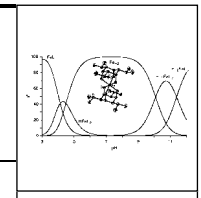
A rigid, cyclohexane-based polyamino-polyalcohol as a versatile building block for tailored chelating agents



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Selective, tailored chelators are of importance in medicine for the treatment of metal intoxication, or to stabilise metal cations in diagnostic radiopharmaceuticals and paramagnetic contrast agents. In this report, the co-ordination chemistry of polyamines, polyalcohols, and polyamino-polyalcohols is examined and some general prerequisites for a successful design of tailored chelators are summarised. The metal binding properties of 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (taci), a rigid, cyclohexane-based polyamino-polyalcohol, are reviewed. Concepts for the design of selective chelators which are based on the taci structure are presented, and the potential of such ligands for medical applications is briefly discussed.

1 Design and application of selective chelating agents

The design of tailored chelating agents represents one of the basic challenges in the field of synthetic co-ordination chemistry. Tailored chelators can be used to govern the stability of a complex or to modulate the electronic properties of the metal cation (redox potential, spin state).[1] Specific control of such properties is of particular importance in medicine, where selective ligands are used to treat metal intoxication (chelation therapy) or to stabilise metal cations in diagnostic radiopharmaceuticals and paramagnetic contrast agents.[1] A number of prerequisites must be fulfilled for the successful use of a chelating agent in medicine. For diagnostic applications, where the entire complex is introduced into a patient, sufficiently high kinetic and thermodynamic stability is required to prevent decay of the complex in the body. This is of particular importance for diagnostic agents with toxic metal cations such as Gd^{III} or radionuclides. In addition, rapid clearance and suitable biodistribution of the complex are of importance. In the therapy of metal intoxication a high selectivity of the ligand towards the target metal is one of the key properties. Again, a suitable biodistribution is necessary to reach the deposits of the toxic metal in the body. The free ligand itself must be non-toxic and should not be metabolised or excreted too rapidly. On the other hand, the complex itself should be excretable and should be cleared promptly.

A variety of chelators have been developed for the treatment of metal intoxication.[1] 2,3-Dimercaptopropan-1-ol (BAL, British Anti-Lewisite) is one of the first examples which has been developed specifically with respect to the treatment of heavy metal poisoning. D-Penicillamine is used to cure copper overload, and $[Ca(EDTA)]^{2-}$ is an antidote for lead intoxication. The well known microbial siderophore desferriferrioxamine B is currently used for the treatment of iron overload. Due to the increasing contamination of the environment by other toxic heavy metals such as Ni, Cd or Pu, the general interest in tailored chelating agents has further grown within the last few years.

The metal binding properties of a multidentate ligand can be influenced by the choice of the donor atoms and by the steric demands of the ligand backbone, and a systematic optimisation of these two properties must be considered to be the major tool for the design of selective chelators. The affinity of a specific metal cation for a donor atom may be described in terms of empirically derived correlations such as the HSAB principle.[2] For a given donor, the efficacy in metal binding in a defined aqueous medium can be tuned by optimising its basicity. Most common donors in a chelating agent are Brønsted bases and competition with the proton must be taken into account. As long as the same type of donor atom is involved, this competition can be described by simple linear free energy correlations.[1] In terms of absolute stability, more basic ligands form more stable ligand–metal bonds. However, the apparent (or 'conditional') stability in a given aqueous medium may be different.[3] Under acidic conditions the more basic ligand may in fact be less effective due to the strong competition with the proton (Fig. 1). For example, the strongly basic catecholate forms a tris complex with Fe^{III}, having an exceptionally high stability, whereas the corresponding stability of the less basic oxalate is much lower. Consequently in an alkaline solution of about pH 10 the tris-catecholate complex is readily formed and is stable while in the

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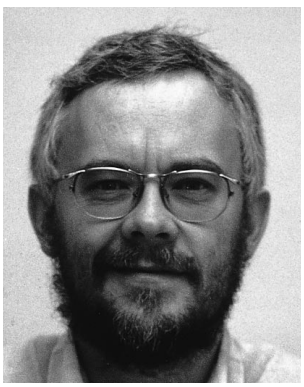


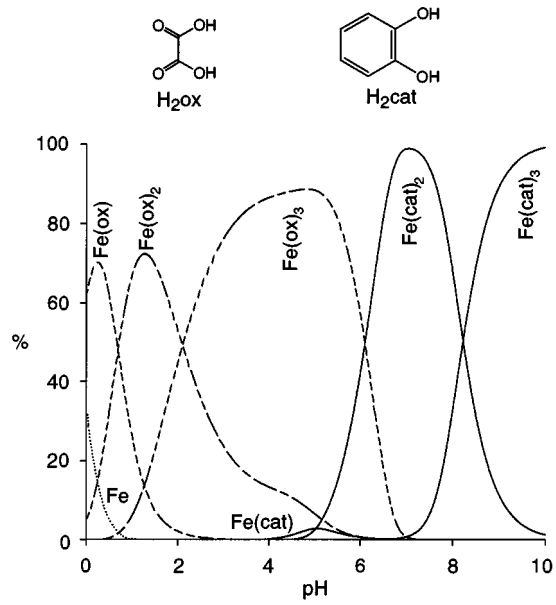


Fig. 1 Species distribution for an equilibrated solution of $Fe(NO_3)_3$, catechol (H_2cat) and oxalic acid (H_2ox) with total concentrations of 1 mmol dm^{-3} (Fe^{III}) and 3 mmol dm^{-3} (cat and ox). pK_a values used: 1.1 and 3.6 for H_2ox, 9.3 and 13.1 for H_2cat. Overall formation constants β_i ($1 \leq i \leq 3$) used: 7.6, 13.8, 18.6 for $[Fe(ox)_i]^{3-2i}$ and 21.0, 35.9, 45.1 for $[Fe(cat)_i]^{3-2i}$ (data from NIST Standard Reference Database 46, *Critically Selected Stability Constants of Metal Complexes*, Gaithersburg, MD 20899, USA). Reduction of Fe^{III} by the organic ligands and formation of mixed oxalato–catecholato complexes are not considered.

sole presence of oxalate solid FeOOH precipitates. In an acidic solution of about pH 3, the tris-catecholate complex decomposes completely due to protonation of the ligand. The tris-oxalato complex is, however, stable. One can show that for a given ligand optimal conditions are reached if pH equals the average pK_a values of the donor atoms (Fig. 2).

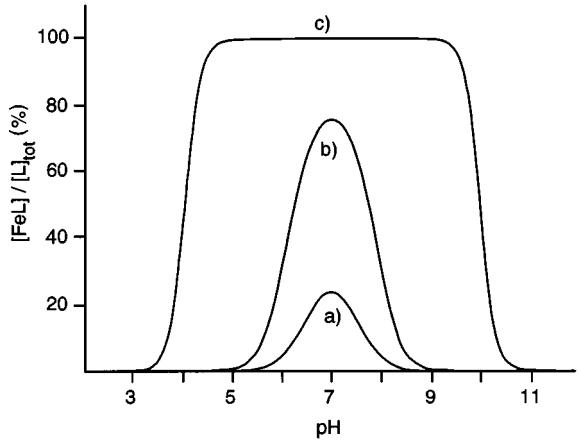


Fig. 2 Sequestering ability of a hypothetical hexadentate ligand H_6L (pK_1 = 5, pK_2 = 6, pK_3 = 7, pK_4 = 7, pK_5 = 8, pK_6 = 9). The ratio [FeL] : total [L] is shown assuming excess of solid FeOOH and variable stability for FeL: a) log K_{FeL} = 23, b) log K_{FeL} = 25, c) log K_{FeL} = 30; $K_w = 10^{-14}$, K_{so} (FeOOH) = 10^{-42}.

Steric strain within the complex can be used to stabilise or destabilise specific co-ordination geometries.[4] It is, for example, well known that due to Jahn–Teller distortion, Cu^{II} preferentially forms complexes with a tetragonal 4 + 2 co-ordination environment and consequently, tridentate ligands with a tripodal arrangement of the donor atoms (which is restricted to a *facial* co-ordination) show a comparably low affinity for this cation. Molecular mechanics methods have been established as a useful and efficient tool to analyse this type of strain in terms of simple force field calculations. Other effects, such as the influence of solvation, are much more difficult to predict and are seldom considered in these discussions.

Various synthetic routes to different types of multidentate ligands have been established in the literature. The use of suitable molecular building blocks of lower denticity, which can be coupled to the target ligand, is one straightforward strategy. It is particularly successful if a template method is used, where the donor set is already preorganised for the coupling reaction by co-ordination to a suitable metal cation.[5] The topic of this review is the fascinating co-ordination chemistry of polyamino-polyalcohols (sections 2 and 3) and the possibility of using these compounds as building blocks for the design of selective, tailored ligands (section 4). This is illustrated by a brief overview of some selected biomedical studies (section 5), which underline the potential of these compounds for such applications. A comprehensive discussion of these applications will, however, be given elsewhere and is not a subject of the present report.

2 Metal binding of polyamines, polyalcohols and polyamino-polyalcohols

2.1 Polyamines

Organic, saturated polyamines are a well known group of complexing agents for transition metal cations and innumerable reports of their co-ordinating properties have appeared in the literature.[6] These ligands are of interest since the donor atom can either be present as a primary, secondary or tertiary amine. An N-donor can thus act as a ramification point and can be used to build up branched structures. The systematic investigation of metal complex formation with aliphatic polyamines in aqueous solution started with the pioneering work of Schwarzenbach and co-workers.[7] Macrocyclic polyamines have been of particular interest in the last two decades owing to their ability to form metal complexes of exceptionally high thermodynamic and kinetic stability.[8] Saturated polyamines are fairly strong bases in water and competition with H^+ must generally be considered in acidic aqueous solutions [eqn. (1)].

$$[L–M]^{z+} + n\ H^+ \rightleftharpoons H_nL^{n+} + M_{aq}^{z+} \quad (1)$$

For a strong, oxophilic Lewis acid, the protonation of the amine can be coupled with the formation of hydroxo complexes (or of the solid metal hydroxide) and eqn. (1) changes to eqn. (2).

$$[L–M]^{z+} + m\ H_2O \rightleftharpoons H_mL^{m+} + [M(OH)_m]^{(z-m)+} \quad (2)$$

This reaction does not depend on pH.

2.2 Polyalcohols

Interactions of aliphatic or alicyclic, saturated polyalcohols such as the sugar alcohols or the cyclitols with metal ions are generally weak and complex formation of a neutral polyalcohol is usually not significant in aqueous solution. However, deprotonated polyalcohols represent rather strong and efficient metal binding agents.[9–11] Polyols are only weak acids (pK_a > 12), *i.e.* a deprotonated polyolato ligand represents an even stronger base than a polyamine, and by analogy with eqn. (1), polyolato metal complexes decompose readily in the presence of acid. It is, however, possible to reduce the basicity of the alkoxo group by the introduction of electron withdrawing substituents. As has been reported, perfluoropinacol has a pK_a of about 6 and forms a stable complex with Fe^{III} in neutral aqueous solution, whereas pinacol itself does not bind Fe^{III} in water.[12]

The ability of a variety of naturally occurring polyalcohol ligands such as glycerol or sorbitol to act as sequestering agents,

preventing formation of solid metal oxides or hydroxides in alkaline aqueous solution, has been well known for many years.[13] However, the correct structures of the complexes that were formed could not be elucidated until very recently. In the last few years, a number of crystal structures analyses have been reported,[14,15] allowing a correct assignment of the structure of such polyolato complexes. These studies showed that the co-ordinated alkoxo group has a pronounced tendency to bind an additional metal cation and to form polynuclear, alkoxo-bridged species.

With regard to the design of tailored ligands, a significant difference between the polyalcohols and the polyamines should be considered. A negative oxygen donor can only bind one C-atom of the ligand backbone and can thus not be used as an interconnecting structural motif for the construction of extended ligand architectures.

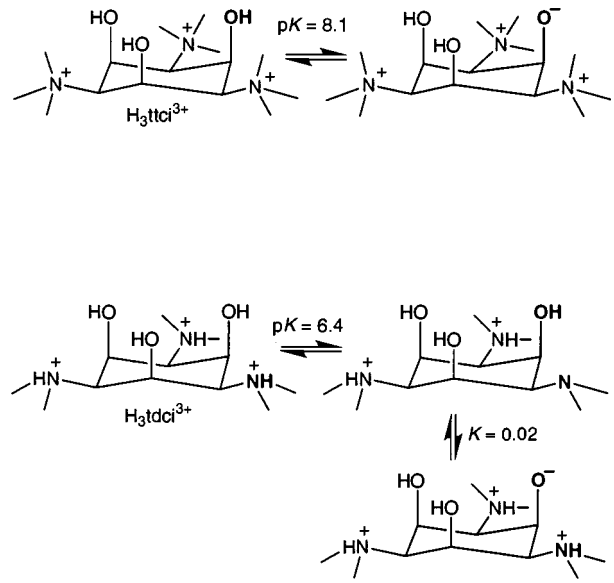
2.3 Polyamino-polyalcohols

Although the co-ordinating properties of polyamino-poly-alcohols (papas) have only scarcely been investigated,[11,16,17] these compounds exhibit a rich and interesting co-ordination chemistry. Both the oxygen and the nitrogen donors of a papa-ligand are regarded as hard Lewis bases in terms of the HSAB concept. The hydroxy group is, however, apparently harder than the amino group, and soft metal cations are preferentially bound to the nitrogen donors.

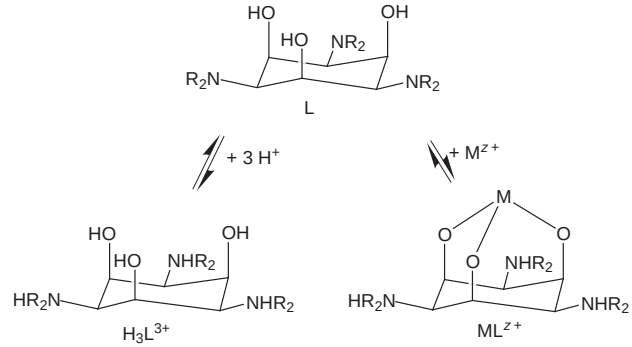
The co-ordination chemistry of the papa-ligands is an illustrative example that a complex system cannot be discussed simply in terms of the combination of the single components. Papas can, of course, act as simple polyamines or polyols by binding a metal cation using the oxygen donors, the nitrogen donors, or a combination of both (mixed N–O-co-ordination). However, the interplay of amino groups and hydroxy groups opens the possibility of further interactions which are not possible for the two individual components. As shown in eqn. (3), the amino groups can act as internal bases, facilitating the deprotonation of the hydroxy groups.

$$R_2N–R'–OH \rightleftharpoons R_2N(H)^+–R'–O^- \qquad (3)$$

This reaction represents an intramolecular proton transfer and results in the formation of a zwitterionic form of the ligand. By analogy to eqn. (2), the equilibrium constant of this reaction does not depend on H^+ concentration and (in contrast to a pure polyol-ligand) the generation of the deprotonated oxygen donor required for metal binding does not depend on the addition of an external base. Although the negative charge on the oxygen donor is stabilised by the positive charge of the ammonium group, the intrinsic acidity of the aliphatic hydroxy group is usually not sufficient to generate the zwitterionic form of the *free* ligand to a substantial extent. An estimate of this acidity for a fully protonated papa-ligand can be obtained by using a corresponding model compound with permanent positive charges (Scheme 1). Comparison of the 1,3,5-trideoxy-1,3,5-tris(trimethylammonio)-*cis*-inositol (H_3ttci^{3+}) cation with the triply protonated 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol (H_3tdci^{3+}) revealed a pK_1 of 8.1 and 6.5, respectively (25 °C, 1 M KCl).[18] If we accept these two values as the intrinsic (microscopic) acidity of the hydroxy group and the dimethylammonio group of the two trications, the zwitterionic form of H_2tdci^{2+} does not form in a greater amount. Co-ordination of a highly charged metal cation to the oxygen donors increases, however, the acidity of the hydroxy groups and the generation of the zwitterion will then predominate. This implies a dramatic stabilisation of the complex in terms of an increased conditional stability at low pH (see section 1 and Scheme 2: competitive protonation of such a papa ligand is significantly reduced since it occurs at the amino groups, having a comparably weak basicity, whereas metal binding occurs at



Scheme 1



Scheme 2

the highly nucleophilic alkoxo groups). The dramatic increase in conditional stability can be exemplified by comparing complex formation of *cis*-inositol (= ino) and tdci with Fe^{III}.[15,19] The former forms the hexanuclear complex $[OFe_6\{(ino)_6 - 21H\}]^{5-}$ in alkaline aqueous solution. In acidic media, this complex is not stable, and hydrolyses completely. For tdci, however, stable, mononuclear species are observed over the entire pH range (Fig. 3)!

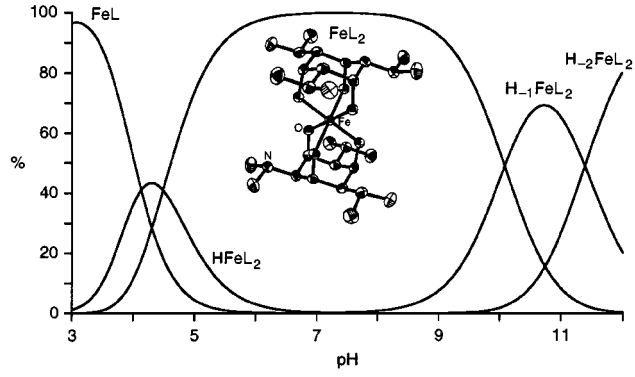


Fig. 3 Molecular structure of $[Fe(tdci)_2]^{3+}$ and species distribution of the Fe^{3+}–tdci system (charges omitted) in equilibrated aqueous solutions. Total Fe = 10^{-3} and total tdci (= L) = 2×10^{-3} mol dm^{-3} (reproduced with permission from *Chem. Eur. J.*, 1995, **1**, 74).

The peripheral (non co-ordinated) ammonium groups in such a papa-complex can of course also be deprotonated and these

groups represent a reservoir of weakly acidic protons. The degree of protonation can be altered simply by varying the pH, allowing the overall charge of the complex to cover a broad range. For example, tdci forms a bis complex with Ta^V, with the metal centre bound to the six alkoxo groups of the two ligand molecules (Fig. 4).[20] In acidic solution, the cation $[Ta(tdci)_2]^{5+}$

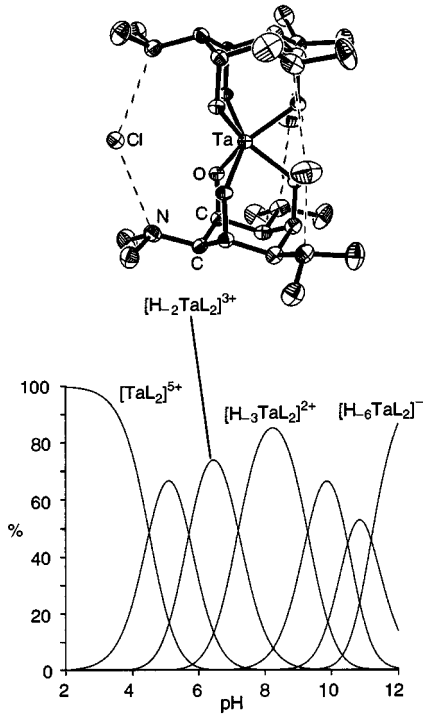
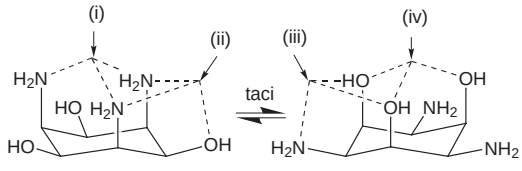


Fig. 4 Molecular structure of $[H_{-2}Ta(tdci)_2]Cl_3$ showing a trigonal prismatic rather than octahedral structure (reproduced with permission from *Angew. Chem.*, 1997, **109**, 2052; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1964) and pH-dependent species distribution (25 °C, 0.1 mol dm^{-3} KCl) for $[H_{-x}Ta(tdci)_2]^{5-x}$ (pK_a-values: 4.5, 5.7, 7.2, 9.3, 10.5, 11.2).

is observed and the two tdci-ligands are present as neutral zwitterions. Increase of the pH results in successive deprotonation and in sufficiently alkaline medium the anion $[Ta(H_{-3}tdci)_2]^-$ is formed. It is thus possible to alter the overall charge of this complex from +5 to −1 without changing the basic structure of the $Ta(tdci)_2$-unit. Such behaviour could be of importance with regard to medical applications where the generation of uncharged species is often required for the transfer across biomembranes.

3 The co-ordination chemistry of 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol

The rigid 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (taci) is an illustrative representative for a papa ligand.[21] As the two chair conformations are of similar energy, this ligand offers a total of four different modes for metal binding (Scheme 3). Mode (i)



Scheme 3

and mode (iv) represent complex formation as a pure polyamine or a pure polyalcohol while modes (ii) and (iii) represent mixed N–O co-ordination. All four binding modes are restricted to a *facial* co-ordination of the ligand. It is, however, interesting that the steric requirements for a symmetric adamantane-like type (i) and type (iv) structure are distinctly different from the asymmetric type (ii) and type (iii) structures. It has been shown by a series of molecular mechanics calculations that the adamantane-like structures are particularly favourable for small metal cations, whereas large cations are bound preferentially to the asymmetric type (ii) or type (iii) sites (Fig. 5).[22] This ability

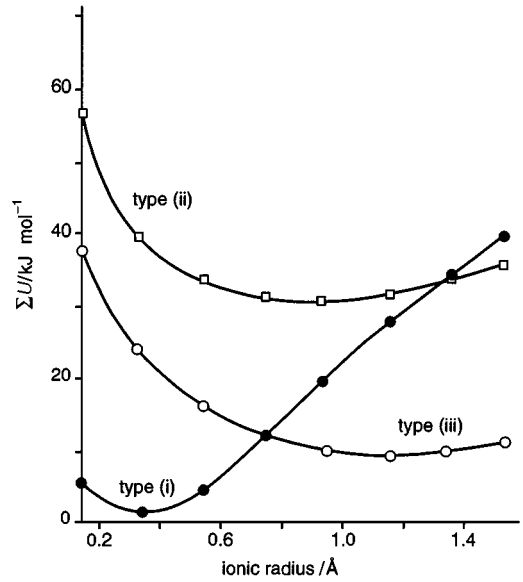


Fig. 5 Molecular mechanics calculation for the M(taci)-fragment where M denotes a generalised metal ion with a constant force field, having a type (i), type (ii) or type (iii) structure. The strain energy ΣU is shown as a function of the metal ionic radius (reprinted from K. Hegetschweiler, M. Wörle, M. D. Meienberger, R. Nesper, H. W. Schmalk and R. D. Hancock, *Inorg. Chim. Acta*, **250**, 35, Copyright 1996, with permission from Elsevier Science).

to bind a metal centre either by oxygen or nitrogen donors, together with the different steric requirements of the four co-ordination modes and the possibility of co-ordination in either a zwitterionic or a non-zwitterionic form, make taci a very versatile ligand. The co-ordinating properties of this ligand have been investigated thoroughly.[23] Complex formation with more than 30 different elements has been verified by crystal structure analysis (Fig. 6), and the stability constants of most of the

H														
Li	**Be**											B	C	N
Na	**Mg**											**Al**	Si	P
K	**Ca**	Sc	**Ti**	V	**Cr**	**Mn**	**Fe**	**Co**	**Ni**	**Cu**	**Zn**	**Ga**	**Ge**	As
Rb	**Sr**	Y	Zr	Nb	**Mo**	Tc	Ru	Rh	Pd	Ag	**Cd**	**In**	**Sn**	Sb
Cs	**Ba**	**La**	Hf	Ta	W	**Re**	Os	Ir	Pt	Au	Hg	**Tl**	**Pb**	**Bi**
Ce	Pr	Nd	Pm	Sm	**Eu**	**Gd**	Tb	Dy	Ho	Er	Tm	Yb	Lu	

Fig. 6 Section of the periodic table. The bold faced symbols represent elements where complex formation with taci has been verified by X-ray structure analysis.

complexes have been determined. For a systematic discussion of these results, the different affinity of a metal cation for oxygen or nitrogen donors, the different steric requirements of the symmetric and asymmetric binding sites and the charge of the metal cation must all be taken into account. A classification of metal cations M^{z+} into five categories proved helpful in reviewing the co-ordination properties of taci:[24]

(1) With the sole exception of Be^{2+}, metal cations of Group 1 and Group 2 elements, having a d^0 configuration with $z \leq 2$ form mononuclear type (iv) bis complexes. These cations are weak acids and consequently, a transfer of the protons from O to N (generation of the zwitterionic form) is not observed, *i.e.*

taci acts in these complexes as a simple polyalcohol. Li^+, Na^+ and Mg^{2+} show octahedral co-ordination. For the heavier elements such as K^+, Ca^{2+}, Sr^{2+} and Ba^{2+} higher co-ordination numbers (up to 9) are realised by co-ordination of additional ligands such as H_2O or a counter ion. As mentioned in section 2.2, neutral polyalcohols are only poor ligands and consequently these complexes are of rather low stability and they dissociate readily in aqueous solution (Mg^{2+}: $\beta_1 \approx 1$ mol^{-1} dm^3).

(2) Small d^0 and d^{10} metal cations with $z \geqslant 3$ also form mononuclear bis complexes $[M(taci)_2]^{z+}$ with exclusive co-ordination *via* the oxygen donors in an octahedral fashion. However, due to the higher charge, the ligands co-ordinate in the zwitterionic form. This mode has been established for $[Al(taci)_2]^{3+}$, $[Ti(taci)_2]^{4+}$, $[Ge(taci)_2]^{4+}$ and $[Sn(taci)_2]^{4+}$. As discussed in section 2.3, the adoption of the zwitterionic form results in a significant stabilisation and consequently these complexes exhibit high stability in aqueous solution.

(3) Divalent transition- and d^{10}-metal cations generally tend to adopt a bis-type (i) structure. This has been found for Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and also for the trivalent Tl^{3+}. The ligand behaves as a simple, tripodal amine and the stabilities of these complexes in aqueous solution fall in the range observed for a triamine. Maximum stability is observed for Ni^{2+} ($\log \beta_2 = 20.94$, Cu^{2+}: $\log \beta_2 = 18.79$). As mentioned in section 1, this deviation from the Irving–Williams behaviour is a consequence of the Jahn–Teller distortion of Cu^{II}.

(4) Some of the trivalent transition metal ions and small trivalent d^{10} metal ions form mononuclear bis complexes with a mixed type (i)–type (iv) co-ordination. The oxygen-bound ligand co-ordinates as a zwitterion. This mixed MN_3O_3 co-ordination mode represents an intermediate case between the two categories (2) and (3). It has been established for Fe^{III} and Ga^{III} in the solid state by crystal structure analysis of the isomorphous $[M(taci)_2](NO_3)_3 \cdot 3H_2O$ salts, and also in aqueous solution by NMR and Mössbauer spectroscopy.

(5) Large sufficiently hard trivalent metal cations such as Bi^{3+} and the lanthanides form trinuclear species of the composition $[M_3(H_{-3}taci)_2]^{3+}$ by co-ordinating simultaneously the three type (iii) sites of taci.[25,26] Each of the three metal cations binds to an amino group and to two deprotonated alkoxo groups (Fig. 7). The two ligands which are present as trianions

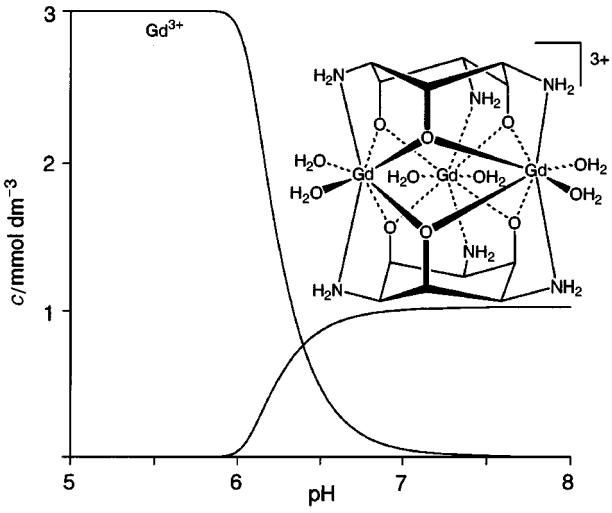


Fig. 7 Molecular structure of $[Gd_3(H_{-3}taci)_2(OH_2)_6]^{3+}$ and species distribution of the Gd^{3+}–taci system in equilibrated complex solutions with total Gd = 3×10^{-3} and total taci (= L) = 2×10^{-3} mol dm^{-3} (reprinted with permission from R. Hedinger, M. Glisletta, K. Hegetschweiler, É. Tóth, A. E. Merbach, R. Sessoli, D. Gatteschi and V. Gramlich, *Inorg. Chem.*, 1998, **37**, 6698. Copyright 1998 American Chemical Society).

encapsulate the equilateral triangle formed by the metal centres and give rise to a cage structure with six μ_2-alkoxo bridges. In the lanthanide complexes, the co-ordination sphere is completed by peripheral ligands such as H_2O or counter ions. In the Bi complex only very weak interactions with Cl^- counter ions are observed, probably due to the presence of a stereochemically active lone pair at the Bi^{III} centres.

Although this classification is useful for an overview of the rich co-ordination chemistry of taci, some metal centres do not fit into this scheme. Be^{2+}, for example, is a very small and strong Lewis acid, having a strictly tetrahedral co-ordination geometry. With taci, a trinuclear complex of the composition $[Be_3(taci)_3]^{6+}$ is formed in solution and in the solid state (Fig. 8).[21] In this complex, the three ligands co-ordinate the three

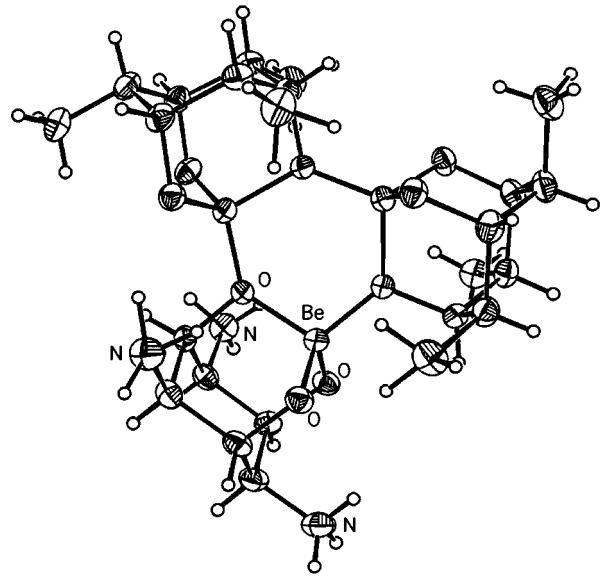


Fig. 8 Molecular structure of $[Be_3(taci)_3]^{6+}$.

Be^{2+} centres exclusively *via* the oxygen donors, and, by analogy with category (2), the ligands adopt a zwitterionic structure. However, to realise a tetrahedral environment around the Be^{2+} centre, one of the oxygen donors undergoes bridging to a neighbouring Be^{2+} centre, giving rise to a six-membered Be–O–Be–O-Be–O–ring. Co^{III} is known to be rather inert and it is thus possible to isolate different isomers which may not correspond to the most stable form of this complex. A variety of Co^{III}–taci complexes have been characterised in which type (i), type (ii) and type (iii) co-ordination modes have been established.[23] Type (ii) co-ordination is actually very rare and besides Co^{III}, it has only been observed in the Re^{I} complex $[(CO)_3Re(H_{-1}taci)]$,[27] and in a trinuclear cluster of the $Mo_3S_4^{4+}$ unit.[22] For Pb^{II}, a trinuclear species of the composition $[Pb_3(H_{-3}taci)(\mu_3\text{-}OH)]^{2+}$ was identified in solution,[28] and this trinuclear structure was also observed in the solid state, where OH^- was replaced by a bridging nitrate.[25] The structure of the $[Pb_3(H_{-3}taci)]^{3+}$ moiety corresponds to the $M_3(H_{-3}taci)_2$-cage described in category (5), with one of the ligands dissociated.

4 Derivatisation of taci: the design of tailored ligands

4.1 Synthetic strategies

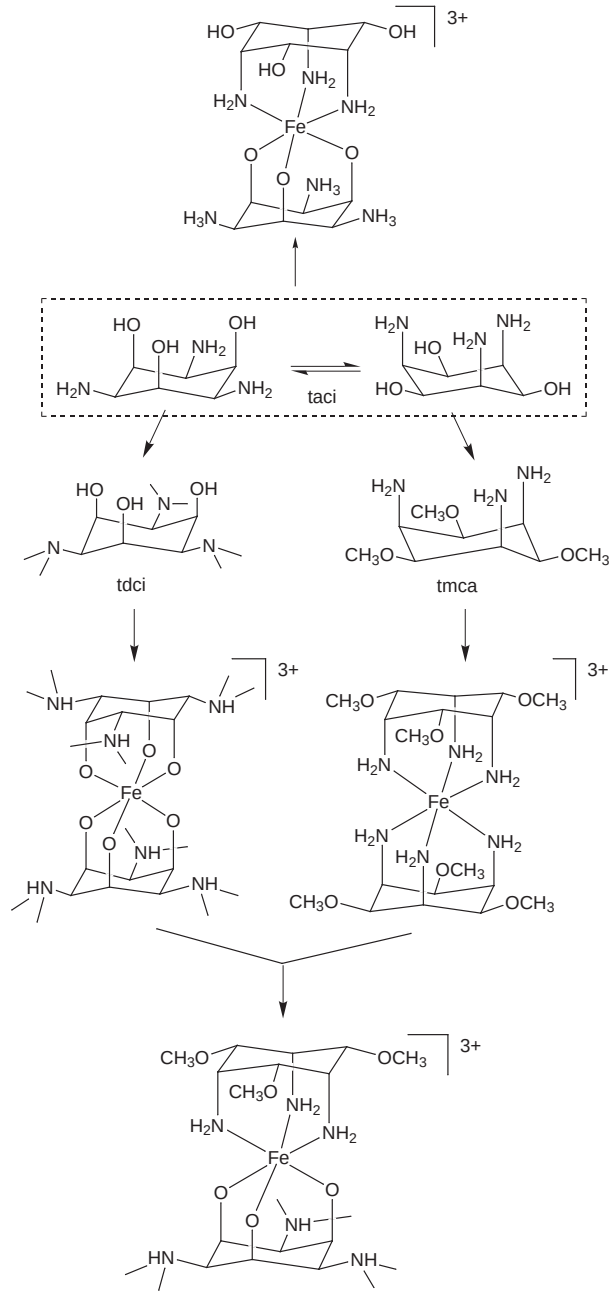
Because of the high number of functional groups present in the taci ligand, a variety of synthetic modifications can be performed. These modifications are of particular interest with regard to a systematic modulation of the co-ordinating properties. However, the multifunctionality may render a specific synthetic modification difficult to control, and several strategies have been developed for a selective substitution either at the

oxygen or nitrogen atoms.[18,29] The synthesis of *O*-alkylated derivatives, for example, proved particularly troublesome, since direct treatment of taci with alkylating agents resulted in *N*- rather than *O*-alkylation. A variety of classical protecting groups for the primary amine functions were investigated. Although such groups could readily be attached to the nitrogen atoms, the resulting compounds showed no significant reactivity towards the alkylating agent. Obviously, the large steric demands of the protecting groups enforced *equatorial* orientation of the nitrogen donors and consequently the hydroxy groups were in the less reactive *axial* positions. The combination of an *equatorial* position for the hydroxy groups and effective protection of the amino groups could be achieved by using $[Ni(taci)_2]^{2+}$ as starting material.[29] This procedure allowed an almost quantitative and selective alkylation of the oxygen atoms. A systematic investigation of such substituted taci derivatives has been undertaken, and these compounds were shown to have a number of interesting properties.[19,29–32] Some examples will be discussed in the following sections (4.2–4.6).

4.2 Methylated derivatives

The introduction of methyl groups on either the oxygen or nitrogen donors generates a set of rather selective ligands.[19,29] In 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol (tdci, Scheme 1), the conformer with three *axial* dimethylamino groups is destabilised by non-bonding (*intra*-ligand) repulsion and only the conformation with three *axial* hydroxy groups is available for metal binding. Also additional *inter*-ligand repulsion between co-ordinated dimethylamino groups substantially increases steric strain in a bis-complex of tdci with MN_6 co-ordination. Similar considerations are valid for all-*cis*-2,4,6-trimethoxycyclohexane-1,3,5-triamine (tmca), where preferential co-ordination by three *axial* nitrogen atoms is observed. The Fe^{III} complexes of taci, tdci and tmca illustrate this behaviour (Scheme 4): $[Fe(tdci)_2]^{3+}$ has an FeO_6 structure whereas $[Fe(tmca)_2]^{3+}$ is one of the rare examples of a ferric hexaamine complex.[30] As mentioned in section 3, $[Fe(taci)_2]^{3+}$ exhibited a mixed FeN_3O_3 co-ordination, which demonstrates that for high spin Fe^{III} the mixed O–N environment is of lowest energy. This was further confirmed by the facile formation of $[Fe(tmca)(tdci)]^{3+}$, which was obtained almost quantitatively by a simple metathesis reaction of $[Fe(tdci)_2]^{3+}$ and $[Fe(tmci)_2]^{3+}$. The two types of methylated ligands can therefore be used to direct co-ordination modes which would not be preferred with taci. Since the steric properties of the *syn-triaxial* binding sites are similar for the three ligands, it is possible to elucidate the intrinsic electronic influence of oxygen and nitrogen donors on the properties of the central metal cation. $[Fe(taci)_2]^{3+}$ and $[Fe(tdci)_2]^{3+}$ as well as the mixed $[Fe(tdci)(tmca)]^{3+}$ are high-spin and labile, whereas $[Fe(tmca)_2]^{3+}$ is low-spin and inert. Clearly, it is the N-ligand which generates the low spin co-ordination and more than three N-donors are required.

With respect to selectivity, tdci is an efficient ligand for hard and highly charged cations such as Fe^{3+}, Al^{3+} or Ti^{4+} ($\log \beta_{FeL_2} = 32.6$);[19] tmca on the other hand represents an effective ligand for late divalent transition metal cations such as Ni^{2+}.[29] It is of particular interest that compared to taci (which carries both co-ordination sites combined in one molecule) the stabilities of the bis complexes of tmca with late divalent transition metal cations and of tdci with the highly charged oxophilic centres exceed those of taci by up to seven orders of magnitude, even though no significant structural differences were observed within the co-ordination spheres or the ligand backbones of corresponding structures. It is not obvious how this increase of stability can be explained. At least for tdci, the donor groups have a higher degree of preorientation than in taci, since the possibility for chair conversion is inhibited. However, an improved preorientation of the donor groups alone cannot explain such a large increase in stability for both cases (*i.e.* tdci *and* tmca) and other reasons, *e.g.* a more favourable solvation of the complex (in terms of a more favourable entropy of solvation), must probably account for this observation.



Scheme 4 Adapted with permission from K. Hegetschweiler, M. Weber, V. Huch, M. Veith, H. W. Schmalle, A. Linden, R. J. Geue, P. Oswath, A. M. Sorgeson, A. C. Willis and W. Angst, *Inorg. Chem.*, 1997, **36**, 4121. Copyright 1997 American Chemical Society.

4.3 Substituents with additional donor groups

If substituents are used which carry additional donor groups, the taci ligand can be extended to a potentially penta- or hexadentate chelator. As an example, the condensation of taci with three equivalents of salicylic aldehyde, followed by hydrogenation of the C=N double bonds, generates the tris-*N*-alkylated 1,3,5-trideoxy-1,3,5-tris[(2-hydroxybenzyl)amino]-*cis*-inositol (H_3thci) providing three aliphatic amino groups, three aliphatic hydroxy groups and three phenolic hydroxy groups for the co-ordination of a cation.[31] The Re^{V} complex

[ReO(thci)] is an example where all three types of donor atoms are involved in metal binding (Fig. 9). In this complex, the

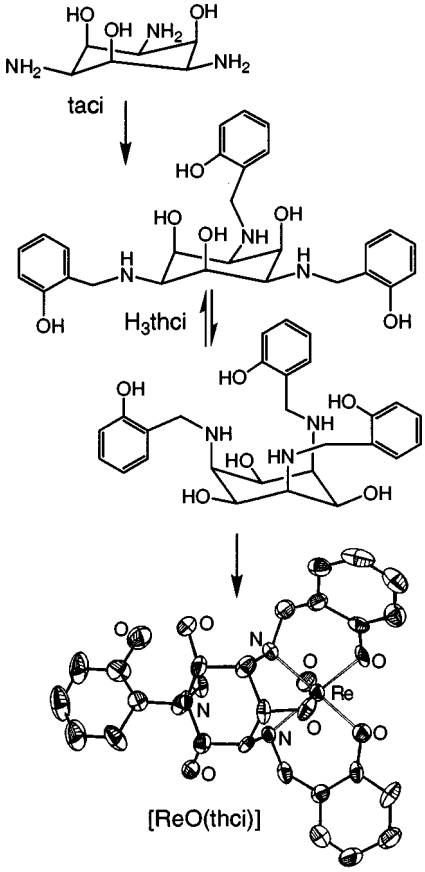
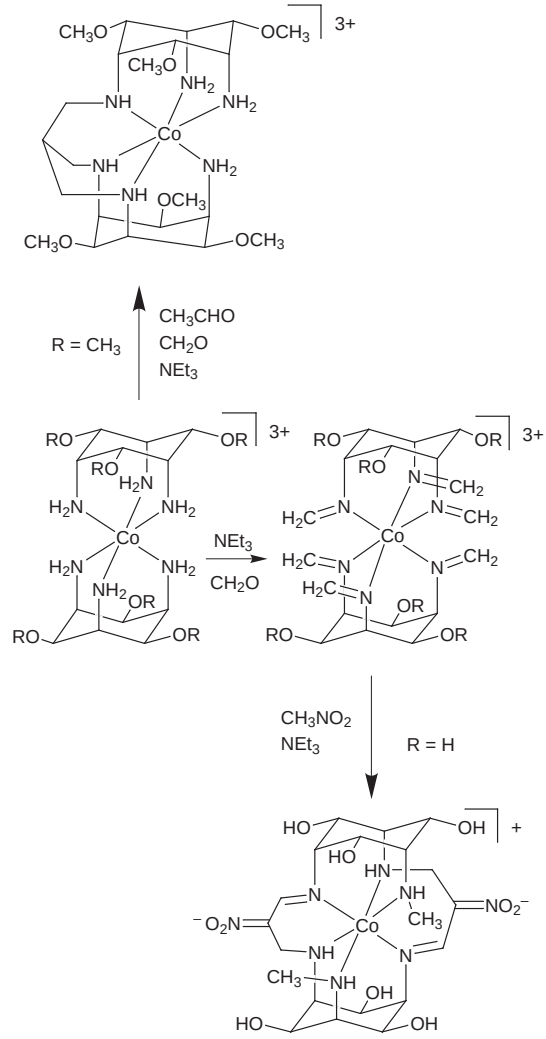


Fig. 9 Formation and molecular structure of [ReO(thci)] (Reprinted with permission from K. Hegetschweiler, A. Egli, R. Alberto and H. W. Schmalle, *Inorg. Chem.*, 1992, **31**, 4027. Copyright 1992 American Chemical Society).

Re=O unit binds to the 'asymmetric' type (ii) site. The co-ordinated aliphatic oxygen is deprotonated. In addition, two amino groups together with their pendant *o*-phenoxy substituents are co-ordinated to the cation. It is of particular interest to note that the third amino group together with its pendant aromatic substituent is not involved in metal binding and the ligand $thci^{3-}$ exhibits pentadentate co-ordination. This clearly illustrates the ability of this ligand to adapt its co-ordination behaviour to a specific metal cation.

4.4 Template methods

Coupling of two taci molecules by linking *via* nitrogen donors represents an additional promising route to novel hexadentate chelators. The synthesis of such bis-taci ligands is straightforward, if a template method is used as mentioned in section 1. For this purpose, the two hexaamine complexes $[Co(taci)_2]^{3+}$ and its *O*-methylated derivative $[Co(tmca)_2]^{3+}$ have been prepared and they were subsequently converted to the corresponding hexa-imino derivatives.[32] This method was originally developed by Sargeson and co-workers (as reviewed in ref. 5). The two hexa-imines proved to be stable in acidic aqueous solution and could be isolated as solids. With nucleophiles such as a hydride or a carbanion, a rapid addition reaction was observed, and in the presence of acetaldehyde or nitromethane and base the two tridentate ligands could readily be coupled, yielding corresponding Co^{III} complexes of new macrocyclic ligands (Scheme 5). Demetalation of these complexes and isolation of the free ligands have, however, not been described as yet.



Scheme 5 Adapted with permission from K. Hegetschweiler, M. Weber, V. Huch, R. J. Geue, A. D. Rae, A. C. Willis and A. M. Sorgeson, *Inorg. Chem.*, 1998, **37**, 6136. Copyright 1998 American Chemical Society.

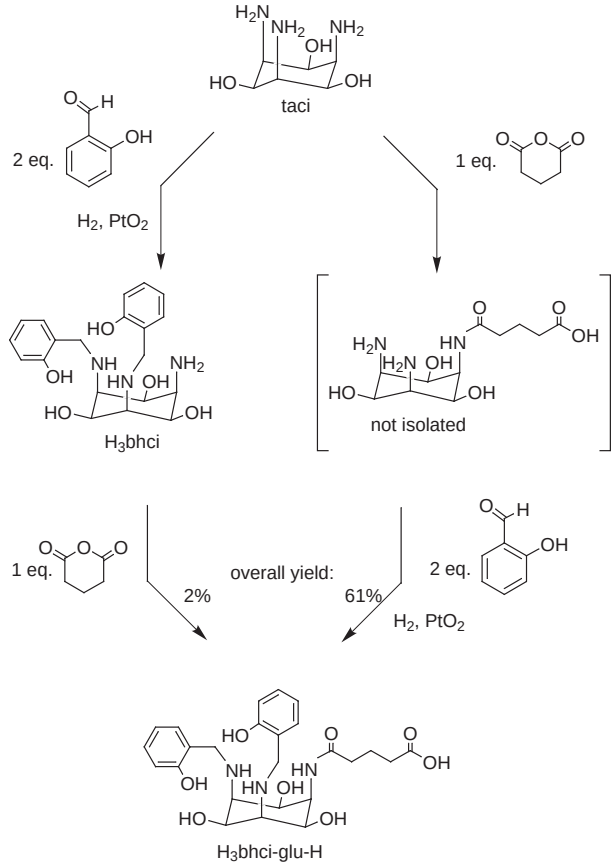
4.5 Variation of lipophilicity

Replacement of the H–O or H–N hydrogen atoms by organic substituents inherently increases the lipophilicity of the ligand. Already tdci, the tris-*N*,*N*-dimethylated derivative of taci, is clearly a much more lipophilic molecule than its parent. The unsubstituted taci behaves similarly to a sugar and is only soluble in water and to a very limited extent in MeOH, while tdci is readily soluble in chloroform or even in boiling hexane.[18] The difference in lipophilicity is also of relevance to the metal binding properties as exemplified by the significantly different behaviour of the Pb^{II} complexes of taci and tdci. The solution chemistry of the Pb^{II}–taci system is restricted to water. In aqueous media, the trinuclear $[Pb_3(H_{-3}taci)(OH)]^{2+}$ (see section 3) is formed.[28] A related species was observed for tdci in MeOH, having the composition $[Pb_3(H_{-3}tdci)(\mu_3\text{-}OCH_3)]^{2+}$. Here, hydroxide is replaced by a μ_3-methoxo ligand. However, tdci also forms the neutral species $[Pb_3(H_{-3}tdci)_2]$ which has a rather unpolar surface.[33] Due to the high lipophilicity and the lack of charge, this complex is insoluble in water but soluble in organic solvents and, despite the rather high molecular weight, it is volatile and sublimes at 250 °C (14 mbar N_2). Volatile metal complexes are of interest for metal organic chemical

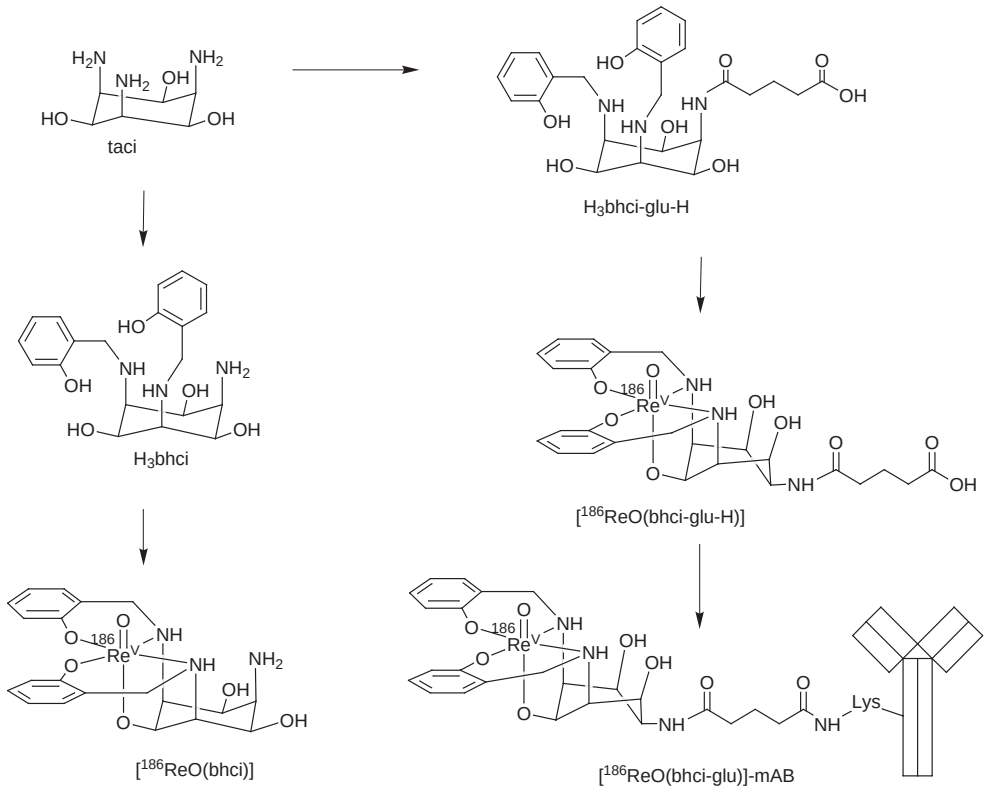
vapour deposition (MOCVD) and in a recent study it has been shown that this compound can be used as a precursor for the deposition of thin films of lead and lead(II) oxide on various substrates by the MOCVD technique.[33]

4.6 Bifunctionalisation

Finally, the introduction of suitable substituents could be of use to generate bifunctionalised derivatives, where one of the substituents serves as a linker to attach the complex covalently to a protein or to an ion exchange resin. Such modifications are of particular interest with regard to medical applications (see section 5.3). The potentially pentadentate H_3bhci–glu–H provides an example of bifunctionalisation where one type of substituent is used to extend the ligand system (the two *o*-hydroxybenzyl substituents) and another is used for the introduction of a linking unit (the glutaric acid moiety).[34] The different synthetic routes shown in Scheme 6 once again demonstrate the difficulties encountered with the high multifunctionality of this system. Although the ligand H_3bhci could be synthesised by condensation of two equivalents of salicylic aldehyde with taci and subsequent reduction of the imines to amines, this process gave rise to a mixture of 1 : 1, 1 : 2 and 1 : 3 products. Subsequent derivatisation of H_3bhci with glutaric anhydride resulted in the formation of a crude mixture of various compounds and the desired product was only obtained in poor yield. The reverse procedure, in which the monoamide was formed first and was further derivatised with salicylic aldehyde, was more successful, since the intermediate amide is of low solubility and precipitates out of solution. The subsequent reduction of the imines was easily performed and good yields of the bifunctional ligand H_3bhci–glu–H were achieved. The two Re^V complexes [ReO(bhci)] and [ReO(bhci–glu–H)] have been prepared for potential radiopharmaceutical applications (Scheme 7).[34] Inspection of the structural features of the two complexes revealed a remarkable difference in the conformation of the cyclohexane rings. In [ReO(bhci)] an almost ideal chair is observed, while [ReO(bhci–glu–H)] exhibited a twisted boat conformation. This difference can be



Scheme 6 Reprinted with permission from A. Kramer, R. Alberto, A. Egli, I. Novak-Hofer, K. Hegetschweiler, U. Abram, P. V. Bernhard and P. A. Schubiger, *Bioconjugate Chem.*, 1998, **9**, 691. Copyright 1998 American Chemical Society.



Scheme 7 Adapted with permission from A. Kramer, R. Alberto, A. Egli, I. Novak-Hofer, K. Hegetschweiler, U. Abram, P. V. Bernhard and P. A. Schubiger, *Bioconjugate Chem.*, 1998, **9**, 691. Copyright 1998 American Chemical Society.

explained on the basis of the different types of intramolecular hydrogen bonds which are formed in the two complexes, underlining though the importance of hydrogen bonding between different substituents for the structural properties of complexes with such cyclohexane-based polyamino-polyalcohol ligands.

5 Applications

5.1 Iron overload

Iron overload is mainly caused by regular blood transfusions which are necessary to treat genetically imposed disorders of haemoglobin production such as Thalassaemia.[35] The ability of the body to excrete excess iron is very limited and repeated blood transfusions inevitably lead to an accumulation of iron in the body. In a first step, excess iron is accumulated in specific storage proteins such as ferritin. Further uptake of iron results in the deposition of solid FeOOH in tissues and organs and the patients will finally die owing to severe damage to these organs. Administration of a specific iron binding chelator is the method of choice to solve this problem. The use of desferrioxamine B for the removal of excess iron has already been mentioned in the introduction (section 1). However, this hydroxamate-based ligand has some severe disadvantages. It is inactive when administered orally and has a very short biological half life. Thalassaemia is responsible for some 100 000 child deaths per year and consequently the search for selective iron chelating agents is of particular importance. Although considerable efforts have been made to develop more suitable iron chelators in the last two decades,[35] a completely satisfactory compound has not yet been found. The high affinity of tdci for hard and highly charged Lewis acids and its low tendency to form complexes with divalent transition metal cations make it an ideal candidate for the treatment of iron overload. The excellent selectivity of tdci can be attributed to (a) the restriction to only one chair conformation which disfavours the competitive binding of Cu^{2+} and Zn^{2+}, and (b) the poor donor capacity of the (neutral) hydroxy groups which renders the interactions with the ubiquitous Mg^{2+} and Ca^{2+} very weak. In fact, the oxygen donors of tdci are only effective in metal binding if they are deprotonated and the divalent Mg^{2+} and Ca^{2+} are not acidic enough to cause the required proton transfer from the hydroxy groups to the amino groups (see section 3).[19] In the complex with the trivalent Fe^{III}, however, co-ordination to alkoxo groups is possible even in acidic media (the generation of the tautomeric form is not dependent on pH, see Scheme 1, Fig. 3, and also section 2.3).

Animal studies revealed a rather low toxicity of tdci (LD_{50} > 1 g kg^{-1}) and a preliminary *in vitro* screening exhibited very favourable kinetics for the dissolution of solid FeOOH.[36] Moreover, a recent animal study with the ^{59}Fe labelled bis-tdci complex showed excellent clearance when the complex was administered subcutaneously. Over 80% of the injected $[^{59}Fe(tdci)_2]^{3+}$ was excreted through the kidneys within 24 h.[37] Other ligands such as the currently used desferrioxamine B have considerably longer retention times. However, studies with iron overloaded rats revealed an almost negligible removal of iron when the free ligand was administered subcutaneously. This disappointing result clearly indicates that tdci itself cannot be used as a therapeutic agent to treat iron overload. The reason for the failure of tdci to sequester substantial amounts of Fe is not clear. The ligand could be metabolised too rapidly or an improper biodistribution might impede rapid loading of the ligand with Fe. These problems may be circumvented by adding different substituents to the nitrogen donors, however, to date, such efforts have not brought success.

5.2 Contrast agents for magnetic resonance imaging (MRI)

In the last two decades, nuclear magnetic resonance (NMR) imaging has been developed as a powerful non-invasive diagnostic tool for acquiring images of tissues as topological representations of NMR parameters.[38] The lack of ionising radiation is a particularly attractive advantage of this method. Although the use of a contrast enhancing agent is not an essential prerequisite for MRI, it increases lesion detection and diagnostic accuracy. Since nearly all NMR clinical imaging involves proton magnetic resonance, and the principal proton species that generates the NMR signal is the water molecule, an effective contrast enhancer basically operates by affecting the NMR properties of body water (faster proton relaxation). For this purpose a variety of paramagnetic metal complexes have been studied. Owing to the high number of unpaired electrons, Gd^{3+} complexes are of particular interest. The free Gd^{3+} aqua ion is, however, toxic, and it must therefore be administered in the form of a complex of sufficient stability. The ability of such a complex to decrease the relaxation time of the surrounding water protons is governed by the number of inner sphere water molecules, the rate of water exchange, rotation and electronic relaxation. Currently, Gd^{III} complexes with suitable polyamino polycarboxylates are utilised as contrast agents for MRI.[38]

As has been shown in section 3, the trivalent lanthanide cations form trinuclear complexes of the composition $[M_3(H_{-3}taci)_2(H_2O)_6]^{3+}$. The corresponding Gd^{III} complex could be of particular interest in the context of MRI, owing to the compact structure, the high amount of paramagnetism induced by three Gd^{III} centres, and the total of six water ligands which are attached to the metal atoms. A comprehensive study has been performed to elucidate the structure, as well as the electronic and solution properties of this complex.[26,39] Magnetic susceptibility measurements showed that only weak antiferromagnetic coupling is present within the trinuclear core and at room temperature the full magnetic moment corresponding to 21 unpaired electrons was observed. The water exchange has been investigated by ^{17}O-NMR measurement. It is considerably slower than in the Gd^{3+} aqua ion and has much more associative character. The difference in the exchange rate can be explained by the rigidity of $[Gd_3(H_{-3}taci)_2(H_2O)_6]^{3+}$ which slows down the transition from the eight co-ordinate ground state to the nine co-ordinate transition state. The rotational correlation time of the complex is unexpectedly low and this has been interpreted in terms of the spherical structure with a large hydrophobic surface, which prevents the formation of a substantial hydration sphere around the trinuclear complex molecule.

The stability of this complex in water was investigated by an NMR study and pH-metric titrations. These measurements showed that $[Gd_3(H_{-3}taci)_2(H_2O)_6]^{3+}$ readily forms in alkaline media but decomposes immediately if the pH falls below 6 (Fig. 7). The inability of taci to bind lanthanide cations in acidic aqueous media is based on the very unfavourable proton balance of the formation reaction (4).

$$2\ H_3taci^{3+} + 3\ Eu^{3+} + 12\ OH^- \rightarrow [Eu_3(H_{-3}taci)_2]^{3+} + 12\ H_2O \qquad (4)$$

In the context of MRI, the potential use of $[Gd_3(H_{-3}taci)_2(H_2O)_6]^{3+}$ as a contrast agent is thus limited by its insufficient stability under physiological conditions. The trinuclear complex is, however, an interesting model for studying the effects of intramolecular Gd–Gd interaction on electronic relaxation, and consequently on proton relaxivity. Increased stability could be achieved by connecting the two taci frameworks by an N–$(CH_2)_2$–NH–$(CH_2)_2$–N or N–$(CH_2)_2$–O–$(CH_2)_2$–N bridge (section 4.4) or by introducing substituents onto the nitrogen atoms which carry additional donor groups

(section 4.3). The investigation of such ligands is currently being carried out in our laboratory.

5.3 Radiopharmaceutical applications

Labelling of tumour seeking monoclonal antibodies (MAB) with radioactive nuclides is another well established diagnostic tool and is of particular use for the location of cancer metastases. In addition, this method is relevant to therapeutic applications.[40] Due to favourable γ-decay characteristics and ready availability, radioimmunoconjugates labelled with ^{99m}Tc are used for diagnostic imaging of specific organs. The β-emitting rhenium isotopes ^{186}Re and ^{188}Re are suited for therapeutic purposes (radioimmunotherapy, RIT).[40] Based on the chemical relationship between rhenium and technetium, the same ligands that are used for ^{99m}Tc labelling may also be applicable for $^{186/188}$Re. Currently, MAG3, a tetradentate N_3S ligand originally developed for renal function measurement with ^{99m}Tc, is used as a ligand in tumour therapy with $^{186/188}$Re. The Re–MAG3 system showed some promising results, although the labelling protocols have not proved to be convenient for routine application. There is thus considerable demand for new suitable chelators which form stable complexes with Re and which could be attached to a protein. A broad range of possible oxidation states is known for Re. Re^V has proved to be suitable as it forms stable chelate complexes which can be prepared readily from ReO_4^-.[1] The design of a specific, pentadentate, bifunctionalised chelator for the Re^V=O moiety has been described in section 4.6 (Schemes 6 and 7).[31,34] The derivatisation of H_3bhci with glutaric acid not only offers the possibility of linking the ligand to a protein but also prevents co-ordination of a cation to the three nitrogen atoms. In this way, a competitive binding of biologically relevant, divalent transition metal cations such as Cu^{2+} or Zn^{2+} can be avoided. The ligand $bhci^{3-}$ and its bifunctionalised analogue $bhci–glu^{4-}$ both encapsulate the Re^V centre efficiently yielding a distorted octahedral co-ordination geometry, and the rigid cyclohexane backbone together with the preorientation of the N_2O_3 donor set lead to the high stability of the complex. Neither [ReO(bhci)] nor $[ReO(bhci–glu)]^-$ showed any detectable decomposition in human serum or under *in vivo* conditions, while ligands with an analogous N_3O_3 donor set but lacking the cyclohexane core decomposed in blood serum over a period of three days.

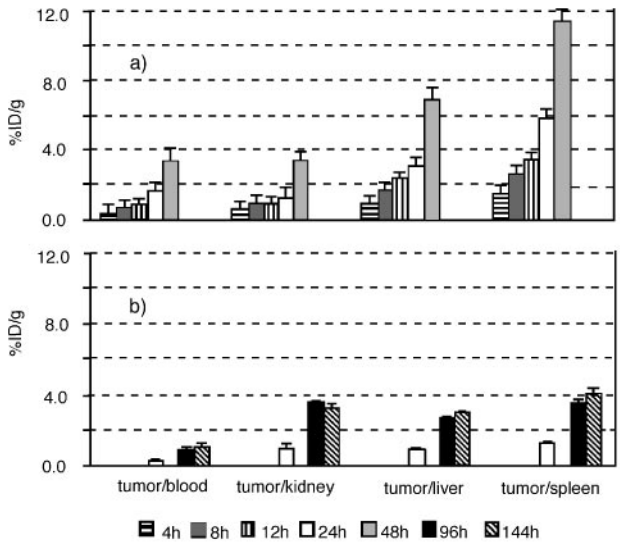


Fig. 10 Tumour to organ ratios of [^{186}ReO(bhci–glu)]-labelled mAb-35 in tumour bearing nude mice. The ratios were determined at 4, 8, 12, 24 and 48 h post injection (a) for the labelled $F(ab')_2$ fragment and at 24, 96 and 144 h post injection (b) for the labelled intact antibody (Reprinted with permission from A. Kramer, R. Alberto, A. Egli, I. Navak-Hofer, K. Hegetschweiler, U. Abram, P. V. Bernhard and P. A. Schubiger, *Bioconjugate Chem.*, 1998, **9**, 691. Copyright 1998 American Chemical Society).

The bifunctionalised H_3bhci–glu–H was applied in a pre-labelling protocol to $^{186/188}$Re (Scheme 7) and subsequently, the anti colon cancer antibody mAb-35 was labelled with [$^{186/188}$ReO(bhci–glu–H)] with full retention of immuno-reactivity. Biodistribution of ^{186}Re labelled mAb-35 in tumour bearing mice revealed good tumour uptake with no significant accumulation of radioactivity in normal tissue.[34] Since it is known that $F(ab')_2$ fragments may present advantages for RIT compared to intact antibodies in terms of better tumour penetration and faster clearance from the body, both intact mAb-35 and its $F(ab')_2$ fragment were labelled and tested as radio immuno conjugates in a comparative study. Animal experiments showed promising results in terms of biodistribution and clearance from the body, especially of the labelled mAb-35 $F(ab')_2$ fragments (Fig. 10). The results with this novel [ReO(bhci–glu)] label clearly indicate its potential for $^{186/188}$Re labelling of antitumour antibodies and for their use in RIT.

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