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Synthesis of calix[4]crowns containing soft and hard ion binding sites *via* click chemistry†

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A series of triazole-modified calix[4]crowns, 3, containing hard and soft ion binding sites were synthesized in good yields *via* click chemistry. The hard and soft ion binding sites may selectively complex alkali metal or transition metal cations. Compound 3a shows good complex selectivity towards Pb^{2+} and 3c shows the highest Li^+/K^+ extraction ratio, suggesting that the triazole groups play an important role in metal ion binding.

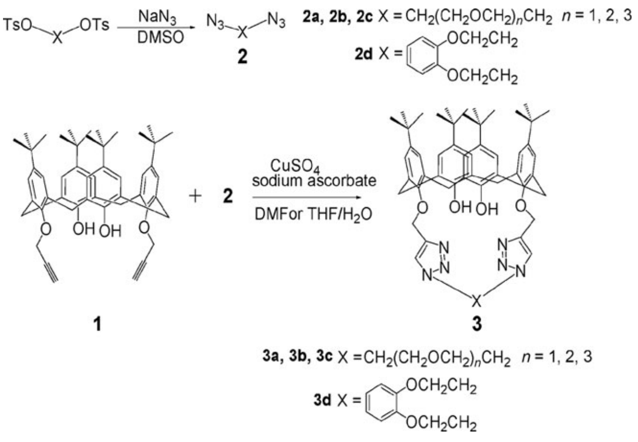
With the aim of advancing the ability of multiple recognition and the mutual effects of binding subunit occupation, considerable attention has been focused on polytopic systems combining two or more binding sites within the same architecture.[1] Calixcrowns[2] comprise a family of calixarenes[3] that exhibit a superior recognition ability towards metal cations by the cooperation of calixarene and crown moieties. Until now, to the best of our knowledge, only three cases concerning calixcrown-based polytopic systems were known. In 1997, Vicens *et al.* synthesized calix[4]-triaza-oxa-benzo-crown-6, containing hard and soft ion binding sites.[4] Chen *et al.* subsequently reported a C_s-symmetrical *p-tert*-calix[6]-1,4-crown-4-2,6-dioxo-diaza crown-4 with hard and soft ion binding sites.[5] Most recently, we reported calix[4]diazacrown-4 oligomers containing hard and soft ion binding sites.[6]

In calixarene chemistry, intramolecular bridging is generally much more difficult to achieve due to the quite complicated products and their low yields.[2] Whereas in click chemistry, click reactions are modular, tolerant of a wide range of solvents and functional groups, simple to perform, and very high yielding.[7] Click reactions have already been used successfully to prepare water soluble[8] and hybrid[9] calixarenes. Therefore, we wanted to employ a new synthetic strategy to bridge intramolecularly calixarenes *via* click chemistry. Furthermore, the triazole groups and the crown ether unit, as soft and hard ion binding sites, were introduced to the calixarene cavity by a one-step pathway. In this Letter, with our continued interest in calixcrown-based polytopic systems, we wish to report the synthesis of a calix[4]crown containing hard and soft ion binding sites *via* click chemistry in good yields, and also its extraction ability towards different metal cations by its hard and soft ion binding sites.

Under our selected conditions, a series of calix[4]crowns were synthesized *via* click chemistry, as shown in Scheme 1. At first, a series of azide-type bridging reagents were readily synthesized in high yields and without further purification by reacting oligoethylene glycol ditosylates and 1,2-bistosyloxyethoxybenzene with NaN_3 in DMSO at 50 °C.[10] Then, the reactions of alkynylcalixarene,[11] **1**, with **2a**, **2b** and **2c** (n = 1, 2, 3) were carried out in DMF at 90 °C with copper(II) sulfate and sodium ascorbate to afford triazole-modified calix[4]crown-3, **3a**, calix[4]crown-4, **3b**, and calix[4]crown-5, **3c**, in yields of 81, 62 and 68%, respectively.[9] However, with **2d** as the bridging reagent, complicated mixtures were obtained.

After much effort with the more polar mixed solvents THF/H_2O, triazole-modified calix[4]benzocrown-4, **3d**, was obtained in 89% yield by recrystallization.[8] **3b** and **3c** were also synthesized with the THF/H_2O system, but no improved yield was observed.

The structures of these compounds were characterized by EI(+)MS spectra, elemental analyses, and ^1H and ^{13}C NMR studies. The EI(+)MS spectra of **3a**, **3b**, **3c** and **3d** show the expected molecular ion peaks, which indicate that the calix[4]arene moiety is intramolecularly-bridged by the crown unit *via* the triazole groups. In the ^1H NMR spectra of the synthesized calix[4]crowns, two signals for the aromatic protons, two doublets for the bridging methylene groups and two singlets for the *tert*-butyl groups suggest that all of the compounds are in a cone conformation. For compound **3a** and **3d**, the cone conformation was also corroborated by the presence of two peaks for the methylene resonances in the ^{13}C NMR spectrum.[12] Furthermore, the structure of



Scheme 1

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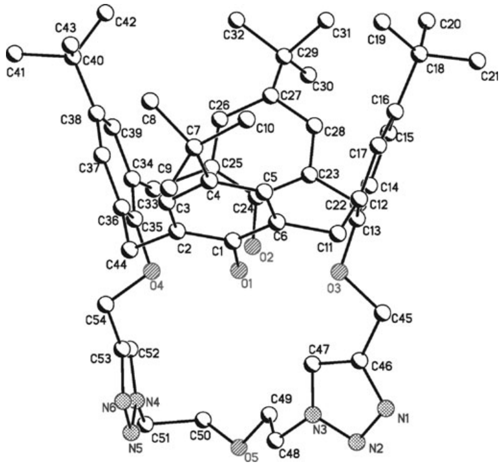

Fig. 1 The X-ray crystal structure of compound **3a**.

compound **3a** was further confirmed by an X-ray crystallographic analysis.†

Calix[4]crown derivative **3a** adopts a cone conformation (Fig. 1);[13] the connecting methylene carbon atoms forming an approximate plane. The interplanar angles between this plane and the rings carrying the crown are 73.47 and 68.98°, while these angles are 44.10 and 50.17° for those carrying the OH groups. Thus, the presence of a crown attached to the phenyl rings of the calix[4]arene pushes them away. The two opposite arenes bearing the crown have an interplanar angle of 37.58°, and between the second pair the angle is 85.75°, showing that the ring pair having the crown attached to them are pointed into the cavity while the other pair are almost perpendicular to each other, as has been seen previously in substituted *p*-tert butylcalix[4]arenes.[14] The torsion angles C(51)–C(50)–O(5)–C(49) and C(48)–C(49)–O(5)–C(50) are 110.8 and 112.9°, respectively. The two triazole groups have an interplanar angle of 65.52°. Because the single-crystal diffraction measurement of the crystal was carried out at a lower temperature (200 K), there are CH_2Cl_2 and water molecules in the crystal's unit cell.

An examination of CPK molecular models reveals that compounds **3a**, **3b**, **3c** and **3d** are well preorganized for the extraction of cations. The ion binding properties of triazole-modified calix[4]crowns **3** were investigated by extracting picrate salts from the aqueous to the organic phase.[15] In order to determine the influence of the 1,2,3-triazole groups on the extraction, *p*-tert-butylcalix[4]crown-5,[16] **4**, was used as a reference compound. The percentage extraction of hosts **3a**, **3b**, **3c**, **3d** and reference compound **4** towards alkali metal cations is summarized in Table 1. The extraction results for transition metal cations are displayed in Fig. 2. From the data given in Fig. 2, triazole-modified calix[4]crowns show good extraction abilities towards transition metal cations. This could be attributed to the nitrogen atom-containing 1,2,3-triazole groups, which are preferable for complexing the more polarizable transition metal cations. The phenomenon might also reflect the "principle of hard and soft acids and bases" introduced by Ho.[15] Meanwhile, triazole-modified calix[4]-crown-3 **3a** exhibited a high affinity towards Pb^{2+} ions. According to the literature,[17] Pb^{2+} can be bound *via* the coordination of two triazole groups. Therefore, the high selectivity towards Pb^{2+} could because the two crown-3-linked triazole groups facilitate strong Pb^{2+} ion binding.

Table 1 The percentage extraction of alkali metal cations

Host	Li^+	Na^+	K^+	Cs^+	Li^+/K^+
3a	36.9	25.2	27.9	24.7	1.32
3b	21.9	8.7	7.4	6.4	2.96
3c	13.1	7.3	2.1	8.0	6.24
3d	15.5	5.1	5.9	7.3	2.63
4[a]	0.08	0.3	11.8	—	<0.01

[a] These data are quoted from ref. 16.

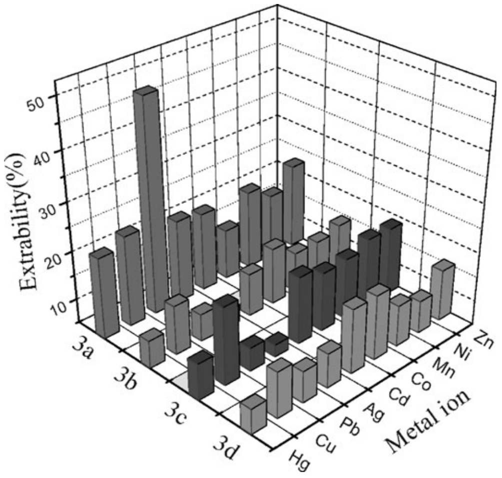

Fig. 2 The extraction capacity of calix[4]crowns **3a**, **3b**, **3c** and **3d** towards transition metal cations.

It can be seen from Table 1 that host **3a** showed the higher extraction abilities towards alkali metal cations. It is tempting to explain the higher percentage extractability of **3a** by a change in the 1,3-alternate conformation facilitated by the short crown chain, but ^1H NMR studies gave no indication of such a conformational change. In comparison with **4**, triazole-modified *p*-tert-butylcalix[4]crown-5, **3c**, showed a higher extraction selectivity towards Li^+. The extraction ratio Li^+/K^+ of compound **3c** is up to 6.24, whereas with compound **4** it is only up to 0.0068. It is pertinent to note that the polyether chain of **3c** is able to coil and bring about the collapse of the cavity to form a larger pseudocircular crown unit, which can then accommodate a larger potassium ion. However, for host **3c**, the pseudocircular crown unit was much smaller than that of compound **4** due to the introduction of the triazole groups. Therefore, the smaller lithium ion fitted into the cavity composed from the crown unit, emphasizing the importance of the size-fit effect. At the same time, it revealed that the triazole groups inflected the extraction ability and selectivity of the hard ion binding site, composed from the crown unit, towards the lithium ion.

Experimental

General

^1H NMR spectra were recorded on Varian Mercury VX400 and 600 instruments at ambient temperature with TMS as the internal standard. ^{13}C NMR spectra were recorded on a

Varian Mercury VX400 instrument at ambient temperature with TMS as the internal standard. EI-MS were recorded on a Finnigan LCQ-Advantage instrument. UV-vis spectra were obtained using a Scinco S-3100 UV-Vis recording spectrophotometer. All chemicals were A.R. grade and were purified by standard procedures.

General procedure for the synthesis of compounds 3a, 3b and 3c

1 (241 mg, 0.333 mmol), $CuSO_4\cdot5H_2O$ (50 mg, 0.201 mmol) and sodium ascorbate (100 mg, 0.505 mmol) were added to a solution of **2a** (78 mg, 0.50 mmol) in DMF (10.0 mL). The mixture was heated at 90 °C for 10 h, and then diluted with ethyl acetate (10 mL) and washed with water (3 × 5 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was recrystallized from CH_2Cl_2/MeOH to afford **3a** as a white solid in 81% yield. Compounds **3b** and **3c** were prepared under identical conditions. Purification by column chromatography eluting with hexane/ethyl acetate (v/v = 2 : 1, 1 : 1) afforded **3b** and **3c** as white solids in yields of 62 and 68%, respectively.

Compound 3a. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (s, 18H, $C(CH_3)_3$), 1.30 (s, 18H, $C(CH_3)_3$), 3.34 (d, J = 13.0 Hz, 4H, $ArCH_2Ar$), 3.90 (t, J = 4.6 Hz, 4H, OCH_2), 4.26 (d, J = 13.0 Hz, 4H, $ArCH_2Ar$), 4.51 (t, J = 4.8 Hz, 4H, OCH_2), 5.27 (s, 4H, $ArOCH_2$), 6.74 (s, 4H, ArH), 6.91 (s, 2H, NCH), 7.10 (s, 4H, ArH), 8.22 (s, 2H, ArOH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.7, 30.9 (CH_3), 31.5, 31.7 ($ArCH_2Ar$), 33.8 ($C(CH_3)_3$), 50.4 (CH_2N), 69.2 (CH_2O), 71.4 ($ArOCH_2$), 125.3, 125.6, 127.7, 132.0, 145.4, 147.5, 149.5, 150.3 (ArC), 124.9 (NCH), 142.1 (NC); EI(+)MS m/z = 882.0 (MH_2^+). Anal. calc. for $C_{54}H_{68}N_6O_5$: C, 73.61; H, 7.78; N, 9.54; found: C, 73.56; H, 7.71; N 9.52%.

Compound 3b. ^1H NMR ($CDCl_3$, 600 MHz): δ 0.97 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$), 3.29 (d, J = 12.9 Hz, 4H, $ArCH_2Ar$), 3.40 (s, 2H, OCH_2), 3.60 (s, 2H, OCH_2), 3.70 (s, 4H, OCH_2CH_2), 3.95 (s, 2H, OCH_2), 4.16 (d, J = 12.9 Hz, 4H, $ArCH_2Ar$), 4.63 (s, 2H, OCH_2), 5.25 (s, 4H, $ArOCH_2$), 6.81 (s, 4H, ArH), 7.04 (s, 4H, ArH), 7.02 (s, 2H, NCH), 8.28 (s, 2H, ArOH); EI(+)MS m/z = 926.2 (MH_2^+). Anal. calc. for $C_{56}H_{72}N_6O_6$: C, 72.70; H, 7.84; N, 9.08; found: C, 72.74; H, 7.81; N, 9.10%.

Compound 3c. ^1H NMR ($CDCl_3$, 600 MHz): δ 0.92 (s, 18H, $C(CH_3)_3$), 1.28 (s, 18H, $C(CH_3)_3$), 3.24 (d, J = 13.2 Hz, 4H, $ArCH_2Ar$), 3.39 (s, 2H, OCH_2), 3.54 (s, 2H, OCH_2), 3.68 (s, 4H, OCH_2), 3.93 (s, 4H, OCH_2), 4.17 (d, J = 13.2 Hz, 4H, $ArCH_2Ar$), 4.64 (s, 4H, OCH_2), 5.23 (s, 4H, $ArOCH_2$), 6.74 (s, 4H, ArH), 6.93 (s, 2H, NCH), 7.03 (s, 4H, ArH), 8.27 (s, 2H, ArOH); EI(+)MS m/z = 969.4 (MH^+). Anal. calc. for $C_{58}H_{76}N_6O_7$: C, 71.87; H, 7.90; N, 8.67; found: C, 71.91; H, 7.87; N, 8.64%.

Procedure for the synthesis of compound 3d

A mixture of **1** (241 mg, 0.333 mmol), $CuSO_4\cdot5H_2O$ (50 mg, 0.201 mmol) and sodium ascorbate (100 mg, 0.505 mmol) were added to a solution of **2d** (124 mg, 0.50 mmol) in THF and water (v/v = 2 : 1, 30.0 mL), and stirred vigorously at 50 °C for 10 h. The mixture was extracted three times with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was recrystallized from CH_2Cl_2/MeOH to afford **3d** as a white solid in 89% yield.

Compound 3d. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.99 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$), 3.30 (d, J = 13.0 Hz, 4H, $ArCH_2Ar$), 4.19 (d, J = 13.0 Hz, 4H, $ArCH_2Ar$), 4.49 (t, J = 4.6 Hz, 4H, OCH_2), 4.80 (t, J = 4.6 Hz, 4H, OCH_2), 5.27 (s, 4H, $ArOCH_2$), 6.84 (s, 4H, ArH), 6.87 (s, 4H, ArH), 7.03 (s, 4H, ArH), 7.42 (brs, 2H, ArOH), 8.35 (s, 2H, NCH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.7, 31.0 (CH_3), 31.5, 31.7 ($ArCH_2Ar$), 33.8, 33.9 ($C(CH_3)_3$), 50.4 (CH_2N), 68.1 (CH_2O), 72.9 ($ArOCH_2$), 115.9, 125.2, 125.6, 125.9, 127.7, 132.5, 145.0, 147.3, 148.3, 150.1, 150.3 (ArC), 125.0 (NCH), 141.8 (NC); EI(+)MS m/z = 973.0 (MH^+). Anal. calc. for $C_{60}H_{72}N_6O_6$: C, 74.04; H, 7.46; N, 8.64; found: C, 74.01; H, 7.42; N, 8.68%.

Solvent extraction experiments

Picrate extraction experiments were performed by following Ho's procedure.[15] 2 mL of a 5×10^{-5} M aqueous picrate solution and 1 mL of a 5×10^{-4} M solution of calixarene in $CHCl_3$ were vigorously agitated for 5 min in a stoppered glass tube with a mechanical shaker, magnetically stirred in a thermostated water bath at 25 °C for 2 h and finally left to stand for an additional 30 min. The concentration of picrate ions remaining in the aqueous phase was then determined by UV spectra from the resulting absorbance at 380 nm. Blank experiments showed that no picrate extraction occurred in the absence of calixarene.

Acknowledgements

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