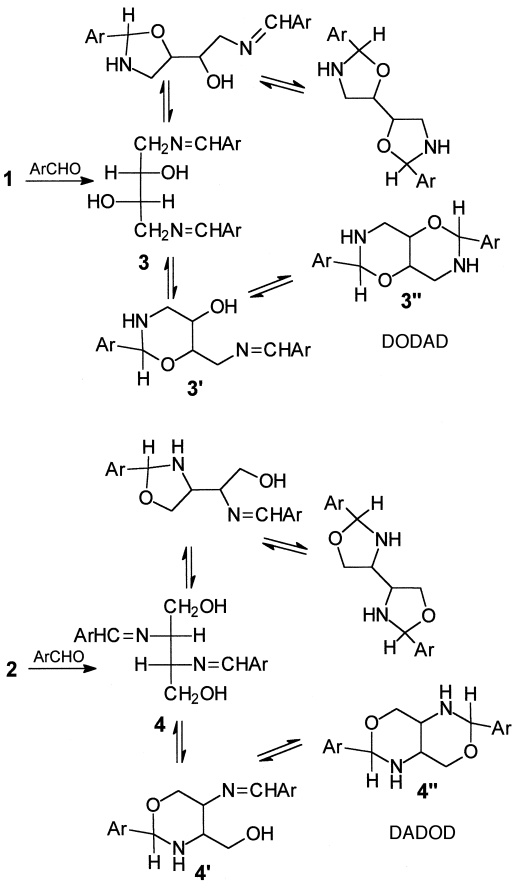
Dioxadiazadecalin/Salen Tautomeric Macrocycles and Complexes: Prototypal Dynamic Combinatorial Virtual Libraries**

Alexander Star, Israel Goldberg, and Benzion Fuchs*

We recently described[1, 2] the reactions of the isomeric *threo*-1,4- and *threo*-2,3-diaminobutanediols (**1** and **2**, respectively) with aldehydes to give the new isomeric *cis*-1,5-dioxa-3,7-diazadecalin (DODAD) and *cis*-1,5-diaza-3,7-dioxadecalin (DADOD) systems,[1] out of the whole variety of possible ring–chain tautomers (Scheme 1).[2] Different 2,6-*para*-aryl substituted derivatives were investigated, and the tautomeric



Scheme 1. All possible products (diimines, mono- and diacetals) from the reaction of *threo*-1,4- and *threo*-2,3-diaminobutanediols (**1**, **2**) with aromatic aldehydes; the six-membered bicyclic systems are the *cis*-dioxadiazadecalins (DODAD) and *cis*-diazadioxadecalins (DADOD).

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ratios, which express the relative stability of these dioxadiazadecalin systems, were shown to be affected by the electronegativity of the 2,6-*p*-aryl substituents.[2a] Whereas *cis*-DADOD systems were more stable than their parent Schiff bases in all cases, the *cis*-DODADs prevailed only with electron-withdrawing substituents. In earlier detailed studies[3] of ring–chain tautomerism in 1,3-oxazanes, it was shown that *ortho*-substituted 2-aryl systems are exceptional[3c] due to hydrogen bonding in addition to electronic and steric effects. This bears upon *N*-salicylideneamino derivatives, which are related to the well-known salen systems.[4, 5]

The Schiff bases **3** and **4** (Ar = *o*-C_6H_4OH),[2b, 6] prepared by the reaction of salicylaldehyde with the L-1,4- and D-2,3-diaminobutanediols (**1** and **2**, respectively), exhibited ring–chain tautomerism,[2] with some formation of the isomeric dioxadiazadecalin systems. The open forms prevail due to strong internal hydrogen bonding involving the 2-hydroxyphenyl groups, which can be avoided[3c] by O-alkylation. Indeed,[2b] O-methylation resulted in higher dioxadiazadecalin yields in both the DODAD (**3″**, Ar = *o*-C_6H_4Me) and the DADOD (**4″**, Ar = *o*-C_6H_4OMe) series; the latter was exclusively isolated. This stability of the bicyclic forms can be partly attributed to intramolecular N–H···OR hydrogen bonds, although these are still somewhat weakened by steric interference of the two OMe groups.

This interference can be avoided by connecting the two phenolic termini, which meets our aim of preparing macrocyclic systems from these platforms. We probed the length of the best-fitting spacer by molecular mechanics and modeling (CFF91-Insight II, MSI) of various spacers with the O···O distance as criterion. For O–CH_2–CH_2–O, this distance coincided with that of a hypothetical unsubstituted and strainless molecule.

The reaction of 1,2-bis(*o*-formylphenoxy)ethane (**5**)[7] with **1** and **2** proceeded smoothly at high dilution to give (2*R*,6*R*;9*S*;9,10-*P*)-2,6-(1′,2′;7′,8′-dibenzo-3′,6′-dioxa-1′,8′-octanylidene)-*cis*-1,5-dioxa-3,7-diazadecalin (**6″**) and (2*R*,6*R*;9*S*;9,10-*M*)-2,6-(1′,2′;7′,8′-dibenzo-3′,6′-dioxa-1′,8′-octanylidene)-*cis*-1,5-diaza-3,7-dioxadecalin (**7″**), respectively (Scheme 2), in almost quantitative yields.

The DODAD macrocycle **6″** exists in $CDCl_3$ entirely without Schiff base tautomers, even on heating. However, heating **6″** in [D_6]DMSO in a variable-temperature NMR study led to increasing formation of the open Schiff bases **6** and **6′** (3.5 and 1.5% at 298 K; 45 and 47% at 410 K, respectively) and less than 5% oxazolidine tautomers. Strong intramolecular NH···OR hydrogen bonding in **6″** and **7″** is manifested in a clear triplet for the NH group with large *anti* vicinal coupling constants, and by strong deshielding ($\Delta\delta = 2$) of these protons relative to known *p*-nitrophenyl-substituted compounds.[2] The structure of **6″**, obtained from an X-ray diffraction analysis (Figure 1), confirms the presence of these strong intramolecular hydrogen bonds, which are probably responsible in part for the smooth macrocyclization reaction.

Lehn[8a] recently introduced the concept of dynamic combinatorial chemistry/virtual combinatorial libraries (DCC/VCL).[8] These molecular or supramolecular libraries are virtual because their constituents may not necessarily exist in significant amounts in the absence of an assembling target (for

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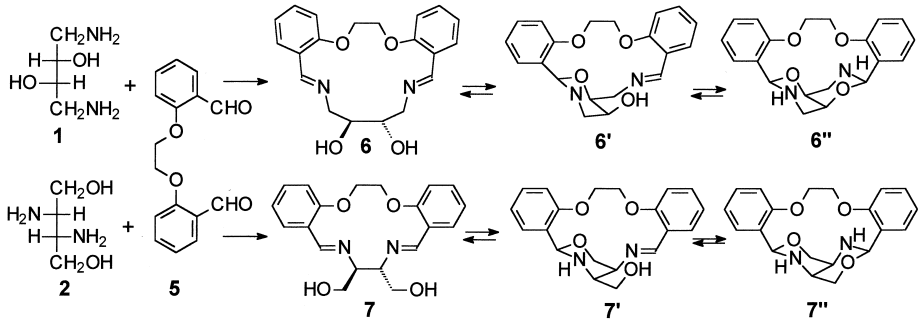


Scheme 2. The tautomeric macrocyclic products in the DODAD (**6″**) and DADOD (**7″**) series from the [1+1] reaction of 1,2-bis(*o*-formylphenoxy)ethane (**5**) with **1** and **2**, respectively.

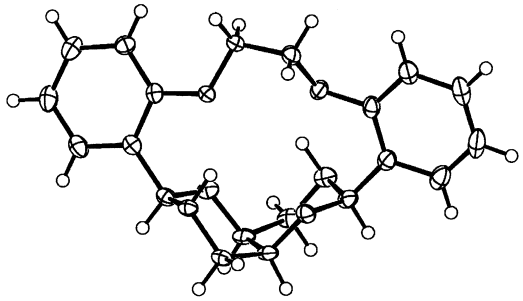


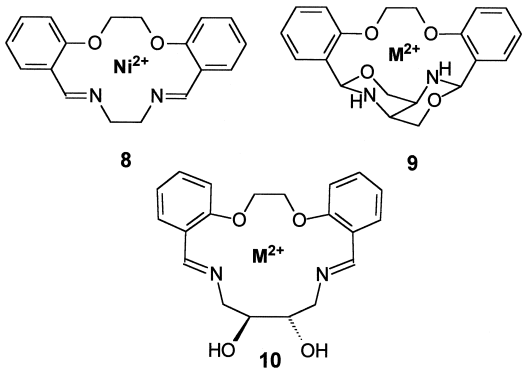
Figure 1. ORTEP plot of **6″** with 50% probability thermal ellipsoids. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137663. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). See also Supporting Information.

most recent related accounts, see ref. [9]). A pertinent passage there states: "Tautomerism, in particular in heterocyclic compounds, gives rise to dynamic diversity, allowing a shift towards one of the tautomeric states in response to interaction with the target or to environmental factors"; we now report a prototypal library of this kind.

The double Schiff base (e.g., **3**) formed in the reaction (Scheme 1) of an aromatic aldehyde with L-1,4-diamino-2,3-butanediol has two possible reaction pathways, namely, reversible consecutive ring closures to give five-membered and/or six-membered ring systems. The resulting five conceivable coexisting species can be considered a dynamic combinatorial virtual library (DCVL). The processes depicted in Scheme 2 represent only one of these options (or a subset of the above DCVL), that is, the six-membered ring closure (Scheme 1, bottom). The latter is also kinetically preferred,[2] since in accordance with Baldwin's rules,[10] the *endo-trig* ring closure is favored for 1,3-oxazanes (6-*endo-trig*), but disfavored for oxazolidines (5-*endo-trig*).

Note that we are not dealing here with an unbiased, isoenergetic DCL, as postulated by Lehn.[8a] This requirement is, after all, strongly phase- and medium-dependent and therefore of only limited pertinence. The **6** and **7** series (Scheme 2) are in fact biased libraries, in which one of the members of each series is strongly favored, such as the stable DODAD macrocycle **6″**, which can be destabilized by heating in DMSO to give **6** and **6′**. This allows the DCVL to be "scanned" for its constituents by changing the temperature and/or solvent. However, in the diazadioxadecalin series (**7**), the closed form **7″** prevails even on heating due to the intrinsic high stability of *cis*-DADOD.[2]

In a biased but target-driven library, in which one constituent is highly favored, the preferred interaction of a virtual (or minor) constituent with the target may overturn the equilibrium situation. Hence, we probed the influence of chelation of selected metal ion targets on ring–chain tautomerism in the **6** and **7** macrocyclic series. In this context, we recalled that Armstrong and Lindoy[7] had prepared the Ni^{II} complex **8** of the related diimine macrocycle (i.e., **7** without the two hydroxyethyl



pendant groups), by condensation of the dialdehyde **5** with ethylenediamine and complexation in situ. Their attempts to isolate the macrocyclic ligand by removing it from the nickel complex **8** were unsatisfactory and, in the presence of other diamines, **8** underwent amine exchange reactions to form more stable complexes of nickel.

Complexation of **7″** with $NiCl_2$ in methanol proceeded slowly at room temperature with formation of transient imine forms ($\delta = 8.5$ by NMR spectroscopy during complexation), but no evidence for a diimine macrocyclic complex similar to **8** was found in the product. The final product was clearly a DADOD complex, but it was apparently formed via **7**·Ni^{II}, which underwent tautomeric ring closure to the more stable **7″**·Ni^{II} complex. The FAB-MS spectrum of the latter has a peak at *m*/*z* 447 (20%) that fits exactly the $[NiLCl]^+$ species. All FAB-MS peak assignments were confirmed by comparison with simulated isotope patterns.

A similar complexation of **7″** with $Ni(ClO_4)_2$ in acetonitrile was carried out with UV monitoring of the complexation process (Figure 2). Addition of nickel salt affords a slight hypsochromic shift with sizable intensity increase and a 1/1 complexation stoichiometry, as determined by Job's method[11] (Figure 2, inset). Attempts to obtain a lead complex of **7″** in methanol failed. Indeed, the Ni^{2+} ion of small ionic radius (0.69 Å) can readily inhabit the DADOD **9** cavity, which the larger Pb^{2+} ion (1.18 Å) can not, and tautomeric

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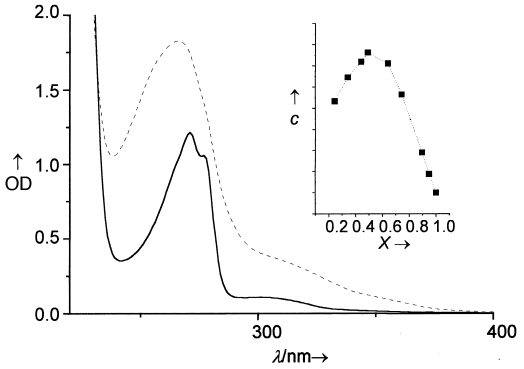

Figure 2. UV spectrometry of the complexation of **7″** with $Ni(ClO_4)_2$ (5×10^{-4} M) in MeCN: —— ligand; ---- [1:1] complex (OD = 1.82). Inset: determination of the ligand/complex ratio, by Job's method[11] (X = "molar fraction").

ring opening to give the similarly sized **7**·M^{II} (cf. **8**) is ineffective.

In the dioxadiazadecalin (DODAD) macrocyclic series (Scheme 2, top), on complexation of **6″** with $NiCl_2$, the final methanol solution shows exclusively (NMR) the dioxadiazadecalin complex. Under FAB-MS conditions, however, the occurrence of peaks at m/z 447 (30%) for $[NiLCl]^+$ and at 411 (65%) for $[NiL-H]^+$ indicate the additional presence of the tautomeric diimine complex. This general and diagnostic difference exists in all FAB mass spectra of complexes of the macrocycles in the **6** and **7** series: the complexes of both the bicyclic DODAD (**6″**) and DADOD (**7″**) exhibit $[MLX]^+$ ions, but only in the ring–chain tautomeric **6** series can one find an $[ML-H]^+$ ion, characteristic of the dimine **6**.

Interestingly and in contrast to the DADOD series (see above), addition of $Cd(ClO_4)_2$ or $Pb(ClO_4)_2$ to **6″** in methanol led to the precipitation of the complexes in each case. These could be dissolved, however, in $[D_6]$DMSO for NMR purposes. Thus, it became evident that **6″** underwent tautomeric ring opening during complexation with Cd^{2+}, and all forms (**6**, **6′**, and **6″**) are present, as is also shown by FAB-MS (peaks at m/z 567 (25%) $[CdL(ClO_4)]^+$, 467 (7%) $[CdL-H]^+$, and 465 (15%) $[CdL-3H]^+$). In the case of lead, however, the NMR spectrum in $[D_6]$DMSO shows only the diimine complex **6**·Pb^{II}, with FAB-MS peaks characteristic of the open-chain form (561 (70%) $[PbL-H]^+$ and 559 (140%) $[PbL-3H]^+$). It appears that the larger Cd^{2+} (0.97 Å) and Pb^{2+} (1.18 Å) ions are readily accomodated by **6″** (in contrast to **7″**) due to its ability to modify its cavity size by a successive ring-opening process (Scheme 2), ending with a ring expansion by two atoms to give **10** (M = Pb). Eventually, the latter may undergo gradual reverse macrocycle folding, which provides a mechanism of fine-tuning until an optimum cavity size for ion bonding is reached. Thus, Ni^{II}, Cd^{II}, and Pb^{II} are complexed by **6**–**6″** in different tautomeric modes that depend on the size of the cation.

To highlight another aspect of DCVLs, the condensation of **1** and **2** with the known 1,10-phenanthroline-2,9-dicarbaldehyde (**11**)[12] was carried out in ethanol (Scheme 3) to give the macrocycles **12″** and **13″**, respectively. Evidently, a [2+2] condensation took place, since the utilization of the long and rigid dialdehyde **11** rendered the [1+1] mode improbable. In fact, according to FAB-MS, **13″** was accompanied also by some [3+3] macrocyclic product. These reactions are closely related to the previously described[13] nontemplate condensation of **11** with 1,2-diaminoethane or 1,4-diaminobutane to give the corresponding tetraimine macrocycles, except that our system has additional 2-hydroxyethyl pendant groups which turn it into a tautomeric manifold and consequently into a DCVL.

The NMR spectra of the sparingly soluble macrocycles **12″** and **13″** could be recorded in chloroform/methanol or DMSO. According to variable-temperature NMR spectra in $CDCl_3$/$[D_4]$MeOH from $-50\,^\circ$C to room temperature and in $[D_6]$DMSO from room temperature up to $120\,^\circ$C, these macrocycles exist as tautomeric mixtures, without apparent preference for any tautomer.

According to the same reasoning as in the simple cases (**3**, **4**; see above), the [2+2] macrocycles can occur in 18 tautomeric forms, with a subset of seven oxazine tautomers (**13**–**13″**, Scheme 4). In case of the [3+3] macrocyclic manifold, 67 components of the tautomeric mixture are theoretically possible, sixteen of them in the oxazine subset (Figure 3, bottom).

Contrary to the [1+1] macrocycles, with their strongly favored DODAD (**6″**) and DADOD (**7″**) components, the [2+2] macrocycles form partly unbiased, isoenergetic dynamic combinatorial libraries over a wide temperature range, whereby certain equilibrating constituents are of sufficiently similar free energy to generate a Boltzmann distribution with comparable populations for these constituents (states). As with the smaller [1+1] species, the [2+2] and [3+3] series are truly DCVLs (Figure 3), but with numerous components, some of which are less stable and likely absent. Further experiments are in progress to produce biased and template-induced forms.

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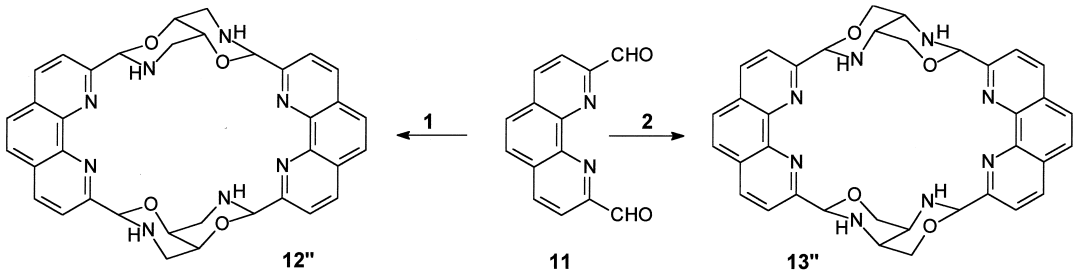

Scheme 3. The fully closed macrocyclic products in the DODAD (**12″**) and DADOD (**13″**) series from the [2+2] reaction of 1,10-phenanthroline-2,9-dicarbaldehyde (**11**) with **1** and **2**, respectively.

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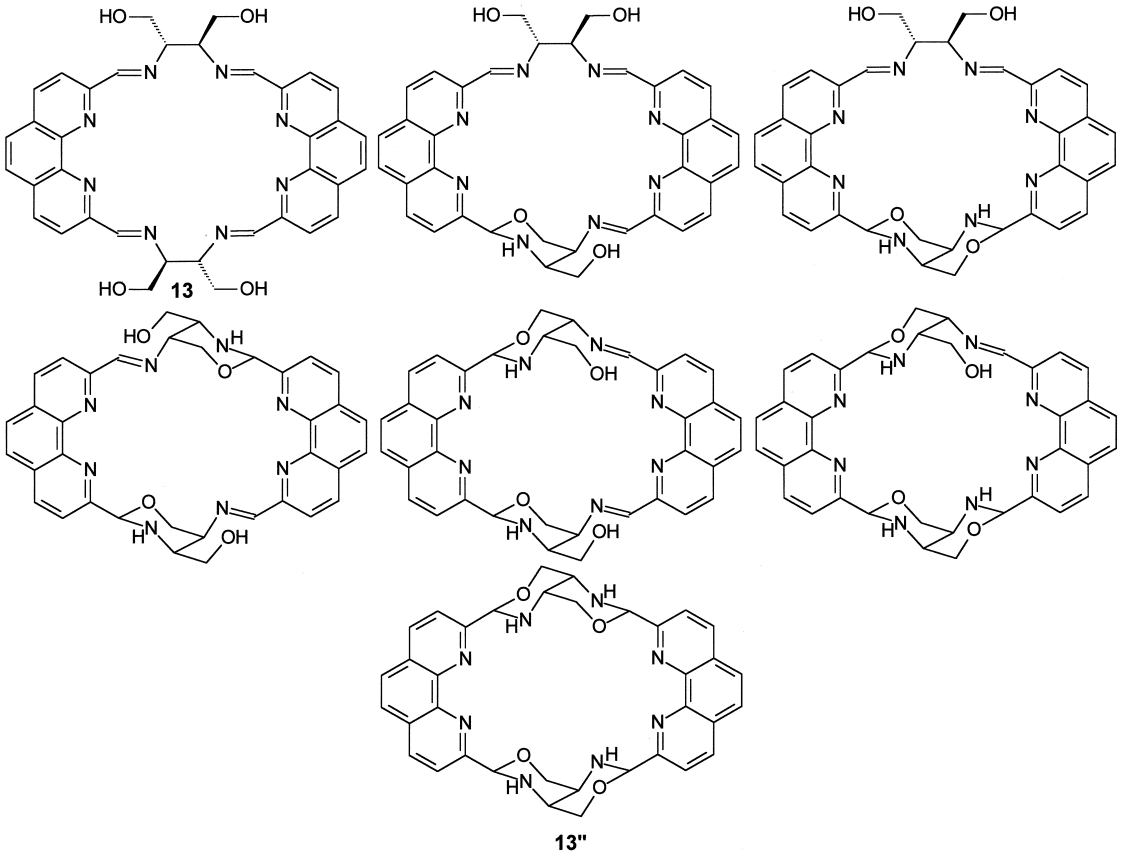

Scheme 4. The full tautomeric set of macrocycles (**13**–**13**″) in the six-membered DADOD series.

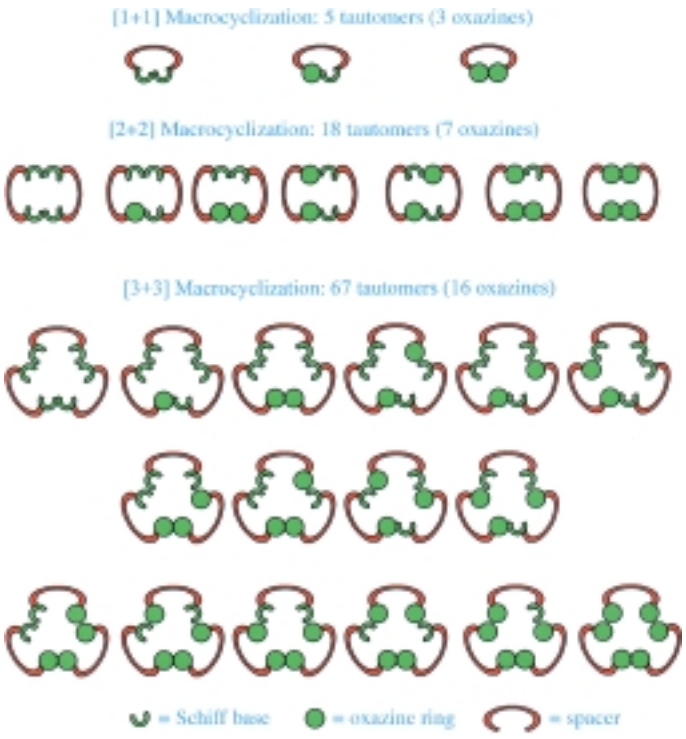

Figure 3. Schematic representation of dynamic combinatorial virtual libraries (DCVLs) comprising the macrocycles in any of the equilibria involving the six-membered DODAD and DADOD systems, bridged by ligating spacers (see Scheme 2 for the [1+1] mode and Scheme 4 for [2+2]).

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Lanthanide [15]Metallacrown-5 Complexes Form Nitrate-Selective Chiral Cavities

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In 1989 we described a strategy using a metal salt and a bifunctional hydroxamic acid for the synthesis of metallomacrocycles known as metallacrowns.[1a] Metallacrowns are preorganised molecules that can be prepared in a variety of structure types[1b–f] in yields ranging from 60 % to quantitative. Remarkably, the molecules are robust: they retain their structure in solution and carry out cation and anion exchange reactions without decomposition.[1g,h] Recently, we have shown that resolved amino hydroxamic acids[1i–k] can be used as precursors for the preparation of macrocycles that can have molecular weights greater than 1500 Daltons,[1k] contain multiple resolved centers, and may be amphiphilic. There is current interest in developing materials capable of anion recognition, particularly through the use of macromolecules such as calixarenes,[2a,b] porphyrins,[3a,b] and macropolycyclic polyammonium molecules[4a–c] which can require multiple step syntheses. Herein we show for the first time that one can exploit the asymmetry of the chiral metallacrown motif to realize molecular cavities that are capable of selective anion recognition by using molecules that are made in a one-step reaction from simple starting materials.

The metallacrown dimer $[(\mathbf{1})Cl_2]^{4+}$[5] (Figures 1 and 2a, Table 1)[6, 7] is prepared using L-tyrosinehydroxamic acid (H_2tyrha) as a ligand.[8] The molecule contains five tyrosinehydroximate ligands and five Cu^{II} ions in each of the two [15]metallacrown-5 (15MC-5) disks, with a Gd^{III} ion captured in the core of each metallamacrocycle to give a stoichiometry of $[C_{45}H_{50}N_{10}O_{15}Cu_5Gd]^{3+}$. The metallacrowns have rotational symmetry, and therefore, the use of L-tyrosinehydroxamic acid provides face differentiation as the side chains are all oriented to the same "hydrophobic" face. The metallacrowns in the dimer are related to one another by a C_2 axis that is parallel to the plane of the disc, and thus are orientated with

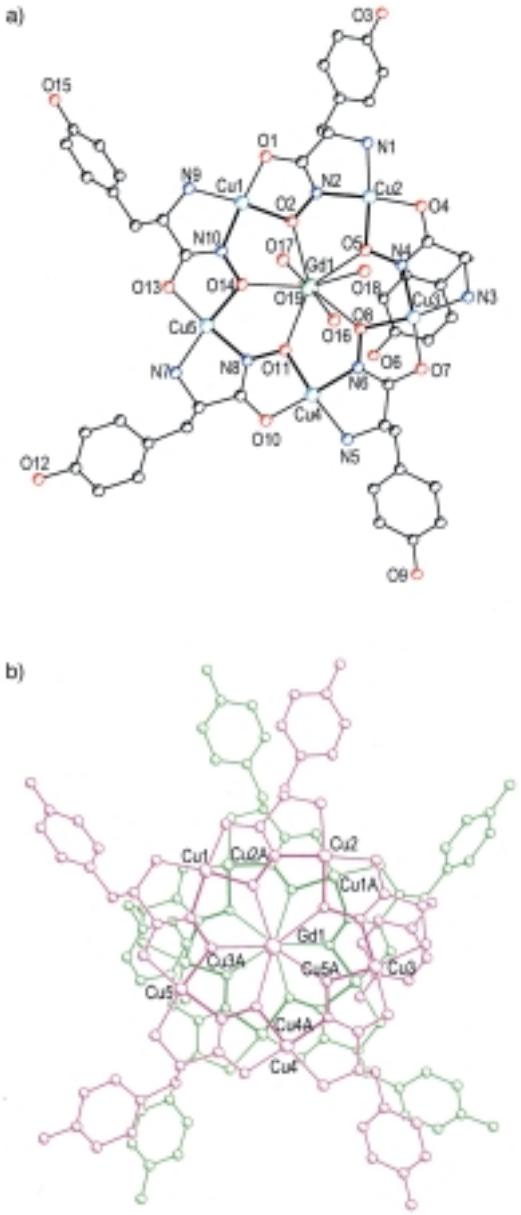

Figure 1. PLUTO diagram of $[\mathbf{1}\cdot(Cl)_2]^{4+}$ with chloride ions removed for clarity. a) Monomer and b) dimer shown looking down the psuedo fivefold axis, with the C_2 axis in the plane of the page.

the hydrophobic faces towards each other. As viewed down the pseudo fivefold axis the MC that is on top has clockwise (C) rotational symmetry (Cu-O-N-Cu); therefore, the bottom metallacrown is anticlockwise (A) when viewed from this perspective, thus giving a C/A isomer. While four phenol groups from each metallacrown are extended into solution, the remaining two wrap into the cavity and bond to a ring copper ion from the opposite metallacrown ($Cu{-}O_{tyr}$ = 2.872 Å). The ring oxygen atoms are nearly perfectly staggered, with an O–O twist angle (defined as the torsion angle O2-Gd1-Gd1A-O2A) between the two metallacrowns of the dimer of 35.7°. However, because the metallacrowns have C/A rotational symmetry, the Cu–Cu twist angle (Cu1-Gd1-Gd1A-Cu2A) is 11.4°, which makes the ring copper ions closer to being eclipsed than staggered. The result is a weakly

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