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New amino-functionalized 1,3-alternate calix[4]arene bis- and mono-(benzo-crown-6 ethers) for pH-switched cesium nitrate extraction

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Abstract—Four calix[4]arene benzo-crown-6 ethers functionalized with primary amine groups in various positions have been synthesized. The cesium extraction behavior under alkaline and acidic conditions has been measured for these compounds and compared with that of non-amine containing analogs. Extraction strength when the amine group is neutral is not affected by the amino substituent, but protonation causes a marked decrease in extraction strength, permitting pH-switched back-extraction. Published by Elsevier Science Ltd.

Calixarene-crowns or calixcrowns, macrocyclic compounds that combine calixarene and polyether units, are being studied intensively in many laboratories as hosts for selective ion recognition. Many variations of these compounds have been reported, as distinguished by different crown chain lengths and structures and by different substituents on the lower and upper rims.[1] However, there are only a few papers devoted to the synthesis and properties of calix[4]crowns with amino groups.[2] We have recently become interested in calix[4]crowns with pendant primary amines as building blocks for more complex molecules that might find utility in a number of applications, among them, metal ion separation by solvent extraction. Especially useful would be enhanced release of a bound metal ion upon protonation of the amino group, thereby increasing the overall efficiency of binding-release cycles via pH switching. Calix[4]arene-crown-6 ethers in the 1,3-alternate conformation[3] in particular have attracted significant interest in recent years as extremely selective extractants for large alkali metal cations for possible applications such as nuclear-waste remediation,[4] sensing,[5] and radiopharmacy.[6] In this paper, we report syntheses of three types of calix[4]arene-crown-6 ethers categorized according to the location of appended amino groups attached to the crown-ether moiety, to the alkoxy substituents, or to the calixarene unit. We also report a preliminary evaluation of the feasibility of the use of these compounds as pH-switchable extractants for cesium nitrate ion pairs.

The synthesis of the amino-substituted calix[4]crowns of the first type—with the amino group attached to the crown-ether moiety—was performed according to Scheme 1. Bis-1,2-[2′(2″-hydroxyethoxy)ethoxy]-4-cyano-benzene **2** was prepared in 74% yield from commercially available 3,4-dihydroxybenzonitrile by reaction with 2-(2-chloroethoxy)-ethanol in dry dimethylformamide in the presence of K_2CO_3.[7] Reaction of **2** with methanesulfonyl chloride in dichloromethane in the presence of Et_3N afforded the dimesylate **3**[8] in 90% yield. It was shown recently that whereas both dimesylates and ditosylates can be used for the calixcrown synthesis, using dimesylates can lead to improved yields.[9] Reaction of bis-*n*-octyloxy-calix[4]arene **4**[10] with one equivalent of dimesylate **3** was carried out with Cs_2CO_3 in dry acetonitrile in a closed heavy-wall glass reaction vessel at 110°C to give the new 1,3-alternate bis-*n*-octyloxy-calix[4]arene 4-cyano-benzo-crown-6 **5**.[11] Reduction of **5** using $(CH_3)_2S{\cdot}BH_3$ in dry THF gave the desired bis-*n*-octyloxy-calix[4]arene 4-amino-methyl-benzo-crown-6 ether **6**[12] in 90% yield.

The biscrown analogue, calix[4]arene bis[(4-amino-methyl)-benzo-crown-6] **8** was obtained in a similar manner. Thus, reaction of calix[4]arene with two equivalents of dimesylate **3** afforded calix[4]arene bis(4-

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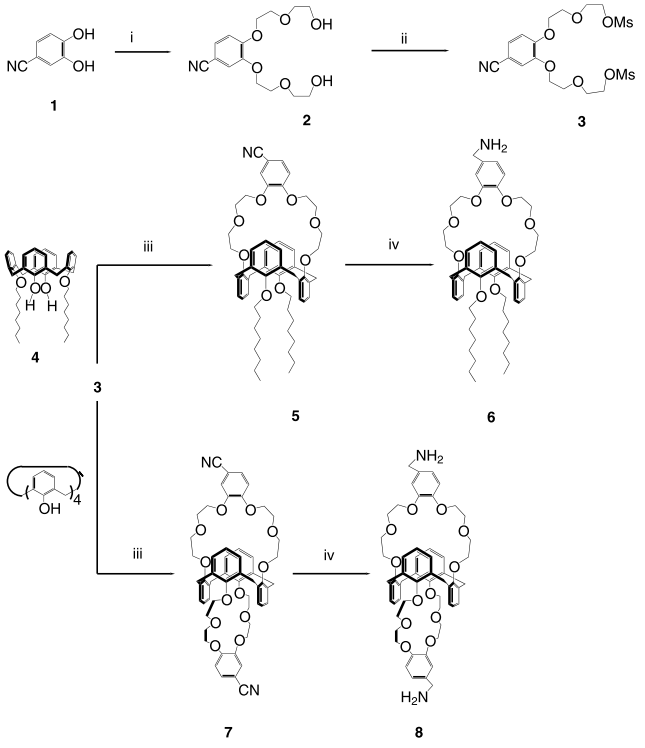
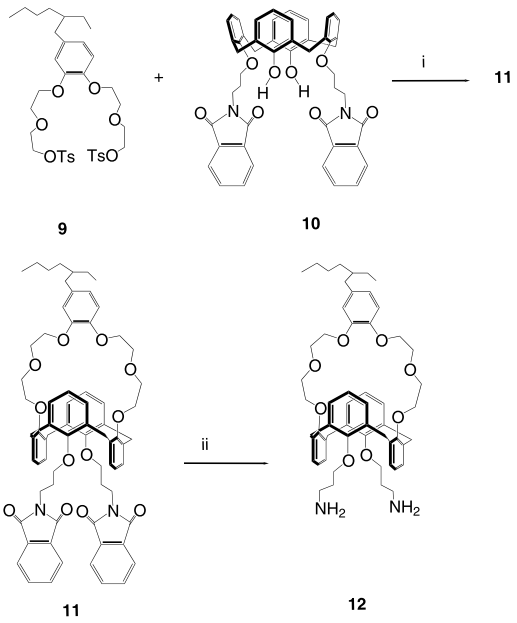
cyano-benzo-crown-6) **7**[13] in 35% yield. Reduction of **7** afforded the new calix[4]arene biscrown **8**[14] in 60% yield.

The second type of calix[4]arene-crown-6 ether—with amino-groups attached to the alkoxy groups in positions 25 and 27 of the calixarene unit—was synthesized according to Scheme 2. 25,27-Bis(phthalimidopropoxy)calix[4]arene 4-(2-ethylhexyl)benzo-crown-6 **11** was prepared in 71% yield from 25,27-bis(3-phthalimidopropoxy)-calix[4]arene **10**[2a] with one equivalent of ditosylate **9**[15] under the same reaction conditions used to prepare compounds **5** and **7**.[16] The phthalimido groups were removed using the conditions described for the synthesis of bis(3-aminopropoxy)-calix[4]arene crown[10] to give the new 25,27-bis-(3-aminopropoxy)-calix[4]arene-4-(2-ethylhexyl) benzo-crown-6 ether **12**[17] in 83% yield.

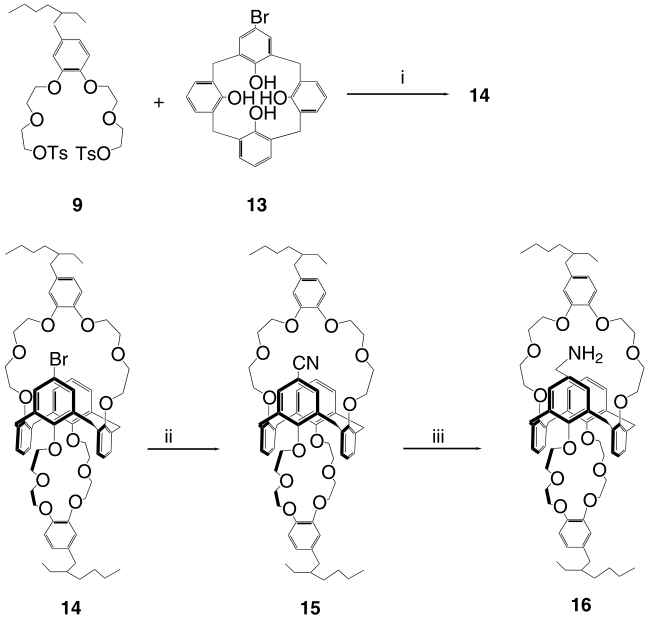
The compound of the third type—with one aminomethyl group attached to the calixarene unit—was synthesized according to Scheme 3. Bromocalix[4]arene - bis(4 - (2-ethylhexyl)benzo - crown - 6 - ether) **14** was prepared in 55% yield from bromocalix[4]arene **13**[18] by reaction with ditosylate **9** and Cs_2CO_3 in acetonitrile under the same reaction conditions described above.[19] The bromide was replaced with a cyano group by treatment of **14** with CuCN in *N*-methyl-pyrrolidinone to afford **15** in 72% yield.[20] Reduction of **15** using $(CH_3)_2S{\cdot}BH_3$ in dry THF gave the desired aminomethyl-calix[4]arene bis(4-(2-ethylhexyl) benzo-crown-6) **16** in 92% yield.[21]



Scheme 1. *Reagents and conditions*: (i) $ClCH_2CH_2OCH_2$-CH_2OH, K_2CO_3, DMF, 80°C, 48 h; (ii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, rt, 48 h; (iii) Cs_2CO_3, CH_3CN, 110°C; (iv) $(CH_3)_2S{\cdot}BH_3$, THF, refluxing.



Scheme 2. *Reagents and conditions*: (i) Cs_2CO_3, CH_3CN, 110°C, 4 days; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, 110°C.



Scheme 3. *Reagents and conditions*: (i) Cs_2CO_3, CH_3CN, 110°C, 4 days; (ii) CuCN, NMP, 200°C, 48 h; (iii) $(CH_3)_2S{\cdot}BH_3$, THF, refluxing, 24 h.

Extraction results demonstrated proof-of-principle for pH-switched extraction and release. The new calix[4]arene monocrowns **6** and **12** and calix[4]arene biscrowns **8** and **16** were compared to calixcrowns **17**[10] and **18**[10] without amino groups as controls (Fig. 1). The organic phase in each case consisted of a calixcrown at 2.5 mM in nitrobenzene, a diluent chosen for its high polarity, which promotes solubility of the calixcrowns and their complexes and which discourages ion-pairing.

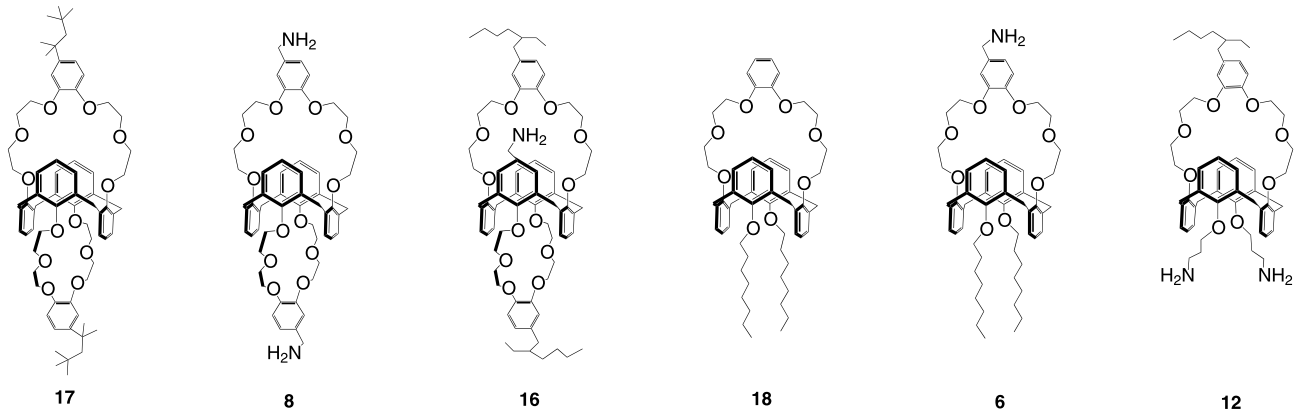


Figure 1. Calixcrowns used in extraction tests.

The absence or weakening of ion-pairing was expected to maximize the repulsive effect of the protonated amino group on binding of the Cs cation. In the case of the control compounds **17** and **18** without amino groups, 2.5 mM of tri-*n*-octylamine (TOA) was also added to the organic phase to serve as a control for the presence of an amine group. It may be noted that alkylation of the benzo group in calix[4]arene-benzo-crown-6 compounds has only a very minor effect on cesium extraction strength.[6,10]

Extractions were carried out from alkaline (1 M $NaNO_3$, 0.05 M NaOH, 10^{-4} M $CsNO_3$) and acidic (0.95 M $NaNO_3$, 0.05 M HNO_3, 10^{-4} M $CsNO_3$) aqueous solutions containing $^{137}CsNO_3$ radiotracer (0.58 μCi/mL). A back-extraction (stripping) of the organic phase previously contacted with the alkaline aqueous phase was carried out using an acidic aqueous phase (0.95 M $NaNO_3$, 0.05 M HNO_3) containing no cesium or tracer. These aqueous conditions were selected so that the driving force for cesium nitrate extraction, as controlled by the aqueous nitrate concentration, was approximately constant in all cases. Hence, differences in extraction behavior on pH swing would be only due to the pH effect. In each case, equal phase volumes were equilibrated by gentle agitation in capped vials for 90 min at 25°C. The cesium distribution ratio D_{Cs} is defined as $[Cs]_{org}/[Cs]_{aq}$.

Results presented in Figure 2 demonstrate large decreases in cesium extraction strength, as much as two orders of magnitude, upon acidification of the aqueous phase. Under alkaline conditions, it may be seen that, except for the bis-amino-propoxy calix[4]crown **12**,[22] the presence of the amino group does not change D_{Cs} significantly. On extraction from acidic solution, the controls **17** and **18** exhibit decreased extraction (ca. 2–3-fold), an effect that may be taken as inhibition of cesium nitrate extraction by a common-ion effect due to nitric acid extraction. This inhibition is expected in all cases based on Le Chatelier's principle and supports the extraction of cesium nitrate as dissociated ion pairs. Extraction under the acidic conditions decreases significantly for all the amino substituted compounds, and most significantly for the aminomethyl calix[4]arene

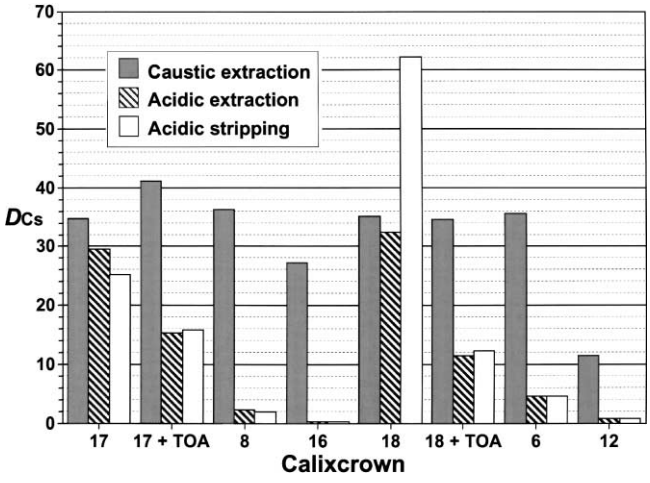


Figure 2. Cesium extraction results for calixcrowns presented in Fig. 1 (at 2.5 mM in nitrobenzene) under alkaline and acidic conditions.

biscrown **16**. Stripping under acidic conditions gives approximately the same value of the cesium distribution ratio D_{Cs} as extraction under nitric acid conditions, confirming that back-extraction is enhanced. Combination of high extraction ability under basic conditions and high stripping efficiency under acidic conditions make compound **16** an attractive extractant candidate among the amino substituted calix[4]arene crowns synthesized thus far.

In conclusion, syntheses of the new calix[4]arene-crown-6 ethers with amino groups in different positions are reported. Extraction strength when the amino group is neutral is not affected by the amino substituent, but protonation causes a marked decrease in extraction strength, permitting pH-switched back-extraction. Amino-methyl-calix[4]arene biscrown **16** appeared to be the most promising extractant. Further studies of the extraction behavior of the amino substituted calix[4]arene crowns **6**, **8**, **12**, and **16** and their derivatives are being carried out.

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7. **2**: Solid, m.p. 74–76°C; ^{1}H NMR (400.13 MHz; $CDCl_3$, 23°C): δ 3.62–3.79 (m, 8H), 3.86–3.95 (m, 4H), 4.15–4.25 (m, 4H), 6.90 (d, $J=8.4$, 1H), 7.10 (d, $J=1.8$, 1H), 7.27 (dd, $J=1.8$, $J=8.4$, 1H); ^{13}C NMR (100.61 MHz; $CDCl_3$, 23°C): (selected) δ 118.9 (*C*N). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.86; H; 7.02; N, 4.49%. ^{1}H and ^{13}C NMR for all other compounds were obtained under the same conditions unless otherwise noted.
8. **3**: Oil. ^{1}H NMR: δ 3.05 (s, 3H) 3.07(s, 3H), 3.83–3.85 (m, 4H), 3.86–3.88 (m, 4H), 3.41–4.22 (m, 4H) 4.38–4.43 (m, 4H), 6.91 (d, $J=8.4$, 1H), 7.11 (d, $J=1.9$, 1H), 7.27 (dd, $J=1.9$, $J=8.4$, 1H); ^{13}C NMR: (selected) δ 119.6 (*C*N). Anal. Calcd for $C_{17}H_{25}NO_{10}S_2$: C, 43.67; H, 5.39; N, 3.00. Found: C; 43.63; H; 5.66; N, 3.08%.
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11. **5**: Solid, m.p. 124–126°C; ^{1}H NMR: δ 0.92 (t, $J=7.0$, 6H), 1.17–1.36 (br m, 24H), 3.45–3.57 (m, 8H), 3.74 (s, 8H), 3.70–3.81 (m, 8H), 4.10–4.18 (m, 4H), 6.62 (t, $J=7.5$, 2H), 6.76 (t, $J=7.5$, 2H), 6.97-7.05 (m, 9H), 7.20 (d, $J=1.9$, 1H), 7.33 (dd, $J=1.9$, $J=8.4$, 1H); ^{13}C NMR: (selected) δ 38.05 (Ar*C*H$_2$Ar), 118.07 (*C*N). Anal. Calcd for $C_{59}H_{73}NO_8$: C, 76.67; H, 7.96; N, 1.66. Found: C; 76.38; H, 8.00; N, 1.73%.
12. **6**: Solid, m.p. 238–240°C; ^{1}H NMR: δ 0.91 (t, $J=7.0$, 6H), 1.10–1.56 (br m, 24H), 3.25–4.45 (m, 20H), 3.75 (s, 8H), 6.65 (br t, $J=7.2$, 2H), 6.79 (br t, $J=7.2$, 2H) 6.92 (br s, 2H), 7.00–7.04 (br m, 9H); ^{13}C NMR: (selected) δ 38.31 (Ar*C*H$_2$Ar), 43.67 (*C*H$_2$NH$_2$). Anal. Calcd for $C_{59}H_{77}NO_8\cdot 2H_2O$: C, 73.48; H, 8.48; N, 1.45. Found: C, 73.84; H, 8.37; N, 1.41%.
13. **7**: Solid, m.p. 258–260°C; ^{1}H NMR: δ 3.50–3.65 (m, 12H), 3.78 (s, 8H), 3.68–3.83 (m, 12H), 4.10–4.20 (m, 8H), 6.67 (t, $J=7.5$, 4H), 6.99 (d, $J=8.3$, 2H), 7.04-7.10 (m, 8H), 7.20 (d, $J=1.4$, 2H), 7.34 (dd, $J=1.4$, $J=8.3$, 2H); ^{13}C NMR: (selected) δ 38.27 (Ar*C*H$_2$Ar), 118.54 (*C*N). Anal. Calcd for $C_{58}H_{58}N_2O_{12}$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.56; H 6.08; N, 2.94%.
14. **8**: Solid, m.p. 237–239°C; ^{1}H NMR: δ 3.48–3.63 (m, 16H), 3.64–3.74 (m, 8H) 3.77 (s, 8H), 3.84 (s, 4H), 4.06–4.20 (m, 8H), 6.70 (t, $J=7.5$, 4H), 6.90–7.04 (m, 6H), 7.06 (d, $J=7.5$, 8H); ^{13}C NMR: (selected) δ 38.38 (Ar*C*H$_2$Ar), 46.80 (*C*H$_2$NH$_2$). Anal. Calcd for $C_{58}H_{66}N_2O_{12}$: C, 70.86; H, 6.77; N, 2.85. Found: C, 70.60; H, 6.81; N, 2.78%.
15. **9**: Engle, N. L.; Bonnesen P. V.; Tomkins, B. A.; Haverlock, T. J.; Moyer, B. A. To be submitted to *Solv. Extr. Ion Exch.*
16. **11**: Solid, m.p. 107–109°C; ^{1}H NMR: δ 0.85–0.90 (m, 6H), 1.23–1.35 (br m, 8H), 1.50–1.65 (m, 5H), 2.48 (m, 2H), 2.56–2.62 (m, 4H), 3.4–3.9 (m, 16H), 3.78 (s, 8H), 4.00–4.25 (m, 4H), 6.65 (t, $J=7.5$, 2H), 6.70–6.94 (m, 5H), 7.04 (br d, $J=7.5$, 8H), 7.65–7.70 (m, 4H), 7.76–7.82 (m, 4H); ^{13}C NMR: (selected) δ 38.26 (Ar*C*H$_2$Ar), 168.53 (*C*=O). Anal. Calcd for $C_{72}H_{76}N_2O_{12}$: C, 74.46; H, 6.60; N, 2.41. Found: C, 74.24; H, 6.68; N, 2.35%.
17. **12**: Solid, m.p. 124–126°C; ^{1}H NMR: δ 0.83–0.89 (m, 6H), 1.23–1.32 (br m, 8H), 1.50–1.63 (m, 5H), 2.40–2.50 (m, 2H), 3.40–3.90 (m, 32H), 4.00–4.30 (m, 4H), 6.68 (t, $J=7.5$, 2H), 6.70–6.95 (m, 5H), 7.00–7.20 (m, 8H); ^{13}C NMR: (selected) δ 38.00 (Ar*C*H$_2$Ar), 41.11 (*C*H$_2$NH$_2$). Anal. Calcd for $C_{56}H_{72}N_2O_8\cdot H_2O$: C, 73.18; H, 8.13; N, 3.04. Found: C, 73.39; H, 7.85; N, 2.96%.

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19. **14**: Solid, m.p. 82–84°C; ^{1}H NMR: δ 0.87 (t, 12H), 1.27 (br s, 16H), 1.45–1.60 (br m, 2H), 2.40–2.60 (br m, 4H), 3.40–3.90 (m, 32H), 4.05–4.12 (m, 4H), 4.14–4.25 (m, 4H), 6.68 (t, $J=7.4$, 4H) 6.70–6.85 (m, 4H), 6.88 (d, $J=8.1$, 2H), 7.00–7.15 (m, 6H), 7.22 (s, 2H); ^{13}C NMR: (selected) δ 37.49 (Ar*C*H$_2$Ar), 37.81 (Ar*C*H$_2$Ar). Anal. Calcd for $C_{72}H_{91}BrO_{12}$: C, 70.40; H, 7.47. Found: C, 70.15; H, 7.37%.
20. **15**: Solid, m.p. 93–95°C; IR (deposit from CH_2Cl_2 solution on KCl plate, cm^{-1}): ν 2255 (CN); ^{1}H NMR: δ 0.87 (t, 12H), 1.27 (br s, 16H), 1.45–1.60 (br m, 2H), 2.40–2.52 (m, 4H), 3.44–3.82 (m, 32H), 4.00–4.20 (m, 8H), 6.62 (t, $J=7.5$, 2H), 6.65–6.83 (m, 6H), 6.88 (m, 2H), 7.00–7.10 (m, 6H), 7.46 (s, 2H); ^{13}C NMR: (selected) δ 37.38 (Ar*C*H$_2$Ar), 37.72 (Ar*C*H$_2$Ar), 119.94 (*C*N). Anal. Calcd for $C_{73}H_{91}NO_{12}$: C, 74.65; H, 7.81; N, 1.19. Found: C, 74.66; H, 7.73; N, 1.09%.
21. **16**: Solid, m.p. 106–108°C; ^{1}H NMR: δ 0.83–0.90 (m, 12H), 1.10–1.35 (br m, 16H), 1.45–1.60 (br m, 2H), 2.40–2.52 (br m, 4H), 3.48–3.80 (m, 26H), 4.00–4.20 (m, 10H), 4.40–4.50 (br m, 2H), 4.59 (br s, 2H), 6.16 (br s, 1H), 6.65 (t, $J=7.5$, 2H), 6.68–6.95 (m, 9H), 7.02–7.10 (m 4H), 7.24 (s, 2H); ^{13}C NMR: (selected) δ 37.48 (Ar*C*H$_2$Ar), 37.74 (Ar*C*H$_2$Ar), 44.62 (*C*H$_2$NH$_2$). Anal. Calcd for $C_{73}H_{95}NO_{12}\cdot 2H_2O$: C, 72.18; H, 8.15; N, 1.18. Found: C, 72.63; H, 8.15; N, 1.18%.
22. The weaker extraction by **12** implies an additional effect, which we suggest may arise from a negative allosteric influence of intramolecular hydrogen binding. This possibility is under investigation.