Pergamon

Tetrahedron 58 (2002) 10205–10212

TETRAHEDRON

Synthesis and alkali metal picrate extraction studies of lower rim functionalized *p-tert*-butylcalix[4]arene crown ethers

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Received 12 September 2002; accepted 21 October 2002

Abstract—The syntheses of four new calix[4]arene receptors, i.e. **4**–**7**, each of which contains an oxahexacyclic cage moiety, are reported. The structures of two of these receptors, i.e. **4** and **7**, have been established via single crystal X-ray structural analysis. The complexation properties of **4**–**7** were determined via a series of alkali metal picrate extraction experiments. Two of the cage-functionalized calix[4]arene-crown-5 hosts, i.e. **4** and **5**, display somewhat greater extraction avidity toward Na^+ picrate vis-à-vis the remaining alkali metal picrates. By way of contrast, host systems **6** and **7** function effectively as a moderately selective K^+ extractants and display significantly increased extraction avidity toward K^+ picrate vis-à-vis **4** and **5**.

1. Introduction

Readily available calix[4]arenes[1] have been used extensively as starting materials for the synthesis of metal cation-selective ionophores.[1b] A variety of calix[4]arene-based receptors which possess unusually-shaped cavities have been prepared via 'upper' and 'lower' rim functionalization.[2] The complexation properties of these molecules appear to be highly dependent upon the nature, number of donor groups, and the conformation of the calix[4]arene moiety.[3] In particular, calix[4] crown ethers that contain polyethylene glycol units have been prepared;[4] several of these host systems display significant levels of selectivity and avidity toward complexation with alkali metal cations.[5]

Previously, we reported the synthesis and the results of alkali metal picrate extraction studies of several cage-functionalized crown ethers and cryptands[6] and also of some lower rim functionalized calix[4]arenes.[7] Incorporation of a cage moiety confers both rigidity and lipophilicity upon the resulting crown ethers and cryptands; both factors have been shown to affect the selectivity and avidity of the resulting host systems.[8] In the present study, we report the synthesis and alkali metal picrate extraction capabilities of novel cage-annulated calix[4]arene receptors **4**–**7**.

Keywords: calixarenes; cage compounds; host compounds; X-ray crystal structures.

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2. Results and discussion

2.1. Syntheses of *p-tert*-butylcalix[4]arenes functionalized at the lower rim by cage-annulated crown ethers

The syntheses of cage-annulated calix[4]arenes **4** and **5** are shown in Scheme 1. The cage annulated podand that serves as the linking agent, i.e. diiodide **3**, possesses C_s symmetry. Attachment of this podand to the lower rim of calix[4]arene (**1**) affords **4** with concomitant reduction of overall molecular symmetry in the calixarene unit.

Cage-annulated podand **3** was prepared via reaction of the corresponding ditosylate, **2**,[6b] with NaI–acetone. Subsequent base-promoted reaction of *p-tert*-butylcalix[4]arene (**1**) with a solution of **3** in THF produced **4** in 43% yield (Scheme 1). Compound **5** was prepared in 68% yield via base-promoted *O*-methylation of the two phenolic hydroxyl groups in **4**. The structures of **4** and **5** were confirmed via analysis of their respective ^1H NMR and ^{13}C NMR spectra (vide infra; also, see Section 4). In addition, the X-ray crystal structure of **4** has been obtained (see Fig. 1).

Subsequent base-promoted reaction of **4** with **2**-tosylethyl methyl ether[9] afforded a mixture mono-*O*-alkylated calix crown ether, **6** (45% yield) and the corresponding bis-*O*-alkylated compound (i.e. **7**, 42% yield; see Scheme 2). The structures of **6** and **7** were confirmed via analysis of their ^1H NMR and ^{13}C NMR spectra (vide infra; also, see Section 4). In addition, the X-ray crystal structure of **7** has been

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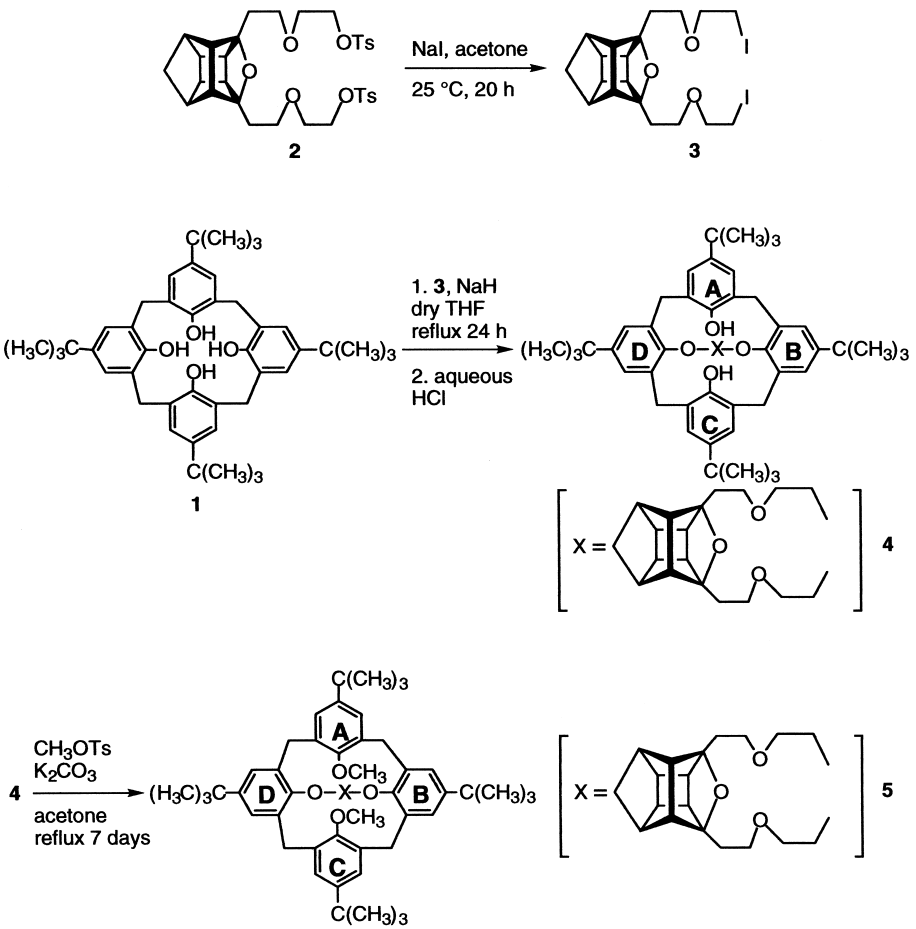
PII: S0040-4020(02)01360-1



Scheme 1.

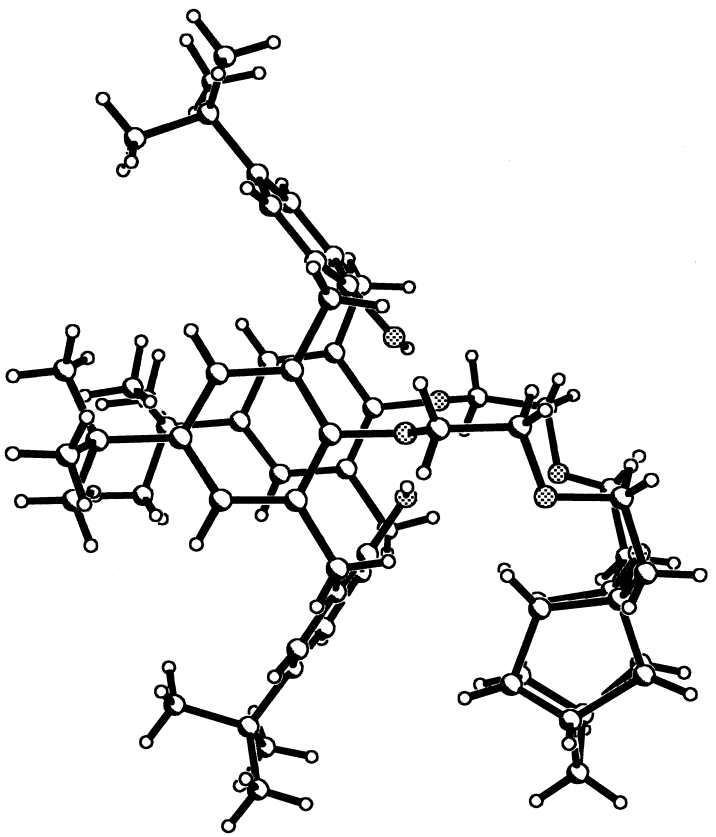
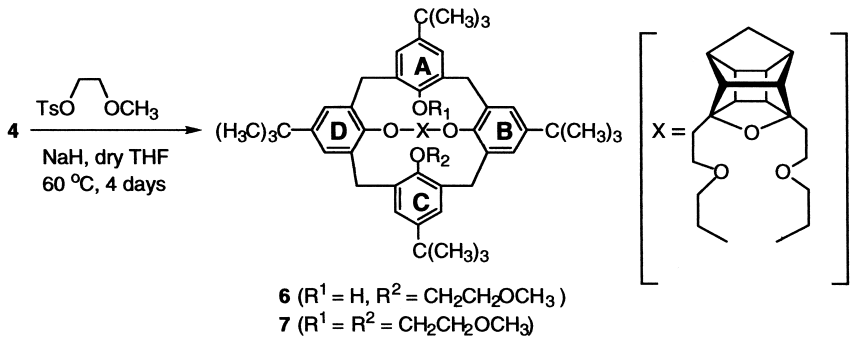


Figure 1. X-Ray structure drawing of **4**. For clarity, the water molecule in the unit cell has been omitted. Atoms are shown as spheres of arbitrary size.



Scheme 2.

obtained (see Fig. 2). Therein, it can be seen that **7** occupies a partial cone configuration in the solid state.

2.2. Some features of the proton NMR spectra of 4–7

A summary of selected absorption patterns that appear in the ^{1}H NMR spectra of **4**–**7** are listed in Table 1.

The appearance of Ar–CH_2–Ar proton absorption patterns in ^{1}H NMR spectra, together with the appearance of the *t*-butyl proton absorption region, has been used extensively to assign conformation in lower rim functionalized *p-t*-butylcalix[4]arenes.[10] In the present study, compounds of the type **4**–**7** (Schemes 1 and 2) each contain an oxahexacyclic cage unit in the crown ether moiety. It should be recognized that the symmetry properties associated with lower-rim cage functionalization confers 'left-right' symmetry but not 'front-back' symmetry on the resulting calix[4] crown ether. Thus, substituted phenyl rings **B** and **D** (i.e. the rings situated 'left' and 'right' of the symmetry plane that bisects C(1) and C(4) in phenyl rings **A** and **C**) are equivalent by symmetry, but rings **A** and **C** are not.

The ^{1}H NMR spectrum of **4** contains AB patterns at δ 3.30, 4.29, and 4.35 that correspond to its various Ar–CH_2–Ar protons. In addition, the ^{1}H NMR spectrum of **4** contains two *t*-Bu singlets at δ 0.84 and 1.30 (ratio 1:1). Since the symmetry properties of **4** in the cone or partial cone conformation are the same, the ^{1}H NMR spectral results are consistent with either conformation for **4** in solution, providing that the absorptions of the *t*-Bu groups situated on rings **A** and **C** are accidentally degenerate (i.e. the magnetic environments of these *t*-Bu groups are not affected by the subtle difference between front-back asymmetry due to the distant cage moiety in **4**). However, the overall appearance of the ^{1}H NMR spectrum of **4** suggests that it exists primarily in its cone conformation in $CDCl_3$ solution.

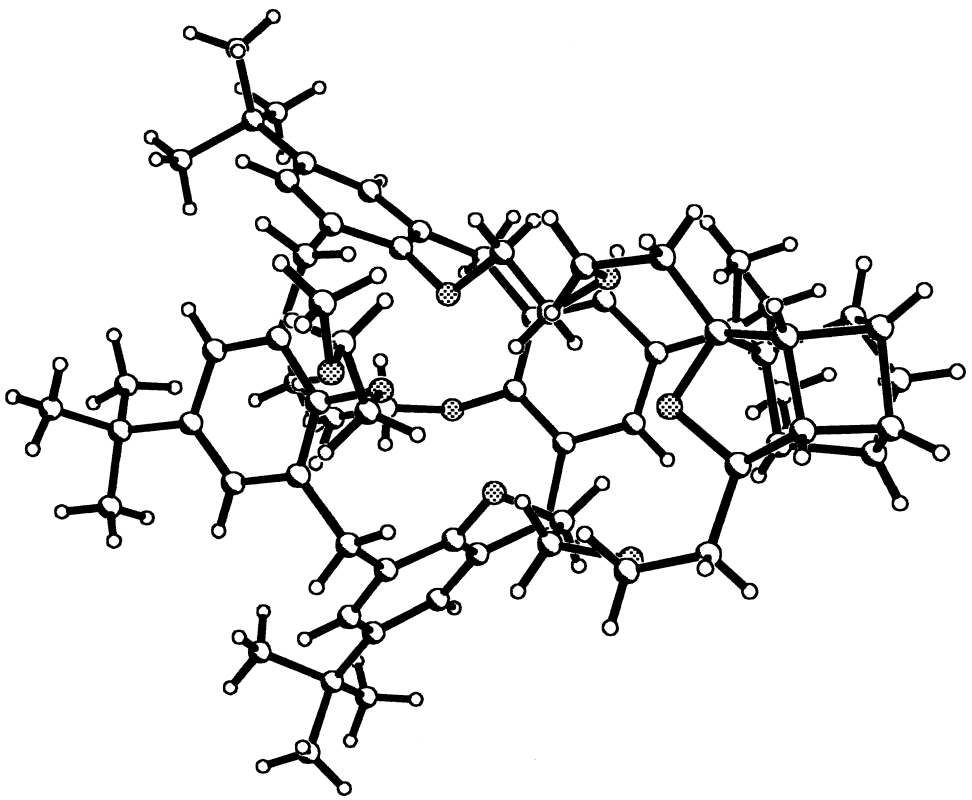


Figure 2. X-Ray structure drawing of **7**. For clarity, atoms are shown as spheres of arbitrary size.

Table 1. Proton NMR spectral data for **4**–**7**

Compound	Aromatic protons	CH_2 protons	*t*-Bu pattern	Comments
4	Two singlets, δ 6.65, 7.04 (ratio 1:1)	δ 3.30 (H_{eq}: J_{AB}=13.2 Hz); δ 3.60–4.15 (m, 12H, due to H_{eq} overlapping with other proton signals) δ 4.29 (H_{ax}: J_{AB}=12.8 Hz); δ 4.35 (H_{ax}: J_{AB}=12.8 Hz)	Two singlets, δ 0.84, 1.30 (ratio 1:1)	Predominant isomer is flattened cone conformer (see X-ray structure drawing in Fig. 1). A small quantity of another conformational isomer appears to be present; a small *t*-Bu signal appears at δ 1.15
5	Two broad singlets, δ 6.40, 7.12 (ratio 1:2)	δ 3.10 (H_{eq}, m); δ 4.22 (H_{ax}, m) are discernible in the 2D COSY NMR spectrum of **6**	Three singlets, δ 0.80, 1.02, 1.32 (ratio 1:1:2)	^{1}H NMR indicates that the material as isolated appears to be a mixture of conformational isomers. An additional *t*-Bu resonance is present at δ 1.57
6	Three singlets, δ 6.71, 6.97, 7.15 (ratio 1:2:1)	δ 3.14 (H_{eq}: J_{AB}=16.2 Hz); δ 4.22 (H_{ax}: J_{AB}=16.2 Hz) are clearly discernible	Three singlets, δ 1.08, 1.28, 1.41 (ratio 2:1:1)	^{1}H NMR indicates that the material as isolated appears to be a mixture of conformational isomers. Small *t*-Bu resonances also are present at δ 1.21 and 1.43.
7	Two singlets, δ 6.42, 7.09 (ratio 1:1)	δ 3.15 (H_{eq}: J_{AB}=16.2 Hz); δ 4.41 (H_{ax}: J_{AB}=16.2 Hz)	Two singlets, δ 0.82, 1.33 (ratio 1:1)	X-Ray structure (Fig. 2) indicates partial cone conformation. Two OCH_3 singlets are observed (δ 3.41 and 3.43, ratio 1:1)

The Ar–CH_2–Ar proton absorptions in the ^{1}H NMR spectrum of **5** cannot readily be identified by inspection of the one-dimensional spectrum. However, Ar–CH_2–Ar proton absorptions at δ 3.10 (H_{eq}, m); δ 4.22 (H_{ax}, m) can be seen as cross-peaks in the 2D COSY NMR spectrum of **5**.

It is instructive to examine the features of lower rim functionalized calix[4]arenes in which rings **B** and **D** have been bridged by a flexible crown ether moiety and rings **A** and **C** are symmetrically functionalized by identical OR groups. Several such systems have been prepared, and features of their ^{1}H NMR spectra have been reported.[9,11,12] Some representative examples in this regard, e.g. **9**–**11**, appear in Table 2.

Comparison of the ^{1}H NMR data obtained for **4**–**7** (Table 1) with the corresponding NMR data contained within Table 2 provides additional insight into the conformational preferences of the lower rim functionalized calix[4]arenes prepared in the present study. The ^{1}H NMR spectra of **4**, **9**, **10a**, and **11** all diplay two *t*-Bu singlets (ratio 1:1); all four compounds appear to occupy cone conformations. By way of contrast, **5**, **6**, and **10b** display three *t*-Bu singlets (ratio 1:2:1). The ^{1}H NMR spectra of **5** and **6** are quite complex, thereby indicating that each compound is present in more than one conformation in solution.

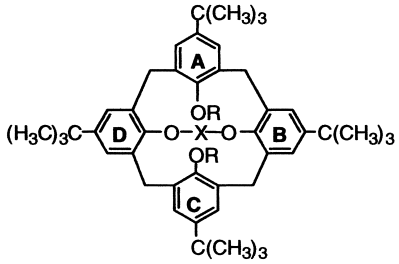
X-Ray structural analyses of **7** (vide supra) and of **10b**[11] reveal that each of these compounds exists in a partial cone conformation in the solid state. The corresponding ^{1}H NMR data for **10b** in $CDCl_3$ solution appear to be consistent with this conclusion as well.[11] However, the ^{1}H NMR spectrum of **7**, which displays only two *t*-Bu singlets (ratio 1:1) and one set of AB patterns for the ArCH_2Ar protons at δ 3.15 and δ 4.41 suggests that this compound exists primarily in its cone conformation in solution. This conclusion is reinforced by the very small difference between the chemical shift values for the two nonequivalent OCH_3 groups in **7**, i.e. δ 3.41 and 3.43. If **7** were to occupy a partial cone conformation in solution, the two OCH_3 groups in this molecule would experience very different environments, which should lead to a correspondingly larger difference between their respective chemical shift values.

It appears that the spatial requirements of the two mobile $OCH_2CH_2OCH_3$ groups in **7** preclude conformation interconversion between cone and partial cone conformations in solution.[13] Thus, we are left with the conclusion that the solution NMR results obtained for **7** do not appear to be consistent with the corresponding (solid state) X-ray crystallographic results. A possible explanation might reside in the single crystal chosen for the X-ray crystallographic study, which might not have been typical of the bulk sample. In an effort to pursue this possibility further, several attempts were made to obtain additional crystals of **7** for X-ray structural analysis; however, despite our best efforts, none of these attempts were successful.

2.3. Alkali metal picrate extraction studies

In an effort to investigate the complexation properties of ligands **4**–**7**, a series of alkali metal picrate extraction

Table 2. Proton NMR spectral data for **9**–**11**



8 [R = H; X = $CH_2CH_2(OCH_2CH_2)_3$]
9 [R = CH_3; X = $CH_2CH_2(OCH_2CH_2)_3$]
10a [R = CH_2 Ph; X = $CH_2CH_2(OCH_2CH_2)_3$ (major isomer)]
10b [R = CH_2 Ph; X = $CH_2CH_2(OCH_2CH_2)_3$ (minor isomer)]
11 [R = H, X = (*R,R*)- $CH_2C(O)OCH(CO_2Et)$-$CH(CO_2Et)OC(O)CH_2$]

Compound	Aromatic protons	CH_2 protons	*t*-Bu proton pattern	Comments
9[a]	Two singlets, δ 6.50, 7.13 (ratio 1:1)	δ 3.14 (H_{eq}: J_{AB}=12.3 Hz); δ 4.37 (H_{ax}: J_{AB}=12.3 Hz)	Two singlets, δ 0.81, 1.31 (ratio 1:1)	Analysis of the ^{1}H NMR spectrum of **9** suggests that this compound occupies the cone conformation[a]
10a[a,b]	Two singlets, δ 6.42, 7.08 (ratio 1:1)	δ 3.02 (H_{eq}: J_{AB}=12.9 Hz); δ 4.32 (H_{ax}: J_{AB}=12.9 Hz)	Two singlets, δ 0.81, 1.33 (ratio 1:1)	Analysis of the ^{1}H NMR spectrum of **10a** suggests that this compound occupies the cone conformation[a]
10b[c,d]	^{1}H signals due to aryl protons in the calix[4]-arene moiety overlap with $PhCH_2Cl$ aryl proton signals	δ 2.91 (H_{eq}: J_{AB}=12.0 Hz); δ 4.19 (H_{ax}: J_{AB}=12.0 Hz)	Three singlets, δ 0.78, 1.17, 1.43 (ratio 1:2:1)	Analysis of the ^{1}H NMR spectrum of **10b** suggests that this compound occupies a partial cone conformation in solution.[c] In addition, the results of X-ray structural analysis indicate that **10b** occupies a partial cone conformation in the solid state[c]
11[e]	δ 6.97–7.06 (m, 8H)	δ 3.31 (H_{eq}: J_{AB}=12.6 Hz); δ 3.39 (H_{eq}: J_{AB}=12.6 Hz; δ 4.22 (H_{ax}: J_{AB}=12.6 Hz); δ 4.23 (H_{ax}: J_{AB}=12.6 Hz)	Two singlets, δ 1.15, 1.22 (ratio 1:1)	Analysis of the ^{1}H NMR spectrum of **11** suggests that this compound occupies the cone conformation[e]

[a] Ref. 9.
[b] Compound **10a** is the major isomer (73%) formed via base promoted reaction of **8** with $PhCH_2Cl$.[11]
[c] Ref. 11.
[d] Compound **10b** is the minor isomer (17%) formed via base promoted reaction of **8** with $PhCH_2Cl$.[11]
[e] Ref. 12.

Table 3. Results of alkali metal picrate extraction experiments

Host molecule	Percent of picrate extracted (%)[a]				
	Li^+	Na^+	K^+	Rb^+	Cs^+
4	0.9±0.5	11.6±0.7	3.6±0.4	1.3±0.8	4.5±0.6
5	4.2±0.6	16.9±0.5	4.9±0.5	7.5±1.0	5.3±0.7
6	7.7±0.4	10.3±0.5	36.4±1.1	23.1±0.9	19.2±0.5
7	2.4±0.7	8.5±0.6	56.3±0.9	18.9±0.4	6.6±0.5

[a] Averages and standard deviations calculated for data obtained from three independent extraction experiments.

experiments were performed. The results thereby obtained are shown in Table 3.

Inspection of the data in Table 3 indicates that **4** and **5** are relatively inefficient alkali metal picrate extractants; however, they display somewhat greater avidity toward Na^+ picrate vis-à-vis the remaining alkali metal picrates. By way of contrast, host systems **6** and **7**, which incorporate one and two $CH_2CH_2OCH_3$ 'lariats' at the lower rim of the calix[4]arene moiety, respectively, display significantly increased extraction avidity toward K^+ picrate vis-à-vis **4** and **5**. Indeed, the results shown in Table 3 indicate that only host systems **6** and **7** function effectively as a moderately selective K^+ extractants.

3. Summary and conclusions

Novel lower-rim functionalized calix[4]arene receptors that contain a cage moiety, i.e. host systems **4**–**7**, have been prepared. The results of single crystal X-ray structural analysis of **4** and **7** reveal that the former system occupies a flattened cone conformation in the solid state, whereas the latter compound occupies a partial cone conformation in the solid state (see Figs. 1 and 2, respectively). Inspection of their respective ^1H NMR spectra suggests that calix[4]arene moieties occupy the cone conformation. This conclusion has been confirmed via X-ray structural analysis of **4** and **7**. However, the appearance of the ^1H NMR spectrum of **7** suggests that this compound exists primarily in its cone conformation in solution. The ^1H NMR spectra of **5** and **6** are complex, thereby suggesting that each of these compounds exists in solution as a mixture of conformational isomers at ambient temperature.

The complexation properties of host molecules **4**–**7** have been evaluated via the results of alkali metal picrate extraction experiments. Only **6** and **7** showed more than modest avidity and/or selectivity as alkali metal cation extractants. Both **6** and **7** appear to function effectively as moderately selective K^+ extractants and display significantly increased extraction avidity toward K^+ picrate vis-à-vis **4** and **5**.

4. Experimental

4.1. General

Melting points are uncorrected. Absorption intensities of alkali metal picrate solutions were measured at $\lambda = 374$ nm by using a Hewlett–Packard Model 84524 Diode Array UV–visible spectrophotometer. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode.

4.1.1. Synthesis of 3. To a solution of **2** (311 mg, 0.488 mmol) in acetone (10 mL) was added NaI (363 mg, 2.44 mmol), and the resulting mixture was stirred at ambient temperature during 20 h. The reaction mixture was concentrated in vacuo, and water (10 mL) was added to the residue. The resulting aqueous suspension was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were washed sequentially with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc–hexane. Pure **3** (211 mg, 79%) was thereby obtained as a colorless waxy semi-solid; IR (film) 2995 (br, s), 2861 (s), 1262 (m), 1096 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (*AB*, J_{AB}=13.3 Hz, 1H), 1.82 (A*B*, J_{AB}=13.3 Hz, 1H), 2.12 (t, J=11.1 Hz, 4H), 2.31–2.62 (m, 8H), 3.21 (t, 4H). 3.50–3.84 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 4.10 (t), 33.1 (t), 42.2 (d), 44.3 (t), 45.1 (d), 59.2 (d), 68.2 (t), 72.1 (t), 95.2 (s). Exact mass (CI HRMS) calcd for $C_{19}H_{26}O_3I$: $[M_r+H]^+$ m/z 557.0050. Found: $[M_r+H]^+$ m/z 557.0046.

4.1.2. Cage-functionalized calix[4]arene 4. To a boiling suspension of NaH (obtained as a 60% dispersion in mineral oil, 35.4 mg, 0.92 mmol) in dry THF (26 mL) was added dropwise with stirring a mixture of calix[4]arene (**1**, 100 mg, 0.154 mmol) and **3** (85.6 mg, 0.154 mmol) in dry THF (5 mL) during 0.5 h. After the addition of **1** had been completed, the reaction mixture was refluxed during 24 h and then was allowed to cool gradually to ambient temperature. The reaction mixture then was acidified via careful, dropwise addition of 1N aqueous HCl (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water (30 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc–hexane. Pure **4** (95 mg, 65%) was thereby obtained as a colorless microcrystalline solid: mp 296–297°C; IR (film) 3474 (br, m), 2957 (s), 2860 (m), 1485 (s), 1126 (m), 884 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 18H), 1.30 (s, 18H), 2.00–2.20 (m, 10H), 2.60 (br s, 2H), 2.75–2.85 (m, 2H), 3.30 (*AB*, J_{AB}=13.2 Hz, 4H), 3.60–4.15 (m, 12H), 4.29 (*AB*, J_{AB}=12.8 Hz, 2H), 4.35 (A*B*, J_{AB}=12.8 Hz, 2H), 6.38 (s, 1H, peak disappears when NMR sample is shaken with D_2O), 6.47 (s, 1H, peak disappears when NMR sample is shaken with D_2O), 6.65 (s, 4H), 7.04 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 31.0 (q), 31.1 (q), 31.3 (s), 31.7 (s), 32.8 (s), 33.8 (s), 41.5 (d), 42.7 (t), 43.9 (d), 48.4 (d), 59.0 (d), 68.8 (2C, t), 70.5 (2C, t), 76.8 (2C, t), 94.4 (s), 124.9 (4C, d), 125.3 (4C, d), 127.9 (s), 128.0 (s), 132.1 (s), 132.2 (s), 141.2 (s), 141.3 (s), 146.7 (s), 149.9 (s), 150.4 (s), 150.7 (s). Exact mass (CI HRMS) calcd for $C_{63}H_{80}O_7$: $[M_r]^+$ m/z 948.5904. Found: $[M_r+H]^+$ m/z 948.5894.

4.1.3. Cage-functionalized calix[4]arene 5. To a solution of **4** (100 mg, 0.105 mmol) in acetone (25 mL) were added K_2CO_3 (145 mg, 1.05 mmol) and CH_3OTs (39 mg, 0.21 mmol), and the resulting mixture was refluxed during 7 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was acidified via careful, dropwise addition of 1N aqueous HCl (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water (30 mL), dried (M_gSO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc–hexane. Pure **5** (70.1 mg, 68%) was thereby obtained as a colorless, waxy solid: mp 182–183°C; IR (film) 3040 (s), 1423 (m), 1210 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 8H), 1.02 (s, 7H), 1.32 (s, 17H), 1.57 (s, 4H, due to *t*-Bu peak in minor conformer), 1.75–2.15 (m, 6H), 2.22–2.60 (m, 8H), 3.05–3.25 (m, 6H), 3.55–4.05 (m, 18H), 4.25–4.43 (m, 4H), 6.40 (s, 2H), 7.12 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 31.7 (q), 32.3 (q), 33.0 (s), 33.1 (s), 34.1 (s), 34.6 (s), 41.9 (d), 44.1 (t), 44.3 (d), 48.6 (d), 59.3 (q), 59.4 (q), 61.9 (d), 69.8 (t), 70.0 (t), 71.61 (t), 71.66 (t), 71.73 (t), 71.9 (t), 92.2 (s), 124.6 (d), 124.76 (d), 124.78 (d), 124.81 (d), 124.84 (d), 124.91 (d), 125.6 (d), 125.8 (d), 132.3 (s), 136.5 (s), 144.6 (s), 146.2 (s), 154.1 (s), 154.2 (s), 156.3 (s). Exact mass (CI HRMS) calcd for $C_{65}H_{84}O_7$: $[M_r+H]^+$ *m/z* 977.62953. Found: $[M_r+H]^+$ *m/z* 977.62952.

4.1.4. Cage-functionalized calix[4]arenes 6 and 7. To a solution of **4** (225 mg, 0.24 mmol) in 1:1 acetone–toluene mixed solvent (15 mL) under argon was added K_2CO_3 (346 mg, 2.5 mmol). To the resulting mixture was added 2-methoxyethyl tosylate (130 mg, 0.56 mmol), and the resulting mixture was refluxed under argon during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature, and $CHCl_3$ (5 mL) then was added. The resulting mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 15% EtOAc–hexane. Pure **7** (108 mg, 45%) was thereby obtained as a colorless microcrystalline solid: mp 127–128°C; IR (film) 2960 (s), 2909 (s), 1481 (s), 1123 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 18H), 1.36 (s, 18H), 2.01–2.12 (m, 4H), 2.39–2.45 (m, 2H), 2.55–2.65 (m, 2H), 2.71–2.85 (m, 4H), 3.15 (*AB*, J_{AB}=16.2 Hz, 4H), 3.41 (s, 3H), 3.43 (s, 3H), 3.68–3.81 (m, 4H), 3.85–3.95 (m, 8H), 4.05–4.11 (m, 5H), 4.21–4.35 (m, 5H), 4.41 (A*B*, J_{AB}=16.2 Hz, 4H), 6.45 (s, 4H), 7.12 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 31.6 (q), 32.2 (q), 32.7 (2C, s), 34.0 (s), 34.5 (s), 42.0 (d), 44.0 (t), 44.4 (d), 49.6 (d), 59.0 (q), 59.1 (q), 60.4 (d), 69.5 (t), 70.2 (2C, t), 71.9 (2C, t), 72.0 (t), 72.5 (t, 2C), 74.09 (t), 74.15 (t), 94.5 (s), 124.9 (2C, d), 125.9 (4C, d), 126.0 (2C, d), 132.32 (s), 132.39 (s), 135.9 (s), 144.7 (s), 145.3 (s), 152.7 (s), 155.3 (s). Exact mass (CI HRMS) calcd for $C_{69}H_{92}O_9$: $[M_r+H]^+$ *m/z* 1065.6820. Found: $[M_r+H]^+$ *m/z* 1065.6808.

Continued elution of the chromatography column afforded **6** (101 mg, 42%) as a colorless microcrystalline solid: mp 299–301°C; IR (film) 2961 (s), 2907 (s), 1481 (s), 1202 (s), 1026 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 18H), 1.28 (s, 9H), 1.41 (s, 9H), 1.61–1.82 (m, 4H), 1.91–2.10 (m, 4H), 2.21 (*AB*, J_{AB}=18.0 Hz, 4H), 2.75–2.88 (m, 2H), 3.15 (A*B*, J_{AB}=18.1 Hz, 2H), 3.30 (s, 3H), 3.45–3.60 (m, 5H), 3.61–3.96 (m, 14H), 4.01–4.15 (m, 2H), 4.21 (A*B*, J_{AB}=18.0 Hz, 2H), 6.71 (br s, 2H), 6.96 (br s, 4H), 7.18 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 31.8 (2C, s), 31.9 (q), 32.4 (q), 32.6 (q), 33.2 (s), 34.5 (s), 38.5 (t), 42.10 (d), 42.13 (d), 42.18 (d), 43.8 (t), 44.1 (d), 46.50 (d), 46.53 (d), 46.59 (d), 59.3 (q), 61.7 (d), 69.1 (2C, t), 70.8 (t), 71.2 (2C, t), 72.3 (t), 74.5 (2C, t), 94.8 (s), 125.2 (d), 126.58 (d), 126.62 (d), 126.65 (d), 126.75 (d), 126.86 (d), 128.17 (d), 128.21 (s), 132.5 (t), 133.28 (t), 133.35 (t), 133.6 (t), 141.2 (s), 144.2 (s), 145.7 (s), 151.3 (s), 152.6 (s). Exact mass (CI HRMS) calcd for $C_{66}H_{86}O_8$: $[M_r+H]^+$ *m/z* 1007.6401. Found: $[M_r+H]^+$ *m/z* 1007.6391.

4.2. X-Ray crystal structure determination of 4

All data were collected on a Bruker Smart 1000 CCD-based diffractometer at 170 K. The frames were edited with the SAINT software package[14] by using a narrow-frame algorithm. The structure was solved and refined by using SHELXTL,[15] and the structure was checked by using PLATON.[16] Compound **4** belongs to space group *P*-1 with a=114.359(1) Å, b=15.116(1) Å, c=15.462(1) Å and α=117.509(1)°, β=104.819(1)°, and γ=97.407(1)°. The structure refines to R=0.0840 for 7181 reflections ($I>2\sigma$) and R=0.1025 for all data with a goodness-of-fit (GOF) of 1.034. X-Ray data for **4** are listed in Table 4. There are two intramolecular hydrogen bonds, O(4)–H(4)–O(3) (O(4)–O(3)=2.938(5) Å) and O(6)–H(6)–O(5) (O(6)–O(5)=2.804(4) Å). The water molecule O(8) exhibits no short intermolecular contacts, although there is a void volume of 46.4 $Å^3$, which might contain an additional molecule of water. Complete crystallographic details are available as supplementary material, and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 192564).[17]

4.3. X-Ray crystal structure determination of 7

All data were collected on a Bruker Smart 1000 CCD-based diffractometer at 293 K. The frames were edited with the SAINT software package[14] by using a narrow-frame algorithm. The structure was solved and refined by using

Table 4. X-Ray structure data for **4** and **7**

Compound	**4**	**7**
Formula	$C_{63}H_{80}O_7(H_2O)$	$C_{69}H_{90}O_9{\cdot}2H_2O$
Size (mm)	0.60×0.35×0.27	0.32×0.29×0.18
Space group	*P*-1	$P2_1/c$
a (Å)	14.359(1)	13.655(3)
b (Å)	15.116(1)	13.551(3)
c (Å)	15.462(1)	35.164(7)
α (°)	117.509(1)	90
β (°)	104.819(1)	96.780(5)
γ (°)	97.407(1)	90
V ($Å^3$)	2755.6(3)	6461(2)
Z-value	2	4
D_{calc} (g cm^{-3})	1.165	1.130
μ (mm^{-1})	0.075	0.075
T (K)	170(2)	293(2)
θ range (°)	1.53–22.50	1.17–22.50
Total reflections	11587	26962
Independent reflections	7181	8441
R_{int}	0.0221	0.1626
Data/restraints/parameters	7181/0/659	8441/0/760
$R1$, $wR1$	0.0840, 0.2073	0.1039, 0.2537
Goodness-of-fit on F^2	1.034	0.851

SHELXTL,[15] and the structure was checked by using PLATON.[16] Compound **7** belongs to space group $P2_1/c$ with a=13.655(3) Å, b=13.551(3) Å, c=35.164(7) Å and β=96.780(5)°. The structure refines to R=0.1039 for 8441 reflections ($I>2\sigma$) with a goodness-of-fit (GOF) of 0.851. The structure contains a void of 120 Å^3, which contains a highly disordered solvent molecule. The molecule was omitted in the refinement, although inclusion of random peaks reduces the R factor significantly. X-Ray data for **7** are listed in Table 4. Complete crystallographic details are available as supplementary material, and have been deposited at the Cambridge Crystallographic Data Centre (CCDC 192565).[17]

4.4. Alkali metal picrate extraction experiments

The extraction experiments were performed by using 5 mM solutions of each compound in $CHCl_3$. The procedure that was used for this purpose has been described previously.[6a]

Acknowledgements

We thank the Robert A. Welch Foundation (Grants B-963 (A. P. M) and P-074 (W. H. W.)) and the US Department of Energy (Grant DE-FG07-98ER14936 (A. P. M.)) for financial support of this study. In addition, we thank Professor Jennifer S. Brodbelt (Department of Chemistry, University of Texas at Austin) for having kindly obtained the high-resolution chemical ionization mass spectral data reported herein.

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