MJF designed into topologically constrained azamacrocycles results in the stable metal complexes predicted by these concepts. Such topologically constrained ligands can be synthesized by a variety of synthetic strategies, as seen in the middle section of this review. One particular strategy, condensation synthesis, has given rise to an especially interesting family of cross-bridged tetraazamacrocycles that exhibit extreme kinetic stability in their transition metal complexes. This stability, along with the other desirable characteristics of the complexes for biomimicry, has been exploited in a Mn^{2+} complex to produce an active and selective oxidation catalyst for use in aqueous solution. This is likely only the initial example of utility from a group of ligands with a very bright future.

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