

Adamanzanes—bi- and tricyclic tetraamines and their coordination compounds †

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Structural modification of the important tetraaza macrocyclic ligands such as cyclen and cyclam involving ethylene and trimethylene bridging of the non-adjacent nitrogens represents a new class of macrobicyclic ligands, so-called bowl-adamanzanes. The molecular topology and size confer special properties to these amines and the most prominent features of their metal ion coordination complexes are extreme inertness and stabilization of low oxidation states. Strapping of the two secondary amine groups in the bicyclic bowl-adamanzanes leads to tricyclic tetraamine cages in which the nitrogen atoms form a nearly tetrahedral geometry. These new amines, so-called cage-adamanzanes, have been intensely studied over the last decade. Medium-sized cage-adamanzanes have a center to nitrogen distance of about 2 Å which makes them obvious candidates for the encapsulation of metal ions. This fascinating goal, however, has yet to be seen. The present article describes the synthesis and properties of cage- and bowl-adamanzanes and the metal ion coordination compounds which have appeared recently.

Introduction

Coordination compounds of macrocyclic, macrobicyclic and macrotricyclic ligands are of current interest because of their importance as model systems within bioinorganic chemistry, their application in medicine and as catalysts. Design, synthesis, and coordination chemistry of new polyamine ligands continue to stimulate intense research efforts due to the realized and potential applications.^{1–3} Structural modifications of the important macrocyclic ligands cyclen and cyclam involving ethylene and trimethylene bridging of the non-adjacent nitrogens have been reported during the last decade. The resulting

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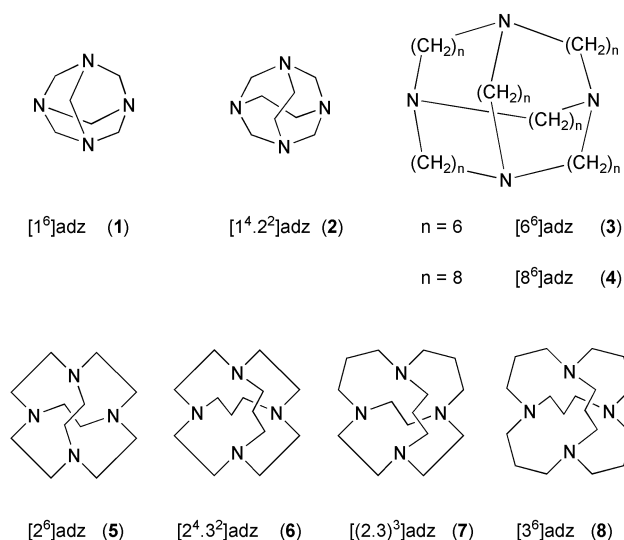


Johan Springborg

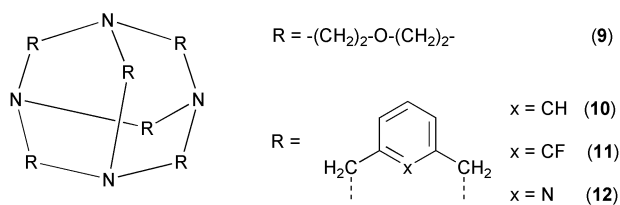
compounds represent a new class of macrobicyclic ligands, so-called bowl-adamanzanes. These amines have very special acid–base properties and their metal ion coordination complexes are inert. Low oxidation states are stabilized and there is a preference for uncommon coordination geometries. Addition of a second alkyl bridge connecting the secondary amine groups in the bicyclic bowl-adamanzanes leads to tricyclic tetraamine cages in which the nitrogen atoms form a nearly tetrahedral geometry. These new amines, so-called cage-adamanzanes, have been intensely studied over the last decade. Medium-sized cage-adamanzanes have a center to nitrogen distance of about 2 Å which makes them obvious candidates for the encapsulation of metal ions. This fascinating goal, however, has yet to be seen. The present article describes the synthesis and properties of cage- and bowl-adamanzanes and the metal ion coordination compounds which have appeared recently.

Cages

Cage-adamanzanes are tricyclic tetraamines with aliphatic chains. An overview of the cage-adamanzanes **1–8** is shown in Scheme 1 and the simplified nomenclature used throughout this paper is given in the Appendix. The smallest member in this family, hexamethylenetetraamine (**1**), was prepared more than a century ago, and its crystal structure, reported by Dickinson and Raymond in 1923, was the first structure of an organic compound obtained by X-ray diffraction.⁴ In this compound and another small adamanzane **2** the lone pairs are directed outwards, whereas the lone pairs are directed towards the inside in all the medium sized adamanzanes **5–8**. The cage-adamanzanes resemble the cryptates and tricyclic amines reported by Lehn, Alder and others.^{2,3} Some closely related compounds are the 3-oxapentamethylene bridged tetraamine **9** ('soccer ball') reported by Lehn *et al.*⁶ and the xylylene bridged tetraamine **10** and its analogues **11** and **12** reported by Inazu, Takemura *et al.* (Scheme 2).^{7,8}



† Electronic supplementary information (ESI) available: tables of variations in $N_{ax}-M-N_{ax}$ angles as a function of cavity size and the radius of the central ion. See <http://www.rsc.org/suppdata/dt/b3/b300510k/>



Scheme 2

Syntheses

The first cage adamanzanes, apart from the small cages **1** and **2**, were reported by Schmidtchen⁹ who synthesized the large cages [6⁶]adamanzane (**3**) and [8⁶]adamanzane (**4**). The synthetic route, outlined in Scheme 3, is based on three successive cyclizations under high dilution conditions. Schmidtchen's method has the advantage that in principle it can be used to synthesize cage-adamanzanes with any combination of sizes of the aliphatic bridges. The drawback is that the condensations require the use of very dilute solutions in order to minimize the formation of polymeric by-products and that the overall yields are low (2–5%) as a consequence of the many synthetic steps. The method was later used by Ichikawa and coworkers to synthesize [5⁶]adamanzane, [5².6⁴]adamanzane and [(5.6)².6¹.5¹]adamanzane.¹⁰ The tetramethylated quaternary ammonium derivatives of these compounds have been the subject of detailed studies of their capacity to encapsulate anions, react with biologically important compounds such as AMP, ATP and NAD and catalyze bimolecular nucleophilic organic substitution reactions.^{10–13}

The first medium sized cage, [2⁴.3²]adamanzane (**6**), was synthesized by us using the reaction of the parent bowl-adamanzane with the ditosylate of trimethylene diol (Scheme 4).¹⁴ The synthesis requires no special use of dilute reactant solutions and the product was isolated as the inside protonated form [H[2⁴.3²]adz]ClO₄ in a reasonable yield (57%). It seems general that the smaller cages are obtained as their inside mono-protonated forms as discussed below. The same method was later used by Miyahara, Inazu and coworkers¹⁵ to prepare the small and highly symmetrical cage H[2⁶]adz⁺. A much more optimistic approach was later used by us studying the reaction between 1,5,9-triazacyclododecane and tris(3-chloropropyl)amine.^{16,17} From almost any point of view this method would be expected to give only polymeric products. Contradicting such expectations the reaction gave a reasonable yield (27%) of [H[3⁶]adz]Br as shown in Scheme 5. Similarly, starting with 1,4,7-triazacyclononane the cage [H[(2.3)³]adz]Br was obtained (yield 38%).¹⁸ In both cases formation of polymeric products does take place, but the pure products can be obtained by simple reprecipitation procedures and the method seems to be quite general.

These cages are obtained as inside mono-protonated forms and it seems certain that the proton is encapsulated during the synthesis and not taken up by the cage after its formation. In fact, several observations point to the notion that these syntheses are template-assisted with a coordinated proton serving as the template. In the synthesis of H[2⁴.3²]adz⁺ (Scheme 4) the

reactant is protonated with one proton bound to the two bridgehead nitrogen atoms. Thereby these groups are prevented from reacting with the tosylate causing quaternary side-product and the intermediate **15** is forced into a conformation which favours the final ring-closure reaction (Scheme 4). A similar hydrogen-bond stabilized intermediate, **16**, has been suggested for the synthesis starting with a triazamacrocycle as illustrated in Scheme 5.

Inertness of the inside coordinated proton

In the crystal structure of [H[3⁶]adz]Br the proton is located at one of the four identical nitrogen atoms (Fig. 1).¹⁷ However, in solution the ¹H and ¹³C NMR spectra reflect a tetrahedral symmetry meaning that the proton must shuttle rapidly—on the NMR time scale—between all four nitrogen atoms.¹⁶ A similar result has been found for H[2⁶]adz⁺ and H[(2.3)³]adz⁺, whereas in H[2⁴.3²]adz⁺ the proton in the solid is hydrogen bonded equally to two non-adjacent nitrogen atoms.^{14,15,18} In the ¹H NMR spectrum the inside coordinated proton presents itself as a relatively sharp singlet with δ varying from 9.8 to 15.2 ppm for the four small cages discussed above. In H[2⁶]adz⁺ a small splitting (1 Hz) of the proton signal is observed and this has been ascribed to coupling with the neighbouring methylene protons.¹⁵ In H[2⁴.3²]adz⁺, H[3⁶]adz⁺ and H[(2.3)³]adz⁺ no splitting of the proton signal was observed, but in the two former species a distinct coupling (COSY NMR) with neighbouring methylene protons was observed.¹⁹ The absence of coupling in the latter compound is not understood. The iminium cage **17** (Scheme 6) exhibits splitting of the proton signal (6 Hz) as well as coupling with the methylene protons. Recent DFT calculations by Galasso²⁰ give chemical shift values for the inside coordinated proton in excellent agreement with the observed ones. The study also included calculation of vibrational spectra and structural parameters with nice agreement between theory and experiment. Similarly, DFT studies of the relationship between basicity, strain and intramolecular hydrogen-bond energy in adamanzanes and related tricyclic proton sponges have been reported by Howard.^{21,22} Finally

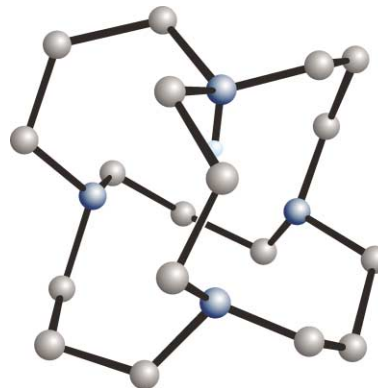
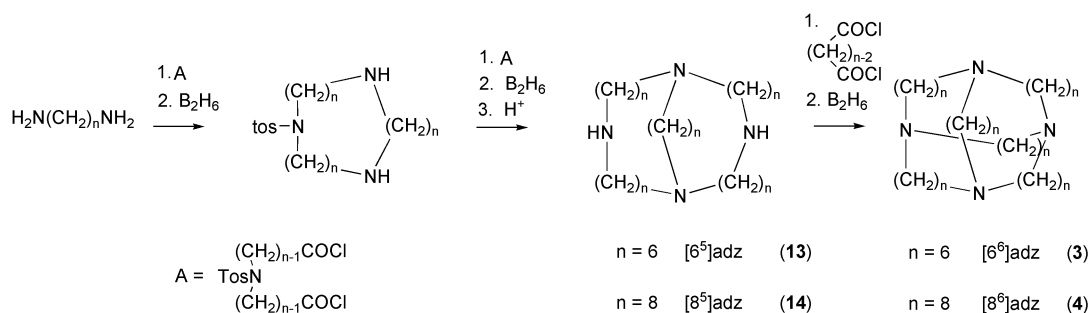
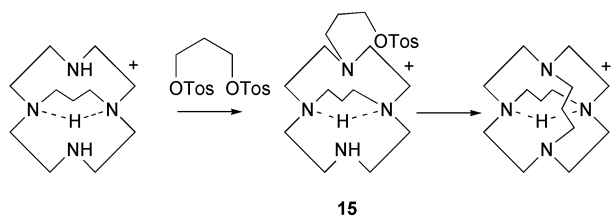


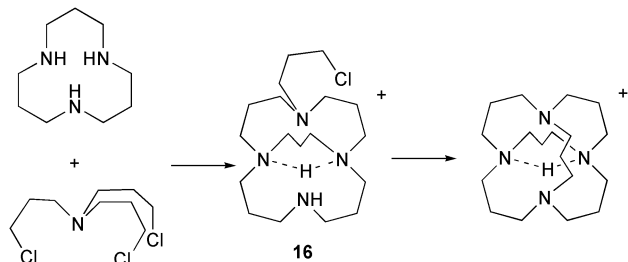
Fig. 1 The cation in the crystal structure of [H[3⁶]adz]Br. In the amines, in this and the following figures, only the hydrogen atoms bound to nitrogen are shown.



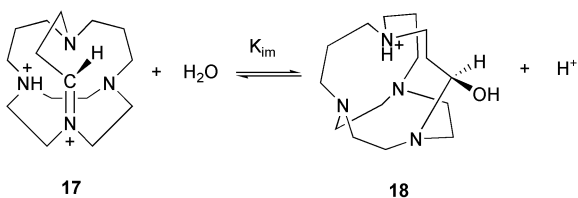
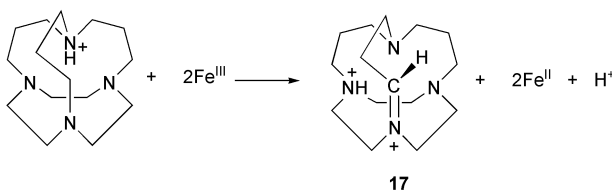
Scheme 3



Scheme 4



Scheme 5



Scheme 6

Knop and coworkers²³ have studied the intramolecular hydrogen bond in H[2⁴.3²]adz⁺ and related systems.

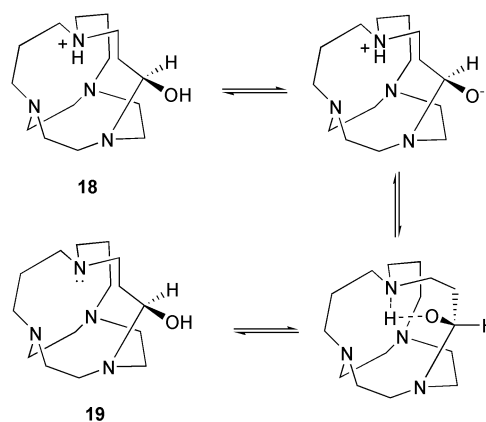
The inside coordinated proton is completely encapsulated by the organic framework of the macrotricyclic cage as seen in Fig. 1. This encapsulation explains the extreme robustness of the proton. Exchange of the inside coordinated proton with a deuteron in D₂O solution has not been observed and for all small cages the half life for the H/D exchange reaction in 1 M NaOD is estimated to be greater than one year, *i.e.* $k_{\text{ex}} < 10^{-8} \text{ s}^{-1}$. Recent experiments show that even when treated with strong basic or reducing agents such as NaBH₄, NaB(CN)H₃ and LiBu in aprotic, organic solvents the cages survive without any detectable sign of formation of unprotonated species (long term treatment at elevated temperature at these conditions, however, do result in decomposition).²⁴ The p*K*_{a1} values for the protonated cage therefore remains unknown. In fact it can not be excluded that the free amine is a weak base, *i.e.* it is possible that it may be even more difficult to insert a proton into the cage than to pull it out.

Outside protonation

Outside protonation, established by NMR studies, has been reported for most of the smaller cages. The cage H[3⁶]adz⁺ forms di- and tri-protonated species $\text{i}^+, \text{i}, \text{i}, \text{o}^+ - \text{H}_2[3^6]\text{adz}^{2+}$ and $\text{i}^+, \text{i}, \text{o}^+, \text{o}^+ - \text{H}_3[3^6]\text{adz}^{3+}$. The diprotonated cation is the dominant species in the region 0.1–3.0 M DCl, whereas the triprotonated species is a very strong acid. Even in 6 M DCl it is only present in minor amounts. However, this species can be isolated as a salt, which has been characterized by its crystal structure.¹⁷

Iminium cages

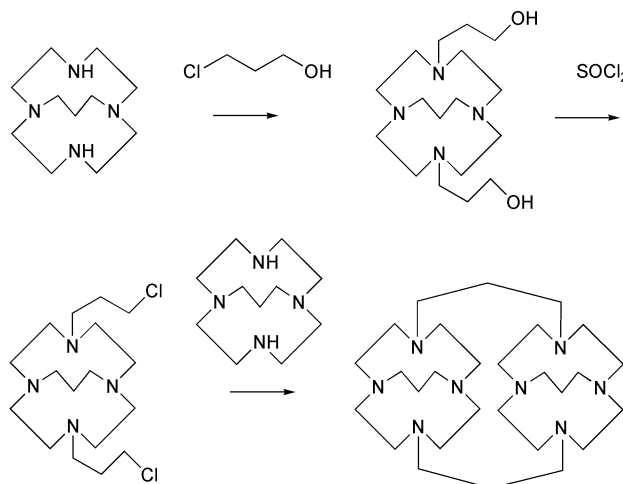
The small cages react with iron(III) quantitatively to form iminium ions as shown in Scheme 6 for H[(2.3)³]adz⁺. The iminium compound 17, which has been characterised by its crystal structure, is in a fast equilibrium with the hemiaminal 18 [$K_{\text{im}} = 1.57(1) \times 10^{-5} \text{ M}$].¹⁹ In basic D₂O solution the inside coordinated proton of 18 is rapidly exchanged with deuterons. In 1 M NaOD the half life is only 7 s at 25 °C, *i.e.* more than one million times shorter than that reported for H[(2.3)³]adz⁺, which differs from the hemiaminal only by substitution of a hydrogen atom with a hydroxy group at a carbon atom. This tremendous increase in rate is clearly not due to different steric hindrance and has been explained by the mechanism outlined in Scheme 7.¹⁹ In basic solution a small part of the hydroxy group in the hemiaminal will be deprotonated to an oxy group. The oxy group flips into the cavity, binds to the proton and then flips out again carrying the hydrogen ion away. In D₂O solution the OH group in 19 is rapidly converted into OD, and the reverse process carries a deuteron from the solvent into the cage and the net result is a H/D exchange in the iminium cage. The mechanism is thus a model for the passive transport of protons through biological membranes.



Scheme 7

Dimers

Two bowl adamanzanes may be bound together by two alkyl chains *via* the secondary nitrogen atoms, thus forming a dimer. They are interesting molecules in their potential to coordinate two, possibly different, metal ions inside the cavity and thereby offering the opportunity to study metal–metal interaction between encapsulated units. The only known example²⁵ so far is synthesized as shown in Scheme 8. The amine was isolated as a



Scheme 8

tetraprotonated salt having one proton coordinated inside and one outside each tetraamine unit (Fig. 2). The acid dissociation constants of the two outward-oriented protons are $pK_{a1} = 4.23$ and $pK_{a2} = 5.43$, whereas the inside-coordinated protons act as proton sponges with $pK_a > 15$. Attempts to insert metal ions have failed so far, probably due to steric hindrance.

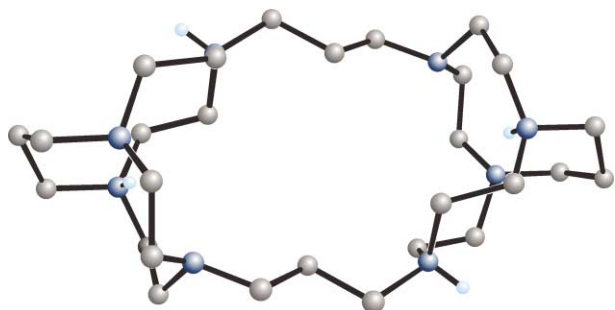
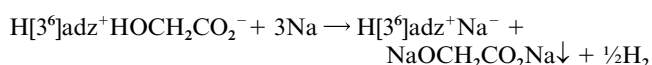


Fig. 2 The cation in the crystal structure of $\{[3^2]\text{bis}(i^+,i,i,o^+-\text{H}_2[2^4.3^1]\text{adz})\}[\text{ZnCl}_4]_2 \cdot 1.5\text{H}_2\text{O}$.

Alkalides

Recently Dye and coworkers²⁶ published the synthesis of the sodide $\text{H}[3^6]\text{adz}^+\text{Na}^-$. The golden crystals were obtained by the overall reaction shown below:



The reaction is performed at low temperature ($-78/-196\text{ }^\circ\text{C}$). The compound decomposes around $-25\text{ }^\circ\text{C}$. It seems possible

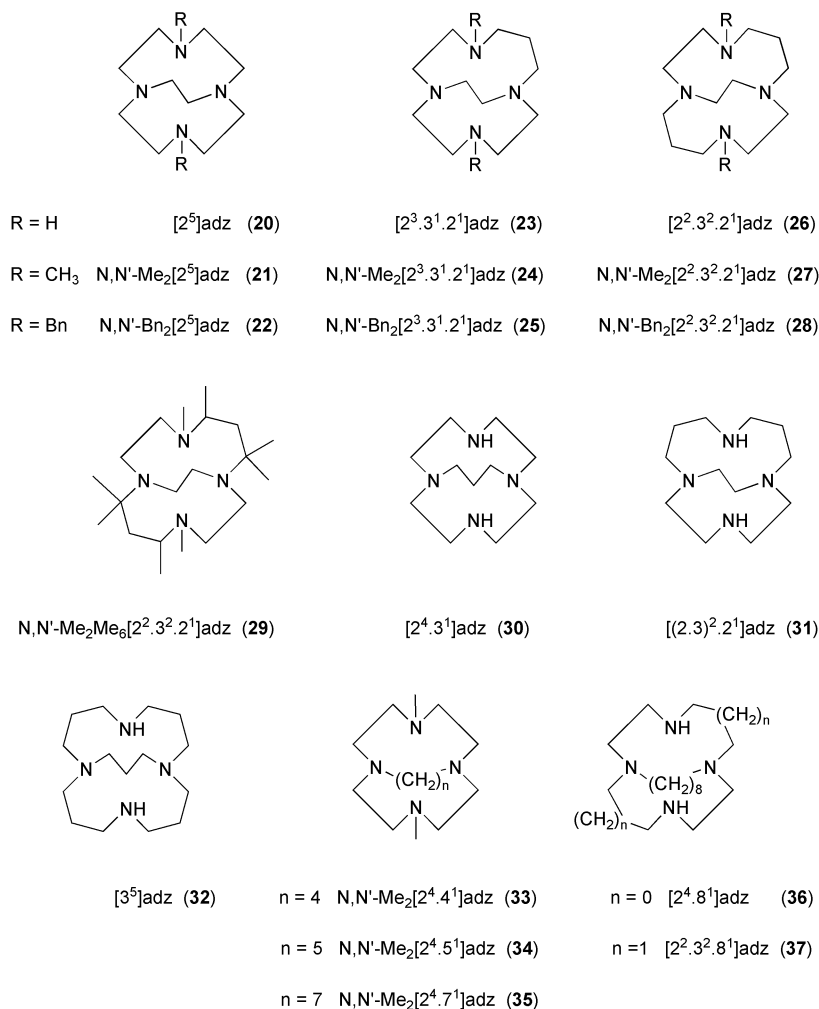
that the inside protonated cage adamanzanes and related adamanzane compounds in future may serve as useful counter cations and permit the synthesis of new alkalides and electrides.

Bowl-adamanzanes

Syntheses

An overview of the bowl-adamanzanes discussed in the following is given in Scheme 9 and the simplified nomenclature used throughout this paper is given in the Appendix. As early as in 1980 Schmidtchen⁹ reported the synthesis of the first bowl-adamanzanes built up by hexamethylene and octamethylene chains. The synthetic strategy is outlined in Scheme 3. However, these amines (**13** and **14**) are probably too large to be suitable as tetradentate ligands for metal ions and no reports on their ligating properties have appeared.

The first small bowl-adamanzane was made by Weisman *et al.*,²⁷ based on a very elegant use of condensation of glyoxal with cyclam to give a tetracyclic bisaminal, followed by highly regioselective *N,N'*-dialkylation to give a bis-quaternary ammonium species and subsequent reduction as shown in Scheme 10. The method is simple and provides a good yield of the free amine *N,N'*-Me₂[2².3².2¹]adz (**27**). The method was later used to synthesize a series of *N,N'*-dibenzyl bowl-adamanzanes (**22**, **25** and **28**) and their parent unsubstituted amines (**20**, **23** and **26**).²⁸ The latter compounds were obtained by Pd/C catalyzed reduction with hydrogen of the benzyl derivatives. The amine **29** has been obtained from racemic tetB using the same method.³⁰ The kinetic, thermodynamic and structural aspects of the glyoxal condensation and the regioselectivity in the dialkylation reaction have been studied in depth including

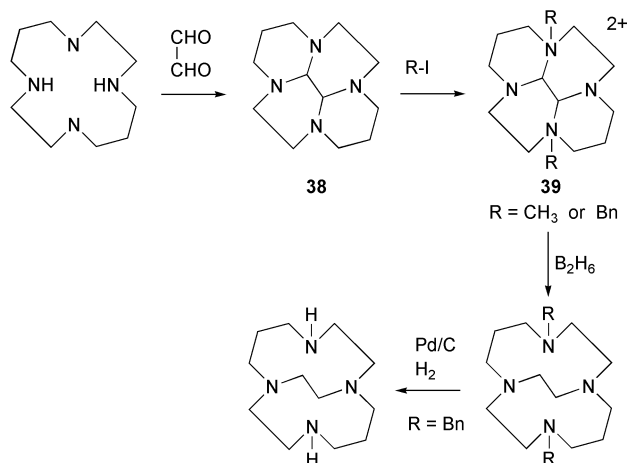


Scheme 9

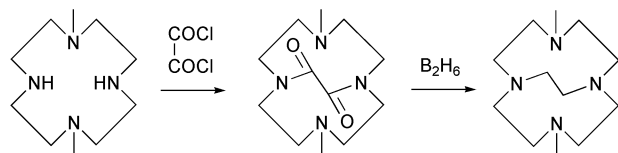
Table 1 Acid dissociation constants of bowls at 25 °C

Free amine	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}	Solvent	Ref.
<i>N,N'</i> -Me ₂ [2 ⁵]adz	—	<2	5.95(1)	>13	0.15 M NaCl	31
<i>N,N'</i> -Me ₂ [2 ⁴ .4 ¹]adz	—	<2	7.8(1)	>13	0.15 M NaCl	32
<i>N,N'</i> -Me ₂ [2 ⁴ .5 ¹]adz	—	<2	6.94(3)	11.55(3)	0.15 M NaCl	33
<i>N,N'</i> -Me ₂ [2 ⁴ .7 ¹]adz	—	—	7.86 ^a	12.00(6)	0.15 M NaCl	34
[2 ⁴ .3 ¹]adz	<-1	3.202(7)	7.242(8)	>15	1 M NaBr	35
<i>N,N'</i> -Me ₂ [2 ³ .3 ¹ .2 ¹]adz	—	<2	6.71(2)	>13	0.1 M NaNO ₃	42
<i>N,N'</i> -Me ₂ Me ₆ [2 ² .3 ² .2 ¹]adz	—	<2	11.45(3)	>13	0.1 M NaNO ₃	42
[(2.3) ² .2 ¹]adz	<1	<1	8.5 ^a	~13	1 M NaCl	18,38
[2 ² .3 ² .2 ¹]adz	3.77 ^a	-2.38 ^a	10.20 ^a	12.42 ^a	0.1 M KCl	40
<i>N,N'</i> -Me ₂ [2 ² .3 ² .2 ¹]adz	—	—	10.8 ^a	>13.5	D ₂ O ^b	27
[3 ⁵]adz	1-2	1-2	9.65(2)	12.09(4)	1 M NaBr	37

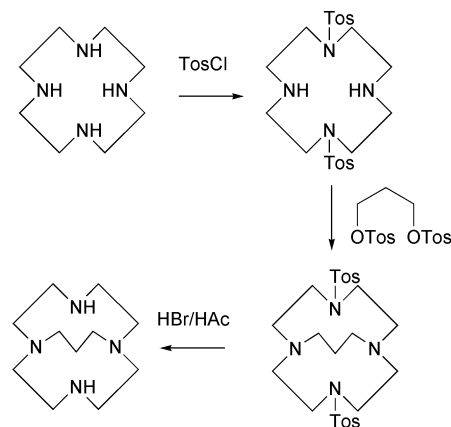
^a Standard deviation not reported. ^b pK_{a4} = 24.9 in CH₃CN.

**Scheme 10**

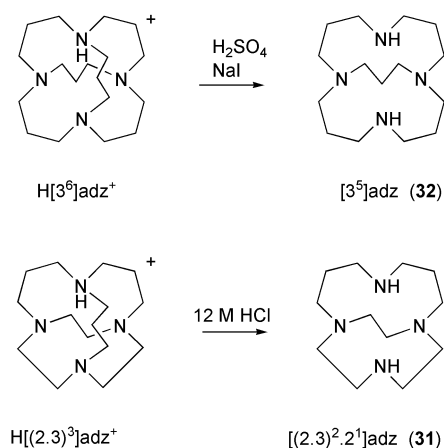
X-ray crystallographic characterization of the intermediates.^{29,30} The bowl [2⁵]adamanzane (**20**) has also been synthesized using, later, Schmidtchen's method (Scheme 3).¹⁵ The limitation to ethylene-bridged bowls in the Weisman method is not present, when the introduction of the bridge is achieved as shown in Scheme 11. The method requires protection of the non-adjacent amine groups and using *trans*-diprotected cyclen (*N,N'*-dimethyl derivative). Bencini *et al.* have synthesized ethylene and tetra-, penta- and hepta-methylene bridged bowl-adamanzanes (**21**, **33**, **34** and **35**).³¹⁻³⁴

**Scheme 11**

The synthesis of [2⁴.8¹]adamanzane (**36**)³⁵ is interesting because in this case the protection of the non-adjacent amine groups is obtained by protonation; *i.e.* reaction of cyclenH₂²⁺ with 1,8-dichlorooctane yields the bowl in high yield (61%), whereas the same reaction with cyclen as a free base only affords a yield of 17%. The corresponding cyclam derivative [2².3².8¹]adamanzane (**37**) has also been reported and it was made from cyclam without any use of protecting groups.³⁵ We have used the reaction of the ditosylate of 1,3-propane diol with cyclen (*trans* ditosylated) to prepare [2⁴.3¹]adamanzane in 23% yield (Scheme 12).³⁶ The method has the advantages that variable bridge size can be obtained and that the reduction step is avoided. Some bowl-adamanzanes have been synthesized from their parent cages.^{18,37} Treatment of H[3⁶]adz⁺ with sodium iodide in sulfuric acid results in a surprisingly clean process with cleavage of one and only one bridge forming the

**Scheme 12**

corresponding bowl [3⁵]adamanzane (**32**) in 60% yield (Scheme 13).³⁷ Similarly, hydrolysis of H[(2.3)³]adz⁺ (reflux in 12 M hydrochloric acid) gives cleavage of one trimethylene bridge and the corresponding bowl [(2.3)².2¹]adamanzane (**31**) was isolated in reasonable yield (40%) (Scheme 13).¹⁸ This bowl has also been obtained from base hydrolysis of the iminium derivative of [(2.3)³]adamanzane (**17**).¹⁹ Finally, *N,N'*-pendant arm carboxylic acid derivatives have been reported by Weisman *et al.*²⁹ and by us³⁸ and will be discussed in relation to their Cu(II) complexes below.

**Scheme 13**

Acid dissociation constants of bowls

In Table 1 pK_a values of bowl-adamanzanes are summarized. A common feature is the strong base strength of the free amines. In several cases the monoprotonated amines have pK_a values larger than 15 acting as proton sponges. Even in 1 M sodium hydroxide the amine remains protonated. Another common feature is the extreme acidic properties of the tetraprotonated

species which nearly all have pK_{a1} values below 2 and in one case below -1 . Both features can be explained by stabilization of the tri- and mono-protonated species, respectively, by intramolecular hydrogen bonds as exemplified in the following for the trimethylene bridged species $[2^4.3^1]$ adamanzane.³⁶ The crystal structure of the triprotonated species (Fig. 3) shows that two of the hydrogen atoms are bound to the secondary nitrogen atoms while the third one is hydrogen bonded to both bridgehead nitrogen atoms. This symmetrical hydrogen-bonding has a stabilizing effect, thus explaining why it is difficult to add a fourth proton, *i.e.* why $pK_{a1} < -1$. Similarly, the remarkably increased basicity of the free base ($pK_{a4} > 15$) is explained by a hydrogen-bond stabilization of the monoprotonated species. In $[3^5]$ adamanzane the distance between the two bridgehead nitrogen atoms becomes larger resulting in a weakening of the hydrogen-bond stabilization and a concomitant decrease in base strength ($pK_{a4} = 12.09$). The observation⁴⁰ that the cyclam based amine $[2^2.3^2.2^1]$ adz has pK_{a1} larger than pK_{a2} is surprising although a similar but not so pronounced behaviour is known for cyclam itself.⁴¹

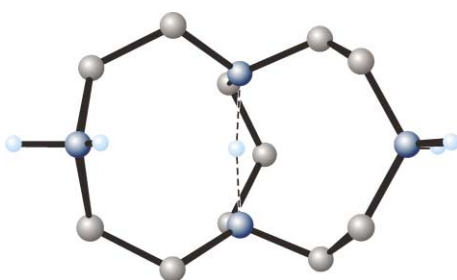


Fig. 3 The cation in the crystal structure of $[H_3[2^4.3^1]adz]Br_2(ClO_4)$.

Coordination compounds with bowl-adamanzanes

Since Weisman in 1990 reported the synthesis of the first small bowl-adamanzane, N,N' -Me₂[2².3².2¹]adamanzane, and briefly described its coordination compounds with Li(I) and Na(I), it took five years before more work in this direction appeared. However, over the last few years a large number of coordination compounds with bowl-adamanzanes have been reported, including the metal ions Cu(I), Cu(II), Ni(II), Co(II), Co(III), Fe(II), Fe(III), Mn(II), Mn(III), Ga(III), In(III), Pd(II) and Zn(II). Octahedral, trigonal bipyramidal, square pyramidal and tetrahedral geometries have been observed. In the octahedral complexes the macrobicyclic occupies two axial and two *cis* equatorial sites of a distorted octahedron and the remaining neutral or anionic ligand(s) occupy the remaining *cis* equatorial sites. Octahedral geometry has been observed for all metal ions studied except Pd(II). Five-coordinated complexes have been found for most Cu(II) complexes and for some Ni(II) and Co(II) complexes, which all exhibit distorted trigonal bipyramidal or square pyramidal geometry. Tetrahedral coordination has until now been found only for Co(II) and Zn(II), in both cases with a pronounced distortion. Six-coordinate geometry has been observed for all bowls, but a general trend seems to be that the larger amines more fully engulf the metal ion, thereby favouring four- and five-coordinate geometry. This is illustrated by structural data for some octahedral Ni(II) and Co(III) complexes.

Table S1 (ESI) shows how the N_{ax} -Ni- N_{ax} angle (N_{ax} refers to the two secondary nitrogen atoms of the macrobicyclic) for six-coordinated Ni(II) complexes increases as the size of the cavity increases thus demonstrating how the metal ion fits increasingly well into the larger cavity, *i.e.* bowls with larger cavities (larger rings and larger bridge) engulf the metal ion more fully than do bowls with smaller cavities. A similar trend is observed for the Co(III) complexes, also listed in Table S1. Following these lines it is found that in nearly all complexes with the smaller bowls the hydrogen atoms of the secondary amine groups point toward the fifth (and sixth) ligands, whereas

in complexes with the larger bowl, $[3^5]$ adamanzane, the amine hydrogen atoms point away due to a configurational shift. Another important trend is that for a given macrobicyclic the smaller ions form a less distorted octahedron than the larger cations as illustrated by a smooth increase in the N_{ax} -Ni- N_{ax} angle as the radius of the pseudo-octahedral cation increases. For Mn(II), Fe(II), Zn(II), Co(II), Cu(II) and Ni(II) the radius of the high-spin six-coordinated cations decrease in the given order and for the corresponding complexes with the ligand N,N' -Me₂[2⁵]adz the N_{ax} -Ni- N_{ax} angles decrease in (almost) the same order as shown in Table S2.

Lithium(I) and sodium(I) complexes

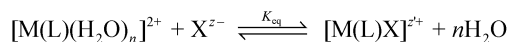
Complexes of alkali metal ions with bowl-adamanzanes have until now only been reported for N,N' -Me₂[2².3².2¹]adamanzane, and no solid compounds have been isolated.²⁷ It was found that Li(I) binds about 200 times better than Na(I).

Copper(II) complexes

Coordination compounds of Cu(II) display numerous examples of five-coordinated trigonal bipyramidal (TBP) or square pyramidal (SP) structures and great variations of the distribution between TBP and SP geometries are reported. The complexes with bowl-adamanzanes are no exception. Apart from a brief comment³⁴ on the Cu(II) complex with N,N' -Me₂[2⁴.7¹]adz, the first well-characterized Cu(II) complexes, reported by Weisman *et al.*, were obtained by reaction of $CuCl_2 \cdot H_2O$ in methanol or ethanol with the free ligands, which afforded dark green crystals of $[Cu(N,N'-Bn_2[2^2.3^2.2^1]adz)Cl]Cl \cdot H_2O$ and blue crystals of $[Cu([2^2.3^2.2^1]adz)]Cl \cdot 3H_2O$, respectively.^{28,29} The first-mentioned complex has a distorted square pyramidal geometry with one benzyl group folded toward the metal ion, essentially occupying the empty sixth coordination site with an interesting interaction between Cu(II) and an *ortho*-hydrogen atom of one of the benzyl rings ($Cu \cdots H-C$ 2.7 Å). Using the same synthetic strategies, Weisman *et al.* have also reported five-coordinated perchlorato complexes with $[2^2.3^2.2^1]adz$ and N,N' -Me₂[2².3².2¹]adz, respectively.²⁹ We have reported a series of five-coordinated complexes $[Cu(L)X]^{2+}$ with $L = [2^4.3^1]$ adamanzane and $X = Br^-$, I^- , OH^- , NH_3 and H_2O .⁴⁸

The synthetic route for these complexes starts with the bromo complex from which the remaining complexes in this series are made by ligand exchange reactions (Table 2). The bromo complex is made from aqueous solution by reacting the protonated form of the macrobicyclic with $[Cu(NH_3)_4]^{2+}$ using an ammonia/ammonium buffer, which acts as a buffer as well as a complexing agent. Heating of the reaction mixture yields $[Cu([2^4.3^1]adz)(NH_3)_3]^{2+}$ and subsequent acidification with hydrobromic acid and perchloric acid affords blue crystals of $[Cu([2^4.3^1]adz)Br]ClO_4$ in high yield (87%). The presence of ammonia prevents the formation of insoluble Cu(II) hydroxide or (when heating the reaction mixture) black Cu(II) oxide and at the same time it keeps the solution basic, which is necessary from a thermodynamic point of view (uptake of the proton from the amine, which is a proton sponge). Addition of excess iodide to an aqueous solution of the chloro complex gave green crystals of $[Cu([2^4.3^1]adz)I]$ (yield 72%). Crystal structures of these compounds show that the coordination geometry of the bromo complex (Fig. 4) is best described as being halfway between the two idealized structures square pyramidal and trigonal bipyramidal, whereas the iodo complex is approximately trigonal bipyramidal.⁴⁸ The observation that relatively small changes in the fifth ligand may cause a drastic change in the ratio between TBP and SP geometry is interesting, indicating how difficult it is to predict the geometry of these complexes. The $[Cu([2^4.3^1]adz)(OH)]^+$ species reacts in carbonate buffer to form a trinuclear species with ferromagnetic coupling (Fig. 5).⁴⁹ Similarly, reactions also in aqueous ammonia/ammonium buffer have led to $[Cu([(2.3)^2.2^1]adz)Br]^+$ and $[Cu([3^5]adz)Br]^+$,

Table 2 Thermodynamic data ($I = 1.0 \text{ M}$ and 25°C) for the equilibrium:



$[\text{M}(\text{L})\text{X}]^{z+}$	$K_{\text{eq}}/\text{M}^{-1}$	$\Delta H^\circ/\text{kJ mol}^{-1}$	$\Delta S^\circ/\text{J mol}^{-1} \text{K}^{-1}$	Ref.
$[\text{Cu}(\{2^4.3^1\}\text{adz})(\text{NH}_3)]^{2+}$	$2.49(9) \times 10^3$	-42.9(46)	-79(16)	48
$[\text{Cu}(\{2^4.3^1\}\text{adz})(\text{OH})]^{+a}$	$5.02(13) \times 10^4$	-19.6(33)	24(11)	48
$[\text{Cu}(\{2^4.3^1\}\text{adz})\text{I}]^+$	12.35(55)	-13.2(33)	-23(11)	48
$[\text{Cu}(\{2^4.3^1\}\text{adz})\text{Br}]^+$	8.33(18)	-8.4(18)	-11(6)	48
$[\text{Cu}(\{(2.3)^2.2^1\}\text{adz})\text{Br}]^+$	4.8(3)	1.7(9)	19(3)	44
$[\text{Cu}(\{3^5\}\text{adz})\text{Br}]^+$	4.55(2)	-4.5(3)	-2.6(1)	44
$[\text{Ni}(\{2^4.3^1\}\text{adz})(\eta^2\text{-NO}_3)]^+$	2.5(3)			43
$[\text{Ni}(\{2^4.3^1\}\text{adz})(\eta^2\text{-NO}_2)]^+$	380(20)			43
$[\text{Ni}(\{(2.3)^2.2^1\}\text{adz})(\eta^2\text{-NO}_2)]^+$	61(4)	-32(6)	-74(18)	38
$[\text{Ni}(\{3^5\}\text{adz})\text{Cl}]^+$	9.1(4)	-7.9(27)	-8.1(87)	44
$[\text{Ni}(\{3^5\}\text{adz})(\eta^2\text{-NO}_3)]^+$	62(4)	-33(4)	-75(15)	44
$[\text{Ni}(\{3^5\}\text{adz})\text{Br}]^+$	1.0(3)			44

^a For $[\text{Cu}(\{2^4.3^1\}\text{adz})(\text{H}_2\text{O})_2]^{2+}$ these values give the parameters $K_a = 7.93(21) \times 10^{-10} \text{ M}^{-1}$, $\Delta H^\circ = 37.7(33) \text{ kJ mol}^{-1}$ and $\Delta S^\circ = -48(11) \text{ J mol}^{-1} \text{K}^{-1}$.

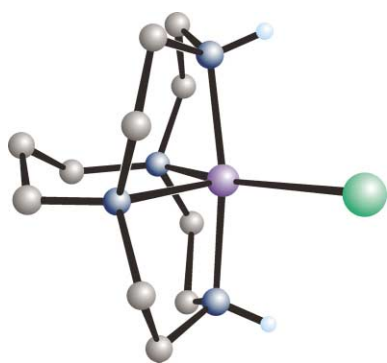


Fig. 4 The cation in the crystal structure of $[\text{Cu}(\{2^4.3^1\}\text{adz})\text{Br}](\text{ClO}_4)$.

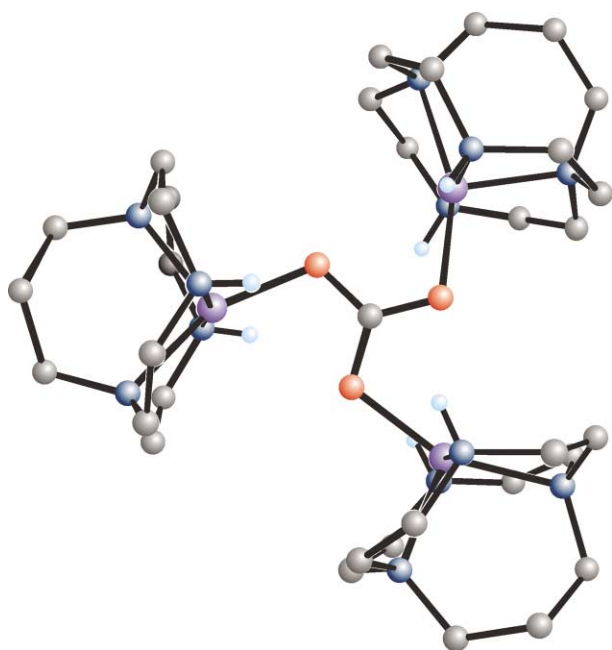


Fig. 5 The cation in the crystal structure of $[\{\text{Cu}(\{2^4.3^1\}\text{adz})\}]_3-(\mu_3\text{-CO}_3)(\text{ClO}_4)_4 \cdot 2\text{H}_2\text{O}$.

respectively.⁴⁴ Hubin *et al.* reported the crystal structures of square pyramidal $[\text{Cu}(N,N'\text{-Me}_2[2^2.3^2.2^1]\text{adz})\text{Cl}]\text{Cl} \cdot 2\text{H}_2\text{O}$ and trigonal bipyramidal $[\text{Cu}(N,N'\text{-Me}_2\text{Me}_6[2^2.3^2.2^1]\text{adz})\text{Cl}]\text{Cl} \cdot \text{H}_2\text{O}$.³⁰

Weisman *et al.* presented the first example of a Cu(II) complex with a pendant arm carboxylate bowl-adamanzane.²⁹ The complex $[\text{Cu}\{N,N'\text{-(CH}_2\text{CO}_2)_2[2^2.3^2.2^1]\text{adz}\}]$ was shown to have an octahedral geometry with both carboxylate groups coordinated in the two *cis* positions. The same structure was

later proposed for the analogous complex $[\text{Cu}\{N,N'\text{-(CH}_2\text{CO}_2)_2[(2.3)^2.2^1]\text{adz}\}]$.³⁸

Macrocyclic chelators and their metal complexes have widespread applications in the biomedical sciences and it is not surprising that bowl-adamanzanes have found their way into this field. The use of copper radionuclides in radiopharmaceuticals is increasing and recently Weisman and coworkers investigated the radiochemistry and biological evaluation of ⁶⁴Cu labelled Cu(II) complexes of $[2^2.3^2.2^1]\text{adamanzane}$ and pendant arm derivatives such as $N,N'\text{-(CH}_2\text{CO}_2)_2[2^2.3^2.2^1]\text{adamanzane}$.⁴⁰ All complexes were found to survive the serum conditions for days. In normal rats the positively charged complexes all exhibited rapid uptake in the liver and kidneys with slow liberation, whereas the neutral complex $[\text{Cu}\{N,N'\text{-(CH}_2\text{CO}_2)_2[2^2.3^2.2^1]\text{adz}\}]$ was liberated rapidly from all tissues. These macrobicyclic ligands thus seem to have a promising potential for labelling copper radionuclides to biological molecules for diagnostic imaging and targeted radiotherapy.

Copper(I) complexes

The only Cu(I) complex reported is obtained by reaction of the free amine $L = N,N'\text{-Bn}_2[2^2.3^2.2^1]\text{adz}$ in pyridine with $[\text{Cu}(\text{CH}_3\text{-CN})_2]\text{PF}_6$ which gives crystals of $[\text{Cu}(\text{L})](\text{PF}_6)$ in which the Cu(I) ion is four-coordinated in a strongly distorted tetrahedron with both benzyl groups folded toward the metal ion, essentially occupying the empty fifth coordination site.⁵⁰ Since Cu(I) is a d^{10} system with no ligand field stabilization (hence no colour) the pale yellow–green colour reported⁵⁰ for this compound probably stems from impurities of the Cu(II) complex. The Cu(I) compound is oxidized in air to give the dark green square pyramidal Cu(II) complex $[\text{Cu}(\text{L})(\text{NCCH}_3)](\text{PF}_6)_2$.⁵⁰

Nickel(II) complexes

Many Ni(II) complexes of bowl-adamanzanes have been reported. With few exceptions they all have distorted octahedral geometry. A series of complexes with $[2^4.3^1]\text{adamanzane}$, $[(2.3)^2.2^1]\text{adamanzane}$ and $[3^5]\text{adamanzane}$ have been described by us.^{43,44,38} Ni(II) complexes with $L = [2^4.3^1]\text{adamanzane}$ have been obtained starting with the dinuclear species $[\{\text{Ni}(\text{L})\}_2(\mu\text{-Br})_2](\text{ClO}_4)_2$, which has been synthesized by the reaction of NiBr_2 with the free ligand (made *in situ* by deprotonation using NaH) in DMF.⁴³ Treatment of this compound with hydrochloric acid affords the corresponding dichloro-bridged dinuclear species $[\{\text{Ni}(\text{L})\}_2(\mu\text{-Cl})_2](\text{ClO}_4)_2$. In dilute aqueous solution both dinuclear species form the corresponding diaqua species, which was isolated as $[\text{Ni}(\text{L})(\text{H}_2\text{O})_2]\text{S}_2\text{O}_6 \cdot 2\text{H}_2\text{O}$. Reaction of aqueous solutions of this complex with nitrite gave $[\text{Ni}(\text{L})(\eta^2\text{-NO}_2)]\text{PF}_6$ and with nitrate $[\text{Ni}(\text{L})(\eta^2\text{-NO}_3)]\text{ClO}_4$.⁴³ The crystal structures of the above-mentioned complexes show

that the coordination geometry about Ni(II) is a distorted octahedron and the nitrite and nitrate ligands are O,O'-chelate bound. Cyclic voltammetry of the diaqua species in 1 M HClO₄ showed a quasi-reversible redox behaviour ($\Delta E = 83$ mV) with a halfwave potential of $E_{1/2} = 1.07$ V. This value is significantly higher than the reported values for Ni(II)/(III) couples of octahedral complexes with Ni([9]aneN₃)₂^{2+/3+} (0.72 V) and with Ni([16]aneN₅)(H₂O)₂^{2+/3+} (0.79 V).

Halide and nitrate complexes with the larger bowl L = [3⁵]adamanzane have been synthesized directly from the free amine and the appropriate hydrated Ni(II) salt.⁴⁴ Maintenance of excess metal ion was crucial to the yields (89–95%), which were quite dependent on the choice of solvents as well. Contrary to the synthesis above with [2⁴.3¹]adamanzane strictly anhydrous conditions were not found to be important. This is probably explained by the difference in basicity of the two amines. Ethanol was found to give the best result for the purple six-coordinated chelate nitrate complex, [Ni(L)(η^2 -NO₃)]NO₃, whereas the use of methoxyethanol optimized the synthesis of the green five-coordinated trigonal bipyramidal halide compounds: [Ni(L)Cl]Cl and [Ni(L)Br]Br. The blue chelated perchlorate complex [Ni(L)(η^2 -ClO₄)]ClO₄ was made⁴⁴ from the chloro complex by reaction in dilute HClO₄ using Hg²⁺ assisted removal of chloride, and represents a relatively rare⁵¹ example of a chelate coordination mode of perchlorate (Fig. 6). The crystal structures of these compounds were reported.⁴⁴ In the structures of the perchlorate and nitrate complexes the angle around the nickel ion show distortion with respect to those of a regular octahedron. This is mainly due to the very small O–Ni–O angle which is 59.2 and 61.9°, respectively, for the nitrate and perchlorate complexes with the consequence that the molar absorptivities are relatively high for both species. The aqua species [Ni(L)(H₂O)]²⁺ was only characterized in solution and its five-coordinated structure inferred from spectral data (lack of reduction in the molar absorptivities). This species equilibrates rapidly in aqueous solution with nitrate, chloride and bromide, respectively, to form the corresponding η^2 -nitrate, dichloro and dibromo complexes. The thermodynamical parameters have been determined (see discussion below in relation to Table 2).

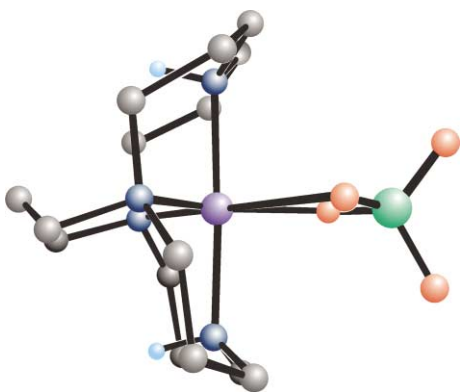


Fig. 6 The cation in the crystal structure of [Ni([3⁵]adz)(η^2 -ClO₄)]ClO₄.

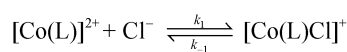
Similarly, six-coordinated Ni(II) complexes with L = [(2.3)².2¹]adamanzane have been reported. Using methoxyethanol as solvent without anhydrous conditions, a putative dimeric Ni(II) complex, [(Ni(L))₂(μ -Br)₂]Br₂ has been obtained.³⁸ From this complex purple [Ni(L)(H₂O)₂]Br₂·2H₂O and reddish [Ni(L)(η^2 -NO₂)]ClO₄ have been synthesized. The crystal structure shows that the diaqua complex has a distorted octahedral geometry. The chelate coordination of nitrite was established from spectral data by comparison with the above mentioned complex with [2⁴.3¹]adamanzane. Cyclic voltammetry of the diaqua species gave $E_{1/2} = 0.97$ V (1 M HClO₄)

which is similar to that reported for the analogous complex with [2⁴.3¹]adamanzane.

Hubin *et al.* have reported the synthesis of a series of complexes with the ethylene bridged bowls *N,N'*-Me₂[2⁵]adz, *N,N'*-Me₂[2².3².2¹]adz, *N,N'*-Me₂[2³.3¹.2¹]adz and *N,N'*-Me₂Me₆-[2².3².2¹].⁴² Purple high spin diaqua and acetylacetonato complexes were made by reaction of [Ni(acac)]⁺ with free ligand in THF. Their octahedral geometry was established from crystal structures. From reaction of NiCl₂ with free ligands in anhydrous DMF green octahedral dichloro complexes were obtained.

Cobalt(II) complexes

We have prepared a series of Co(II) complexes.⁴⁴ With L = [3⁵]adamanzane the purple compound [Co(L)Cl]Cl was made in high yield (83%) by reaction of CoCl₂·6H₂O with the free ligand in methoxyethanol. The crystal structure showed trigonal bipyramidal geometry and the compound is isostructural with the corresponding complexes of Ni(II) and Cu(II). The solution chemistry of [Co(L)Cl]Cl is quite intriguing in that four-, five- and six-coordinated species may be formed. In 12 M HCl it dissolves as five-coordinated [Co(L)Cl]⁺, whereas solutions in methanol give six-coordinated [Co(L)YX]²⁺ (X, Y = Cl⁻ or MeOH). In dilute aqueous solutions it forms either a six-coordinated diaqua species or a four-coordinated tetrahedral species. The six-coordinated diaqua complex was isolated (Hg²⁺ assisted removal of Cl⁻) as the pale green [Co(L)(H₂O)₂](ClO₄)₂·H₂O. The proposed structure of the diaqua species is based upon spectral data (molar absorptivities approximately 1/10 of those of the five-coordinated or tetrahedral species). In 5 M HCl solutions of [Co(L)Cl]Cl an equilibrium between five-coordinated [Co(L)Cl]⁺ and tetrahedral [Co(L)]²⁺ is formed.



The equilibrium constant has been determined, $K_{\text{eq}} = 0.2 \text{ M}^{-1}$ (5 M HCl and 25 °C), and the first-order rate constants are $k_1 = 1.4 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-1} = 7 \times 10^{-4} \text{ s}^{-1}$ (in ref. 44 the rate-constants k_1 and k_{-1} have been accidentally interchanged and the unit for k_1 was erroneously given without M^{-1}). The tetrahedral species has been isolated from an aqueous solution of the chloro compound as pink [Co(L)][ZnCl₄] (yield 76%). This complex is a rare example of a tetrahedral Co(II) amine complex, which is stable in aqueous solution and is resistant to air-oxidation (Fig. 7). The crystal structure shows a distorted tetrahedral coordination in which the N–Co–N angle for the bridgehead nitrogen atoms is 104.31(11)° and for the secondary nitrogen atoms 126.22(11)°. The compound is isostructural with the analogous Zn(II) complex, [Zn(L)][ZnCl₄], mentioned below. The pink colour of the [Co([3⁵]adz)]²⁺ ion stems from the much higher ligand field strength of the amine macrocycle compared to that of the anionic ligands present in the more

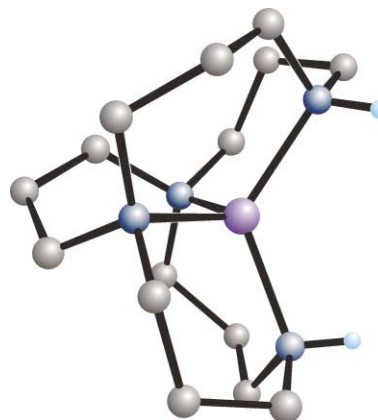
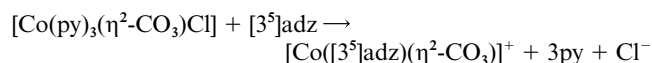


Fig. 7 The cation in the crystal structure of [Co([3⁵]adz)][ZnCl₄].

prevalent blue tetrahedral Co(II) complexes. The position of the visible absorption band (543 nm) is nearly identical to that of the reported tetrahedral $[\text{Co}(\text{[16]aneN}_4)]^{2+}$ ion (540 nm).⁵²

Cobalt(III) complexes

Six-coordinated low-spin Co(III) complexes of $[2^4.3^1]$ adamanzane and $[3^5]$ adamanzane have been reported by us.^{38,45} A very convenient method is the reaction of free amine in ethanol with another Co(III) complex exemplified by the formation of the carbonate complex.⁴⁵



The purple compound $[\text{Co}([3^5]\text{adz})(\eta^2\text{-CO}_3)]\text{Cl}$ was isolated in good yield (92%). Reaction in perchloric acid affords the corresponding hydrogencarbonato complex, which was isolated as blue $[\text{Co}([3^5]\text{adz})(\eta^2\text{-HCO}_3)][\text{ZnBr}_4]\cdot\text{H}_2\text{O}$, which is a rare example of a complex having chelate bound hydrogen carbonate (Fig. 8). Reaction in sulfuric acid yields turquoise $[\text{Co}([3^5]\text{adz})(\eta^2\text{-SO}_4)]\text{AsF}_6\cdot\text{H}_2\text{O}$. The crystal structures of these compounds are discussed below. Co(III) complexes with $[2^4.3^1]$ adamanzane, which is a proton sponge, were best obtained using anhydrous conditions starting with Co(II).³⁸ The reaction of CoBr_2 with the free ligand (made *in situ* by deprotonation using NaH) in DMF yields a pink Co(II) complex which is easily oxidized by atmospheric oxygen. The air sensitivity of this Co(II) complex follows the normal behaviour of Co(II) amine complexes, in striking contrast to the inertness with respect to air-oxidation of the $[3^5]$ adamanzane Co(II) complexes discussed above. It is tempting to propose that this difference is caused by a greater stabilization of the smaller oxidized ion by the smaller cavity offered by $[2^4.3^1]$ adamanzane relative to the larger $[3^5]$ adamanzane.

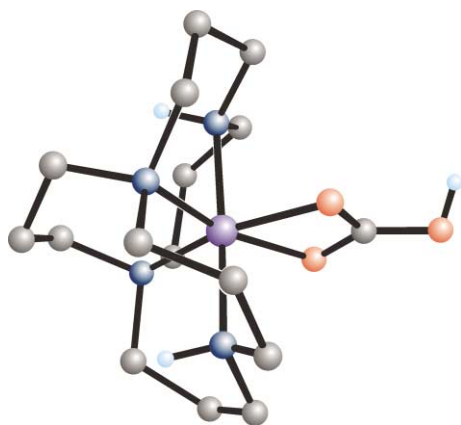


Fig. 8 The cation in the crystal structure of $[\text{Co}([3^5]\text{adz})(\eta^2\text{-CO}_3\text{H})][\text{ZnBr}_4]\cdot\text{H}_2\text{O}$.

The very special properties of the carbonate and hydrogen carbonate complexes with $[3^5]$ adamanzane mentioned above deserve some comments. Both complexes are robust with respect to cobalt–oxygen bond cleavage even in strong acidic solvents.⁴⁵ The acid dissociation constant of the blue $[\text{Co}([3^5]\text{adz})(\eta^2\text{-HCO}_3)]^{2+}$ complex was determined spectrophotometrically giving $\text{p}K_{\text{a}1} = 0.27$ at 25 °C ($I = 5 \text{ M}$), which is similar to $\text{p}K_{\text{a}1}$ values previously reported by Springborg and Schäffer⁵³ ($[\text{Co}(\text{py})_4(\eta^2\text{-HCO}_3)]^{2+}$, $\text{p}K_{\text{a}} = 0.15$) and by Buckingham and Clark⁵⁴ ($[\text{Co}(\text{NH}_3)_4(\eta^2\text{-HCO}_3)]^{2+}$, $\text{p}K_{\text{a}} = 0.0$). From the crystal structure it was shown that the proton is situated at the non-coordinated carbonyl oxygen in the solid and from spectral data it could be concluded that it is at the same position in solution. These observations are in agreement with the assumption that the reactive intermediate in the acid hydrolysis of carbonate complexes is protonated on the carbonyl ring

oxygen and not at the non-coordinated carbonyl oxygen.⁵⁴ The reaction in 5 M trifluoromethanesulfonic acid gives the diaqua complex and the pseudo first-order rate constant is $k_{\text{obs}} = 7.9 \times 10^{-6} \text{ s}^{-1}$ (25 °C). The unusual slowness of the decarboxylation process has been explained by steric factors: The hydrogen atoms of the secondary amine groups point away from the anionic oxo ligand. This configuration of the $[3^5]$ adamanzane ligand leaves the metal deeply imbedded in the organic framework of the macrocycle giving rise to a certain degree of sterical shielding of the carbonate moiety. Similarly, the slow hydrolysis of $[\text{Co}(\text{py})_4(\eta^2\text{-HCO}_3)]^{2+}$ was explained by steric shielding of the central ion.⁵³

Iron(II) and iron(III) complexes

Fe(II) complexes with the ethylene crossbridged cyclen and cyclam ligands N,N' -Me₂[2⁵]adamanzane and N,N' -Me₂[2².3².2¹]adamanzane, respectively, have been obtained by reaction of $[\text{Fe}(\text{py})_2\text{Cl}_2]$ in acetonitrile with the free ligands under strictly anhydrous conditions.⁴⁷ The crystal structure of the brown compounds $[\text{Fe}(\text{L})\text{Cl}_2]$ showed distorted octahedral geometry. Oxidation with bromine gave the corresponding octahedral yellow–orange Fe(III) complexes $[\text{Fe}(\text{L})\text{Cl}_2]\text{PF}_6$ although no crystallographic data were reported.⁵⁵

Manganese(II) and manganese(III) complexes

Octahedral high spin Mn(II) and Mn(III) have been reported by Hubin *et al.*^{47,55} Mn(II) complexes with the ethylene crossbridged cyclen and cyclam ligands N,N' -Me₂[2⁵]adamanzane and N,N' -Me₂[2².3².2¹]adamanzane, respectively, have been obtained by the reaction of $[\text{Mn}(\text{py})_2\text{Cl}_2]$ in acetonitrile with the free ligands under strictly anhydrous conditions.⁴⁷ The crystal structure of the pale blue–green compounds $[\text{Mn}(\text{L})\text{Cl}_2]$ showed distorted octahedral geometry. Oxidation with bromine gave the corresponding octahedral red–brown Mn(III) complexes $[\text{Mn}(\text{L})\text{Cl}_2]\text{PF}_6$ although no crystallographic data were reported.⁵⁵ Cyclic voltammetry showed reversible redox processes for the Mn(II)/Mn(III) and Mn(III)/Mn(IV) couples. In aqueous solution all compounds hydrolyze to the corresponding aqua complexes. The octahedral species $[\text{Mn}(N,N'\text{-Me}_2[2^2.3^2.2^1]\text{adz})(\text{H}_2\text{O})_2]^{2+}$ was characterized in solution and shown to have $\text{p}K_{\text{a}1} = 10.87$, which agrees well with the value found for $[\text{Mn}(\text{H}_2\text{O})_6]^{2+}$ ($\text{p}K_{\text{a}1} = 10.9$). Similarly, the corresponding Mn(III) species $[\text{Mn}(N,N'\text{-Me}_2[2^2.3^2.2^1]\text{adz})(\text{H}_2\text{O})_2]^{3+}$ was characterized in solution and shown to have $\text{p}K_{\text{a}1} = 1.6$ which is close to the value reported for $[\text{Mn}(\text{H}_2\text{O})_6]^{3+}$ ($\text{p}K_{\text{a}1} = 0.83$). The Mn(II) complex with N,N' -Me₂[2².3².2¹]adz reacts with hydrogen peroxide and other oxidizing agents to produce a Mn(IV) complex and the catalytic effect of this species has been assessed in the epoxidation reaction of carbamazepine and the hydrogen abstraction reaction with 1,4-hexadiene.⁵⁵ These results have proved important to industrial processes such as the development of bleaching agents.⁵⁵

Gallium(III) complexes

Gallium radionuclides are important radiopharmaceuticals⁵⁶ and the fact that bowl-adamanzanes endow their metal complexes with unusual inertness encouraged the study of gallium complexes. Two Ga(III) complexes have been reported.⁵⁷ Reaction of anhydrous GaCl_3 with the free ligands in acetonitrile using rigorously anhydrous conditions gave $[\text{Ga}([2^5]\text{adz})\text{Cl}_2]\text{Cl}\cdot\text{H}_2\text{O}$ (yield 68%) and $[\text{Ga}([2^2.3^2.2^1]\text{adz})\text{Cl}_2]\text{Cl}\cdot 0.5\text{H}_2\text{O}$ (yield 53%). The crystal structure of the $[2^2.3^2.2^1]$ adamanzane complex showed a distorted octahedral geometry with an $N_{\text{ax}}\text{-Ga-N}_{\text{ax}}$ angle of 169.3°.

Indium(III) complexes

Compounds similar to those discussed above for Ga(III) have been reported.⁵⁷ The crystal structure of $[\text{In}([2^5]\text{adz})\text{Br}_2]\text{Br}\cdot\text{H}_2\text{O}$

showed a very distorted octahedral geometry with an $N_{ax}-In-N_{ax}$ angle of 144° (Fig. 9). The distortion is much more pronounced than for the Ga(III) complex. This is explained by *both* its larger ionic size [94 ppm for In(III) *versus* 76 ppm for Ga(III)] and the smaller cleft of the [2⁵]adamanzane ligand compared to that of [2².3².2¹]adamanzane.

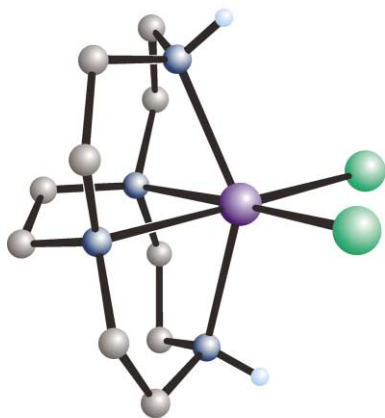


Fig. 9 The cation in the crystal structure of $[In([2^5]adz)Br_2]Br$.

Palladium(II) complexes

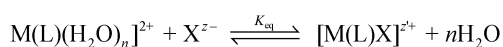
The coordination geometry of Pd(II) complexes is usually square-planar. Other geometries are normally only found when the steric or topological demands of the ligand outweigh the loss in ligand field stabilization due to the geometric distortion, and the only known bowl-adamanzane complex with Pd(II) represents such an example. Dark blue crystals of $[Pd(N,N'-Me_2[2^2.3^2.2^1]adz)Cl]Cl \cdot 2H_2O$ were obtained (yield 55%) by the reaction of $[Pd(MeCN)_2Cl_2]$ with the free ligand in acetonitrile.⁵⁸ The crystal structure showed a five-coordinated square-pyramidal structure.

Zinc(II) complexes

Weisman *et al.* reported the syntheses of Zn(II) complexes by reaction of Zn(II) dichloride with the free ligand in methanol.⁵⁹ Starting with $ZnCl_2 \cdot 6H_2O$ the reaction gave an aqua complex in which the $ZnCl_4^{2-}$ counter ion is coordinated to the Zn(II) amine entity by a chloro-bridge $[(H_2O)([2^2.3^2.2^1]adz)Zn(\mu-Cl)ZnCl_3]$, whereas anhydrous conditions gave colourless crystals of a dichloro-bridged compound $[\{Zn([2^2.3^2.2^1]adz)\}_2(\mu-Cl)_2]Cl_2 \cdot 4MeOH$. Similarly, also using methanol as solvent the compound $Zn([3^5]adz)Br_2$ has been prepared.⁴⁴ No structural data were reported, but comparison with the findings above might suggest a dibromo-bridged structure. From aqueous solution this complex can be crystallized as $[Zn([3^5]adz)][ZnCl_4]$. The crystal structure shows that the coordination polyhedron around the Zn(II) tetraamine entity is a slightly distorted tetrahedron and the compound is isostructural with the corresponding Co(II) complex mentioned above.

Equilibrium studies

The inertness of bowl adamanzanes with respect to hydrolysis of the macrobicyclic amine facilitates thermodynamic studies of substitution reactions at the two labile *cis* positions since interference due to metal–nitrogen(macrocycle) bond breaking or isomerization reactions do not occur. We have studied equilibria of five- and six-coordinated species of Cu(II) and Ni(II) using traditional spectrophotometric methods.^{38,43,44,48} The thermodynamic data are given in Table 2.



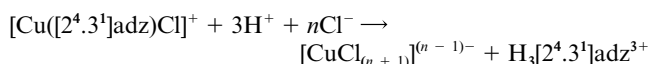
The equilibrium constants for the $[Cu(L)Br]^+$ complexes are similar for the three bowl-adamanzanes studied and correspond well with those reported for other macrocyclic tetraamines, all having values of $K_{eq}(Br^-)$ in the region $2-20 M^{-1}$.⁶⁰ The formation constant for the hydroxo complex $[Cu([2^4.3^1]adz)(OH)]^{2+}$ is very large compared to *e.g.* $[Cu(NH_3)_4(OH)]^+$ ($K_{eq}(OH^-) = 9.3 M^{-1}$),⁶¹ which is in keeping with the observation that an equatorial aqua ligand is a much stronger acid than axially coordinated water in five-coordinated Cu(II) amine complexes. This trend is followed for the ammine complex $[Cu([2^4.3^1]adz)(NH_3)]^{2+}$ which has a much larger formation constant than *e.g.* $[Cu(NH_3)_5]^{2+}$ ($K_5 = 84 M^{-1}$).⁶¹

Formation constants for Ni(II) complexes with three bowl-adamanzanes have been reported. The thermodynamic data shows a nine-fold increase in the equilibrium constants for the formation of the $[Ni([3^5]adz)X]^+$ species when crossing from bromide to chloride and a further approximate five-fold increase upon changing to nitrate. The nitrate ion is generally considered to be of weak ligating power. However, the results obtained for these Ni(II) complexes correlate with the acidity of the corresponding strong acids; the stronger the acid, the weaker the anion is bound to the positively charged nickel-adamanzane moiety. Accordingly, the binding of the perchlorate ion appears to be insignificant in aqueous solution, although a chelate perchlorate complex was isolated in the solid. The binding of the nitrate ion is 25 times more efficient in $[Ni([3^5]adz)(\eta^2-NO_3)]^+$ than in $[Ni([2^4.3^1]adz)(\eta^2-NO_3)]^+$.

Kinetic properties

One of the most prominent features of coordination compounds with bowl-adamanzanes is the exorbitant inertness with respect to cleavage of the metal ion from the macrobicyclic sometimes referred to as metal extrusion. In hydrochloric acid the adamanzane complexes are cleaved slowly to form the hexa-aquametal(II) ions or the tetrachlorometallate(II) anions plus the corresponding protonated amines as shown by several kinetic studies in our laboratory.^{38,43,44,48}

As an example the reaction of $[Cu([2^4.3^1]adz)Cl]^+$ in 5 M HCl may be considered.⁴⁸



The reaction follows first-order kinetics with $k_{cleavage} = 1.48 \times 10^{-6} s^{-1}$. The corresponding reaction of $Cu(cyclen)^{2+}$ in 5 M HCl is very much faster, $k_{cleavage} = 0.72 s^{-1}$. The extreme difference in reactivity may be explained by different geometry and flexibility of the two ligands: in the cyclen complex the Cu(II) ion is coordinated 0.5 Å above the plane formed by the four nitrogen atoms of cyclen, making the cleavage of one of the Cu–N bonds as well as the subsequent formation of a Cu–Cl or Cu–OH₂ bond facile, since no substantial conformational change of the relatively flexible amine ligand is required. In contrast, Cu–N cleavage in the bowl complex requires a significant distortion of the very rigid ligand, and furthermore coordination of water or chloride will be sterically hindered by the proximity of the un-coordinated (protonated) nitrogen donor atom.

In the same way other Cu(II) complexes and complexes with Ni(II) and Co(II) have been studied using visible spectroscopy, whereas a Zn(II) complex has been studied with ¹H NMR. The kinetic data are collected in Table 3. The dissociation of the macrobicyclic ligand from the metal ion is a multi-step process for which the nature of the rate-determining step is not known. The products of the dissociation reactions differ, from tetrachloro- to hexaqua-ions. These facts dictate extreme caution when attempting comparison of the rates and kinetic parameters for the present systems.

Table 3 Kinetic parameters for the metal extrusion in 5 M HCl at 25 °C

	$k_{\text{cleavage}}/\text{s}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$	Ref.
$[\text{Cu}(\text{[2}^4.3^1\text{]adz})\text{Cl}]^+$ ^a	$1.48(2) \times 10^{-6}$	89(6)	-60(14)	44,48
$[\text{Cu}(\text{[(2.3)}^2.2^1\text{]adz})\text{Cl}]^+$	$1.79(5) \times 10^{-6}$	93(4)	-42(9)	44
$[\text{Cu}(\text{[3}^5\text{]adz})\text{Cl}]^+$	$2.28(6) \times 10^{-7}$	121(4)	32(14)	44
$[\text{Ni}(\text{[2}^4.3^1\text{]adz})(\text{H}_2\text{O})_2]^{2+}$	$1.7(9) \times 10^{-9}$	110(5)	-45(15)	38,43
$[\text{Ni}(\text{[(2.3)}^2.2^1\text{]adz})(\text{H}_2\text{O})_2]^{2+}$	$8.1(17) \times 10^{-9}$	116(3)	-10(7)	38
$[\text{Ni}(\text{[3}^5\text{]adz})\text{Cl}]^+$	$1.4(6) \times 10^{-9}$	126(6)	8(17)	44
$[\text{Co}(\text{[3}^5\text{]adz})]^{2+}$	$1.12(2) \times 10^{-4}$	84(2)	-39(15)	44
$[\text{Zn}(\text{[3}^5\text{]adz})]^{2+}$	$1.60(6) \times 10^{-4}$	82(2)	-44(7)	44

^a At 40 °C $k_{\text{cleavage}} = 8.6(3) \times 10^{-6} \text{ s}^{-1}$ in 5 M HCl (S2 in ref. 44), $k_{\text{cleavage}} = 2.0(1) \times 10^{-7} \text{ s}^{-1}$ in 1 M HCl⁶² and $k_{\text{cleavage}} = 2.2(1) \times 10^{-8} \text{ s}^{-1}$ in 1 M HClO₄.⁶²

When comparing only the [3⁵]adamanzane complexes the general expectation is that the rate of cleavage should increase in the order Ni(II) < Co(II) < Zn(II) < Cu(II). Accordingly the dissociation of the five-coordinated Ni(II) complex is by far the slowest and for the two tetrahedral complexes Co(II) is cleaved slower than the Zn(II) complex. However, the order is reversed for Co(II) and Cu(II), the latter being cleaved about 1000 times slower than the Co(II) species. The pronounced decrease in reactivity of the Cu(II) complex is very surprising, although a possible explanation could be a difference in the geometry of the reactants.

There is no trend in the variation of the dissociation rates for the three Cu(II) complexes. The activation parameters, on the other hand, display a general increase with the increase in ligand size, ending up with a change of sign of the activation entropy for the dissociation of the [Cu([3⁵]adz)Cl]⁺ complex. The dissociation of the latter complex exhibits much larger enthalpies of activation than the rest. Again this might be due to structural differences and it has been proposed that the orientation of the NH hydrogen atoms may be responsible for this difference in reactivity. In the [Cu([3⁵]adz)Cl]⁺ complex [and the corresponding Ni(II) complex] the NH hydrogen atoms are pointing away from the chloride ligand, whereas in all the other complexes in Table 3 they point toward the inorganic ligand(s), which might cause a different reaction mechanism for the dissociation of the macrocyclic ligand from the metal ion. The reactions of the three Ni(II) complexes follow the same lines as discussed above for Cu(II).

Cleavage of the Cu(II) complex with the ligand *N,N'*-Me₂-[2².3².2¹]adamanzane has been reported to have $k_{\text{cleavage}} < 4 \times 10^{-9} \text{ s}^{-1}$ in 1 M HClO₄ (40 °C), but no kinetic data were given.⁴⁷ In any case this complex is very inert and the upper limit value for the rate constant is at least five times smaller (although far from 1000 times smaller as claimed in ref. 47, which compares kinetic data for 1 M HClO₄ with data obtained in 5 M HCl) than the rate-constant⁶² for cleavage of [Cu[2⁴.3¹]adz]Cl]⁺ at the same conditions (Table 3). It is noted that cleavage of [Cu[2⁴.3¹]adz]Cl]⁺ at 40 °C in 1 M HClO₄ is about ten times slower than cleavage in 1 M HCl and about 300 times slower than cleavage in 5 M HCl (Table 3). Care must be taken when comparing kinetic data obtained from different solvents.

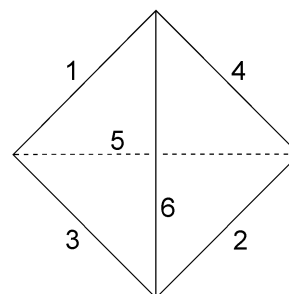
Summary and outlook

The studies of adamanzanes have given many results which are interesting in themselves and also important to medicine and industry. The cage adamanzanes have only been synthesized as inside protonated forms and attempts to synthesize the free cage amines have failed until now. The properties of the free amines will undoubtedly be very different from those of the protonated species, and, in keeping with the chemistry of the tricyclic diamines studied by Alder,¹ one important aspect would be the study of their redox properties. The notion that reduction of the inside coordinated proton *in principle* may lead to compounds in which a hydrogen atom is encapsulated is very interesting and if realized might bring the adamanzane

chemistry into the field of nanochemistry and quantum computers.⁶³ Following the same line it is seen that cage-adamanzanes in which the inside coordinated proton is substituted with T⁺ due to the radioactive decay of tritium to helium (half-life twelve years) might give a compound in which a helium atom is encapsulated. Compounds with metal ions inside the cage adamanzanes would be extremely interesting to study since four-coordinate tetraamine metal ion complexes with tetrahedral (or approximately tetrahedral) geometry are unknown for most metal ions. The formation of such compounds, however, represents a tantalizing synthetic challenge. From the present knowledge it seems certain that insertion of metal ions into the free amine cages is not possible and an obvious strategy might be to build the cage around the metal ion, *i.e.* using a metal ion coordinated to a bowl-adamanzane as precursor. The coordination chemistry of bowls has produced compounds with unusual inertness, redox properties and coordination geometries. Some obvious candidates for future studies are photochemically and redox active metal ions such as rhodium(III), chromium(III), ruthenium(III) and molybdenum(III) just to mention a few examples. Finally, metal ion coordination compounds with dimeric bowl-adamanzanes can probably be synthesized by direct reaction between the metal ion and the amines given the right size of the two cage entities and of the connecting aliphatic chains. The interaction between two encapsulated metal centers might offer interesting redox, spectroscopic and magnetic properties.

Appendix

The simplified nomenclature suggested^{16,17,48} for adamanzanes corresponds to that used for the series of bicyclic systems in which the numbers of carbon (and hetero) atoms in the three chains are given as a prefix in a square bracket.² The diamine 1,6-diazabicyclo[4.4.4]tetradecane is thus given the name [4.4.4]amine. The present cage-adamanzanes are considered as nitrogen analogues to the tetrahedral carbon cages whose smallest member is adamantane, tricyclo[3.3.1.1^{3,7}]decane thereby giving rise to the name **adamanzane** (adamantane + tetraaza + amine) and the above rule for numbering is followed with the additional rule that the carbon chains are listed in the order shown in Scheme 14 using the expression [a.b.c.d.e.f.g]-adamanzane. In order to avoid multiple names for the same



Scheme 14

compound the following rules are applied (a name will always define the structure unambiguously, but without the following rules the opposite will not always be the case): Bridge number 1 and 2 is chosen as small as possible: $a \leq b \leq c, d, e$ and f . In the case of several alternative choices bridge number 3 is chosen to give c as small as possible. The same procedure is then followed with bridge numbers 4 and 5, in that order. Following these rules only one name is possible for each isomer including enantiomers (e.g. [2.6.2.7.2.8]adz and [2.6.2.8.2.7]adz represent a pair of enantiomers). Formulae such as [2.2.2.2.3]adz and [2.3.2.3.2.3]adz, respectively, may be abbreviated as [2⁴.3²]adz and [(2.3)³]adz.

Formulae for the protonated species may be written as, for instance, H[2⁶]adz⁺. The orientation of the lone pairs at each nitrogen are given (if necessary) by suffixes *i* and *o*, respectively, to indicate lone pairs pointing inwards and outwards with respect to the cavity. In protonated forms *i*⁺ and *o*⁺, respectively, are used to designate inwards and outwards coordinated protons. For the most common cases with *i,i,i* the prefix is normally neglected.

Dimers are two adamantane units linked together by two alkylene bridges. One [2⁴.3¹]adz unit and one [3⁵]adz unit linked together by an ethylene and a trimethylene chain is named: [2.3]([2⁴.3¹]adz)([3⁵]adz). More symmetrical dimers such as 1,4,8,11,15,18,22,25-octaazapentacyclo[20.6.2.2⁴.2⁵.2⁸.15.2¹¹.18]-hexatriacontane are named [3²]bis([2⁴.3¹]adz) and for the tetra-protonated form of this compound the orientation of lone pairs and protons at each nitrogen group are given using the rules above. This gives the name [3²]bis(*i*⁺,*i*,*i*,*o*⁺-H₂[2⁴.3¹]adz) for the compound shown in Fig. 2. The nomenclature for bowls follow the above rules and the bridge is given number 5.

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