Selectivity of Asymmetric Macrocyclic Compartmental Lanthanide(III) Complexes towards Alkali and Alkaline-Earth Metal Ions

Alessandro Barge,[a] Mauro Botta,[b] Umberto Casellato,[c] Sergio Tamburini,*[c] and P. Alessandro Vigato[c]

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The asymmetric macrocyclic compartmental ligand H_2L, derived from the [1+1] condensation of 3,3′-(3-oxapentane-1,5-diyldioxy)bis(2-hydroxybenzaldehyde) with 1,5-diamine-3-azamethylpentane, forms the complexes $[LnNa(L)(Cl)_2(CH_3OH)]$ (Ln = La–Nd, Sm–Lu) where the lanthanide(III) ion resides in the N_3O_2 Schiff base coordination site and the sodium ion is located in the O_3O_2 crown-like cavity. The new heterodinuclear complexes $[LnCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl$ (Ln = Tb, Dy, Tm, Yb) were prepared and characterised by single-crystal X-ray diffraction, IR, ^{1}H and ^{13}C NMR spectroscopy and their homogeneity and stoichiometry (Ln:Ca:Cl = 1:1:3 molar ratio) were ascertained by SEM-EDS analysis. The single-crystal X-ray structure of $[YbCa(L)(Cl_2)(EtOH)(H_2O)]\cdot Cl\cdot 2H_2O$ has been determined. The complex is monoclinic, space group $P2_1/c$, with a = 10.033(2), b = 11.702(2), c = 27.796(6) Å and β = 105.51(3)°. The ytterbium ion is seven-coordinate within the N_3O_2 site and is in a pentagonal bipyramidal environment and bonded, in the axial positions, to two chloride ions. The calcium ion is seven-coordinate within the O_3O_2 site and is bonded to the ethyl alcohol oxygen and to one water molecule. The significant contact between the calcium ion and the chloride ions increases the coordination number of the metal ion to eight in a square antiprismatic environment. The selectivity of the etheric site towards alkali and alkaline-earth metal ions has been quantitatively assessed by evaluating, with ^{23}Na NMR spectroscopy, the transmetallation reaction involving the coordinated Na^+ ion in the complexes $[LnNa(L)(Cl)_2 (CH_3OH)]$ (Ln = Tb, Dy, Tm and Yb) and Li^+, K^+ and Ca^{2+}. The affinity constants follow the general order $K_{Ca} >> K_{Li} \geq K_K$. Quantitative kinetic analyses were performed on the complex $[TmNa(L)(Cl)_2(CH_3OH)]$ using variable temperature ^{23}Na NMR spectroscopy in CD_3OD. It was ascertained that the exchange rate Na_{bound}/Na_{free} is independent of the presence of increasing amounts of water in the methanolic solution.

Introduction

In recent years asymmetric compartmental macrocyclic ligands have been designed and extensively studied since they are endowed with two well-defined and different recognition processes at two adjacent sites.[1,2] In these studies, Schiff-base ligands have often been used due to their well known coordinating ability. For the preparation of these systems, appropriate formyl-, keto- or amine-precursors have been condensed under suitable experimental conditions.[3]

Recently we prepared [1+1] cyclic Schiff bases by the condensation of 3,3′-(3-oxapentane-1,5-diyldioxy)bis(2-hydroxybenzaldehyde) or 3,3′-(3,6-dioxaoctane-1,8-diyldioxy)bis(2-hydroxybenzaldehyde) with 1,2-diaminoethane, 1,3-diaminopropane or 1,5-diamine-3-azamethylpentane.[4] These ligands contain one N_2O_2 or N_3O_2 Schiff base site and one O_3O_2 or O_4O_2 crown ether-like site. The N_2O_2 and N_3O_2 sites are particularly suitable for the coordination of transition-metal ions while alkali and alkaline-earth metal ions invariably prefer the O_3O_2 or O_4O_2 sites.[5,6] The 4f-metal(III) ions also prefer the crown ether-like chamber irrespective of the shape and donor atoms of the Schiff base site, as ascertained from X-ray structural determinations.[7,8] However, when this cavity is already filled by an alkali metal ion, the incoming lanthanide(III) ion coordinates to the adjacent chamber if the latter is large enough to accommodate the large 4f-metal ion. This occurs in the N_3O_2 chamber of the above mentioned ligand H_2L, derived from the 1:1 condensation of 3,3′-(3-oxapentane-1,5-diyldioxy)bis(2-hydroxybenzaldehyde) and 1,5-diamine-3-azamethylpentane. Thus, heterodinuclear complexes of the type $[LnNa(L)(Cl)_2(CH_3OH)]$ can be easily prepared.[9] When 1,2-diaminoethane or 1,3-diaminopropane was used, the resultant N_2O_2 site is too small for lanthanide(III) encapsulation although the N_3O_2 group is suitable for such coordination.

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[a] Dipartimento di Chimica I. F. M., Università di Torino,
Via P. Giuria 7, 10125 Torino, Italy
[b] Dipartimento di Scienze dell'Ambiente e della Vita, Università del Piemonte Orientale "Amedeo Avogadro",
Spalto Marengo 33, 15100 Alessandria, Italy
E-mail: mauro.botta@mfn.unipmn.it
[c] Istituto di Chimica Inorganica e delle Superfici-C. N. R.,
Corso Stati Uniti 4, 35127 Padova, Italy
E-mail: sergio.tamburini@icis.cnr.it

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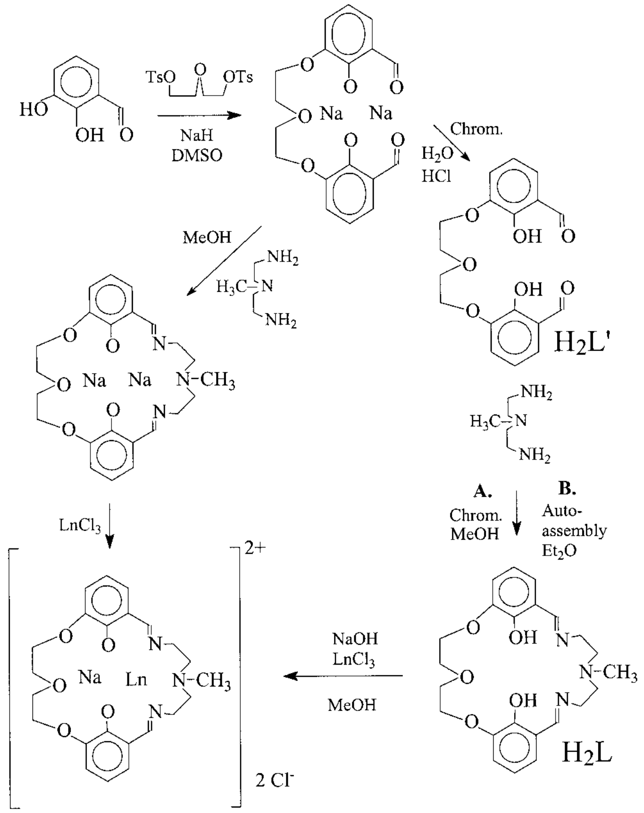
In these complexes, the lanthanide ion coordinated in the N_3O_2 chamber is able to induce a strong paramagnetic shift (LIS) on the Na^+ ion coordinated in the O_3O_2 site. In the case of the Tb, Dy and Tm complexes, the bound shifts are of the order of several hundred ppm (in methanol) which is more than one order of magnitude higher than the values estimated (in water) for the shift reagents currently available.[10–12,15]

These properties make the heterodinuclear Ln-Na complexes very promising candidates for the development of highly effective shift reagents for metal cations of biological interest. The study of the stability of these complexes in solution and the selectivity of the O_2O_3 chamber towards other alkali or alkaline-earth metal ions thus becomes of paramount importance.

In this work, for the complexes $[LnNa(L)(Cl)_2(CH_3OH)]$, we have investigated the rate of exchange between Na_{bound} and Na_{free} (Ln = Tb, Dy, Tm, Yb) and the transmetallation reaction of Na^+ with K^+, Li^+ and Ca^{2+} (Ln = Tm). Furthermore, the heterodinuclear $[LnCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl$ (Ln = Tb, Dy, Tm, Yb) complexes have been prepared and characterised by single-crystal X-ray diffraction, IR, ^1H and ^{13}C NMR spectroscopy and their homogeneity and stoichiometry ascertained by SEM and EDS analyses.



Scheme 1.

Results and Discussion

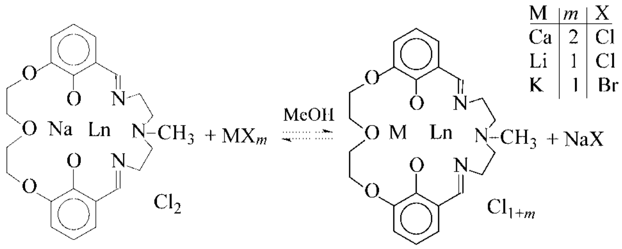
Preparation and Properties of the Macrocycle H_2L and Related Complexes

The H_2L [1+1] macrocyclic ligand and its homo- and heterodinuclear complexes have been prepared according to Scheme 1.

The diformyl precursor 3,3′-(3-oxapentane-1,5-diyldioxy)bis(2-hydroxybenzaldehyde) H_2L' and its related disodium derivative Na_2L' were prepared as pale yellow air-stable and organic solvent soluble solids by the reaction of the appropriate ditosilate with 2,3-dihydroxybenzaldehyde in anhydrous dimethyl sulfoxide in the presence of NaH. Pure H_2L' was obtained by chromatographic workup on silica gel using $CHCl_3$ as the eluent. The IR spectrum of H_2L' shows a strong ν(C=O) absorption at 1659–1646 cm^{-1}. The ^1H NMR ($CDCl_3$) spectrum consists of a singlet at δ = 9.94 ppm due to CH=O protons, a singlet at δ = 10.96 ppm assignable to the phenolic oxygens and multiplets at δ = 7.15, 4.26 and 3.96 ppm associated with the aromatic and the aliphatic protons of the crown ether chain, respectively. The IR and ^1H NMR spectra of Na_2L' are analogous to those of H_2L'.

The [1+1] macrocyclic ligand H_2L was synthesised by self-condensation of H_2L' with 1,5-diamine-3-azamethylpentane (1:1 molar ratio) in methanol. Alternatively, H_2L can be obtained by the same condensation reaction in the presence of $Ba(ClO_4)_2$ as a templating agent. By following this route, the yellow [1+1] macrocyclic complex $[Ba(H_2L)](ClO_4)_2$ can be demetallated by guanidinium sulphate and the resultant macrocycle H_2L extracted from water with $CHCl_3$. Finally, H_2L can be conveniently prepared in high yield by the condensation of H_2L' and 1,5-diamine-3-azamethylpentane in diethyl ether using the high dilution technique. The latter synthetic route was the chosen method since it gives the macrocyclic ligand in high yield without the need for any further purification. H_2L is a yellow solid and its [1+1] cyclic nature was inferred from the presence of the parent peak $[M - H]^+$ at m/z = 428 in the mass spectrum and by the presence, in the IR spectrum, of a strong ν(C=N) band at 1634 cm^{-1}. The bands attributable to ν(C=O) or ν(NH_2) completely disappeared. Moreover the ^1H NMR spectrum in $CDCl_3$ shows a singlet at δ = 8.19 ppm for the iminic protons, multiplets at δ = 6.75 ppm assignable to the aromatic protons and peaks at δ = 4.20 and 3.95 ppm which can be assigned to the methylenic protons of the crown ether chain. Peaks at δ = 3.63 and 2.78 ppm are due to methylenic protons of the iminic chain and a singlet at δ = 2.32 ppm can be assigned to the methyl group. The ^1H NMR spectrum of Na_2L, obtained from the condensation of the acyclic derivative Na_2L' with $H_2N(CH_2)_2N(CH_3)(CH_2)_2NH_2$, is significantly different from that of H_2L owing to the coordination of the Na^+ ions in the N_3O_2 and O_3O_2 coordination chambers.

By treating Na_2L with the appropriate lanthanide(III) trichloride in methanol in a 1:1 molar ratio, the heterodinuclear complexes $[LnNa(L)(Cl)_2(CH_3OH)]$ were obtained. Alternatively, the macrocycle H_2L can be treated with NaOH and the subsequent addition of $LnCl_3$ yields the same heterodinuclear complexes. The complexes are yellow solids which are stable in the solid-state and in solution and yield well formed crystals when recrystallised from alcoholic solutions. The homogeneity of the obtained crystals and the occurrence of the correct Ln/Na/Cl ratio (1:1:2) were checked by electron microscopy and EDS analysis.The IR spectra of $[LnNa(L)(Cl)_2(CH_3OH)]$ show a lower frequency for the ν(C=N) band at 1617–1632 cm^{-1} compared with the free ligand (1634 cm^{-1}). Noticeably, the ν(C=N) resonance lies at 1635–1660 cm^{-1} for the mononuclear complexes $[Ln(H_2L)Cl(H_2O)_4](Cl)_2$ in which the Ln^{3+} ion occupies the O_3O_2 site, with a relevant shift ($\Delta\tilde{\nu}$ = 29–38 cm^{-1}) towards higher wavelengths compared with H_2L. The differences in the C=N stretching frequencies are clearly related to the change in the coordination mode of the lanthanide(III) ion on going from the mononuclear to the heterodinuclear complex.The $[LnCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl$ complexes were prepared by the transmetallation route of $[LnNa(L)(Cl)_2(CH_3OH)]$ with an equimolar quantity of $CaCl_2$ in methanol followed by crystallisation of the resultant powder to eliminate the sodium chloride formed (Scheme 2).



Scheme 2.

The formation of the LnCa(L) complexes was highlighted by elemental analyses as well as IR and NMR spectroscopic measurements and further confirmed by SEM-EDS investigations which indicated the complete disappearance of sodium and the correct Ln:Ca:Cl ratio of 1:1:3. The BSE micrography and the EDX spectra of the complex $[TbCa(L)(Cl)_2(CH_3OH)H_2O]Cl$ are reported in Figure 1.

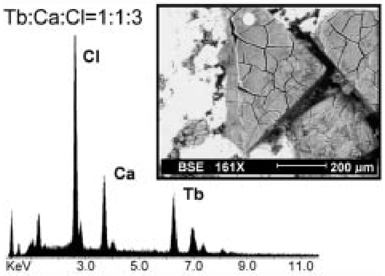


Figure 1. BSE micrography and EDX spectra of the complex $[TbCa(L)(Cl)_2(CH_3OH)H_2O]Cl$.

The ^1H NMR spectra of the paramagnetic calcium complexes closely resemble those of the corresponding sodium complexes. These spectra consist of thirteen resonances spanning a very large chemical shift range. The strict similarity, in terms of chemical shift and bandwidth, between the set of proton resonances for LnCa(L) and LnNa(L) strongly suggests that in both cases the lanthanide ion is coordinated at the N_3O_2 Schiff base site. The IR data also confirm this hypothesis. The ν(C=N) stretching for LnCa(L) is only 2–10 cm^{-1} higher than that of the Ln-Na complex.

Crystal Structure of $[YbCa(L)(Cl)_2(EtOH)(H_2O)]Cl·2H_2O$

Crystals of $[YbCa(L)(Cl)_2(EtOH)(H_2O)]Cl·2H_2O$ were obtained by slow diffusion of Et_2O into an ethanol solution of $[YbCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl·H_2O$. ORTEP representations of the complex and its coordination geometries are shown in Figure 2 (see parts a and b).

The macrocyclic ligand accommodates the ytterbium ion in the O_2N_3 chamber and the calcium ion in the O_2O_3 site. The presence of the calcium ion, as already seen with alkaline ions, forces the coordination of the lanthanide at the iminic site although this is generally unfavourable. The heptacoordination around the lanthanide ion is completed by two chloride ions *trans* to each other and the resultant coordination geometry can be described as pentagonal bipyramidal with the two chlorine atoms [Cl(1) and Cl(2)] in the apical positions. Another chlorine atom and two water molecules are not coordinated and are not reported in the figures. The calcium ion, which is heptacoordinated, is bonded to the two phenolic oxygen atoms which act as a bridge to the ytterbium ion, the three etheric oxygen atoms of the ligand as well as one ethanol and one water molecule. A significant contact is also present between the calcium ion and the chlorine atom Cl(2), [Ca···Cl(2) 3.135(6) Å, the sum of ionic radii being 2.80Å] and this increases the coordination number of the calcium ion to eight. The coordination polyhedron can now be described as a square antiprism.

The Yb–O(phenol) distances are 2.205 Å (mean), the Yb–N(iminic) distances are 2.45 Å (mean) and the Yb–N(2) (aminic) distance is 2.49(1) Å. The difference between the two Yb–Cl distances [2.623(4) Å for Cl(1) and 2.639(4) Å for Cl(2)] is due to the interaction of Cl(2) with the calcium ion. The distance between the two metal ions is 3.565(3) Å. The calcium ion is encapsulated into the O_2O_3 ligand site and the Ca–O(phenol) distances are 2.39(1) Å (mean). The Ca–O(ether) distances are longer and vary between 2.48 and 2.56 Å.

A comparison between this complex [YbCa(L)] and the sodium analogue [YbNa(L)] already published[13] indicates remarkable differences in spite of the very similar ionic radii of the two metal ions (0.97 and 0.99 Å for Na^+ and Ca^{2+}, respectively). Clearly, the charge difference plays an important role. The distances involving the ytterbium ion are comparable in the two complexes as well as the contact distances Yb–Na [3.540(2) Å] and Yb–Ca [3.565(3) Å]. The most important structural difference relates to the coordination geometries of the Na^+ and Ca^{2+} ions. In the former the geometry is pentagonal pyramidal whereas for the latter it is square antiprismatic.

Different spatial arrangements of the ligands are present in the two compounds, although both are in a butterfly-like

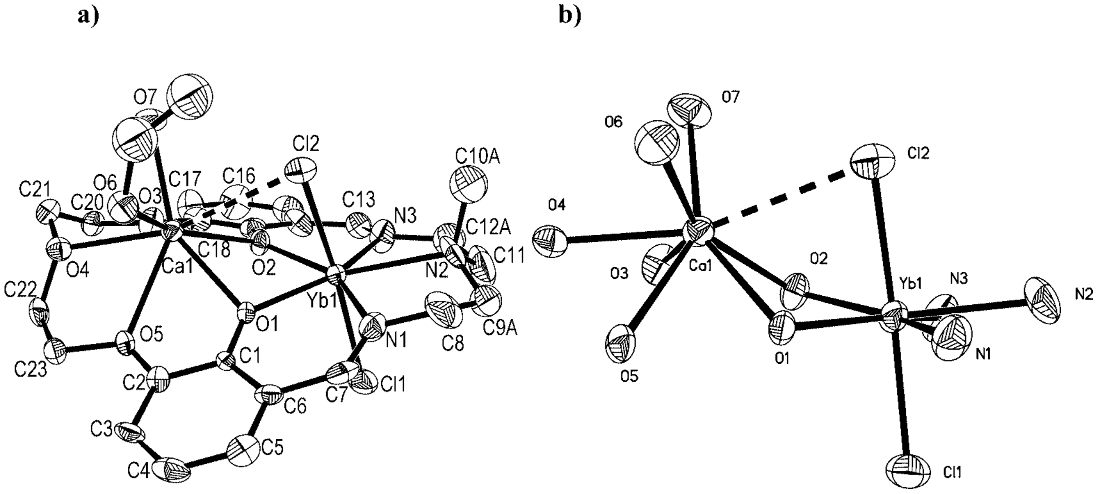


Figure 2. ORTEP representation of (a) the molecular structure of the complex $[YbCa(L)(Cl)_2(EtOH)H_2O]Cl$ and (b) the coordination geometries.

arrangement. The two wings (the two benzene rings) subtend a dihedral angle of 40.7° in the YbNa(L) complex and 32.2° in the YbCa(L) complex. Dissimilar dihedral angles involving the central metals are present and the dihedral angle between Na–O(1)–Yb and Na–O(2)–Yb is 21.1° whereas it increases to 49.3° for the angle between Ca–O(1)–Yb and Ca–O(2)–Yb. A noticeable dissimilarity between the Na–O(etheric) and Ca–O(etheric) bond distances and the torsion angles of the ligand (O–C–C–O and N–C–C–N) is present in the complexes. The conformations of the torsion angles O(3)–C(20)–C(21)–O(4) and O(4)–C(22)–C(23)–O(5) are g^+ and g^- in the Na complex and g^- and g^- in the Ca compound. The conformations of the torsion angles N(1)–C(8)–C(9)–N(2) and N(2)–C(11)–C(12)–N(3) are g^- and g^+ for the Na complex and g^+ and g^- for the Ca complex [because of the presence of disorder, we used the C(9A) and C(12A) atomic positions which show higher population parameters]. The Na–O(etheric) bond distances are 2.38 Å (mean) whereas the corresponding Ca–O(etheric) bond distances are 2.52 Å (mean). The hydrogen bonding networks in the crystal structures of these complexes are remarkable and involve the three chloride anions and all the coordinated and uncoordinated water molecules.

NMR Solution Studies

Selectivity of $[LnNa(L)(Cl)_2(CH_3OH)]$ towards Li^+, K^+ and Ca^{2+} Ions

The LnNa(L) complexes appear to be stereochemically rigid on the NMR timescale and their proton spectra are characterised by sharp and well-separated resonances over a wide interval of temperatures.[9] On the other hand, the ^{23}Na NMR spectra show single resonances assignable to the coordinated sodium cation and markedly shifted from the positions of the free ions. Following addition to the methanolic solution of KBr, LiCl or $CaCl_2$, a transmetallation reaction occurs which can be revealed by the appearance, in the ^{1}H NMR spectra, of a second set of resonances closely corresponding to those of the LnNa(L) complex.[9] Alternatively, the course of the reaction can be followed by monitoring the decrease in the intensity of the ^{23}Na NMR peak of the coordinated sodium cations and the concomitant increase of a new resonance due to the free sodium ions (Figure 3). Thus, the replacement of Na^+ by alkali and alkaline-earth metal ions does not modify the structure or the stereochemical rigidity of the complex.

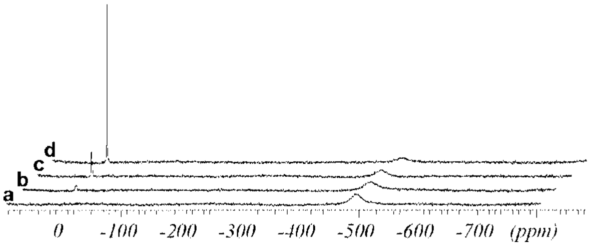


Figure 3. ^{23}Na NMR spectra of $[TbNa(L)(Cl)_2(MeOH)]$ in CD_3OD at 9.4 T and 273 K before (a) and after the addition of equimolar amounts of KBr (b), LiCl (c) and $CaCl_2$ (d).

We have recorded the ^{23}Na NMR spectra of the LnNa(L) complexes (Ln = Tb, Dy, Tm and Yb) in the presence of equimolar amounts of LiCl, KBr and $CaCl_2$ at different temperatures. When LnNa(L) and the lithium, potassium or calcium salts are added together in equimolar amounts, the transmetallation reaction described in Equation (1) assumes a simplified form [Equation (2)] particularly suitable for an NMR study.

$$LnNa(L) + M \leftrightarrow LnM(L) + Na \quad (1)$$

$$K = \frac{[LnM(L)][Na]}{[LnNa(L)][M]} \Rightarrow K = \frac{[Na]^2}{[LnNa(L)]^2} \quad (2)$$

In fact, the equilibrium constant K can be directly assessed by measuring the areas of the ^{23}Na NMR signals corresponding to the free and bound sodium cations. For the different lanthanides investigated, we observed different affinities for the complexes towards alkali and alkaline-earth metal ions. Table 1 reports the K values for the transmetallation reactions of involving the LnNa(L) complexes (Ln = Tb, Dy, Tm, Yb) with Li^+, K^+ and Ca^{2+}.

Table 1. Equilibrium constants for reaction (1) obtained from ^{23}Na NMR spectroscopic data at 9.4 T and 293 K.

Ln	K_{Li}	K_K	K_{Ca}
Tb	4.3×10^{-2}	1.1×10^{-2} [a]	2.4
Dy	2.7×10^{-2}	3.8×10^{-2} [a]	2.7
Tm	3.2×10^{-1}	7.3×10^{-2}	1.2
Yb	6.4×10^{-2}	1.9×10^{-3}	7.6

[a] Measured at 273 K.

The values of the equilibrium constants follow the general order $K_{Ca} >> K_{Li} \geq K_K$. This behaviour is likely to be related to the ionic radii of the metal ions and the dimension of the O_2O_3 coordination site. Both Na^+ (97 pm) and Ca^{2+} (99 pm) fit rather well into the crown-ether cavity whereas Li^+ (76 pm) and K^+ (138 pm) are either too small or too large. On the other hand, a well defined trend as a function of the ionic radius of the lanthanide ion was not observed. The equilibrium constants for the transmetallation reactions with Li^+ and K^+ are higher for Tm than for the other lanthanide cations, whereas the highest affinity for Ca^{2+} is shown by the Yb complex. Clearly, the affinity of the different Ln^{III} cations towards a given alkali or alkaline-earth metal ion is not simply dictated by the variation of the charge density across the lanthanide series. Although this behaviour cannot easily be rationalised in terms of the available data, it could arise from small structural variations of the complexes which occur on passing from the Tb to the Yb complexes involving primarily the crown-ether site. A powder X-ray diffraction analysis on the Dy complex, obtained from a different solvent, was carried out using a Philips X'Pert system in the range 4–90° (2θ). The resultant diffraction pattern is not analogous with that of the Yb analogue and this is consistent with the differences in the structural details.

The selectivity of the complexes to sodium appears greater than that observed for TmDOTP^{5-} [DOTP^{8-} = tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetrakis(methylphosphonate)], the most effective shift reagent currently available.[14] This latter complex forms very stable 1:1 adducts with Ca^{2+} (and Mg^{2+}) and the ^{23}Na shift is significantly reversed for a Ca^{2+}/TmDOTP^{5-} ratio close to 1. Under similar experimental conditions 48% of the sodium remains bound to the Tm complex in our case (20 °C). On the other hand, the Dy complex with a polyoxa tetraaza macrocyclic tetraacetate ligand shows a higher selectivity for Na^+ than for Ca^{2+} although the paramagnetic shift is much smaller.[15]

Determination of the Na^+ Exchange Rate

The rate of exchange of the Na^+ ion between the coordination site of the complex and the solution is of primary importance for the development of efficient shift reagents for biomedical applications. The exchange rate needs to be sufficiently rapid so as to give rise to an exchange-averaged ^{23}Na NMR signal well shifted from the diamagnetic position and to allow a clear discrimination of the peaks of the Na^+ ions present in two different compartments. The ^{23}Na NMR spectra of the LnNa(L) complexes in methanol can be characterised, at low temperature, by the presence of a broad, highly shifted resonance (–614, –157, +340 and –40 ppm for Tb, Dy, Tm and Yb, respectively, at 253 K and 9.4 Tesla) corresponding to the coordinated Na^+ ion and another narrow peak at 0 ppm corresponding to the free ion.[9,13] The magnitudes of the shifts are very large when compared with common lanthanide-based shift reagents. One possible reason is the presence of a very short Ln–Na distance (ca. 3.5–3.6 Å) which is in contrast to the case of the polyaminocarboxylic complexes in which the ion-paired adducts are characterised by Ln–Na distances of about 4.0 Å and the LnDOTA chelate bearing a crown-ether moiety able to bind sodium where the distance is 5.3 Å.[15] In the complexes discussed here, however, the presence of a contact (through bond) contribution to the shift through the bridging phenolic oxygen atoms cannot be excluded. On the other hand, an accurate evaluation of this contribution is not possible because of the lack of an isostructural trend along the lanthanide series.[12]

The narrow resonance arises from the presence of NaCl which cocrystallises during the recrystallisation of the complexes. By increasing the temperature, the paramagnetically shifted resonance begins to sharpen and shift towards the peak corresponding to the free sodium ions. Exchange-averaged signals can be observed at about 320 K (at ca. +80 and –15 ppm for the Tm and Yb complexes, respectively) which sharpen further upon a further increase in temperature. The lanthanide-based shift reagents currently available produce a shift in the ^{23}Na NMR signal which does not exceed 10 ppm in the compartment in which they distribute.[10–12] These heterodinuclear LnNa(L) complexes are much more effective since they show chemical shifts of hundreds of ppm for the "bound" sodium cation. However, their solubility in water is very poor and, at present, this limits their use for biomedical studies. Clearly, a modification of the ligand is necessary in order to improve the solubility in aqueous media. In this work we have recorded a series of ^{23}Na NMR spectra for the TmNa(L) complex, in the presence of an equimolar amount of NaCl, as a function of temperature and increasing amounts of water. We then calculated the rate of sodium exchange. The complex:NaCl:D_2O molar ratios used were as follows: 1:1:0, 1:1:0.2, 1:1:0.4, 1:1:0.7, 1:1:1.4 and 1:1:2.9. Over a wide range of temperatures, from 263 to 315 K, the resonances due to the coordinated (B) and free (F) Na^+ ions are well separated (large $\Delta\nu_{BF}$) and the system is in the slow exchange regime. These two conditions allows us to assume the validity of the following expression: $1/\tau_B \leq \Delta\nu_{BF}/5$, where $1/\tau_B = k_{ex}$.[16] In this case, the transverse relaxation rate of the resonance of Na_F, calculated from the bandwidth at half-height, $\Delta\nu_F$, can be expressed in terms of Equation (3).[16]

$$1/T_{2F} = 1/T_{2F}^{ref} + P_B \times k_{ex} \quad (3)$$

where $1/T_{2F}$ and $1/T_{2F}^{ref}$ (given by: $\Delta\nu_F \times \pi$) are the transverse relaxation rates of the free Na^+ ions in the presence and in the absence of chemical exchange, respectively, P_B is the molar fraction of the coordinated sodium ion $[P_B = [B]/([B]+[F])]$ and k_{ex} is the rate constant of the exchange process. A similar expression holds for the transverse relaxation rate of the resonance of Na_B, see Equation (4).

$$1/T_{2B} = 1/T_{2B}^{ref} + P_F \times k_{ex} \quad (4)$$

The temperature dependence of k_{ex} is given by the Arrhenius equation, see Equation (5).

$$k_{ex}^{T} = k_{ex}^{298} \times T/298.15 \times \exp[\Delta H^{\#}/R \times (1000/298.15 - 1000/T)] \quad (5)$$

where T is the temperature, k_{ex}^{T} is the exchange rate constant at the temperature T, $\Delta H^{\#}$ (kJ mol^{-1}) is the enthalpy of activation of the exchange process and R is the gas constant. Finally, the temperature dependence of the transverse relaxation rate of the NMR signal in the absence of exchange is given by Equation (6).

$$1/T_2^{ref} = (1/T_2^{ref})^{298} \times \exp[E_a/R \times (1000/T - 1000/298.15)] \quad (6)$$

where E_a represents the activation energy of the process.

With the use of Equations 3–6, we have analysed the temperature dependence of the bandwidth of the ^{23}Na peak of the bound sodium ion for the six different solutions and calculated the rate of chemical exchange. The value of k_{ex} was found to be 600 s^{-1} (at 298 K) for all the solutions investigated and is thus independent of the molar fraction of added water. Thus, the derivatisation of the ligand aimed at increasing the solubility of the complexes in water should not compromise their promising properties as ^{23}Na NMR shift reagents, provided that the chemical modification does not affect the structure and rigidity of the coordination cage.

Conclusions

The transmetallation reactions of the complexes $[LnNa(L)(Cl)_2(CH_3OH)]$ (Ln = Tb, Dy, Tm and Yb) by Li^+, K^+ and Ca^{2+} ions have been investigated by ^{23}Na NMR spectroscopy in methanolic solutions. The affinities of the macrocyclic complexes towards the alkali and alkaline-earth metal ions are primarily dictated by the match of the ionic radii with the size of the crown-like cavity of the ligand. Interaction of the cation in the O_2O_3 site with the anions may also contribute to the stabilities of the complexes. Large variations were observed in the affinity of a given metal ion for different lanthanide complexes. Small structural changes which may occurs across the lanthanide series seem to have a strong influence on the stabilities of the heterodinuclear complexes. Clearly, further investigations involving a systematic variation of the crown ether cavity are necessary in order to understand the relationship between the selectivity and the structural details of the complexes. The exchange of sodium between the coordination site and the solution is fast enough at physiological temperatures to cause an exchange averaged NMR signal strongly shifted from the diamagnetic position. The rate of exchange is not influenced by the addition of variable amounts of water to the methanolic solution. This property is promising for the development of water soluble derivatives as highly effective shift reagents for cations of biological relevance for diagnostic applications.[11]

Experimental Section

Materials: All solvents, reagents and the lanthanide chlorides, $LnCl_3 \cdot 6H_2O$, were purchased from Aldrich and Fluka and used without further purification.

Physico-Chemical Measurements: Elemental analyses were carried out by using a Fison 1108 analyser. IR spectra were recorded as KBr pellets on a Mattson FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra for the diamagnetic complexes were recorded on a Bruker AMX300 spectrometer equipped with a broadband multinuclear probe and a variable temperature unit. ^{23}Na spectra were recorded on the same spectrometer on 15–25 mM solutions of the Ln^{III} complexes (Ln = Tb, Dy, Tm, Yb) in CD_3OD. Typically, 2000 transients were necessary to obtain a satisfactory signal to noise ratio. The data were processed using a line broadening of 20 Hz and a baseline correction. ^{23}Na chemical shifts were measured in relation to the ^{23}Na signal of a 5 M solution of NaCl in CD_3OD. Downfield induced shifts are denoted as positive. The chemical shifts (^{23}Na) and the peak widths were determined by fitting the signals to a Lorenzian line function. All the samples examined were dissolved in deuterated methanol which was also used as an internal reference.

XRD investigations were performed on a Philips X'Pert PW3710 diffractometer using Cu-K_α radiation (40 kV, 30 mA), a high-resolution graphite monochromator, rotating sample holder and a proportional detector. Measurements were carried out in the range $4° < 2\theta < 90°$ with a step of 0.02°. The morphology, homogeneity and the lanthanide/alkali or alkaline-earth/chlorine ratios of the complexes were investigated using a Philips XL40 model scanning electron microscope equipped with an EDAX DX PRIME X-ray energy dispersive spectrometer.[17] The solvent contents (H_2O or MeOH) were evaluated from thermal analysis curves recorded using Netzsch STA 429 thermoanalytical equipment. The tests were performed under nitrogen (flux rate 250 mL min^{-1}, heating rate 5 °C min^{-1}) and in air under the same conditions. Neutral alumina (Carlo–Erba, Milano, Italy) was used as reference material. All mass spectrometric measurements were performed on a VG ZAB 2F instrument (VG Analytical Ltd.) operating under fast atom bombardment (FAB) conditions (8 keV Xe atoms bombarding a nitrobenzyl alcohol solution of the sample). Also, ESI-MS spectra were recorded using an LQC mass spectrometer (Finnigan) and methanolic solutions of the samples (10^{-5} M).[18]

Preparation of H_2L' and Na_2L': The diformyl precursor 3,3′-(3-oxapentane-1,5-diyldioxy)bis(2-hydroxybenzaldehyde) (H_2L') and the disodium derivative (Na_2L') were prepared by a modification of the literature procedure.[6,7,19–21]

Preparation of H_2L and $[LnNa(L)(Cl)_2(CH_3OH)]$ (Ln = Y, La, Ce, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu): The asymmetric [1+1] macrocycle 18-methyl-3,5,8-trioxa-15,18,21-triazacyclo-[21.3.1.1[9,13]]octacosa-1(27),9(28),10,12,14,21,23,25-octaene-27,28-diol (H_2L) and its heterodinuclear complexes $[LnNa(L)(Cl)_2(CH_3OH)]$ were prepared according to a literature procedure.[9]

Preparation of $[LnCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl$ (Ln = Tb, Dy, Yb): $[LnNa(L)(Cl)_2(CH_3OH)]$ (Ln = Tb, Dy, Yb) (1 mmol) in methanol (50 mL) was added to an equimolar methanolic solution (50 mL) of $CaCl_2$. The pale brown solution was stirred for 24 h at room temperature. The mixture was then cleared by filtration and the solvent was evaporated to dryness under reduced pressure. The pale yellow residue was treated with *n*-propanol (30 mL), filtered, dried in vacuo and recrystallised by slow diffusion of diethyl ether into a methanol solution which yielded well-formed yellow crystals suitable for X-ray analysis.

$[TbCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl\cdot H_2O$: IR (KBr): $\tilde{\nu}$ = 1631 cm^{-1} (C=N). $C_{24}H_{35}CaCl_3N_3O_8Tb$: calcd. C 36.08, H 4.42, N 5.26; found C 35.82, H 4.71, N 5.02.

$[TmCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl\cdot H_2O$: IR (KBr): $\tilde{\nu}$ = 1630 cm^{-1} (C=N). $C_{24}H_{35}CaCl_3N_3O_8Tm$: calcd. C 35.64, H 4.36, N 5.19; found C 35.43, H 4.97, N 4.89.

$[DyCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl\ H_2O$: IR (KBr): $\tilde{\nu}$ = 1630 cm^{-1} (C=N). $C_{24}H_{35}CaCl_3DyN_3O_8$: calcd. C 35.92, H 4.40, N 5.24; found C 35.51, H 4.62, N 4.98.

$[YbCa(L)(Cl)_2(CH_3OH)(H_2O)]Cl\cdot H_2O\cdot 0.5NaCl$: IR (KBr): $\tilde{\nu}$ = 1627 cm^{-1} (C=N). $C_{24}H_{35}CaCl_{3.5}N_3Na_{0.5}O_8Yb$: calcd. C 34.23, H 4.19, N 4.99; found C 34.98, H 4.22, N 4.64.

X-ray: Diffraction data were collected at room temperature on a Philips PW1100 automatic four-circle diffractometer (FEBO System) using graphite monochromated Mo-K_α radiation and the ω-2θ scan method. Lattice parameters were obtained from least-squares refinements of the setting angles of 30 reflections with $9° \leq 2\theta \leq 23°$. No sign of crystal deterioration was revealed by monitoring three standard reflections after every 200 measurements. The structure was solved by standard Patterson methods and subsequently completed by a combination of least-squares techniques and Fourier syntheses with the SHELX program.[22,23] All benzene rings were refined as rigid bodies, the hydrogen atoms were included in idealised positions with fixed C–H distances (C–H = 0.93Å) and isotropic temperature factors fixed to 1.2 times *U*(eq) of the corresponding carbon atom. Table 2 shows a summary of the crystallographic data and structure refinement. The poor quality of the crystals did not give very good data but the data were, however, very useful in understanding the structure and the connectivity of this complex. In particular, serious disorder was found around N2 and for the coordinated ethanol molecule. Two possible positions for C9, C10, C12 and C25 were refined together with the corresponding population parameters. Additional crystallographic data, atomic coordinates, anisotropic thermal parameters and full listings of bond lengths and angles are available as supplementary material from the CCDC. Final geometrical calculations and drawings were carried out with the PARST program[24] and the XP utility of the Siemens package,[25] respectively, running on a DIGITAL ALPHA-AXP 300 computer.

Table 2. Crystal data for $[YbCa(L)(Cl)_2(EtOH)(H_2O)]Cl\cdot 2H_2O$.

Formula	$C_{25}H_{38}N_3O_9Cl_3CaYb$
F_w	844.0
Crystal system	monoclinic
Space group	$P2_1/c$
a [Å]	10.033(2)
b [Å]	11.702(2)
c [Å]	27.796(6)
β [°]	105.51(3)
Cell volume [$Å^3$]	3145(1)
Z	4
Calcd. density [$g\,cm^{-3}$]	1.783
Absorption μ (mm^{-1}) [Mo-K_α]	3.445
Range of rel. transm. factors[a] [%]	89–100
θ limits [°]	6.9–56
Data collected/unique	4876/4772
Data observed	4521 [$F \geq 3.6\sigma(F)$]
Nr. of param. (observ.per param.)	349/13
R ($\Sigma(\lvert F_o\rvert - \lvert F_c\rvert) / \Sigma\lvert F_o\rvert$)	0.080
R_w [$\Sigma w(\lVert F_o\rvert - \lvert F_c\rVert)^2 / \Sigma w(F_o)^2]^{1/2}$	0.18
Highest map residual ($e\,Å^{-3}$)	1.33

[a] Corrections: Lorentz-polarisation and absorption (empirical, ψ scan).

CCDC-249846 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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