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Regioselective routes to disubstituted dibenzo crown ethers and their complexations†

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Two isomers of bis(carbomethoxybenzo)-24-crown-8 (*cis*-BCMB24C8, **1**, and *trans*-BCMB24C8, **2**) were synthesized regiospecifically with acceptable to excellent yields. Cyclization in the presence of a template reagent, KPF_6, led to an essentially quantitative yield of the potassium complex of the crown ether **1**; the isolated cyclization yield of *pure* ***1*** was a remarkable 89%! The methods not only avoid the very difficult separation of the isomers, but also greatly shorten the synthesis time by eliminating syringe pump usage during cyclization. The complexations of the isomeric BCMB24C8 with dibenzylammonium hexafluorophosphate (**10**) were studied by NMR; association constants (K_a) for **1** and **2** with the dibenzylammonium cation are 190 and 312 M^{-1}, respectively. The X-ray crystal structures of crown ether **2** and the complexes **1**·KPF_6, **2**·KPF_6 and pseudorotaxane **2**·**10** were determined.

Introduction

Dibenzo-24-crown-8 (DB24C8) forms pseudorotaxanes with secondary ammonium salts driven by hydrogen bonding and ion–dipole interactions in low-polarity solvents, such as chloroform and acetonitrile.[1] The dibenzo-24-crown-8 moiety has been widely employed in the construction of pseudorotaxanes, rotaxanes and catananes.[1,2] Rotaxanes and polyrotaxanes derived from mono- or di-functionalized DB24C8 have been reported extensively.[1b,3–5] However, for further development of supramolecular chemistry, substituted crown ethers are required to construct more complicated and delicate designs.

There are two approaches for synthesis of functionalized dibenzo crown compounds. One is the synthesis of the parent macrocycle followed by functionalization through aromatic electrophilic substitution. This usually consists of few steps, but produces mixtures of regioisomers.[5] Our lab has devised another approach using properly pre-functionalized aromatic precursors as starting materials to synthesize single isomers of substituted crown ether macrocycles (cyclophanes). This method has been successful in making di-substituted, "axially" symmetrical bis(*m*-phenylene)-(3x + 2)-crown-x ethers using 5-functionalized resorcinols (Scheme 1) with yields up to 50%.[6–8]

Though, as shown below, the method works for syntheses of disubstituted DB24C8 using catechol analogs, control of the regiochemistry of the product is lost due to the unsymmetric substitution on the catechol rings. The cyclization step produces two positional isomers, which are often difficult, if not impossible, to separate and thus are often used as mixtures.[4e,f,5] Due to the potential differences of the two isomers of di(functionalized benzo) crown ethers in complexation and other physical properties, it is desirable to study the isomers separately. In 1997 Sachleben *et al.* reported syntheses of *cis*-bis-(*tert*-butylbenzo)24C8 and *cis*-bis-(*tert*-octylbenzo)24C8 in 35% and 20% yields, respectively, using pre-linked catechols and tri(ethylene glycol) dichloride with $CsCO_3$ as base at unspecified concentrations.[9] Replacing the catechol rings with resorcinol rings and making alternative crowns with the same ring size to imitate DB24C8 are two ways that have been used to avoid the isomer problem.[10,11] In this paper, using the bis(carbomethoxy) derivatives as examples, efficient routes for synthesis of pure DB24C8 isomers monosubstituted on each aromatic ring are reported. Both of the DB24C8 isomers form complexes with dibenzylammonium hexafluorophosphate, but with different affinities as expected.

Results and discussion

A Syntheses of mixed bis(carbomethoxybenzo)24C8 (BCMB24C8) isomers

First, we synthesized BCMB24C8 employing the traditional method (Scheme 2) with a relatively high cyclization yield, 53%. The product obtained was a mixture of *cis*- and *trans*-BCMB24C8 regioisomers, **1** and **2**. All attempts to separate the two isomers, including derivatization, failed. Thus we turned our attention to other routes.

† Electronic supplementary information (ESI) available: Cyclization yields of **2** and **9** at various starting material concentrations; X-ray crystallographic files (CIF) for *trans*-BCMB24C8 (**2**), complexes of *cis*-BCMB24C8 (**1**) and *trans*-BCMB24C8 (**2**), respectively, with KPF_6, and the complex of *trans*-BCMB24C8 (**2**) with dibenzylammonium hexafluorophosphate (**10**); ^{1}H NMR complexation data for **1**·**10** and **2**·**10** and analysis of K_a and K_{ipd}; preliminary estimates of association constants for **1** and **2** with KPF_6. See http://www.rsc.org/suppdata/ob/b5/b503072m/

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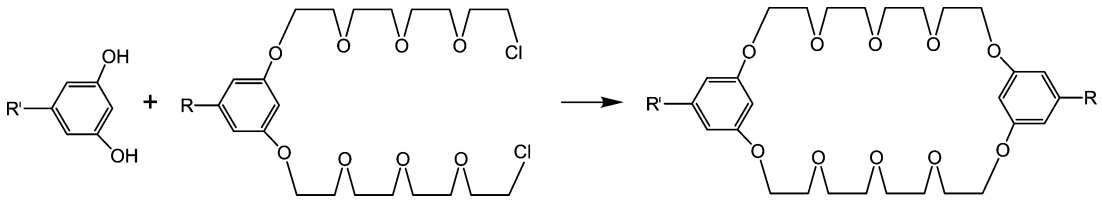
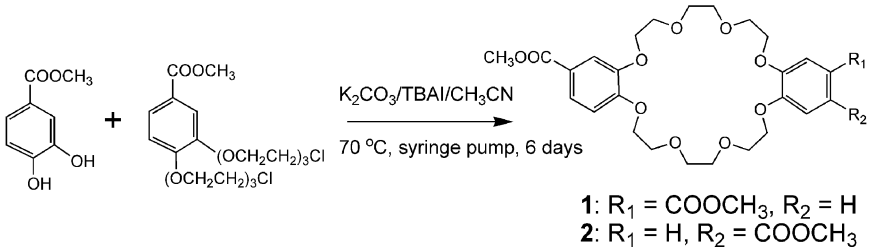


Scheme 1 General cyclization method for making disubstituted "axially" symmetrical bis-(*m*-phenylene)-(3*x* + 2)-crown-*x* ethers.



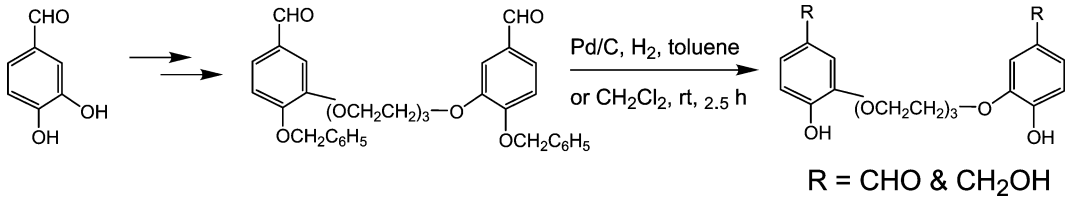
Scheme 2 Synthesis of a mixture of BCMB24C8 isomers **1** and **2**.

B Synthesis of *cis*-BCMB24C8 isomer 1

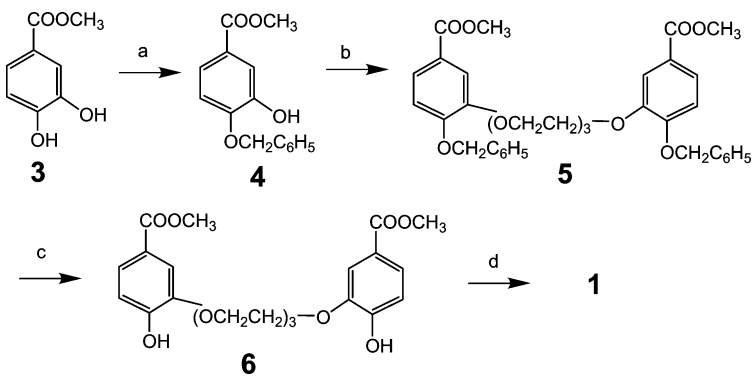
A method reported recently for synthesis of regio-controlled diformyl DB18C6 isomers[12] was initially adapted. 3,4-Dihydroxybenzaldehyde was selectively protected at the 4-hydroxyl group (65%) and coupled *via* tri(ethylene glycol) ditosylate (Scheme 3). The deprotection of the hydroxyl groups was carried out under H_2 atmosphere as reported. However, we found that it was very difficult to control and a mixture of aldehyde and alcohol was always obtained.

To overcome this problem, methyl 3,4-dihydroxybenzoate (**3**) was used in place of the 3,4-dihydroxybenzaldehyde. The 4-hydroxyl group in **3** was selectively protected by reaction with benzyl bromide in DMF to give methyl 4-benzyloxy-3-hydroxybenzoate (**4**) in 51% yield (Scheme 4). In this step acetonitrile is a better solvent than DMF; it gives the same yield, but work-up is much easier due to its lower boiling point. Otherwise, no attempt was made to optimize this step, since the starting materials are relatively inexpensive. The coupling reaction of **4** with tri(ethylene glycol) ditosylate was carried out in acetonitrile to give diprotected precursor **5** quantitatively. The deprotection of **5** gave pure desired diphenolic product, **6**, with a yield of 87%; again we expect that optimization of this step would make it essentially quantitative.

The cyclization of **6** and tri(ethylene glycol) ditosylate was carried out in the presence of potassium hexafluorophosphate as a template reagent. Historically, reactions to form macrocyclic compounds have often been performed under pseudo-high dilution conditions *via* syringe pump reagent addition to suppress the formation of acyclic oligomers.[8b,13,14] It is significant that without using a syringe pump in the cyclization step the isolated yield for pure **1** after recrystallization is 89%. Compared to the conventional synthesis shown in Scheme 2, this method also saves both time and solvent. The templating effect of the potassium cation clearly plays an important role. The initial crude product was the complex of **1** and potassium cation, **1**·$K^{\pm}$, obtained in essentially quantitative yield. Association constants for complexation between DB24C8 and potassium ion in acetonitrile as measured by conductivity and solubility average 7.62 (±1.92) × 10^3 M^{-1}.[15] (See the ESI for preliminary estimates of the association constant for **1** with KPF_6, which is comparable.†) The use of templation in crown ether synthesis[13]



Scheme 3 DB24C8 derivatives *via* protection/deprotection route.



Scheme 4 Synthesis of *cis*-BCMB24C8 (**1**). a. $C_6H_5CH_2Br$, K_2CO_3, CH_3CN, 65 °C/12 h, 51%. b. $Ts(OCH_2CH_2)_3OTs$, K_2CO_3, MeCN, reflux/15 h, 100%. c. H_2, Pd/C, CH_2Cl_2, 12 h, 87%. d. $Ts(OCH_2CH_2)_3OTs$, K_2CO_3, KPF_6, MeCN, 80 °C/24 h, 89%.

dates to their discovery by Pedersen,[2a] but we are unaware of other reports of such cyclization yields for the larger (>18-membered) crown ethers [van Eis *et al.* reported[12a] a 92% yield of *cis*-bis(formylbenzo)-18-crown-6], particularly in bimolecular processes; the highest cyclization yield (95% estimated spectroscopically, not isolated) known to us was reported for unimolecular cyclization to form benzo-18-crown-6 in very dilute, non-preparative conditions (0.52 mM) in the presence of NaBr.[13a]

^{1}H NMR spectra of the crude product before and after washing with water are compiled in Fig. 1. In ^{1}H NMR signals for α- and α′-protons are well resolved in **1**·K^+. In FAB mass spectrometry the complex of **1** with KPF_6 displayed a strong peak at *m*/*z* 603.19 for [**1**·K]$^+$. After washing with water to remove K^+, the signals of α- and α′-protons merge in **1**, while the other signals show up- or down-field shifts relative to **1**·K^+. As these spectra indicate, the cyclization yield is essentially quantitative! The solubility of the crude product before and after washing with water also changed greatly, from easily soluble in methanol to slightly soluble. **1** was purified by recrystallization in methanol.

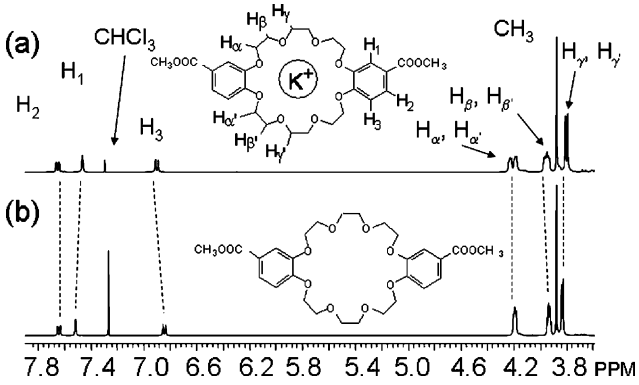


Fig. 1 400 MHz ^{1}H NMR spectra in $CDCl_3$: (a) crude product before washing with water, **1**·K^+ PF_6^-, (b) crude product after washing with water, **1**.

C Synthesis of *trans*-BCMB24C8 isomer 2

Protected phenol **4** was reacted with equimolar tri(ethylene glycol) dichloride[2a] (Scheme 5) to give **7**. Though it was more reactive, tri(ethylene glycol) ditosylate gave a crude product with complicated composition, which was difficult to separate. With tri(ethylene glycol) dichloride the crude product can be easily purified by column chromatography to give pure **7**, which upon deprotection by hydrogenolysis quantitatively affords difunctional precursor **8**. With potassium carbonate as the base, **8** underwent a 1 + 1 cyclization to give the expected product **2**. As in the synthesis of *cis*-BCMB24C8, no syringe pump was employed in the cyclization.

Intramolecular cyclization of **8** leads to the small ring product **9**. We tried to minimize the contribution of the intramolecular process by using more concentrated reaction solutions. The results (see ESI: Table S1†) show that high concentrations do not increase the yield of larger ring **2**, although dilute conditions do favor small ring formation. The highest yield of **2** (44%) was obtained with an initial concentration of 23 mM of precursor **8** in the reaction solution.

As with *cis*-BCMB24C8 (**1**), the *trans*-BCMB24C8 complex with potassium cation (**2**·K^+) was obtained as the crude product before exposure to water. This complex even survives silica gel column chromatography with ethyl acetate as eluent. (See below for its crystal structure and the ESI for an estimate of the association constant for **2** with KPF_6, which is comparable to that reported for DB24C8 with KPF_6.[15]) In FAB mass spectrometry the complex of **2** with KPF_6 displayed a strong peak at *m*/*z* 603.19 for [**1**·K]$^+$. The ^{1}H NMR spectra in Fig. 2 show that α- and α′-proton signals are well resolved for **2**·K^+, while merged in **2**. All the protons except the γ-protons show downfield shifts in the complex compared to uncomplexed **2**.

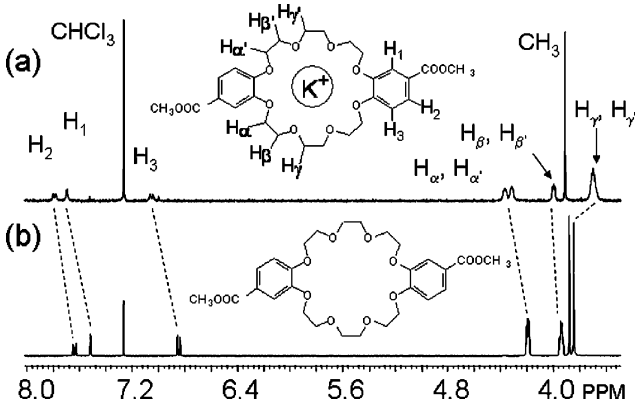
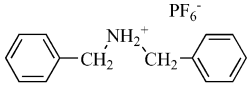


Fig. 2 400 MHz ^{1}H NMR spectra in $CDCl_3$: (a) crude product before washing with water, **2**·K^+ PF_6^-, (b) crude product after washing with water, **2**.

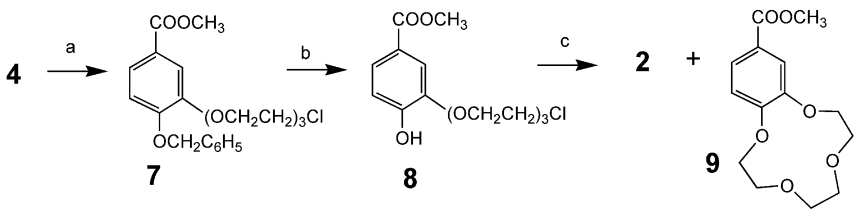
D Complexation of isomeric BCMB24C8 derivatives with dibenzylammonium hexafluorophosphate (10)

For comparison with the previously reported DB24C8 results,[16a] complexation studies of BCMB24C8 isomers, **1** and **2**, with **10** were carried out in 2 : 3 CD_3CN : $CDCl_3$ at 22 ± 1 °C. **1** is soluble up to 30 mM, but the maximum concentration of **2** is 12.4 mM. In the ^{1}H NMR spectra of the solutions (Fig. 3), just as with the model system DB24C8·**10**,[2b,16a] there are two sets of peaks attributable to the free and complexed species of each component, resulting from a slow-exchange complexation based on the NMR time scale. The complexation percentages of the crown ethers were determined by integrations of the well resolved proton H_3 signals in the complexed and free crown ether species. Then the concentrations of each species in the samples were calculated (see ESI: Tables S2 and S3†).



10

The values of the apparent association constant $K_{a,exp}$ = [complex]/([crown]$_o$ − [complex])([**10**]$_o$ − [complex]) varied two- to three-fold with concentration. This result indicates we have to take into account ion-pair dissociation effects, *i.e.*, the fact that the complex is not ion paired but the ammonium salt is ion paired, meaning that it is the ammonium cation (G^+) that is the actual guest and not the salt.[16] The analysis was done



Scheme 5 Synthesis of *trans*-BCMB24C8 (**2**). a. $Cl(CH_2CH_2O)_2CH_2CH_2Cl$, K_2CO_3, MeCN, reflux/3 d, 75%. b. H_2, Pd/C, CH_2Cl_2, 12 h, 100%. c. K_2CO_3, KPF_6, MeCN, reflux/3 d.

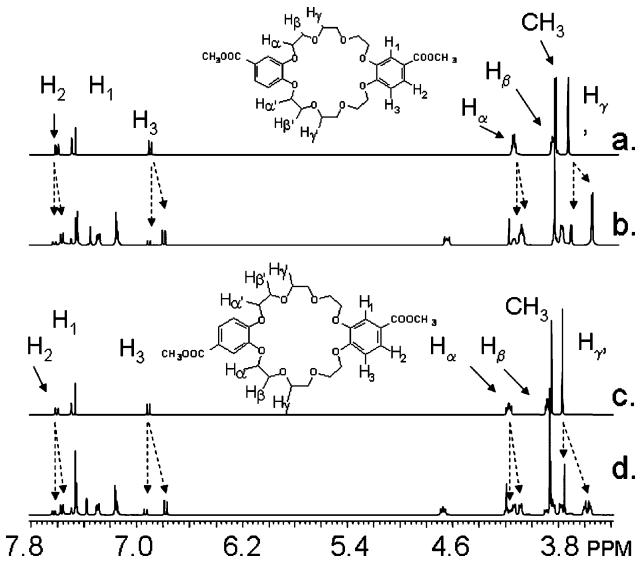


Fig. 3 400 MHz ^{1}H NMR spectra in 2 : 3 CD_3CN : $CDCl_3$: (a) $[\mathbf{1}]_0$ = 20 mM, (b) $[\mathbf{1}]_0 = [\mathbf{10}]_0$ = 20 mM, (c) $[\mathbf{2}]_0$ = 10 mM, (d) $[\mathbf{2}]_0 = [\mathbf{10}]_0$ = 10 mM.

by the method we recently developed for the parent system of DB24C8·**10**.[16a] We found that for complexation of host **1** with the dibenzylammonium cation (G^+) $K_a = 190 \pm 67$ M^{-1}, while the ion pair dissociation constant of **10**, $K_{ipd} = 6.8\ (\pm 5.5) \times 10^{-3}$ M. For complexation of **2** with the dibenzylammonium cation (G^+) $K_a = 312 \pm 35$ M^{-1}, and the independently determined value for K_{ipd} of **10** was 4.4 ($\pm$1.2) $\times$ 10^{-3} M. The two values of K_{ipd} for **10** agree with each other and our previous determination within the error limits (see ESI for details†).

It can be understood that the association constants (K_a) of BCMB24C8 isomers **1** and **2** with the dibenzylammonium cation (G^+) are smaller than that of unsubstituted DB24C8 ($K_a = 560 \pm 60$ M^{-1}).[16a] The two electron-withdrawing carbomethoxy groups reduce the electron density of the oxygen atoms in the crown ether ring both inductively and *via* resonance. Thus the hydrogen bonding of the crown ether oxygen atoms of **1** and **2** with the acidic protons of the dibenzylammonium cation (G^+) become weaker, lowering K_a values. The different K_a values of **1** and **2** with the dibenzylammonium cation (G^+) can be explained by the different symmetry of the substitutions. In *cis*-crown **1**, the two tri(ethylene glycol) tethers differ from each other, because the oxyethylene units *para* to both ester groups become less basic than those *meta*, on account of the stronger resonance effect,[17] resulting in an unbalanced crown. In *trans*-crown **2** the two tri(ethylene glycol) tethers are identically affected by the two ester moieties. Thus the more symmetric crown ether **2** gives a more stable complex than **1**.

MALDI-TOF mass spectrometric characterization of the complexes of **1** and **2** with **10** yielded parent ion signals at *m*/*z* 762.35 for [crown·**10**-PF_6]$^+$. The results corroborate the 1 : 1 complexation observed in solution and solid states (see below).

E X-Ray crystallography of DB24C8 diesters and their complexes

1 Solid state structure of *trans* diester crown ether 2. Attempts to grow suitable crystals of **1** failed, but crystals of **2** were readily obtained. The crystal structure of free **2** (Fig. 4)[18] shows an extended molecule, in which the two aromatic rings

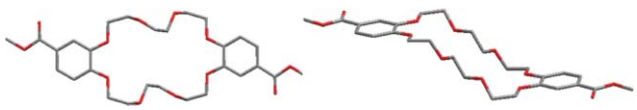


Fig. 4 Solid state structure of **2** (gray: carbon atoms, red: oxygen atoms). Hydrogens are omitted for clarity.

Table 1 Lengths (Å) of ion–dipole interactions between K^+ and ether oxygen atoms in the complexes **1a**·KPF_6 and **2a**·KPF_6

Interaction	**1a**·KPF_6	**2a**·KPF_6	Interaction	**1a**·KPF_6	**2a**·KPF_6
a	2.94	3.00	*f*	2.84	2.82
b	2.75	2.74	*g*	2.73	2.77
c	2.81	2.81	*h*	2.95	2.97
d	2.93	2.94	*i*	2.68	2.65
e	2.97	2.92			

are parallel. It resembles the solid state structure of parent DB24C8.[19]

2 Solid state structures of diester crown ether complexes with KPF_6. In crystals of **1**·KPF_6[20] and **2**·KPF_6[21] the crown molecules fold to a V-shape with a twist so that the planes of aromatic rings have inclination angles of 120.9 and 99.4°, respectively (Fig. 5a,c). Potassium cations reside in the center of the V, bound by ion–dipole interactions with all eight ether oxygen atoms. As shown in Table 1, in both complexes the distances between the potassium cations and the four oxygen atoms adjacent to the γ-carbons are shorter (interactions *b*, *c*, *f* and *g* of **1**·KPF_6 and **2**·KPF_6) than those between the potassium cation and the four phenolic oxygen atoms (interactions *a*, *d*, *e* and *h* of **1**·KPF_6 and **2**·KPF_6). This agrees with the ^{1}H NMR spectral results (Figs. 1 and 2) in that the γ-protons undergo upfield shifts upon complexation. Note that for **1**·KPF_6 interactions *e* and *h* with oxygen atoms *para* to the ester moieties are longer than those *meta* to them, *a* and *d*; this is consistent with the argument made above concerning the inductive and resonance effects of the substituents. Conversely in **2**·KPF_6 this correlation does not hold, perhaps because of packing forces.

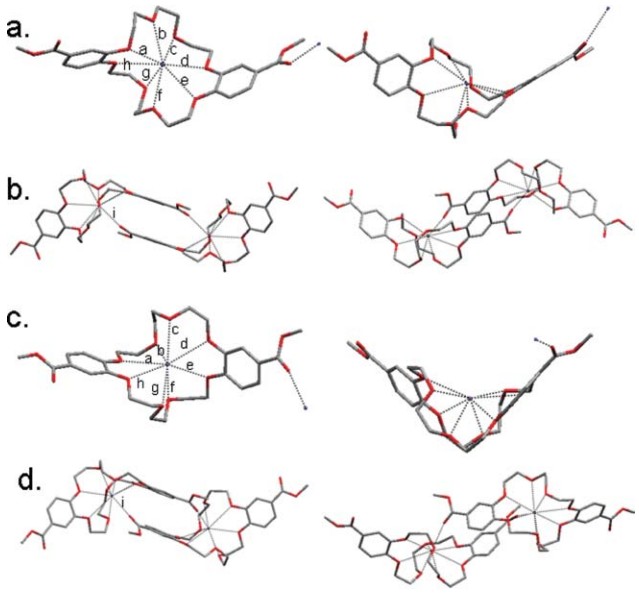


Fig. 5 Solid state structures of complexes of BCMB24C8 isomers with K^+. (gray: carbon atoms, red: oxygen atoms, blue: K^+ cation): (a) **1**·KPF_6, (b) dimer of **1**·KPF_6 (π–π stacking centroid–centroid distance = 3.984 Å, planar inclination angle = 0°), (c) **2**·KPF_6, (d) dimer of **2**·KPF_6 (π–π stacking centroid–centroid distance = 3.648 Å, planar inclination angle = 9.8°). Hydrogen atoms and PF_6^- groups are omitted for clarity.

Both **1**·KPF_6 and **2**·KPF_6 form dimers through ion–dipole interactions between the potassium cations residing in the first crown molecule and the carbonyl oxygen of the second crown molecule; these interactions have the shortest lengths (interactions *i* of **1**·KPF_6 and **2**·KPF_6) among all the interactions of the potassium cations with crown oxygen atoms (Fig. 5b,d). Both dimers are further stabilized by π–π stacking of two of the benzo rings.

Table 2 Hydrogen bond parameters for complex **2a·10**

Hydrogen bond	C(N)–O length (Å)	H–O length (Å)	C(N)–H–O angle (°)
a	3.07	2.15	173
b	2.82	1.90	179
c	3.25	2.60	123
d	3.59	2.64	163
e	3.30	2.47	141
f	3.29	2.32	165

3 Solid state structure of complex 2·10. In the crystal structure of pseudorotaxane **2·10** (Fig. 6a),[22] the crown molecule takes on the conformation of free **2**, but with a little twist so that the two catechol rings have a planar inclination angle of 15.9°. The dibenzylammonium cation threads the crown ring to form the pseudorotaxane complex, stabilized predominantly by two N–H–O (*a*, *b*) and three N–CH–O (*c*, *d*, *e*, *f*; *c* & *d* bifurcated) hydrogen bonds between the NH_2^+ center and the adjacent benzylic CH_2 groups, respectively, and ether oxygen atoms of **2** (Table 2). π–π overlap between one of the catechol rings of **2** and one of the phenyl rings of the dibenzylammonium cation further stabilizes the pseudorotaxane complex. Though the complex of **10** with the parent DB24C8 displays two independent conformations,[2b] only one conformation is observed in **2·10**, which in turn forms a dimer, stabilized by π–π stacking interactions between phenyl groups of neighboring dibenzylammonium ions (Fig. 6b).

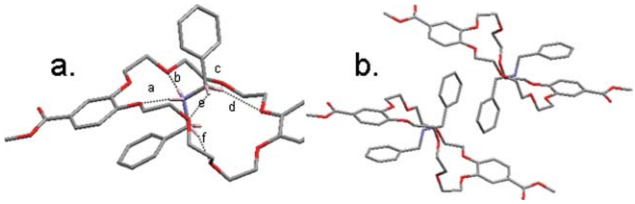


Fig. 6 Solid state structures of **2·10** (a) and its dimer (b) (gray: carbon atoms, red: oxygen atoms, blue: N atoms). Catechol ring of **2** to phenyl ring of **10**: centroid–centroid distance = 3.76 Å, ring plane–ring plane inclination = 7.5°. In the dimer phenyl–phenyl centroid–centroid distance = 3.83 Å, planar inclination angle = 0°.

The length of P–K^+ (7.220 Å) and P–NH_2^+ (7.725 Å) separations in the solid state structures of **1**·K^+, **2**·$K^+$and **2·10**$^+$ are in the range of reported values (7.2 to 8.4 Å) for complexes of DB24C8 with **10** and other ammonium hexafluorophosphate derivatives.[1,2b,23] Thus, no tight or intimate ion pairs exist in the solid state of these three complexes, consistent with the situation in solution deduced from analysis of the association constant for **1·10** and **2·10** (see ESI† and reference 16).

Conclusions

Pure isomeric *cis*- and *trans*-BCMB24C8 derivatives **1** and **2** were synthesized regiospecifically, avoiding the difficult problem of separation of the two isomers. There are three significant advantages over the traditional synthesis route: 1) the cyclizations are carried out at normal concentrations without use of a syringe pump; 2) thus, the reaction time is shortened from five days to one day (*cis*-BCMB24C8, **1**) or 3 days (*trans*-BCMB24C8, **2**); 3) the macrocyclization templated by potassium cation yielded the salt complex essentially quantitatively and pure *cis*-BCMB24C8 (**1**) in high isolated yield (89%). Other disubstituted dibenzo crown ethers can be made in this way. For example, cyclization of precursor **6** with tetra-, penta- and hexa-(ethylene glycol) ditosylates will afford the unsymmetrical 27-, 30- and 33-membered analogs of **1**.

The two new isomeric crown ether esters **1** and **2** form non-ion paired pseudorotaxanes with dibenzylammonium hexafluorophosphate, (**10**). Under the same conditions, these complexes have lower association constants than that of their parent crown ether, DB24C8, due to the electron-withdrawing carbomethoxy groups on the crown rings. The different positions of the carbomethoxy groups in the two isomers result in differences in their properties, *e.g.*, solubilities and association constants. The carboxylate groups can be easily transformed to diverse functional groups, as we have demonstrated with other crown ethers.[8] Therefore, the availability of the pure isomers will inevitably enhance the study of supramolecular systems constructed with dibenzo crown ethers, as we will demonstrate in subsequent publications.

Experimental

General information

All chemicals were used as received. Melting points were measured with a Mel-Temp II device and are uncorrected. Thin layer chromatography (TLC) was done using Whatman PE SIL G/UV254. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were obtained at ambient temperature on a Varian Unity (or an Inova) 400/100 MHz spectrometer with TMS (δ = 0.00 ppm) as internal standard. High resolution mass spectra (HR MS) were obtained on a JEOL Model HX 110. Crystals were mounted on a nylon CryoLoop™ (Hampton Research) with Krytox® Oil (DuPont) and centered on the goniometer of an Oxford Diffraction XCalibur2™ diffractometer equipped with a Sapphire 2™ CCD detector. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlis.[24] The structure was solved by direct methods and refined using the SHELXTL NT program package.[25] The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms and a riding model for all hydrogen atoms. The program packages SHELXTL NT and PLATON were used to generate crystallographic tables.[25,26] The program packages SHELXTL NT[25] and Mercury were used for molecular graphics generation.

Methyl 3,4-dihydroxybenzoate (3)

A solution of 3,4-dihydroxybenzoic acid (51.32 g, 333 mmol) and *p*-toluenesulfonic acid (1.2 g, 6 mmol) in methanol (250 mL) was refluxed for 3 days. After reaction, solvent was removed by rotoevaporation. The solid was dissolved in ethyl acetate and washed with 10% Na_2CO_3 once and saturated NaCl solution twice. After drying over anhydrous Na_2SO_4, solvent was removed to give 51.4 g (85%) of white solid. Mp. 141.8–142.7 °C (lit. 138.5–139.5 °C[27]); ^{1}H NMR ($CDCl_3$) δ 7.58 (d, $^4J_{HH}$ = 2, 1H), 7.58 (dd, $^4J_{HH}$ = 2, $^3J_{HH}$ = 9, 1H), 6.91 (d, $^3J_{HH}$ = 9, 1H), 5.83 (s, 1H), 5.59 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (acetone-d_6) δ 167.81, 151.51, 146.37, 124.08, 123.64, 117.92, 116.55, 52.63., 52.39; HR MS *m*/*z* (FAB in NBA PEG) calc. for $C_8H_8O_4$ M^+ 169.0501, found: 169.0508.

Methyl 3,4-bis(8′-chloro-3′,6′-dioxaoctyloxy)benzoate

To a solution of **3** (45.1 g, 268 mmol) and tri(ethylene glycol) dichloride (340 mL, ~2 mol) in CH_3CN (350 mL) was added K_2CO_3 (113.33 g, 820 mmol). The suspension was stirred at reflux for 7 days. The solution was decanted from the salts; CH_3CN and unreacted dichloride were removed by distillation

under reduced pressure. To remove residual salts the crude oil was filtered through silica gel; the silica gel was washed with CH_3CN. After removal of the solvent, 90 g (72%) of a viscous yellow oil remained. The oil was purified by column chromatography on silica gel using ethyl acetate : *n*-hexane (5 : 1) or ethyl acetate : petroleum ether (5 : 2). The pure product was obtained as a light yellow oil, 69 g (55%). ^{1}H NMR (acetone-d_6): δ 8.47 (bs, 2H), 7.49 (d, $^4J_{HH} = 2$, 1H), 7.45 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 1H), 6.91 (d, $^3J_{HH} = 8$, 1H), 3.81 (s, 3H). ^{13}C NMR (acetone-d_6): δ 166.64, 150.31, 145.16, 122.90, 122.42, 116.72, 115.36, 51.46, 29.98, 29.80, 29.60, 29.41, 29.21, 29.02, 28.83. Elem. anal.: calc. for $C_{20}H_{30}Cl_2O_8$ C 51.18, H 6.44, Cl 15.11; found: C 51.11, H 6.34, Cl 15.08%.

Mixture of DB24C8 diester isomers (1 and 2)

A solution of **3** (10.38 g, 61.8 mmol) and methyl 3,4-bis(8′-chloro-3′,6′-dioxaoctyloxy)benzoate (28.98 g, 61.8 mmol) in CH_3CN (total ~50 mL) was added at a rate of 0.69 mL h^{-1} to a suspension of K_2CO_3 (80.60 g, 584 mmol) and catalytic amount of tetra-*n*-butylammonium iodide in 3.5 L of CH_3CN at 70 °C. After complete addition the mixture was stirred for six days, cooled and filtered. The solvent was removed from the filtrate by rotoevaporation to give a gray powder. It was recrystallized from a large amount of methanol to give a slightly gray powder. Column chromatography with ethyl acetate–$CHCl_3$ (3 : 1) yielded a white solid, 17.5 g (53%, single spot on TLC). Mp: 135–139 °C. ^{1}H NMR ($CDCl_3$): δ 7.62 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 2H), 7.51 (d, $^4J_{HH} = 2$, 2H), 6.84 (d, $^3J_{HH} = 8$, 2H), 4.19 (m, 4H), 3.94 (m, 4H), 3.87 (s, 3H), 3.84 (bs, H). ^{13}C NMR ($CDCl_3$): δ 166.74, 152.76, 148.14, 123.82, 122.78, 114.08, 111.85, 71.32, 71.39, 69.74, 69.61, 69.46, 69.41, 69.28, 69.23, 51.92. FAB MS (NBA) *m/z*: 603, 19%, $(M + K)^+$; 565, 32%, $(M + H)^+$; 533, 87%, $(M - OCH_3)^+$. Elem. anal.: calc. for $C_{28}H_{36}O_{12}$ C 59.57, H 6.43; found C 59.46, H 6.49%.

Methyl 4-benzyloxy-3-hydroxybenzoate (4)

A solution of **3** (35.0 g, 208 mmol) and K_2CO_3 (28.8 g, 208 mmol) in CH_3CN (250 mL) was stirred at 85 °C for 4 h. To the suspension was added benzyl bromide (24.7 ml, 208 mmol). It was stirred at 65 °C for 12 h. The solid was removed by filtration through a pad of Celite 545. The filtrate was concentrated to give a viscous liquid. It was partitioned in water and ethyl acetate; the water layer was extracted with ethyl acetate 5 times. The combined ethyl acetate solution was washed with saturated NH_4Cl solution 3 times, water once and saturated NaCl solution 3 times, and dried over anhydrous Na_2SO_4. Solvent was removed in a rotoevaporator to give a yellow solid, which was recrystallized in $CHCl_3$ to yield 15.35 g of **4**. The filtrate solution was concentrated and separated by silica gel column chromatography with $CHCl_3$ as eluent to yield an additional 12.0 g of **4** (total yield 51%). Mp. 133.7–135.0 °C (lit. 128 °C[28]); ^{1}H NMR ($CDCl_3$) δ 7.61 (d, $^4J_{HH} = 2$, 2H), 7.59 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 2H), 7.41 (m, 5H), 6.94 (d, $^3J_{HH} = 8$, 2H), 5.70 (s, 1H), 5.17 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.43, 150.22, 146.12, 136.23, 129.52, 129.35, 128.57, 124.37, 123.37, 116.51, 111.86, 71.80, 52.66; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{15}H_{15}O_4$ $(M + H)^+$ 259.0970, found 259.0964.

Tri(ethylene glycol) ditosylate

To an aqueous solution of NaOH (64 g, 1.6 mol, in 600 mL of water) at 0 °C was added a solution of tri(ethylene glycol) (80.04 g, 0.533 mol) in THF (150 mL) dropwise. The mixture was stirred mechanically at 0 °C for 30 min and then at 0 °C a solution of *p*-toluenesulfonyl chloride (254 g, 1.33 mol) in THF (600 mL) was added dropwise. The mixture was stirred at rt 2 d. The organic layer was separated and the water layer was washed with CH_2Cl_2 5 times. The combined organic solution was concentrated to give a liquid, which was dissolved in acetone and chilled in a freezer, yielding white crystals (210 g, 86%). Mp. 82–83 °C (lit. 80–81 °C[29]); ^{1}H NMR ($CDCl_3$) δ 7.79 (d, $^3J_{HH} = 8$, 4H), 7.34 (d, $^3J_{HH} = 8$, 4H), 4.14 (t, $^3J_{HH} = 5$, 4H), 3.65 (t, $^3J_{HH} = 5$, 4H), 3.53 (s, 4H), 2.44 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.51, 133.53, 130.48, 128.56, 71.27, 69.85, 69.33, 22.25; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{20}H_{27}O_8S_2$ $(M + H)^+$ 459.1147, found 459.1143.

α,ω-Bis(2′-benzyloxy-5′-carbomethoxyphenoxy)-3,6-dioxaoctane (dimethyl 4,4′-bis(benzyloxy)-3,3′-oxytri(ethyleneoxy)dibenzoate) (5)

A solution of **4** (11.50 g, 44.5 mmol), K_2CO_3 (12.30 g, 89.0 mmol) and tri(ethylene glycol) ditosylate (9.74 g, 21.3 mmol) in CH_3CN (160 mL) was stirred at reflux for 15 h. After solvent was removed, the residue was partitioned in water and ethyl acetate. The water layer was extracted with ethyl acetate 5 times. The combined ethyl acetate solution was washed with water and saturated NaCl solution, and then dried over anhydrous Na_2SO_4. After concentration in a rotoevaporator, 14.3 g (100%) of a white solid was obtained. Mp. 87.9–89.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 2H), 7.57 (d, $^4J_{HH} = 2$, 2H), 7.35 (m, 10H), 6.90 (d, $^3J_{HH} = 8$, 2H), 5.15 (s, 4H), 4.19 (t, $^3J_{HH} = 5$, 4H), 3.87 (t, $^3J_{HH} = 5$, 4H), 3.87 (s, 6H), 3.72 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 167.44, 153.35, 149.16, 137.22, 129.22, 128.67, 127.92, 124.53, 123.73, 115.44, 113.78, 71.70, 71.46, 70.24, 69.59, 52.64; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{36}H_{38}O_{10}$ M^+: 630.2465, found: 630.2461.

α,ω-Bis(2′-hydroxy-5′-carbomethoxyphenoxy)-3,6-dioxaoctane (dimethyl 4,4′-dihydroxy-3,3′-oxytri(ethyleneoxy)dibenzoate) (6)

To a solution of **5** (11.70 g, 18.55 mmol) in CH_2Cl_2 (100 mL) was added 10% Pd/C (0.20 g). The suspension was shaken under H_2 atmosphere (~50 psi) at rt. After 12 h, TLC showed complete conversion to product. The catalyst was removed by filtration. The filtrate was concentrated to give a white solid, 11.58 g, which was purified by column chromatography with a mixture of CH_2Cl_2 and ethyl acetate as eluent: 7.24 g (87%) of a white solid. Mp. 129.0–130.1 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 9$, 2H), 7.60 (d, $^5J_{HH} = 2$, 2H), 7.50 (s, 2H), 6.96 (d, $^3J_{HH} = 9$, 2H), 4.24 (t, $^3J_{HH} = 5$, 4H), 3.88 (s, 6H), 3.87 (t, $^3J_{HH} = 5$, 4H), 3.79 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 167.49, 152.28, 146.22, 126.08, 122.76, 116.75, 115.97, 71.01, 70.35, 69.92, 52.62; HR MS *m/z* (FAB) calc. for $C_{22}H_{26}O_{10}$ M^+ 450.1526, found 450.1521.

cis-Bis(carbomethoxybenzo)-24-crown-8 (1)

A solution of **6** (3.00 g, 6.66 mmol), K_2CO_3 (5.52 g, 39.9 mmol), KPF_6 (1.50 g, 8.13 mmol) and tri(ethylene glycol) ditosylate (3.06 g, 6.67 mmol) in CH_3CN (150 mL) was stirred in an 80 °C oil bath for 24 h. The solid was removed by filtration. The filtrate was concentrated to give 5.20 g of off-white solid (theoretical yield 4.99 g for **1**·KPF_6). MALDI MS of this KPF_6 complex afforded *m/z* 603.1833 $[\mathbf{1}\cdot K]^+$; see Fig. 1 for its ^{1}H NMR spectrum and Fig. 5 for the X-ray structure. The salt complex was dissolved in $CHCl_3$ and washed with water and saturated NaCl solution. The solution was then dried over anhydrous Na_2SO_4. After removal of solvent by rotoevaporation a white solid was obtained. It was recrystallized in methanol to give 3.35 g (89%) of white solid (**1**). Mp. 137.1–138.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 9$, 2H), 7.51 (d, $^4J_{HH} = 2$, 2H), 6.84 (d, $^3J_{HH} = 9$, 2H), 4.19 (m, 8H), 3.93 (m, 8H), 3.88 (s, 6H), 3.84 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 167.47, 153.45, 148.88, 124.53, 123.54, 114.79, 112.56, 72.22, 72.12, 70.45, 70.33, 70.13, 70.02, 52.66; HR MS *m/z* (FAB) calcd for $C_{28}H_{36}O_{12}$ M^+ 564.2207, found 564.2217.

Methyl 4-benzyloxy-3-{chloroethoxy[ethoxy(ethoxy)]}benzoate (7)

A solution of **4** (20.0 g, 77 mmol), K_2CO_3 (32.1 g, 232 mmol) and tri(ethylene glycol) dichloride (36.2 g, 194 mmol) in CH_3CN

(250 mL) was refluxed for 3 days. The solid was removed by filtration. The filtrate was concentrated to give a yellow oil that was purified by column chromatography with 5 : 1 hexane : ethyl acetate as eluent. A colorless oil (23.7 g, 75%) was obtained. ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 9$, 2H), 7.51 (d, $^4J_{HH} = 2$, 2H), 6.84 (d, $^3J_{HH} = 9$, 2H), 4.19 (d, $^3J_{HH} = 4$, 4H), 3.94 (t, $^3J_{HH} = 4$, 4H), 3.93 (t, $^3J_{HH} = 4$, 4H), 3.87 (s, 6H), 3.85 (s, 4H), 3.84 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 167.43, 153.37, 149.13, 137.20, 129.24, 128.71, 127.94, 124.59, 123.74, 115.53, 113.76, 72.03, 71.65, 71.48, 71.40, 70.35, 69.70, 52.66, 43.40; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{21}H_{25}O_6Cl$ $(M)^+$ 408.1340, found 408.1334.

Methyl 4-hydroxy-3-{chloroethoxy[ethoxy(ethoxy)]}benzoate (8)

A suspension of **7** (3.53 g, 8.63 mmol) and 10% Pd/C (0.092 g) in CH_2Cl_2 (60 mL) was shaken under H_2 atmosphere (~50 psi) at rt. After 12 h, TLC showed complete conversion to product. The catalyst was removed by filtration. The filtrate was concentrated to give 2.75 g (100%) of a pure colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, $^5J_{HH} = 2$, $^3J_{HH} = 8$, 1H), 7.62 (d, $^5J_{HH} = 2$, 1H), 6.94 (d, $^3J_{HH} = 8$, 1H), 4.23 (m, 2H), 3.88 (s, 3H), 3.85 (m, 2H), 3.77 (t, $^3J_{HH} = 6$, 2H), 3.74 (m, 4H), 3.65 (t, $^3J_{HH} = 6$, 2H); ^{13}C NMR ($CDCl_3$) δ 167.41, 152.61, 146.17, 126.29, 122.75, 117.54, 115.79, 72.09, 71.26, 71.11, 70.12, 52.61, 43.35; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{14}H_{19}O_6Cl$ M^+ 318.0870, found: 318.0869.

trans-Bis(carbomethoxybenzo)-24-crown-8 (2) and carbomethoxybenzo-12-crown-4 (9)

A solution of **8** (1.08 g, 3.39 mmol), K_2CO_3 (1.41 g, 10.2 mmol) and KPF_6 (0.31 g, 1.7 mmol) in CH_3CN (150 mL) was stirred at reflux 3 days. The solid was removed by filtration. The filtrate was concentrated to give an off-white solid. It was dissolved in $CHCl_3$ and washed with water and saturated NaCl solution. The solution was then dried over anhydrous Na_2SO_4. After removal of solvent by rotoevaporation, the solid residue was separated by column chromatography. Two white solids were obtained. **9**: 0.34 g (36%); mp. 94.2–95.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 1H), 7.68 (d, $^4J_{HH} = 2$, 1H), 6.96 (d, $^3J_{HH} = 8$, 1H), 4.23 (m, 4H), 3.89 (m, 2H), 3.88 (s, 3H), 3.83 (m, 2H), 3.78 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 167.26, 150.68, 150.55, 125.95, 124.72, 120.74, 116.62, 73.32, 72.08, 71.65, 71.46, 70.43, 70.36; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{14}H_{19}O_6$ $(M + H)^+$ 283.1182, found 283.1183. **2**: 0.42 g (44%); mp. 165.3–166.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (dd, $^4J_{HH} = 2$, $^3J_{HH} = 8$, 2H), 7.52 (d, $^4J_{HH} = 2$, 2H), 6.84 (d, $^3J_{HH} = 8$, 2H), 4.19 (m, 8H), 3.94 (m, 8H), 3.88 (s, 6H), 3.85 (s, 4H), 3.84 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 167.48, 153.48, 148.86, 124.54, 123.52, 114.79, 112.56, 72.22, 72.13, 70.47, 70.34, 70.19, 69.96, 52.65; HR MS *m/z* (FAB in NBA PEG) calc. for $C_{28}H_{36}O_{12}$ M^+ 564.2207, found 564.2217. If the solid was not exposed to water before chromatography, **2**·KPF_6 was isolated upon elution with ethyl acetate; its ^{1}H NMR spectrum is shown in Fig. 2 and its crystal structure is shown in Fig. 5.

Complexation studies

Solutions were prepared by precisely weighing a minimum of 1.00×10^{-2} g of each host and guest component by means of an analytical balance which read to 1.0×10^{-4} g into a 5.00 (±0.02) or 10.00 (±0.02) mL volumetric flask equipped with a ground glass stopper to make a moderately concentrated (nominally 16.0 mM) master solution. This solution was then sequentially diluted (no more than four sequential dilutions per master solution) by transferring specific volumes of the higher concentration solution to a clean volumetric flask *via* a to-deliver volumetric pipette (±0.006 mL) and diluting to the mark. The fresh solutions were filtered through a cotton-filled disposable pipette before 0.500 (±0.006 mL) mL of each solution component (host and guest) at a specified concentration was transferred *via* a to-deliver pipette to a 5.0 mm NMR tube. NMR spectroscopic data were collected on a temperature controlled 400 MHz spectrometer within 1 hour of mixing the host and guest solutions. The fraction of total crown moieties occupied by guest was determined by integration of the complexed and uncomplexed crown signals for H_3 of hosts **1** and **2**; these results were corroborated by similar analyses of H_2 and H_γ. Reproducibilty in fractional binding of the host was shown to be good within 0.29% relative standard error (100 σ_n/mean) using multiple (12) samples and multiple (5) Fourier transformations/integrations for a sample with 24.2% crown bound. The major source of error in calculated K values results from errors in weights and volumes: ~ ±2% maximum possible relative errors in initial concentrations. The complexation percentages' relative error is less than 0.3%. The error bars shown in the ESI were accumulated results of the previously mentioned maximum possible (rather than most probable) concentration errors. The errors for slopes and intercepts are standard errors given by the least squares fitting program in Origin. Though the complexation percentage of the hosts are well controlled in the area of 20 ~ 80%,[30] our experiments show that the complexation percentage of guest is also an important factor influencing the quality of analysis data. The bigger error bars shown in ESI Figure S1b† are mainly due to the high complexation percentage (~ 90%) of the guest in the corresponding NMR samples (Table 2). This directly leads to the large error for K_{ipd}, 6.8 (±5.5) × 10^{-3} M.

Crystal structure determinations

Colorless plates of **1**·KPF_6 (0.35 × 0.20 × 0.03 mm^3) were formed in $CHCl_3$ by vapor diffusion of hexane at rt. Colorless trapezoidal crystals of **2** (0.1 × 0.3 × 0.4 mm^3) and **2**·KPF_6 (0.15 × 0.3 × 0.3 mm^3) were formed in $CHCl_3$ by vapor diffusion of pentane at rt. Colorless needles of **2**·**10** (0.8 × 0.1 × 0.03 mm^3) were formed by slow diffusion of pentane into a mixture of $CHCl_3$–CH_3OH at rt, which were cut into smaller crystals (0.35 × 0.084 × 0.028 mm^3) before being mounted on a nylon CryoLoop™ (Hampton Research).

Systematic absences for **1**·KPF_6 were consistent with the triclinic space group $P\bar{1}$ with unit cell parameters of a = 10.3429(7) Å, b = 12.6823(9) Å, c = 13.1381(9) Å, α = 84°, β = 73°, γ = 78°. Systematic absences for **2** were consistent with the monoclinic space group $P2_1/c$ with unit cell parameters of a = 13.8926(14) Å, b = 12.4235(11) Å, c = 8.2043(8) Å, β = 105.243(9)°; the asymmetric unit of the structure comprises 0.5 crystallographically independent molecules. Systematic absences for **2**·KPF_6 were consistent with the monoclinic space group $C2/c$ with unit cell parameters of a = 16.840(2) Å, b = 19.447(3) Å, c = 19.410(2) Å, β = 91°. The asymmetric unit of the structure comprises one crystallographically independent **2**·KPF_6 complex and two half-PF_6^- anions. Systematic absences for **2**·**10** were consistent with the monoclinic space groups $C2/c$ and Cc. The centric space group $C2/c$ was chosen with unit cell parameters of a = 14.324(6) Å, b = 22.806(6) Å, c = 26.470(8) Å, β = 97.20(3)°. The asymmetric unit of the structure comprises one crystallographically independent **2**·**10** complex and 0.265 methanol solvate molecules. Two residual electron density peaks were modeled as a partially occupied CH_3OH molecule disordered over two symmetrically related positions. The occupancy in the asymmetric unit refined to 26.5%, or 53.0% when disordered over the two sites.§§

§§ CCDC reference numbers 265204–265207. See http://www.rsc.org/suppdata/ob/b5/b503072m/ for crystallographic data in CIF or other electronic format.

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21 Crystal data: $C_{28}H_{36}O_{12}\cdot KPF_6$, $M = 748.64$, monoclinic, $a = 16.840(2)$ Å, $b = 19.447(3)$ Å, $c = 19.410(2)$ Å, $\beta = 91.43(1)°$, $V = 6354(2)$ Å^3, $T = 100(2)$ K, space group $C2/c$ (no. 15), $Z = 8$, μ (Mo Kα) = 0.315 mm^{-1}, 22885 reflections measured, 9339 unique ($R_{int} = 0.0308$). The final R values were $R(F) = 0.0585$ [$I > 2\sigma(I)$] and $wR(F^2) = 0.1926$ (all data).

22 Crystal data: $C_{28}H_{36}O_{12}\cdot[C_{14}H_{16}N][PF_6]\cdot 0.265CH_3OH$, $M = 916.31$, monoclinic, $a = 14.324(6)$ Å, $b = 22.806(6)$ Å, $c = 26.470(8)$ Å, $\beta = 97.20(3)°$, $V = 8579(5)$ Å^3, $T = 100(2)$ K, space group $C2/c$ (no. 15), $Z = 8$, μ (Mo Kα) = 0.154 mm^{-1}, 32751 reflections measured, 12526 unique ($R_{int} = 0.0570$). The final R values were $R(F) = 0.0578$ [$I > 2\sigma(I)$] and $wR(F^2) = 0.1901$ (all data).

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