Discrimination between magnesium(II) and calcium(II) by 1,4,7-tris(2-hydroxyalkyl)-1,4,7-triazacyclononane ligands

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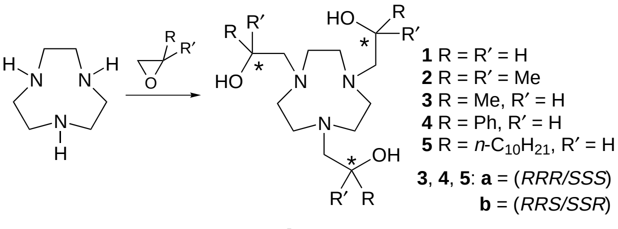
The title ligands and their possible diastereomeric forms show large selectivity differences for complexation of Mg^{II} and Ca^{II} which are related to the twist angle of the plane of coordinating hydroxy groups relative to the plane of macrocyclic ring nitrogens.

Although calcium(II) and magnesium(II) both play vital roles in many biological processes, it is quite problematic to differentiate ‘ionic’ or weakly bound *vs.* tightly bound Mg^{II} in a biological sample due to interference from ubiquitous Ca^{II}. Very few ligands have been reported that show a high enough selectivity for Mg^{II} over Ca^{II} to overcome this problem. This is especially evident in the development of ion-specific electrode methods for Mg^{II} where the current technology requires a substantial correction for both Ca^{II} and pH.[1] We recently described several 1,4,7-triazacyclononane derivatives containing methylene phosphinate ester, methylene phosphinate, or mixed acetate side-arms that showed a selectivity for Mg^{II} over Ca^{II} of, in some cases, more than two orders of magnitude.[2,3] Although the small cyclononane ring usually guarantees a higher Mg/Ca selectivity ($K_{sel} = K_{MgL}/K_{CaL}$) over most other ligand systems,[4] there are significant selectivity differences between known 1,4,7-triazacyclononane derivatives with different side-arm coordinating groups. For example, nota [1,4,7-triazacyclononane-1,4,7-tris(acetic acid)] has a K_{sel} of 5.9[5] while notmp [1,4,7-triazacyclononane-1,4,7-tris(methylene methylphosphinate)] has a K_{sel} of 170.[3] While investigating these selectivity differences in more detail, we discovered that the Mg/Ca binding selectivity of several trisubstituted 2-hydroxyalkyl derivatives of 1,4,7-triazacyclononane varied by three orders of magnitude and learned that stereochemistry of neighbouring side-chain groups defined the metal-ion selectivity. Although the ligands reported here did not bind significant amounts of Mg^{II} or Ca^{II} in aqueous solution, the dramatic selectivity of these systems for binding of Mg^{II} in acetonitrile may serve as guide to developing better ion-specific membrane electrode systems.

All ligands were prepared by the reaction of 1,4,7-triazacyclononane with an excess of the corresponding epoxide (Scheme 1), as described before for **1**.[6] If R ≠ R′, two diastereomers of each derivative were formed when racemic epoxide was used. The ratio between the (*RRR*/*SSS*) (**a**) and the (*RRS*/*SSR*) (**b**) forms of **3**, **4** and **5** was in all cases 1 : 3, as statistically expected. Optically pure **3a** and **4a** were prepared from the corresponding chiral (*S*)-epoxides.



Scheme 1

The magnesium(II) and calcium(II) complexes of these ligands were studied by ^{13}C NMR spectroscopy (125 MHz) at room temp. using CD_3CN as the solvent. The metal-to-ligand ratios were varied from 0–1.5 by the addition of magnesium(II) or calcium(II) perchlorate. In all cases, a 1 : 1 complex, in slow exchange with the free ligand, was formed completely upon addition of a stoichiometric amount of metal perchlorate. For **1** and **2**, single resonances were observed for all ring carbons and for all equivalent nuclei from the side-chains, while for **3a** and **4a** the ring carbons showed two resonances upon metal complexation. In the diastereomeric mixtures of **3**, **4** and **5**, eight equally intense ring carbon resonances could be detected for both MgL and CaL: two arise from the symmetrical (*RRR*/*SSS*)-isomer, while six belong to the unsymmetrical (*RRS*/*SSR*)-isomer. Analogously, the resonances of the side-chain nuclei appear as four equally intense lines.† Identification of the diastereomers of **3** and **4** was accomplished by comparison with the spectra of optically pure **3a** and **4a**, while for **5** the spectra were compared to the data obtained for **3**.

The Mg/Ca selectivities of the ligands were determined by ^{13}C NMR on samples with both Mg^{II} and Ca^{II} in excess. For a sample containing **3a** : **3b** : Mg : Ca = 1 : 3 : 6 : 6, the ^{13}C NMR spectrum (Fig. 1) showed that both Mg^{II} and Ca^{II} formed complexes with **3b** (K_{sel} = 0.25), while **3a** only bound Mg^{II}. Selectivity experiments with pure **3a** indicated that K_{sel} = 590 for this ligand. This led to the conclusion that the orientation of a single methyl group in these ligands results in a Mg/Ca selectivity difference of more than three orders of magnitude. Only **3a**, **4a** and **5a** exhibit good to excellent Mg/Ca selectivities (Table 1), while **1**, **2**, **3b**, **4b** and **5b** barely discriminate between Mg^{II} and Ca^{II}.

To further investigate these large selectivity differences, we used molecular-mechanics calculations‡ to find the optimal

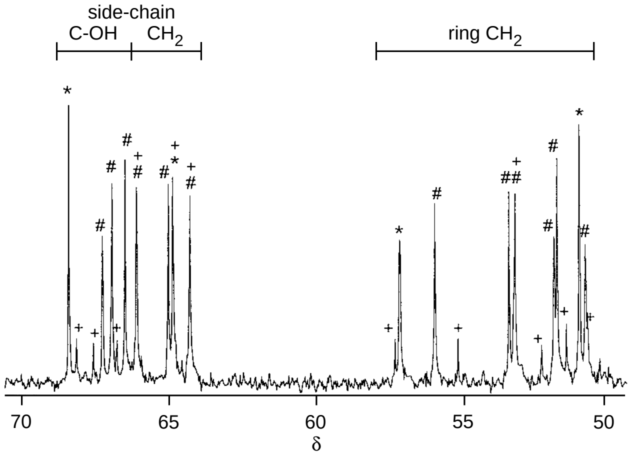


Fig. 1 ^{13}C NMR spectrum of a sample with **3a** : **3b** : Mg : Ca = 1 : 3 : 6 : 6; * Mg(**3a**); + Mg(**3b**); # Ca(**3b**) (methyl resonances not shown)

structures of the magnesium(ii) and calcium(ii) complexes of **1**, **2**, **3a** and **3b**. Local energy minima were observed for structures in which the side-chains adopted one of three possible coordination modes (Fig. 2). The methyl groups in all optimized structures of **3a** and **3b** were pointing out from the centre, causing all side-chains to be in the same orientation for **3a**, while for **3b** two different side-chain orientations were present in each optimized structure. Table 1 shows the coordination mode of the lowest energy state of all magnesium(ii) and calcium(ii) complexes of **1**, **2** and **3**. Only for **3a**, the magnesium(ii) complex had a different structure (AAA) than the calcium(ii) complex (BBB).

The coordination modes AAA, BBB and CCC give rise to different 'twist angles', α, *i.e.* the rotation of the plane of coordinating oxygen atoms compared to the plane of ring nitrogens (Fig. 2). Since the carbon atoms of the macrocyclic ring are positioned alternately above and below the plane of ring nitrogens, these compounds contain an inherent twist of the plane of the side-chain carbon atoms directly connected to the ring nitrogens. Here, we define a positive α as a twist of the plane of coordinating oxygens in the same direction as the plane of side-chain carbons relative to the ring nitrogens. The twist α was large and positive for the AAA configuration, smaller (but positive) for BBB, and negative for CCC.§ Molecular mechanics showed that, for the magnesium(ii) complexes, the large α (AAA) is only favoured when there is a driving force on the side-chains to put a residual R-group away from the centre and if any resulting steric hindrance between two side-chains is absent. As a result, Mg(**1**) adopted the BBB conformation because there is no driving force, while Mg(**2**) and Mg(**3b**) did not adopt AAA or AAB due to resulting steric hindrance between methyl groups of neighbouring side-chains. Only for Mg(**3a**) [and for Mg(**4a**) and Mg(**5a**)] were all factors optimal for adopting the AAA conformation. The large twist (AAA) makes the cavity for the metal ion quite small, so that this conformation is not optimal for the larger Ca^{II} ion, which always preferred the BBB (or ABB) structure.

Table 1 Selectivities, K_{sel} (= K_{MgL}/K_{CaL}),[a] of the macrocyclic ligands (Scheme 1) as obtained from ^{13}C NMR competition experiments, and the preferred side-chain coordination modes (Fig. 2) as obtained from MMX calculations

		Mode	
Ligand L	K_{sel}	MgL	CaL
1	0.18	BBB	BBB
2	3.0	BBB[b]	BBB
3a	590	AAA	BBB
3b	0.25	ABB	ABB
4a	16		
4b	0.06		
5a	60[c]		
5b	0.28		

[a] ±5%. [b] CCC has only slightly higher energy. [c] Lower limit; observed only for a mixture of **5a** and **b**.

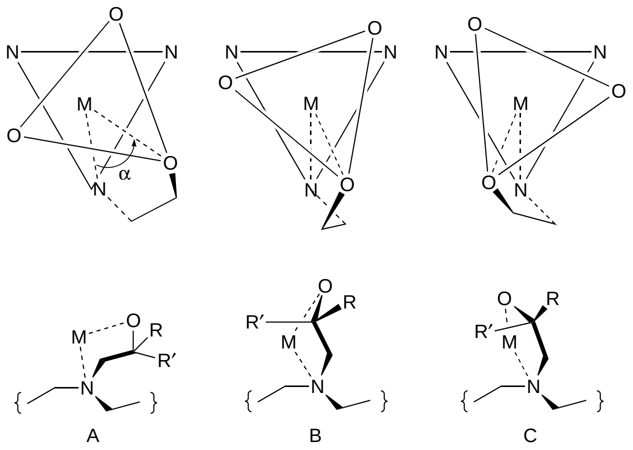


Fig. 2 Schematic front and top views of the possible coordination modes of the side-chains of the metal complexes of **1**, **2** and **3** for which energy minima were observed by molecular-mechanics calculations, and the resulting twist angles, α, of the plane of coordinating oxygens relative to the plane of macrocyclic ring nitrogens

In conclusion, we have found that triazacyclononane derivatives that are able to accommodate Mg^{II} in a small, tight cavity (large α) form complexes with structures (AAA), different from those of Ca^{II} (BBB). This appears to be the origin of the large Mg/Ca selectivity seen for these ligands. Similar conformational changes that depend on the size of the metal ion have been observed in crystal structures of a few transition-metal complexes, *e.g.* the zinc(ii) complex of **3a** adopted the BBB conformation,[7] while the smaller cations Co^{III} and Cr^{III} preferred the AAA structure.[8] For nota, the nickel(ii) and nickel(iii) and chromium(iii) complexes adopted the BBB conformation, while the larger Cu^{II} and Fe^{III} preferred CCC.[9] The present study is the first, however, to relate this phenomenon to a (large) difference in metal ion selectivity. A more elaborate study involving acetate, phosphonate ester, and phosphinate side-chains will be published elsewhere.

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Footnotes

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† In **5**, only the first two carbon nuclei of R (= n-$C_{10}H_{21}$) were thus resolved.

‡ The geometries of the magnesium(ii) and calcium(ii) complexes of **1**, **2** and **3** were optimized using the built-in MMX forcefield of Hyperchem 4.5 on a 486DX, 66 MHz PC. Side-chains were positioned roughly into modes A, B or C (Fig. 2) before optimization, and the position of the OH protons in **1**, **2** and **3**, and of the methyl groups in **3** was varied systematically for observation of the local minima.

§ Trigonal prism: $\alpha = 0$; octahedron: $\alpha = 60°$. Twist angles observed for the magnesium(ii) complexes were approximately +40, +10 and −30° for AAA, BBB, and CCC, respectively, while for the calcium(ii) complexes these were +25, +5 and −20°.

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