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# Molecular Design of Hard-Soft Ditopic Metal-Binding Sites on a Calix[4]arene Platform

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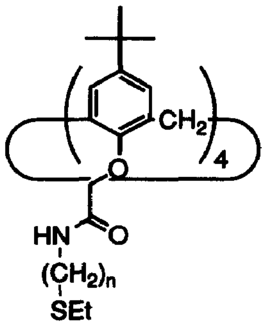
***Abstract***: Ditopic "hard"-"soft" metal binding-sites composed of four $EtS(CH_2)_nNHCOCH_2O$- groups were designed for the first time on a calix[4]arene platform. N = 2 is too short to form a bimetallic complex whereas n = 6 is long enough to accept two metal ions. $^1H$ NMR spectral studies established that although $Cd^{2+}$ bound to the "soft" binding-site excludes $Na^+$ out of the "hard" binding-site, $Ag^+$ can be co-existent with $Na^+$ in the ionophoric cavity.

Molecular design of hard-soft ditopic metal binding-sites has been of much concern as an attractive catalytic site in both enzymatic and artificial systems: a hard metal ion can interact with anionic guests through electrostatic interactions or polarize Lewis-basic functional groups whereas a soft metal ion can mediate electron-transfers or bond-rearrangements which lead to net catalytic reactions.[1-4] We have been interested in designing various recognition sites using calix[n]arenes as a platform. We noticed that calix[4]arenes would be useful as a potential platform for the design of hard-soft ditopic metal binding-sites because the lower rim of calix[4]arenes can be modified into the first binding-site for hard metal ions by introduction of $CH_2C(=O)OR$ or $CH_2CONR_2$ groups[5] and the second binding-site for soft metal ions can be constructed next to the first binding-site by modification of the R groups.[6] Furthermore, it is known that the first binding-site features a unique metal-induced conformational change: that is, in the absence of metal ion four carbonyl groups are turned outward to reduce their electrostatic repulsion whereas in the presence of metal ion ($Na^+$ is particularly effective) they are turned inward to interact with the metal ion (Fig. 1).[7,8] This conformational change induces translocation of the second-binding-site-composing ligand groups (L in Fig. 1): that is, the L----L distance is more separated in the presence of $Na^+$ than in the absence of $Na^+$. One can expect, therefore, that if the spacer groups ($(CH_2)_n$ in Fig. 1) are long enough, they can form hard($Na^+$)-soft ditopic metal complexes whereas if the spacer groups are relatively short, the soft metal complex is destabilized not only by electrostatic repulsion between two metal ions but also by the $Na^+$-induced conformational change. This kind of mutual communication between two metal-binding sites reminds us of allosteric effects frequently seen in enzymatic systems. With these objects in mind we synthesized **1**$_2$ and **1**$_6$ (both immobilized in a cone conformation). Examination of CPK molecular models allows us to predict that in **1**$_2$ the $Na^+$-binding inevitably decomposes the soft metal complex whereas in **1**$_6$ the formation of a hard-soft ditopic complex is possible even though the $Na^+$-induced rotation of the carbonyl groups takes place. Here, we chose $Cd^{2+}$ and $Ag^+$ as soft metal ions.



**1**$_n$

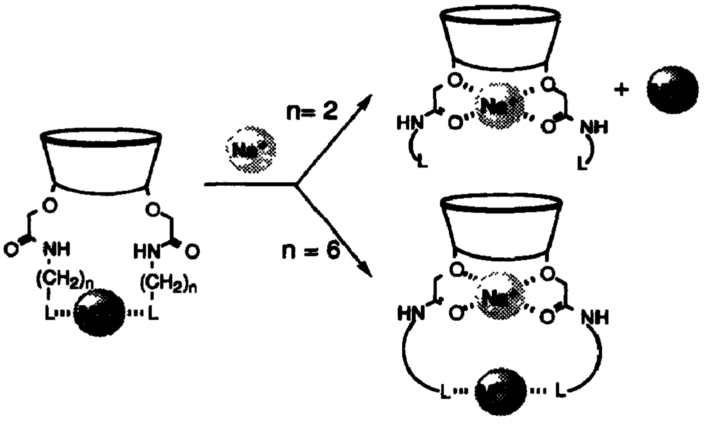


Fig. 1. Na$^+$-Induced conformational change. Two of the four ester groups are omitted for clarity.

Compounds **1**$_2$ (mp 215 °C) and **1**$_6$ (mp 186 °C) were synthesized from 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene (**2**) and $H_2N(CH_2)_nSEt$. Compound **2** was treated with oxalyl chloride in $CCl_4$ and then allowed to react with $H_2N(CH_2)_nSEt$ in THF in the presence of triethylamine. The products were identified by IR, $^1H$ NMR spectral evidence and elemental analyses.[9]

First, we estimated the affinity of alkali metal cations (added as $MClO_4$) for **1**$_2$ by $^1H$ NMR spectroscopy (400 MHz, $CDCl_3$:$CD_3CN$ = 10:1 v/v, 30 °C). Since the signals for the **1**$_2$ •M$^+$ complex appeared separately, the association constants ($K$) could be readily determined from the ratio of each integral intensity. As shown in Fig. 2, Na$^+$ showed the highest affinity with **1**$_2$. Thus, we hereafter employed Na$^+$ as a hard metal ion.

As recorded in Table 1, not only the **1**$_n$•Na$^+$ complexes but also **1**$_n$•Cd$^{2+}$ complexes (added as $Cd(ClO_4)_2$) gave the $^1H$ NMR signals independent of those of free **1**$_n$, indicating that their exchange rates are slower than the NMR time-scale. The $K$ values for Cd$^{2+}$ were estimated to be log $K$ = 4.03 for **1**$_2$ and 3.37 for **1**$_6$. When Cd$^{2+}$ was added to the solution containing **1**$_n$•Na$^+$ ([Na$^+$] / [ **1**$_n$] = 100 where **1**$_n$ wholly exist as the Na$^+$ comp-

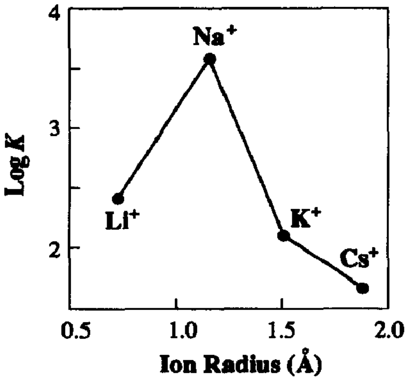


Fig. 2. Association constants of **1**$_2$ for alkali metal cations (added as $MClO_4$: $CDCl_3$: $CD_3CN$ = 10:1 v/v, 30 °C).

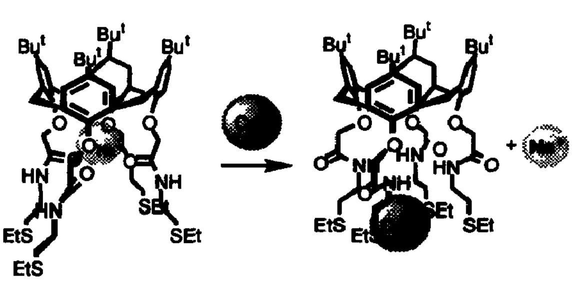


Fig. 3. Template effect of Na$^+$ on the formation of an intramolecualr **1**$_n$•Cd$^{2+}$ complex.

Table 1. Chemical shift changes induced by metal cations ($CDCl_3$:$CD_3CN$ = 1:1 v/v, 30 °C, [$\mathbf{1_n}$]=2.9mM)[a]

| | Δδ / ppm | | | | | | |
|---|---|---|---|---|---|---|---|
| | NH | ArH | $ArCH_2Ar$(endo) | $OCH_2$ | $ArCH_2Ar$(exo) | $CH_2SEt$ | $SCH_2Me$ |
| $\mathbf{1_2}\cdot Na^+$ | -0.68 | +0.28 | -0.28 | -0.05 | +0.14 | +0.02 | +0.02 |
| $\mathbf{1_2}\cdot Cd^{2+}$ | -0.16 | +0.37 | -0.61 | -0.01 | +0.25 | +0.08 | +0.03 |
| $\mathbf{1_6}\cdot Na^+$ | -0.70 | +0.32 | -0.32 | -0.05 | b | b | b |
| $\mathbf{1_6}\cdot Cd^{2+}$ | -0.24 | +0.40 | -0.63 | -0.04 | b | +0.05 | +0.02 |

[a] + denotes the shift to lower magnetic field.

[b] These peaks appeared as multiplet and the chemical shifts could not be determined precisely.

lexes: treatment A), the $^1H$ NMR signals assignable to the $Cd^{2+}$ complexes appeared and the increase was exactly equal to the decrease in the $^1H$ NMR signals of the $Na^+$ complexes. The similar change was observed when $Na^+$ was added to the solution containing $\mathbf{1_n}\cdot Cd^{2+}$ ([$Cd^{2+}$] / [ $\mathbf{1_n}$] = 1.0 where $\mathbf{1_n}$ wholly exist as the $Cd^{2+}$ complexes: treatment B). The results imply that $Na^+$ bound to the "hard" binding-site and $Cd^{2+}$ bound to the "soft" binding-site substitute each other and do not form ditopic bimetallic complexes. Interestingly, we noticed that treatment A results in the $\mathbf{1_n}\cdot Na^+$ / $\mathbf{1_n}\cdot Cd^{2+}$ ratio (1.3:8.7 for n = 2 and 4.2:5.8 for n = 6) lower than treatment B (3.4:6.6 for n = 2 and 4.5:5.5 for n = 6). This is attributed to the "template effect" of $Na^+$: as illustrated in Fig. 3, bound $Na^+$ arranges four thioether groups so that they can form the intramolecular $Cd^{2+}$ complex and subsequently, bound $Cd^{2+}$ efficiently excludes $Na^+$ from $\mathbf{1_n}$. On the other hand, the mixture of $Cd^{2+}$ and non-arranged $\mathbf{1_n}$ partly results in intermolecular complexes, to which $Na^+$ can be bound more easily because of reduced electrostatic repulsion. This rationale was evidenced by dynamic light scattering: only when $Cd^{2+}$ and $\mathbf{1_2}$ were mixed in the absence of $Na^+$, we could observe the presence of aggregated particles with 3900 Å.

Instead of $Cd^{2+}$ we used $Ag^+$ as a soft metal ion which is expected to have the larger *K* values and feature reduced electrostatic repulsion because of the +1 charge. Addition of $Ag^+$ (added as $AgClO_4$) did not

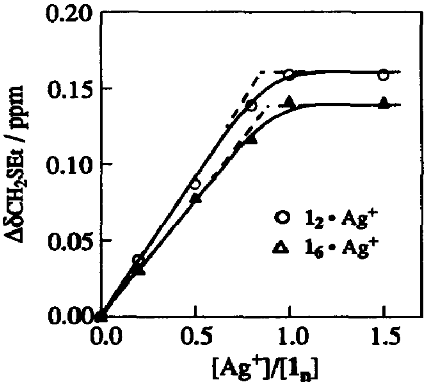


Fig. 4. Plots of $\Delta\delta CH_2SEt$ vs. [$Ag^+$] / [$\mathbf{1_n}$]: $CDCl_3$:$CD_3CN$ = 1:1 v/v, 30 °C. $\mathbf{1_n}$ (2.9 mM) was maintained constant. + denotes the shift to lower magnetic field.

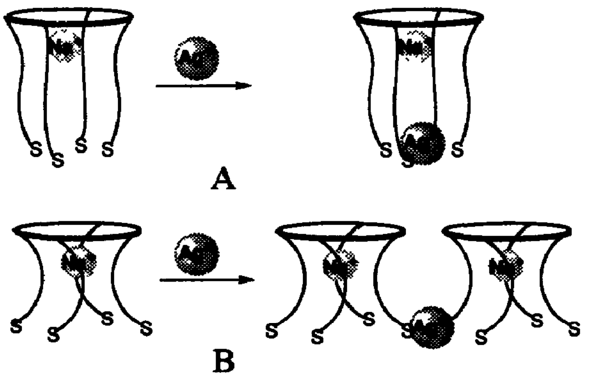


Fig. 5. Schematic representation for the formation of (A) an intramolecular $\mathbf{1_6}\cdot Na^+\cdot Ag^+$ complex and (B) an intermolecular $\mathbf{1_2}\cdot Na^+\cdot Ag^+$ complex.

give new $^1$H NMR signals for the $\mathbf{1}_n$·Ag$^+$ complex but only induced the change in the chemical shifts (400 MHz, $CDCl_3$:$CD_3CN$ = 1:1 v/v, -50 ~ 30 °C), indicating that the exchange rate of Ag$^+$ is faster than the NMR time-scale. Figure 4 shows plots of $\Delta\delta_{CH_2SEt}$ vs. [Ag$^+$] / [$\mathbf{1}_n$]. It is seen from Fig. 4 that $\mathbf{1}_n$ form a 1:1 complex with Ag$^+$ but the $K$ values are too large to determine ($K > 10^5$ M$^{-1}$). When Ag$^+$ was added to the solution containing $\mathbf{1}_n$·Na$^+$ ([Na$^+$] / [$\mathbf{1}_n$] = 100), $\delta_{CH_2SEt}$ moved to lower magnetic field as in Fig. 4 with increasing Ag$^+$ concentration but the peak signals ascribable to $\mathbf{1}_n$·Na$^+$ did not decrease. This implies that bound Ag$^+$ does not exclude Na$^+$ out of the "hard" binding-site: that is, the bimetallic complexes are apparently formed. As mentioned in Introduction, $\mathbf{1}_6$ features the steric flexibility enough to include both Na$^+$ and Ag$^+$ whereas in $\mathbf{1}_2$ inclusion of these two metal ions is sterically impossible because of the negative allostericity between "hard" and "soft" binding-sites. This discrepancy can be explained as follows; $\mathbf{1}_6$ forms an intramolecular $\mathbf{1}_6$·Na$^+$·Ag$^+$ bimetallic complexes (Fig. 5A) whereas in $\mathbf{1}_2$ Ag$^+$ forms an intermolecular complex with $\mathbf{1}_2$·Na$^+$ without excluding Na$^+$ (Fig. 5B). In fact, the $\mathbf{1}_2$·Na$^+$·Ag$^+$ complex resulted in large aggregated particles (1900 Å) detectable by dynamic light scattering.

In conclusion, the present study showed that calix[4]arenes which have been used as a platform for designing ionophores for alkali metal cations are also useful for designing ditopic ionophores bearing both "hard" and "soft" metal binding-sites. We believe that the present system can be applied to novel bimetal-mediated systems such as recognition of small molecules, catalytic reactions, allosteric binding of either "hard" or "soft" metal ions, etc.

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9. $\mathbf{1}_2$ : $^1$H NMR(250 MHz, $CDCl_3$, 25 °C) $\delta$ 7.66 (t, 4H, NH), 6.78 (s, 8H, ArH), 4.52 and 3.26 (d each, 4H each, J=13.1 Hz, $ArCH_2Ar$), 4.49 (s, 8H, $OCH_2CO$), 3.56 (q, 8H, $NCH_2$), 2.72 (t, 8H, $CH_2SEt$), 2.57 (q, 8H, $SCH_2Me$), 1.26 (t, 12H, $CH_3$) and 1.07(s, 36H, Bu$^t$): IR(KBr) 3280 (NH) and 1650 (C=O) cm$^{-1}$. Anal. Calcd for $C_{68}H_{100}N_4O_8S_4$: C, 66.41; H, 8.19; N, 4.56 %. Found: C, 66.29; H, 8.16; N, 4.47 %. $\mathbf{1}_6$ : $^1$H NMR(250 MHz, $CDCl_3$, 25 °C) $\delta$ 7.52 (t, 4H, NH), 6.78 (s, 8H, ArH), 4.47 (m, 12H, $OCH_2CO$ and $ArCH_2Ar$), 3.36 (q, 8H, $NCH_2$), 3.23 (d, 4H, J=13.0 Hz, $ArCH_2Ar$), 2.52 (m, 16H, $CH_2SCH_2$), 1.54 (m, 32H, $(CH_2)_4$), 1.25 (t, 12H, $CH_3$) and 1.08(s, 36H, Bu$^t$); IR(KBr) 3250 (NH) and 1650 (C=O) cm$^{-1}$. Anal. Calcd for $C_{84}H_{132}N_4O_8S_4$: C, 69.38; H, 9.15; N, 3.85 %. Found: C, 69.57; H, 9.04; N, 3.82 %.

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