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# Mono-, Bis-, and Tris(crown ether)s Assembled around 1,3,5-Triaroylbenzene Scaffolds

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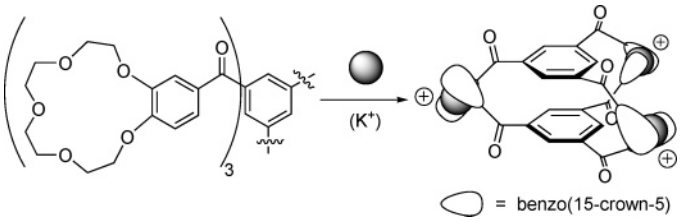


A concise and experimentally straightforward method for assembling multiple benzo(crown ether) units around 1,3,5-triaroylbenzene scaffolds has been developed. Symmetrical tris(crown ether)s possessing three benzo(15-crown-5) or three benzo(18-crown-6) peripheral substituents have been prepared in good yield via cyclotrimerization of monomeric enaminones. Efficient cross-cyclotrimerizations have also been demonstrated through construction of unsymmetrical triaroylbenzenes functionalized with only one or two benzo(15-crown-5) moieties. The alkali cation-binding abilities of these mono- and polytopic crown ethers have been probed through picrate extraction experiments and isothermal titration calorimetry. Thermodynamic binding parameters uncovered using the latter technique reveal increasing $K^+/Na^+$ selectivity in the benzo(15-crown-5) series of compounds as a function of increasing numbers of benzo(crown) units. The data also indicate that the triaroylbenzene-derived bis- and tris-crown ethers do not engage in intramolecular chelation of cations too large to be accommodated by individual crown macrorings. Instead, cation/triaroylbenzene stoichiometries and binding profiles indicate formation of alkali metal-bridged dimers.

## Introduction

Host−guest interactions are a fascinating topic of study within the field of supramolecular chemistry. Inspired largely by nature, researchers over the last several decades have achieved a greater understanding and control over the various intermolecular interactions that govern supramolecular assembly in artificial systems.[1] An emerging area of contemporary interest concerns the design, synthesis, and evaluation of molecular receptors possessing multiple binding sites for targeted guest species. Polytopic receptors capable of binding two or more substrates not only may display altered guest affinities and selectivities relative to their monotopic components (for example, due to cooperative host−guest interactions and/or formation of chelated host−guest assemblies) but also may provide the means to explore multivalent interactions in synthetic systems.[2] Furthermore, polytopic receptors featuring multiple structurally distinct substrate-binding sites may be capable of complexing two (or more) non-identical guest moieties (i.e., heteropolytopic receptors).[3]

Crown ethers are well-recognized as effective alkali and alkaline cation-binding agents, and, in many respects, their discovery by Pedersen represents the genesis of modern supramolecular chemistry.[4] In general, the cation selectivity exhibited by simple crown ethers can be estimated according to the "hole-size" principle. That is, size-complementarity between the crown ether macrocycle and guest cation facilitates formation of ion−crown complexes. Steric factors alone do not account for the

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(1) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons: Chichester, 2000.

(2) (a) Badjić, J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723. (b) Mulder, A.; Huskens, J.; Reinhoudt, D. N. *Org. Biomol. Chem.* **2004**, *2*, 3409.

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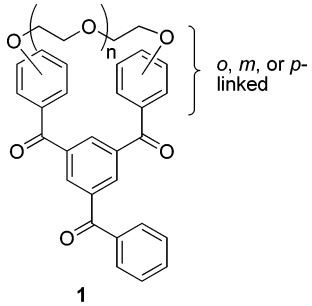
ionophoric activity of crown ethers, however, as cations nominally too large or too small to fit within a given crown may still display significant affinities.[5]

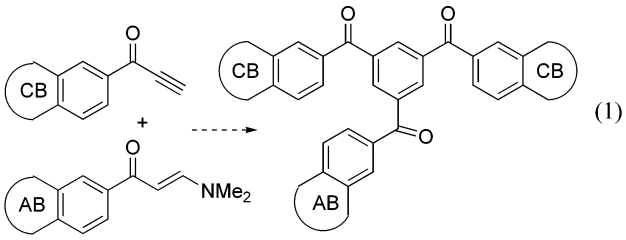
Incorporation of crown ethers into oligomeric assemblies can result in binding of multiple cation substrates. In addition, cation affinities and guest selectivities exhibited by crown oligomers may differ significantly from those manifested by the individual monomeric crown ether units.[6] Using bis(crown ether)s as an example, ionophores derived from 15-crown-5 units may display enhanced selectivity for the binding of $K^+$ and $Rb^+$ (ions too large to fit within individual 15-crown-5 rings) over that of $Na^+$ (an ion that is accommodated by a single 15-crown-5 moiety) due to the formation of chelated sandwich-type crown−cation complexes. Likewise, bis(18-crown-6) derivatives may display enhanced $Cs^+/K^+$ selectivity relative to simpler mono(18-crown-6) congeners.[7]

We have recently demonstrated the utility of alkyne/enaminone cyclotrimerization processes in the construction of structurally elaborate 1,3,5-triaroylbenzene (TAB) derivatives. In particular, dendritic-like triaroylbenzenes have been prepared via cyclotrimerization of linked enaminones,[8] while bis(aryl ethynyl ketones) have been shown to participate in concomitant trimerization−macrocyclization reactions.[9] This latter transformation was subsequently employed to prepare a series of crownophanes (**1**).[10] It was originally envisaged that **1** would provide the basis for construction of new heteroditopic salt-binding receptors with the crownophane portion serving as the site for cation association.[11] Unfortunately, none of the crownophanes prepared in the course of this study exhibited any cation-binding ability, presumably because the crown portions of these cyclophanes are too large and rigid to trap alkali cations (an extreme example of the hole-size principle). This prompted us to consider incorporating more conventional and established crown ether units into future ionophoric receptors. Specifically, we envision using the convergency inherent in enaminone-directed cross-cyclotrimerization reactions to construct heterotopic receptors along the lines indicated in eq 1, in which individual cation- and anion-binding substituents (CB and AB, respectively) are arrayed about a common triaroylbenzene core.




**1**

n = 2, 3, or 4




(1)

CB = cation binding group, AB = anion binding group

Such receptors may function as discrete unimolecular salt-binding ionophores or as components of multi-molecular constructs formed via self-assembly in the presence of suitable cation/anion combinations. This latter possibility offers an opportunity to potentially tune the cation and/or anion specificities of these receptors beyond those exhibited by the individual cation-binding and anion-binding units via polyvalent host−guest interactions. As a prelude to the construction of such salt-binding heterotopic receptors and their associated assemblies, we sought to determine the ionophoric properties of simpler homotopic TAB's decorated with benzo(crown ether) moieties. To that end, we report the synthesis of symmetrical triaroylbenzenes possessing three benzo(15-C-5) or three benzo(18-C-6) groups as peripheral arene substituents. Additionally, unsymmetrical TAB's incorporating one or two benzo(15-C-5) rings have also been prepared. The alkali cation-binding abilities and cation selectivities of these receptors have been examined using picrate extraction experiments and isothermal titration calorimetry (ITC).

## Results and Discussion

The initial synthetic targets of this study were symmetrical triaroylbenzenes functionalized with either benzo(15-C-5) or benzo(18-C-6) groups along the periphery. Although in principle the targeted receptors could be constructed in a single step via 3-fold Friedel−Crafts acylation of benzo(crown ether)s with trimesic acid chloride, we opted to develop a convergent trimerization route in anticipation of preparing unsymmetrical triaroylbenzene-based receptors in the future. The synthesis of these tris(crown ether)s is illustrated in Scheme 1. The 4-acetyl benzocrown derivatives were treated with *N*,*N*-dimethyl formamide dimethyl acetal to afford the corresponding enaminones **2** and **3**. Cyclotrimerization was then effected using established conditions that involve heating the enaminone in a solution of acetic acid and pyridine.[12] The desired tris(benzo(15-C-5)) and tris(benzo(18-C-6)) derivatives **4** (TB15C5) and **5** (TB18C6) were obtained in excellent yields without the need for chromatographic purification.

The preparation of unsymmetrical triaroylbenzenes was next examined. In previous studies involving the construction of dendritic and macrocyclic TAB's,[8−10] we used preformed

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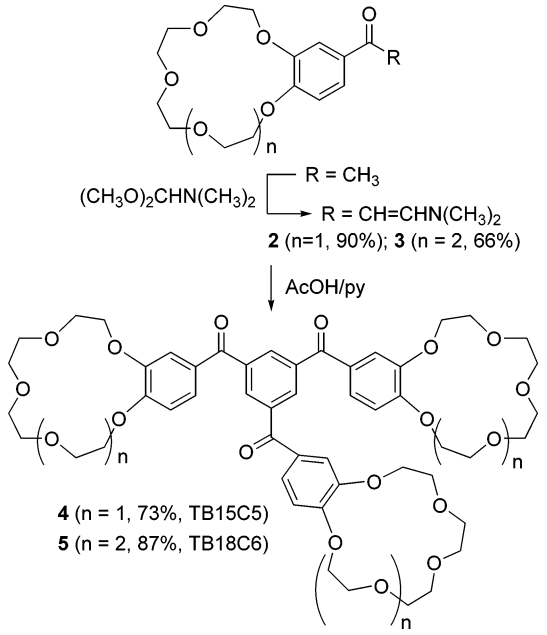
(10) Pigge, F. C.; Ghasedi, F.; Schmitt, A. V.; Dighe, M. K.; Rath, N. P. *Tetrahedron* **2005**, *61*, 5363.

(11) For recent examples of ion pair receptors, see: (a) Cametti, M.; Nissinen, M.; Dalla Cort, A.; Mandolini, L.; Rissanen, K. *J. Am. Chem. Soc.* **2005**, *127*, 3831 and references cited. (b) Mahoney, J. M.; Stucker, K. A.; Jiang, H.; Carmichael, I.; Brinkmann, N. R.; Beatty, A. M.; Noll, B. C.; Smith, B. D. *J. Am. Chem. Soc.* **2005**, *127*, 2922.

(12) Elghamry, I. *Synthesis* **2003**, 2301.

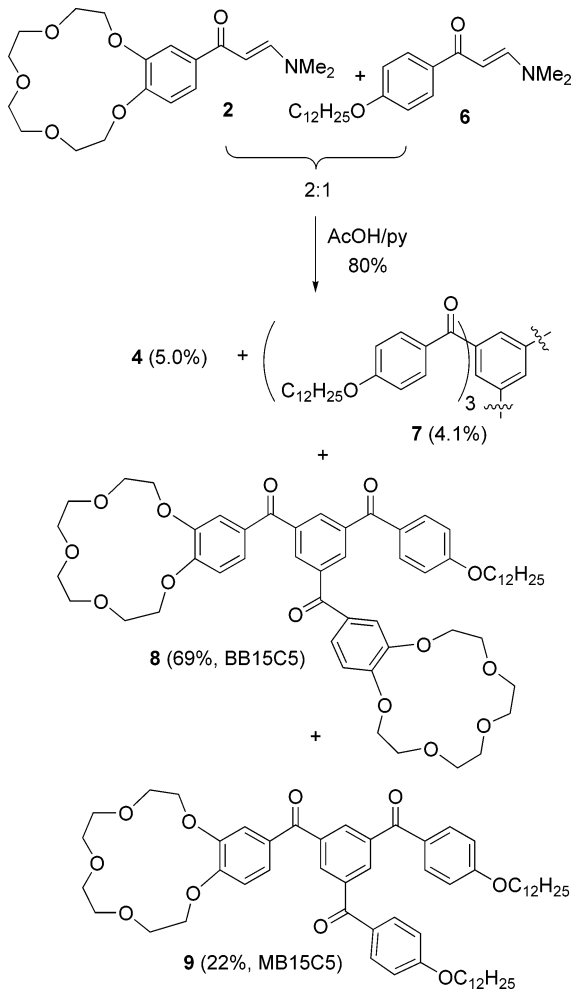
**SCHEME 1. Preparation of Tris[benzo(crown ether)s]**




enaminones as triggers to initiate cyclotrimerization in the presence of excess aryl ethynyl ketone reactants.[13] Application of this method for the synthesis of bis(benzocrown)-functionalized TAB's would thus require preparation of benzo(crown ether) ethynyl ketone derivatives capable of participating in cyclotrimerization with an appropriate aryl enaminone (similar to the hypothetical transformation illustrated in eq 1), and mono-(benzocrown) TAB's would be accessed from reaction of enaminones such as **2** with an excess of an aryl ethynyl ketone. Rather than approach the synthesis of mono- and bis(benzocrown)-substituted TAB's separately via the two routes outlined above, we reasoned that both types of compounds may be constructed simultaneously and in serviceable yield via direct condensation of two different enaminone reactants, either **2** or **3** and a second enaminone not derived from a benzo(crown ether). This approach offers several practical advantages in that the required enaminone starting materials are easily prepared in one step from acetylated arenes (see Scheme 1) and trimerization of enaminones in AcOH/pyridine affords TAB products in high yield at the expense of unwanted oligomers.[14] While co-trimerization of two enaminones can produce up to four different triaroylbenzene products, we expect that the product ratio will be subject to alteration by adjusting the relative stoichiometry of the starting materials. The success of this approach relies on the ability to effectively separate and purify the TAB products; consequently an enaminone possessing a 12-carbon alkoxy group at the para position was selected as a condensation partner to imbue mono- and bis-crown adducts with greater solubility while also attenuating the polarity of such materials, thereby aiding chromatographic separation.

In the event (Scheme 2), enaminone **2** was combined with **6** in a 2:1 ratio and subjected to cyclotrimerization conditions. As expected, four triaroylbenzene products were obtained in combined 80% overall yield. Chromatographic purification of the product mixture resulted in isolation of the symmetrical

**SCHEME 2. Preparation of Unsymmetrical TAB-Based Mono- and Bis-benzo(crown ether)s**




TB15C5 **4** and the symmetrical TAB **7** (obtained from homotrimerization of enaminone **6**) in an approximately 1:1 ratio. Gratifyingly, the mixed triaroylbenzenes possessing two (**8**, BB15C5) and one (**9**, MB15C5) benzo(15-C-5) group(s) proved to be the major products. The observed ratio of TAB's (1:1.2:5.4:16.7 for **7**:**4**:**8**:**9**, respectively) differs somewhat from the theoretical product ratio of 1:8:6:12. Specifically, the amount of tris(benzo-crown) **4** is significantly less than that predicted based upon purely statistical considerations. In part, this may reflect difficulties in isolating **4** via column chromatography due to its affinity for silica gel. Alternatively, the various cyclotrimerizations occurring during the reaction may proceed at different rates that favor generation of heterotrimers. While further studies are needed to clarify this issue, the ease and rapidity with which differentially functionalized TAB's **8** and **9** are obtained is noteworthy. Moreover, TAB's **8** and **9**, together with symmetrical tris(crown ether)s **4** and **5**, represent suitable substrates for an initial assessment of the cation-binding ability and selectivity of ionophores constructed around a triaroylbenzene framework.

The cation-binding abilities of tris(crown ether)s **4** and **5** were first qualitatively examined in picrate extraction experiments.

(13) This method is predicated upon mechanistic studies of the cyclotrimerization reaction reported by Iwamura: Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550.

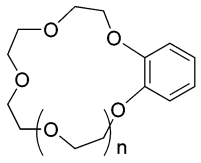
(14) We have observed formation of intractable tars (presumably polymeric in nature) along with desired TAB's in the course of cross-cyclotrimerizations involving enaminones and aryl ethynyl ketones (see refs 8−10).

**TABLE 1. Picrate Extraction by Crown Ethers 4−5 and 10−13**[a,b]

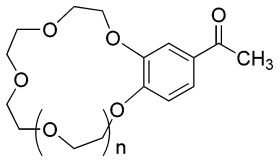
| | percent extraction | | | |
|---|---|---|---|---|
| crown | $Li^+$ | $Na^+$ | $K^+$ | $Cs^+$ |
| **4** (TB15C5)[c] | 4.5 | 10 | 21 | 1.5 |
| **5** (TB18C6)[c] | 2.3 | 9.7 | 100 | 21 |
| **10** (B15C5)[d] | 7.0 | 37 | 22 | 10 |
| **11** (B18C6)[d] | 6.1 | 27 | 100 | 35 |
| **12** (AB15C5)[d] | 3.4 | 13 | 7.3 | 17 |
| **13** (AB18C6)[d] | 8.5 | 14 | 100 | 16 |

[a] Extraction conditions: aqueous phase [MOH] = 0.1 M, [picric acid] = $7.5 \times 10^{-5}$ M, 3 mL; organic phase $CHCl_3$, 3 mL. [b] Experimental % extraction values represent an average of three trials. [c] [Crown] = $1.2 \times 10^{-3}$ M. [d] [Crown] = $3.6 \times 10^{-3}$ M.

For comparison, the parent monotopic benzo(crown ether)s **10** (B15C5) and **11** (B18C6), and acetyl benzo(crown ether)s **12** (AB15C5) and **13** (AB18C6) were examined as well. The results of these experiments are summarized in Table 1. Among the benzo(15-crown-5) derivatives studied, simple B15C5 **10** exhibited the highest extraction ability toward sodium picrate, while the tris(crown) derivative **4** was most active in the extraction of potassium picrate. As it is well known that 15-crown-5 ethers coordinate $K^+$ ions in nonaqueous solvents via formation of 2:1 crown:metal sandwich complexes,[15] the greater extractability of potassium picrate by **4** presumably reflects the ability of two benzo(15-crown-5) units (either from the same or from two different TAB's) to chelate a single metal ion. The slightly diminished overall extraction ability of **4** as compared to **10** may reflect an attenuation of ion-binding caused by the presence of electron-withdrawing carbonyl groups conjugated to the benzo(crown) moieties. Indeed, the acetyl-substituted analogue **12** also displays decreased extraction ability for all ions when compared to **10**.[16] Nonetheless, the benefits of polytopic crown ether receptors with respect to influencing cation-binding selectivity are apparent in the liquid−liquid extraction results obtained for the 15-C-5 series of substrates. In contrast, extraction experiments proved to be ill-suited for analysis of the 18-C-6 series of compounds as all crown ethers (**5**, **11**, and **13**) exhibited 100% extraction of $K^+$ ion under the conditions employed.



**10** (n = 1, B15C5)
**11** (n = 2, B18C6)



**12** (n = 1, AB15C5)
**13** (n = 2, AB18C6)

The extraction experiments described above confirm that assembly of three crown ether units around a central triaroylbenzene core results in viable ionophores, at least toward alkali metal cation guests. We next sought a more quantitative means of assessing the strength of tris(crown)−cation interactions as well as a method for determining the host−guest binding stoichiometry between **4**/**5** and monovalent cations. Comparison of the data obtained for **4** with that obtained for bis- and mono-(crown ether)s **8** and **9** may then provide insight into the relationship between the number of benzo(crown ether) units and cation-binding selectivity. Such information should prove useful in furthering our efforts aimed at designing heterotopic receptors as outlined in eq 1. Additionally, such binding data appear to be largely absent from reports describing the preparation of various other tris(crown ether)s.[17] Consequently, binding assays were performed using isothermal titration calorimetry (ITC) so that all thermodynamic parameters associated with ion binding, including metal ion stoichiometry, could be conveniently obtained simultaneously.[18]

Excess of selected metal salts possessing weakly coordinating lipophilic counterions (NaSCN, KSCN, $CsBPh_4$) was dissolved in acetonitrile and injected into solutions of the crown ethers, and the results of these experiments are shown in Table 2. For comparison, calorimetrically determined binding data for the complexation of $Na^+$ and $K^+$ by B15C5 **10** and B18C6 **11** are also included. Examination of binding stoichiometry for TB15C5 **4** reveals a decreasing cation/**4** ratio (*N*) as a function of increasing cation ionic diameter. Two sodium ions are bound by **4** as compared to 1.5 potassium ions and one cesium ion. A single benzo(15-C-5) macrocycle is well-suited to host a single $Na^+$, so we attribute the incomplete metalation of **4** upon treatment with NaSCN to negative cooperativity, perhaps arising from unfavorable electrostatic interactions between solvated ions and the dicationic $Na_2$**4** adduct.[2a,19] In contrast, benzo(15-C-5) rings are known to interact with $K^+$ ions via formation of bis-(crown)−potassium chelates.[15] The observed $K^+$:**4** ratio of 3:2, then, may indicate assembly of potassium ion bridged assemblies. The exact structure of such assemblies is not known with certainty; however, binding data obtained from bis- and mono-benzo(15-C-5) analogues **8** and **9** seemingly provide some insight into this issue (vide infra). Only a single $Cs^+$ ion is accommodated per molecule of **4**, and the large ionic diameter of this cation also mandates formation of sandwich-type complexes. The favorable entropy term for $Cs^+$ complexation may reflect the ability of a single cesium ion to interact with two benzo(crown ether) units from the same TAB receptor (i.e., intramolecular chelation), resulting in extensive desolvation of both the cation and the receptor. Notably, entropic costs associated with $K^+$ ion binding by **4** are significantly greater, perhaps indicating formation of a larger ternary supramolecular host−guest assembly as discussed below.[20,21] Differences in the average binding constants (log *K*) between **4** and the three cations examined are also apparent, with $K^+$ ion binding

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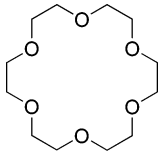
**TABLE 2. Thermodynamic Parameters and Stoichiometry of Alkali Cation Binding by Tris(crown ether)s 4 and 5, Bis(crown ether) 8, and Mono(crown ether) 9 in $CH_3CN$ As Determined by ITC[a,b]**

| crown | cation | $N$[c] | log $K$ | $\Delta H$ (kcal mol$^{-1}$) | $T\Delta S$ (kcal mol$^{-1}$) | $\Delta G$ (kcal mol$^{-1}$)[d] |
|---|---|---|---|---|---|---|
| **4** (TB15C5) | $Na^+$ | 1.89 ± 0.07 | 3.32 ± 0.02 | −6.10 ± 0.31 | −1.57 | −4.53 |
| | $K^+$ | 1.51 ± 0.01 | 4.68 ± 0.02 | −10.60 ± 0.13 | −4.31 | −6.29 |
| | $Cs^+$ | 1.12 ± 0.03 | 3.88 ± 0.04 | −1.43 ± 0.06 | 3.85 | −5.28 |
| **5** (TB18C6) | $Na^+$ | 2.69 ± 0.01 | 4.06 ± 0.01 | −3.94 ± 0.02 | 1.60 | −5.54 |
| | $K^+$ | 2.79 ± 0.01 | 4.26 ± 0.01 | −4.98 ± 0.02 | 0.84 | −5.82 |
| | $Cs^+$ | 1.70 ± 0.01 | 4.36 ± 0.01 | −5.60 ± 0.05 | 0.34 | −5.94 |
| **8** (BB15C5) | $Na^+$ | 1.88 ± 0.04 | 3.37 ± 0.02 | −5.61 ± 0.14 | −1.01 | −4.60 |
| | $K^+$ | 1.09 ± 0.05 | 4.09 ± 0.03 | −12.52 ± 0.99 | −6.93 | −5.59 |
| **9** (MB15C5) | $Na^+$ | 1.05 ± 0.06 | 3.54 ± 0.02 | −4.36 ± 0.31 | 0.47 | −4.83 |
| | $K^+$ | 0.52 ± 0.07 | 3.63 ± 0.02 | −11.30 ± 1.42 | −6.45 | −4.85 |
| **10** (B15C5) | $Na^+$ | 1 | 4.47 | −5.62 | 0.45 | *e* |
| | $K^+$ | 0.5 | 4.74 | −15.42 | −8.97 | *f* |
| **11** (B18C6) | $Na^+$ | 1 | 4.71 | −4.11 | 2.28 | *g* |
| | $K^+$ | 1 | 4.75 | −5.31 | 1.14 | *g* |

[a] Experiments performed using single injection method. Values for $N$, log $K$, $\Delta H$, and $\Delta S$ are averages of three separate trials. [b] $T$ = 298 K. [c] $N$ = number of cations bound/TAB. [d] Calculated from average $\Delta H$ and $\Delta S$ values. [e] Reference 23c. [f] Reference 15c − data obtained in MeOH:$H_2O$ (8:2) solution. [g] Reference 22.

exhibiting approximately an order of magnitude higher log $K$ as compared to $Na^+$ binding (a result that mirrors the cation selectivity displayed in extraction experiments).[22]

Binding parameters for cations and TB18C6 analogue **5** differ in several respects from those observed for **4**. First, cation:**5** binding stoichiometries approach 3:1 for both $Na^+$ and $K^+$ and 2:1 for $Cs^+$. Thus, unlike the situation encountered with the combination of $Na^+$ and **4**, metalation of all three benzo(crown) units does not appear to be precluded in this system. The magnitudes of the average association constants for **5** and all three cations are similar, and each interaction is favored on both enthalpic and entropic grounds (in contrast to the thermodynamic binding profile of **4**). While crown ether−cation interactions in organic solvents are typically enthalpically driven, positive entropy changes have been noted in the binding of various cations with 18-crown-6 itself (**14**) in acetonitrile. This effect has been ascribed to the unique ability of acetonitrile (relative to other aprotic solvents) to solvate the 18-C-6 macroring. Disruption of the solvation shell upon cation binding then contributes to positive $\Delta S$ values.[23] Extensive solution phase solvation of **14** in acetonitrile is supported by results obtained from computational and spectroscopic experiments,[24,25] and indirectly by solid-state structural characterization of a 2:1 $CH_3CN$:**14** complex.[26] In addition, a number of benzo(18-C-6) derivatives have also been shown to form solid-state complexes with multiple acetonitrile molecules.[27] Extensive solvation of **5** in acetonitrile may likewise account for the favorable entropy term apparent in the formation of cation:**5** guest:host adducts. Smaller crown macrocycles (such as 15-crown-5 derivatives) are not expected to exhibit similar solvation phenomena in acetonitrile.[24,25]



**14**

The tris(crown ether) **4** displays an intriguing cation affinity/selectivity profile. To further probe possible cooperative effects operative in this system and to gain insight into the nature of chelated and/or bridged ion/ionophore assemblies, we have also examined the interactions of structurally related bis- and mono-benzo(15-C-5) TAB derivatives **8** and **9** with $Na^+$ and $K^+$ ions (Table 2). Triaroylbenzene **9** possessing only a single benzo-(15-C-5) ring accommodates one $Na^+$ ion and exhibits an association constant comparable to the average log $K$ of the tris(crown) **4**−sodium system. The overall free energy of sodium binding between these two receptors ($\Delta G$) is also similar, although the respective enthalpic and entropic thermodynamic contributions differ slightly with sodium binding to **4** being more enthalpically driven than sodium binding to the mono-crown **9**. Sodium ion complexation by the bis(crown ether) **8** exhibits a thermodynamic profile very similar to that of **4**. Each receptor displays nearly identical affinities for the binding of two $Na^+$ ions while also possessing comparable $\Delta H$, $T\Delta S$, and calculated $\Delta G$ terms. While the average binding constant for sodium does diminish in the series **9** > **8** > **4**, the maximum difference in log $K$ values is only a factor of 1.6, and all binding data compare favorably with similar sodium ion binding measurements obtained on B15C5 (**10**) itself.[15b,23c] Our conclusion, then, is

(20) Solid-state structural data may prove helpful in elucidating the exact nature of the crown−alkali cation complexes discussed; however, attempts to obtain X-ray quality crystals of **4**, **5**, **8**, and **9** along with their metalated derivatives have thus far been unsuccessful.

(21) NMR experiments aimed at characterizing crown−alkali cation interactions were inconclusive. Significant complexation-induced shifts in the $^1H$ NMR spectra of TAB derivatives obtained before and after addition of an excess of metal salt were absent.

(22) Stepwise association constants were not determined. Instead, the log $K$ values shown in Table 2 reflect an average of all binding events. Values obtained for tris(crown)s **4** and **5** are similar to association constants reported for simpler benzo(crown ether)s and alkali cations. For a compilation of binding data, see: Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.

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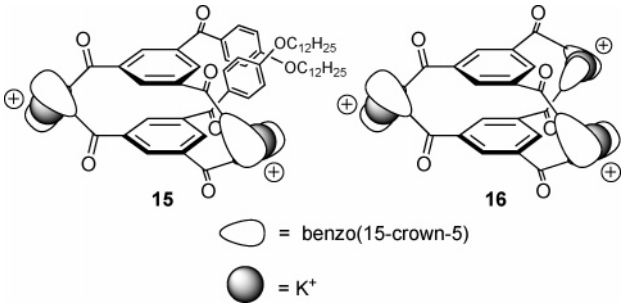


**FIGURE 1.** Schematic representation of $K^+$-bridged TAB dimers formed from bis-crown **8** (complex **15** − TAB:$K^+$ = 1:1) and **4** (complex **16** − TAB:$K^+$ = 2:3).

that while the stoichiometry of $Na^+$ ion binding differs as a function of the number of benzo(15-C-5) substituents, the three TAB derivatives examined function as more or less equivalent sodium ion receptors. Negative cooperativity in the binding of $Na^+$ by **4**, however, seemingly limits the extent of metalation, and one benzo(crown ether) ring remains vacant. Finally, it appears that the presence of dodecyloxy chains in the unsymmetrical TAB's **8** and **9** does not affect ion binding ability.

In contrast to the results obtained with $Na^+$, the affinity of these receptors toward potassium ions is observed to significantly increase with an increase in the number of benzo(15-C-5) groups. Thus, the average binding constant for **4**/$K^+$ is ∼11 times greater than the binding of $K^+$ to **9**, while bis-crown ether **8** exhibits an approximately 3-fold greater $K_a$ relative to the monotopic congener. The binding is enthalpically driven, and the $\Delta H$ values are more negative than those encountered in sodium binding. These favorable enthalpy terms are partially offset, however, by considerably more negative entropic contributions. The binding stoichiometry between mono-benzo(15-C-5) TAB and $K^+$ is consistent with a 2:1 (**9**:$K^+$) complex. Formation of such a supramolecular aggregate is expected to be entropically costly, providing the major contribution to the large negative $T\Delta S$ term observed in the calorimetric binding profile. Indeed, a similarly large and unfavorable entropy term has been recorded for the 2:1 complex between simple benzo-(15-C-5) and KSCN (although this titration was performed in MeOH/$H_2O$ rather than acetonitrile).[15c] Significantly, potassium binding to **8** and **4** also exhibits stoichiometries and entropic costs that can be rationalized by invoking formation of TAB dimers bridged by two (**15**) and three (**16**) $K^+$ ions, respectively (Figure 1). In these cases, we speculate that formation of the first dibenzocrown−$K^+$ assembly is entropically the most costly, but formation of additional $K^+$ ion chelates benefits from a certain degree of pre-organization. A marked decrease in unfavorable entropy is observed for **4**, which may reflect greater desolvation inherent in a triply bridged structure such as **16**. Thus, enhanced $K^+$ ion binding in **4** is a manifestation of positive cooperativity resulting from the presence of three benzo-(15-C-5) rings.[28]

An alternative to the binding arrangement described above exists in that it may be possible for two benzo(crown) substituents on the same TAB to chelate a single metal ion. Examination of molecular models (CPK) reveals that attainment of a face-to-face geometry (an ideal orientation for coordination of a single cation) is unlikely, however, due to the semirigid nature of the triaroylbenzene framework. Inoue and co-workers encountered a similar situation in their studies of potassium ion binding by bis-benzo(15-C-5) ethers connected through linkers possessing varying degrees of flexibility.[15c] It was observed that the 1:1 complex between $K^+$ and a bis-benzo(crown ether) possessing a single methylene linker exhibited a more negative entropic term than that found for the parent intermolecular 2:1 benzo(15-C-5):$K^+$ sandwich. These workers attributed this effect to a partially solvated "open-clam" binding arrangement caused by the inability of the two crown rings to attain a face-to-face orientation. Longer and more flexible tethers led to 1:1 complexes in which intramolecular cation chelation was characterized by higher binding constants and decreased entropic costs. While we also observe a similar trend as a function of increasing numbers of benzo(15-C-5) substituents (i.e., higher log *K* values and decreased entropic costs), the relative ability (or inability) of **4** and **8** to engage in intramolecular $K^+$ chelation does not change. Hence, we speculate that the calorimetrically determined potassium ion binding parameters are a consequence of ternary supramolecular assemblies along the lines of **15**−**16**. Further evidence in support of this assertion can be found in the results of picrate extraction experiments (Table 1). Specifically, Kikukawa and co-workers have noted a "bis-crown" effect in picrate extractions involving linked benzo(crown ether)s capable of chelating alkali metals too large for the individual crown ether components. These bis(crown ether)s were found to be much more effective extraction agents than their monomeric counterparts.[7b] Similar "bis-crown" effects have been observed in other systems as well.[6,29] If a polytopic crown ether such as **4** were capable of intramolecular potassium chelation, then one would expect to observe significantly enhanced $K^+$ picrate extraction as compared to simpler monotopic analogues **10** and **12**. The potassium picrate % extraction values of 21, 22, and 7.3 for **4**, **10**, and **12**, respectively, however, do not appear indicative of such a "polycrown" effect.[30]

Ionophores possessing multiple crown ether groups often display cation-binding selectivities that differ from those exhibited by monotopic analogues. In most instances, this altered selectivity arises from intramolecular interactions between crown components and cation substrates.[6,7] Notably, despite the apparent absence of this metal binding motif in **4** and **8**, enhanced $K^+/Na^+$ selectivity is nonetheless observed. The ratio of $K^+/Na^+$ average binding constants ($K_a$'s) is observed to increase with increasing numbers of benzo(15-C-5) substituents. Thus, the mono-crown conjugate **9** displays the lowest $K^+/Na^+$ selectivity (1.2), which increases to 5.4 for BB15C5 **8** and to 23 for TB15C5 **4**. Although the modest potassium ion selectivity observed in this study is not in a range necessary for practical separation applications, systematic modification of the basic TAB framework designed to enhance not just cation binding ability but also cation selectivity should be possible (e.g., through incorporation of an anion binding moiety as outlined in eq 1). Work along these lines is underway.

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(30) Similarly, the % extraction of $Cs^+$ by the benzo(18-C-6) series of compounds (**5**, **11**, **13**) does not show any enhancement as a function of multiple crown ether substituents.

## Conclusions

We have developed concise synthetic routes to mono-, bis-, and trisbenzo(crown ether)s assembled around 1,3,5-triaroylbenzene (TAB) scaffolds. These materials are conveniently prepared from readily available starting materials via enaminone cyclotrimerization. While benzo(15-C-5) and benzo(18-C-6) building blocks were utilized in this study, we expect other benzo(crown ether) derivatives to display similar reactivity. Thus, the procedures outlined here should represent general and widely applicable methods for construction of polytopic ionophores. The cation binding abilities of tris-benzo(15-C-5) **4** and tris-benzo(18-C-6) **5** were examined using picrate extraction experiments and isothermal titration calorimetry. Additionally, the affinities of bis- and mono-benzo(15-C-5) analogues **8** and **9** toward $Na^+$ and $K^+$ ions were also evaluated via ITC. Taken together, the binding studies appear to indicate that these polytopic crown ethers do not form intramolecular crown ether−metal chelates when exposed to cations too large to be accommodated by individual crown macrorings. Instead, binding occurs through formation of cation-bridged aggregates such as dimeric TAB assemblies **15** and **16**. Positive cooperativity was observed in the binding of $K^+$ ions to **4** in addition to a modest level of $K^+/Na^+$ selectivity. We are currently examining the feasibility of using structurally related TAB frameworks to organize heterotopic receptors for simultaneous binding of cations and anions. Incorporation of anion-binding functionality (such as urea groups[31]) into the hydrocarbon chains in constructs resembling **15** may lead to self-assembly of three-dimensional receptors capable of encapsulating polyvalent salts (e.g., $K_2HPO_4$). In addition, we envision that triaroylbenzene-based crown ether derivatives may serve as useful supramolecular building blocks in the construction of a variety of other functional materials.[32]

## Experimental Section[33]

**Enaminone 2.** 4-Acetylbenzo(15-C-5)[34] (0.95 g, 3.06 mmol) and *N*,*N*-dimethyl formamide dimethyl acetal (3.0 mL) were combined and heated in a 120 °C oil bath for 12 h. The oil bath was then removed, and the mixture was allowed to cool to room temperature to produce a yellow solid. The solid was broken up in hexanes, collected by vacuum filtration, and dried to afford **2** (1.01 g, 90%). Mp 114−116 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$ = 12.3 Hz, 1H), 7.50 (t, $J$ = 8.7 Hz, 2H), 6.84 (d, $J$ = 8.3 Hz, 1H), 5.69 (d, $J$ = 12.4 Hz, 1H), 4.23−4.16 (m, 4H), 3.93−3.89 (m, 4H), 3.76 (s, 8H), 3.02−2.88 (br s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 188.5, 154.8, 152.7, 149.6, 134.6, 122.2, 114.0, 113.0, 92.3, 71.7, 70.9, 70.1, 69.5, 69.3. IR (neat) $\nu$ ($cm^{-1}$) 1640. HRMS (EI) calcd for $C_{19}H_{27}NO_6$ $[M]^+$, 365.1839; found, 365.1841.

**Enaminone 3.** The procedure described above was applied to 4-acetylbenzo(18-C-6)[34] (1.70 g, 4.80 mmol) and 5.0 mL of *N*,*N*-dimethylformamide dimethyl acetal. No solid formed directly from the reaction mixture upon cooling, so the contents of the reaction flask were concentrated in vacuo to afford **3** as a yellow oil that solidified on standing (1.30 g, 66%). Mp 54−56 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 12.3 Hz, 1H), 7.58 (t, $J$ = 14.1 Hz, 2H), 6.86 (d, $J$ = 8.3 Hz, 1H), 5.69 (d, $J$ = 12.3 Hz, 1H), 4.23−4.18 (m, 4H), 3.94−3.90 (m, 4H), 3.77−3.07 (m, 12H), 3.07−2.80 (br s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 187.2, 153.8, 151.5, 148.4, 133.4, 121.4, 113.3, 112.3, 97.6, 70.9, 70.7, 69.4, 69.0. IR (neat) $\nu$ ($cm^{-1}$) 1640. HRMS (ESI) calcd for $C_{21}H_{32}NO_7$ $[M + H]^+$, 410.2179; found, 410.2179.

**Tris-benzo(15-C-5) TAB 4.** Using the trimerization conditions of Elghamry,[12] enaminone **2** (1.00 g, 2.74 mmol) was dissolved in 10 mL of 4:1 AcOH:pyridine and heated in a 120 °C oil bath for 12 h. The solvent was then removed in vacuo to afford a brown residue. Water was added, and the mixture was vigorously stirred for several hours. The desired triaroylbenzene **4** was obtained as a colorless solid collected after filtration and drying under vacuum (0.64 g, 73%). Mp 142−144 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (s, 3H), 7.49 (s, 3H), 7.37 (d, $J$ = 8.4 Hz, 3H), 6.86 (d, $J$ = 8.5 Hz, 3H), 4.21−4.19 (m, 12H), 3.93−3.91 (m, 12H), 3.76 (s, 24H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.0, 153.2, 148.3, 138.0, 132.7, 128.7, 125.5, 113.7, 112.0, 71.2, 70.5, 69.6, 68.4. IR (neat) $\nu$ ($cm^{-1}$) 1658. HRMS (ESI) calcd for $C_{51}H_{61}O_{18}$ $[M + H]^+$, 961.3859; found, 961.3858. Anal. Calcd for $C_{51}H_{60}O_{18}$: C, 63.74; H, 6.29. Found: C, 63.29; H, 6.46.

**Tris-benzo(18-C-6) TAB 5.** Using the procedure given for the preparation of **4**, enaminone **3** (1.30 g, 3.17 mmol) yielded **5** (1.00 g, 86%) as a pale yellow solid. Mp 165−167 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.25 (s, 3H), 7.49 (s, 3H), 7.32 (d, $J$ = 10.3 Hz, 3H), 6.88 (d, $J$ = 8.4 Hz, 3H), 4.23−4.21 (m, 12H), 3.97−3.92 (m, 12H), 3.78−3.69 (m, 36H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.8, 153.6, 148.9, 138.7, 133.0, 129.3, 125.9, 114.1, 111.6, 70.0, 70.6, 69.3, 69.0, 68.9. IR (neat) $\nu$ ($cm^{-1}$) 1658. HRMS (FAB, NBA) calcd for $C_{57}H_{73}O_{21}$ $[M + H]^+$, 1093.4645; found, 1093.4662. Anal. Calcd for $C_{57}H_{72}O_{21}$: C, 62.63; H, 6.63. Found: C, 62.41; H, 6.75.

**Enaminone 6.** 4-Hydroxyacetophenone (0.70 g, 5.14 mmol) and 1-iodododecane (1.38 g, 4.66 mmol) were combined in 15 mL of DMF. Potassium carbonate (0.64 g, 4.70 mmol) was added, and the reaction was heated in a 150 °C oil bath for 12 h. The DMF was evaporated, and the residue was partitioned between $H_2O$ and ether. The layers were separated, and the organic phase was washed sequentially with 5% aq NaOH solution, $H_2O$, and brine. The ether solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford an oily residue, which was purified by flash column chromatography (3:1 hexanes:EtOAc) to afford 4-dodecyloxyacetophenone (0.76 g, 49%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 9.0 Hz, 2H), 6.93 (d, $J$ = 9.0 Hz, 2H), 4.01 (t, $J$ = 6.4 Hz, 2H), 2.54 (s, 3H), 1.80 (m, 2H), 1.45−1.26 (m, 18H), 0.87 (br s, 3H). Without further characterization, this material (0.66 g, 2.17 mmol) was combined with 2.0 mL of *N*,*N*-dimethyl formamide dimethyl acetal and heated in a 120 °C oil bath for 12 h. Volatile liquid was removed in vacuo to afford **6** as a yellow oil that solidified on standing (0.76 g, 97%). Mp 74−76 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.89 (d, $J$ = 7.0 Hz, 2H), 7.78 (d, $J$ = 12.3 Hz, 1H), 6.9 (d, $J$ = 7.0 Hz, 2H), 5.71 (d, $J$ = 12.3 Hz, 1H), 3.99 (t, $J$ = 6.6 Hz, 2H), 3.02 (br d, 6H), 1.81−1.74 (m, 2H), 1.45−1.26 (m, 18H), 0.88 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 187.4, 161.5, 153.7, 132.8, 129.4, 113.7, 91.7, 68.0, 31.9, 29.5, 29.0, 26.0, 22.6, 14.1. IR (neat) $\nu$ ($cm^{-1}$) 1640. HRMS (ESI) calcd for $C_{23}H_{38}NO_2$ $[M + H]^+$, 360.2903; found, 360.2905.

**Co-trimerization of Enaminones 2 and 6. Preparation of TAB's 4 and 7−9.** A mixture of **2** (0.60 g, 1.64 mmol) and **6** (0.29 g, 0.82 mmol) in 7.5 mL of 4:1 AcOH:pyridine was heated in a 120 °C oil bath for 24 h. The solvent was then evaporated, and the residue was combined with $H_2O$ (20 mL) and extracted

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with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 0.63 g (80%) of crude material consisting of a mixture of the four possible triaroylbenzene products. Separation and purification of the desired TAB's was achieved via flash column chromatography using gradient elution (20% EtOAc in hexanes−100% MeOH). The products eluted from the column in the order **7** (22 mg, 4.1%), mono-crown **9** (120 mg, 22%), bis-crown **8** (370 mg, 69%), and tris-crown **4** (27 mg, 5.0%) The combined isolated yield was 539 mg (69% overall, 86% of the crude product).

**Characterization Data. 7.** Waxy semisolid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 3H), 7.84 (d, $J$ = 8.8 Hz, 6H), 6.95 (d, $J$ = 8.8 Hz, 6H), 4.03 (t, $J$ = 6.4 Hz, 6H), 1.83−1.78 (m, 6H), 1.48−2.36 (m, 54H), 0.88 (t, $J$ = 6.8 Hz, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.9, 163.4, 138.7, 133.1, 132.6, 128.9, 114.3, 68.4, 31.9, 29.5, 29.3, 29.0, 22.6, 14.1. IR (neat) $\nu$ (cm$^{-1}$) 1658. HRMS (ESI) calcd for $C_{63}H_{91}O_6$ $[M + H]^+$, 943.6816; found, 943.6806.

**8.** Pale yellow solid. Mp 50−51 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 3H), 7.84 (d, $J$ = 8.8 Hz, 2H), 7.49 (s, 2H), 7.38 (d, $J$ = 8.3 Hz, 2H), 6.96 (d, $J$ = 8.8 Hz, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 4.21−4.19 (m, 8H), 4.03 (t, $J$ = 6.4 Hz, 2H), 3.95−3.91 (m, 8H), 3.77 (br s, 16H), 1.9−1.85 (m, 2H), 1.32−1.26 (m, 18H), 0.87 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.9, 193.8, 163.4, 153.8, 149.1, 138.7, 133.1, 129.3, 126.0, 114.3, 111.6, 71.2, 70.4, 70.3, 69.3, 69.2, 69.0, 68.7, 68.4, 31.9, 29.7, 29.6, 29.5, 29.4, 22.7, 14.1. IR (neat) $\nu$ (cm$^{-1}$) 1649. HRMS (ESI) calcd for $C_{55}H_{70}O_{14}$·Na $[M + Na]^+$, 977.4664; found, 977.4668.

**9.** Colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.26 (s, 3H), 7.84 (d, $J$ = 7.0 Hz, 4H), 7.48 (s, 1H), 7.38 (m, 1H), 6.96 (d, $J$ = 7.0 Hz, 4H), 6.86 (d, $J$ = 8.4 Hz, 1H), 4.21−4.19 (m, 4H), 4.03 (t, $J$ = 6.6 Hz, 4H), 3.95 (m, 4H), 3.76 (br s, 8H), 1.83−1.76 (m, 4H), 1.48−1.26 (m, 36H), 0.87 (t, $J$ = 6.7 Hz, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 194.1, 163.7, 154.0, 149.3, 139.0, 133.3, 132.9, 129.6, 129.1, 126.2, 114.6, 111.9, 71.4, 70.6, 70.5, 69.2, 68.6, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.3, 26.2, 22.9, 14.3. IR (neat) $\nu$ (cm$^{-1}$) 1659. HRMS (ESI) calcd for $C_{59}H_{81}O_{10}$ $[M + H]^+$, 949.5830; found, 949.5823.

**General Procedure for Picrate Extraction Experiments.** A $CHCl_3$ solution of **4** or **5** (3.0 mL, 3.6 × 10$^{-3}$ M) and an aqueous solution (3.0 mL) consisting of alkali metal hydroxide (0.1 M) and picric acid (7.5 × 10$^{-5}$ M) were combined in a test tube and vigorously agitated for 1.5 h. The layers were allowed to separate, and a 2.5 mL aliquot of the aqueous phase was diluted to 5.0 mL. The absorbance of the aqueous phase at 355 nm before and after agitation with the crown solution was compared to determine the % extraction. Extraction experiments involving **10**−**13** were performed using 3.6 × 10$^{-3}$ M solutions of crown ether (i.e., 3 times the concentration of **4** and **5**). Data in Table 1 are averages of three trials.

**Isothermal Titration Calorimetry.** Calorimetric measurements were performed in acetonitrile at 298 K on a computer-controlled VP-ITC microcalorimeter (Microcal, Inc.) against a reference solution of 100% acetonitrile. Acetonitrile (HPLC grade) was purified by passing through a column of activated molecular sieves immediately prior to use. Concentrations of crown ether solutions were 0.5 mM for each experiment. Sodium and potassium titrant solutions were prepared from NaSCN and KSCN (50 mM in MeCN). Cesium titrant solutions were prepared from $CsBPh_4$ (10 mM). Binding isotherms for $Na^+$ and $K^+$ were obtained upon continuous injection of 160 $\mu$L of titrant solution into 1.42 mL of crown ether solution over 1600 s. Evaluation of $Cs^+$ binding was performed similarly except that 280 $\mu$L of titrant was injected over 2800 s. Binding curves were obtained from nonlinear least-squares analysis of the isotherms using the Origin analysis package provided by Microcal, Inc. Data in Table 2 represent averages of three separate trials.

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra, calorimetric data. This material is available free of charge via the Internet at http://pubs.acs.org.

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