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# Novel Ionophores with 2*n*-Crown-*n* Topology: Anion Sensing via Pure Aliphatic C−H···Anion Hydrogen Bonding

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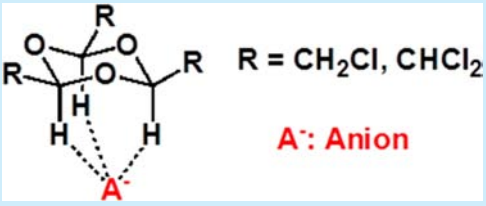
Supporting Information

**ABSTRACT:** A series of novel coronands having a 2*n*-crown-*n* topology based on trioxane (6-crown-3) derivatives are designed and characterized. These neutral hosts can sense anions through pure aliphatic C−H hydrogen bonding (HB) in condensed phases due to the unusual topology of 2*n*-crown-*n*. C−H bonds are strongly polarized by two adjacent oxygen atoms in this scaffold. These hosts provide a rare opportunity to modulate anion binding strength by changing the electronic nature of aliphatic C−H bonds and offer ease of synthesis.




Recently, anion recognition using strongly charged hydrogen bonds and ionic hydrogen bondings (HBs) has been widely studied. Although relatively weaker, interactions between aromatic C−H and anions via HBs in solution media have also been studied,[1] especially cationic imidazolium based anion receptors utilizing strong coulombic interactions.[2] Very recent development based on neutral aromatic C−H HB is worthy of note. Electron-deficient aromatic groups were utilized to recognize anions to form stable structures with anions.[3] The sensing efficiency of an aromatic C−H bond of triazole could be comparable to that of the N−H bond of pyrrole.[3a] The hosts based on triazole C−H hydrogen bonding motifs could be prepared by a very efficient synthetic method.[3b] In a study based on triazolophane structures, the affinities of aromatic and aliphatic C−H hydrogen bonding were compared and the aromatic one was found to be stronger.[3c]

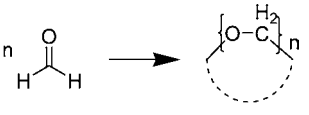
Despite the fact that aliphatic C−H bonds are the most common in organisms, anion hosts utilizing pure aliphatic C−H HBs are very rare.[4d] Although this interaction is weaker than aryl C−H HB, theoretical calculations have revealed that aliphatic C−H HB is also feasible: Aryl C−H HBs are roughly half the strength of conventional O−H and N−H HBs.[4] Furthermore, Pedzisa et al. showed an aliphatic HB element could be very strong (~20 kcal/mol),[4c] which encourages the search for new hosts through pure aliphatic C−H HB elements. The earliest example of pure aliphatic C−H HB was a macrocyclic ether as fluoride anions host in THF solution, and the recognition through aliphatic C−H HB elements was attributed to the presence of large numbers of fluorine atoms.[5] A series of resorcinarene-based cavitands were studied with respect to their binding behavior with anions in the gas phase by ESI-FTICR-MS,[6] and the observed binding affinity was due to four convergent C−H groups polarized by neighboring electronegative heteroatoms. Some anion receptors utilizing positively polarized aliphatic C−H hydrogen bonds by transition metal coordination have also been reported to form stable complexes.[7]

In previously reported anion hosts, C−H bonds are polarized by adjacent electron-withdrawing groups (EWG). These reported hosts are either very complex or activated by metal coordination, and are not amenable to systematic study of aliphatic C−H···anion HB interaction.

No compounds utilizing 2*n*-crown-*n* topology have been previously reported as anion receptors in solution or solid phases.[8] In an effort to identify novel hosts with this topology, we designed, synthesized, and characterized a series of coronands. Unlike the previously reported hosts, trioxane is a simple and neutral host which can be modified by an electron-withdrawing group substitution to polarize C−H bonds.

We first investigated the thermodynamic stabilities of 2*n*-crown-*n* structures (Scheme 1), in which *n* is the number of

**Scheme 1. 2*n*-Crown-*n* Structures from Formaldehyde, where *n* = 2, 3, 4, 5, 6**

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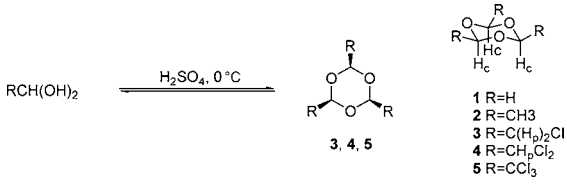
monomeric units. When the starting material is formaldehyde, cyclic multimers would be of 2*n*-crown-*n* topology. Since the crown ethers with $n \geq 3$ have multiple conformations, we calculated many conformers for each $n$ (2−6) to identify a structure with the lowest energy. A simulated annealing procedure was employed for each $n$, using the AMBER 12 package.[9] The conformers for each $n$ were fully optimized without any constraints with the B3LYP/6-311++G** level of theory using the Gaussian 09 program package.[10] All structures were confirmed to be at local minima via frequency calculations.

For $n = 2$, the reaction was endothermic by 1.1 kcal/mol per monomer because of ring strain. With the exception of $n = 2$, 2*n*-crown-*n* structures were predicted to be thermodynamically more stable than their corresponding precursors (formaldehydes) by ∼10 kcal/mol per monomer. Accordingly, computational results indicated the synthetic feasibility of stable 2*n*-crown-*n* architectures for $n \geq 3$.

This theoretically predicted feasibility was verified experimentally under acidic conditions using hydrated formaldehyde,[11] which resulted in the isolation of trimeric hosts (Scheme 2). The $^1$H and $^{13}$C NMR spectra of these three hosts

**Scheme 2. Synthesis of 6-Crown-3 (Trioxane) Hosts**




(Figures S1−6) showed that all protons and carbons were equivalent. Considering the spectroscopic data, there were only two possibilities; that is, all R groups should be either equatorial or axial. We found that for all substituents **2**, **3**, **4**, **5** (Scheme 2), equatorial structures were substantially more favored (>10 kcal/mol) due to steric congestion caused by the bulky R group (Figure 1). The stereospecificities of **3** and **4** were confirmed by

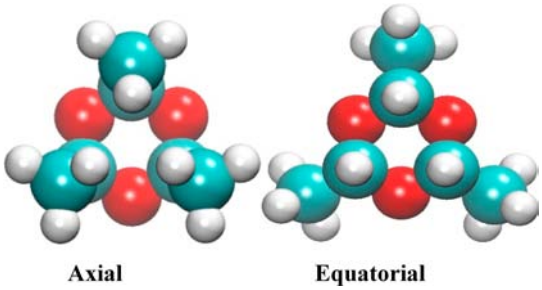



**Figure 1.** Representation of the steric congestion of methyl groups in an all-axial trioxane conformer as compared with the all-equatorial conformer (R = $CH_3$).

X-ray crystallography (Figure 2). These findings indicate that experimentally obtained structures are all-equatorial stereoisomers.

It is remarkable that every isolated reaction product was a single stereoisomer regardless of substitutents (R in Scheme 2). The stereospecificity of these reactions could be useful to study new macrocyclic hosts having a trioxane scaffold.

Because it carries a high positive charge, the hydrogens of the methylene groups of trioxane derivatives should interact with

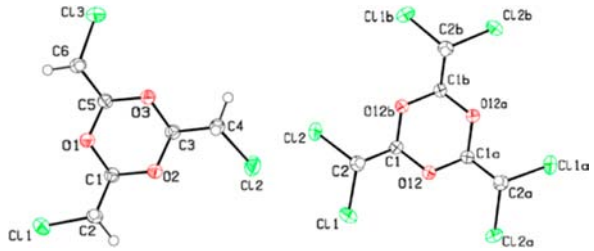



**Figure 2.** Crystal structures of compounds **3** and **4** demonstrating their stereospecificities.

anions more strongly. In addition, because they are parallel to one another, the three C−H bonds are favorably disposed to accommodate anions effectively.

The calculated binding energies of trioxane for nitrite and acetate were −5.1 and −4.7 kcal/mol in the gas phase. The thermal correction was obtained from frequency calculation. For solvation, a polarizable continuum model was used. In benzene solution, the binding free energy values are positive, indicating nonbinding (Table 1). To increase the binding

**Table 1. Binding Energies between Trioxane Derivatives and Anions in Benzene (B3LYP/6-31++G**)[a]**

| | nitrite | | | acetate | | |
|---|---|---|---|---|---|---|
| host | $\Delta E_{BSSEC}$ | $\Delta G_{therm}$ | $\Delta G_{sol}$ | $\Delta E_{BSSEC}$ | $\Delta G_{therm}$ | $\Delta G_{sol}$ |
| **1** | −13.0 | −5.1 | 4.07 | −14.7 | −4.7 | 5.19 |
| **2** | −11.2 | −3.6 | 4.57 | −13.4 | −3.1 | 5.14 |
| **3** | −24.6 | −16.0 | −3.48 | −26.8 | −14.6 | −2.64 |
| **4** | −26.5 | −17.5 | −3.59 | −29.4 | −18.1 | −4.56 |
| **5** | −28.0 | −18.7 | −4.43 | −31.4 | −19.8 | −5.52 |

[a] $\Delta E_{BSSEC}$, binding energy after BSSEC. $\Delta G_{therm}$, Gibbs binding free energy; $\Delta G_{sol}$, binding energy using the structure optimized in benzene followed by frequency calculation. Units are in kcal/mol.

affinity, we introduced electron-withdrawing groups to further polarize C−H bonds. With chloromethyl substitution, hosts **3**, **4**, and **5** were predicted to bind weakly to both nitrite and acetate. For anion sensing, as the number of chlorine substituents is increased, the absolute magnitude of binding energy increases monotonically, indicating the importance of the electronic effect on the C−H bonds (Table 1). The antiperiplanar arrangements of C−Cl bonds and anion-sensing C−H bonds are shown in Figure 3.

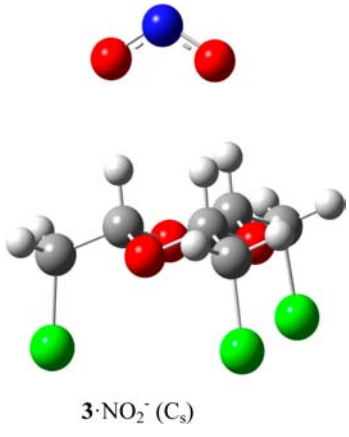



**Figure 3.** Effect of three chloromethyl substitutions on anion sensing.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In order to verify anion recognition experimentally, we chose benzene as a solvent to minimize the solvation of guest anions. We could not observe anion binding with trioxane (**1** in Scheme 2) or its three methyl substituted derivative (**2** in Scheme 2) in benzene, as predicted by theoretical calculations. However, we could detect interactions between anions and **3** and **4**. For **5**, we encountered a stability problem; that is, it decomposed gradually under the experimental conditions. For halides, we conducted titration studies in acetonitrile since TBA·halide salts are not soluble in benzene. Accordingly, the calculations for halides were performed in acetonitrile (Table S2). The binding trend for halides in acetonitrile are very similar to that for other anions in benzene, i.e., the larger the electron-withdrawing effect of the substitutents, the bigger the affinity.

There are two type of hydrogens: one is on trioxane at the center ($\mathbf{H_c}$), and the other at the periphery ($\mathbf{H_p}$). The chemical shifts of $\mathbf{H_c}$ at a $[H_0]/[G_0]$ of 1:1 ratio are shown in Table 2,

**Table 2. Relative Downfield $^1$H Shifts (ppm) of 3 and 4 ($\mathbf{H_c}$) in the Presence and Absence of Guests in d6-Benzene or d3-Acetonitrile: $[H_0] + [G_0] = 8.00$ mM**

| | 3 | | 4 | | 5 |
|---|---|---|---|---|---|
| | $\mathbf{H_c}$ | $\mathbf{H_p}$ | $\mathbf{H_c}$ | $\mathbf{H_p}$ | $\mathbf{H_c}$ |
| $NO_2^-$ | 0.012 | 0.002 | 0.082 | 0.024 | 0.002 |
| $AcO^-$ | 0.017 | 0.004 | 0.128 | 0.049 | 0.004 |
| $Cl^-$ | 0.0031 | −0.0005 | 0.0230 | 0.0015 | N.D.[a] |
| $Br^-$ | 0.0027 | −0.0003 | 0.0146 | 0.0010 | N.D. |
| $I^-$ | 0.0021 | −0.0002 | 0.0076 | 0.0008 | N.D. |

[a]Not detected.

which shows that hosts **3** and **4** bind acetate more strongly (Figure 4). However, host **5** exhibits an abnormal binding affinity with these two anions, because it decomposes to aldehyde monomers.

NMR titrations of hosts **3** and **4** versus acetate, nitrite, and halides were performed keeping $[H_0] + [G_0]$ constant. At a certain concentration of a guest, the chemical shifts of $\mathbf{H_c}$ and $\mathbf{H_p}$ of **3** and **4** are saturated at the same point (Figures S7, S10, S13, S15, S18, S21, S24, S27, S30, S33), and Job plots of $\mathbf{H_c}$ and $\mathbf{H_p}$ chemical shifts (Figures S11, S16) were almost identical for both hosts. Binding stoichiometries were determined from Job plots (Figures 5, S8, S11, S14, S16, S19, S22, S25, S28, S31, S34). The binding constants ($K$) and proton chemical shifts of 1:1-binding HGs (final chemical shift, $\delta_{fin}$) were extrapolated from experiments performed at constant $[H_0] + [G_0]$ (Table 3). For host **4**, substantial chemical shifts of $\mathbf{H_p}$ were observed upon anion binding. We believe this is caused by the very low affinity of host **4** toward anions. That is, instead of being tightly fixed at one site, the guests can move around dynamically. Indeed, during computational structure optimization, we found the peripheral binding structures were not of a much higher energy, while central binding structures were the only local minima for host **4** anion complexes. According to the binding constants obtained, both acetate and nitrite were bound to **3** and **4** through aliphatic C−H HBs. The trend of binding affinity with respect to substituents is consistent with the calculation regardless of the solvent used (benzene or acetonitrile).

In summary, we designed and identified a series of crown ethers with a novel 2*n*-crown-*n* topology. These hosts, which possess a trioxane scaffold, were easily synthesized and

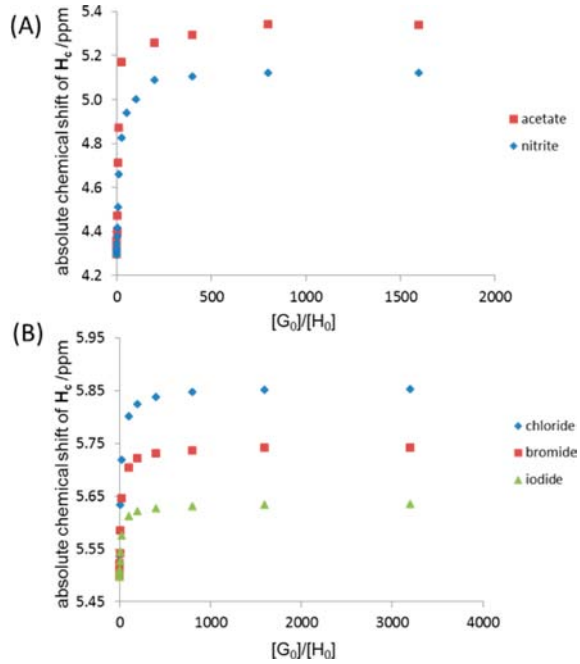


**Figure 4.** $^1$H NMR shifts of $\mathbf{H_c}$ of **4** upon adding anions in d6-benzene (A)or d3-acetonitrile (B). 4 mM of **4** titrated by 100 mM of guests (for acetate, 50 mM).

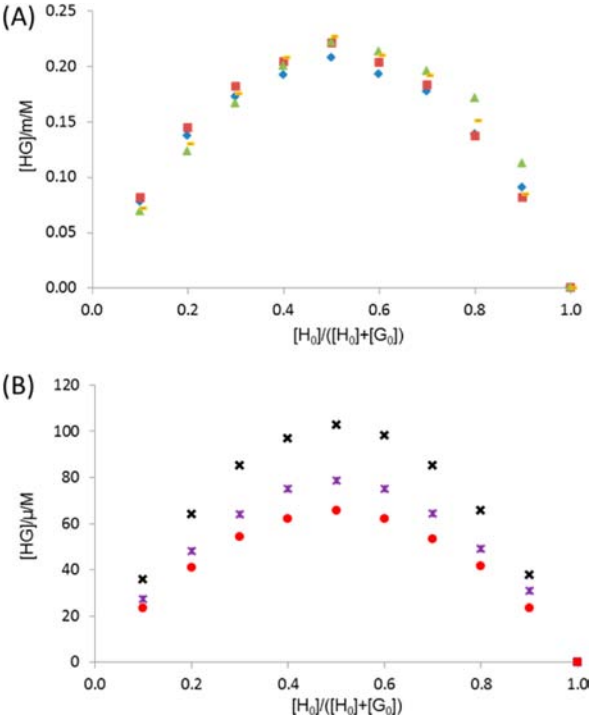


**Figure 5.** Representative Job plots of the interaction between **4** and anions in d6-benzene (A) or d3-acetonitrile (B). Blue diamond: $\mathbf{H_c}$ /$AcO^-$; brown square: $\mathbf{H_p}$/$AcO^-$; green triangle: $\mathbf{H_c}$ /$NO_2^-$; orange hyphen: $\mathbf{H_c}$ /$NO_2^-$; black cross: $\mathbf{H_c}$ /$Cl^-$; purple star: $\mathbf{H_c}$ /$Br^-$; red circle: $\mathbf{H_c}$ /$I^-$. $[H_0] + [G_0] = 8.00$ mM.

modified. Because of their proximities to oxygen, bound methylene groups were significantly polarized. To verify the anion sensing abilities inherent in 2*n*-crown-*n* topology in the condensed phase, we modified trioxane using electron-withdrawing groups and then confirmed the anion binding abilities


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Table 3. Binding Stoichiometries, Binding Constants, and Final Chemical Shifts of 3 and 4 with Nitrite and Acetate in d6-Benzene and Halides in d3-Acetonitrile: $[H_0] + [G_0] = 8.00$ mM

| | 3 ($H_c$) | | | 4 ($H_c$) | | | 4 ($H_p$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $S$[a] | $K$[b] | $\delta_{fin}$ | $S$ | $K$ | $\delta_{fin}$ | $S$ | $K$ | $\delta_{fin}$ |
| $NO_2^-$ | 2 | N.D.[c] | N.D. | 1 | 12.6 | 5.774 | 1 | 13.9 | 5.446 |
| $AcO^-$ | 1 | 9.97 | 4.763 | 1 | 14.7 | 6.766 | 1 | 15.0 | 5.910 |
| $Cl^-$ | 1 | 2.43 | 5.5939 | 1 | 6.58 | 6.3930 | | | |
| $Br^-$ | 1 | 2.98 | 5.5022 | 1 | 4.92 | 6.2390 | | N.A.[d] | |
| $I^-$ | 1 | 2.35 | 5.4648 | 1 | 4.19 | 5.9596 | | | |

[a]Binding stoichiometry (H/G). [b]Binding constant ($M^{-1}$). [c]Not determined. [d]Not available because of insufficient chemical shifts.

of these hosts in solution. The current study is an example of anion sensing hosts through only aliphatic C−H HB motifs, envisioned by previous reports.[3c,4c,d] This study also shows that 2*n*-crown-*n* scaffolds have potential use as anion sensors utilizing pure aliphatic C−H HB interactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) (a) Yoon, J.; Kim, S. K.; Singh, N. J.; Kim, K. S. *Chem. Soc. Rev.* **2006**, *35*, 355−360. (b) Hargrove, A. E.; Nieto, S.; Zhang, T.; Sessler, J. L.; Anslyn, E. V. *Chem. Rev.* **2011**, *111*, 6603−6782. (c) Kwon, J. Y.; Singh, N. J.; Kim, H. N.; Kim, S. K.; Kim, K. S.; Yoon, J. *J. Am. Chem. Soc.* **2004**, *126*, 8892−8893. (d) Xu, Z.; Singh, N. J.; Lim, J.; Pan, J.; Kim, H. N.; Park, S.; Kim, K. S.; Yoon, J. *J. Am. Chem. Soc.* **2009**, *131*, 15528−15533.

(2) Sessler, J. L.; Gale, P. A., Cho, W.-S. *Anion Receptor Chemistry*; RSC Publishing: 2006.

(3) (a) Hua, Y.; Flood, A. H. *Chem. Soc. Rev.* **2010**, *39*, 1261. (b) Hua, Y.; Ramabhadran, R. O.; Karty, J. A.; Raghavachari, K.; Flood, A. H. *Chem. Commun.* **2011**, *47*, 5979. (c) Hua, Y.; Ramabhadran, R. O.; Uduehi, E. O.; Karty, J. A.; Raghavachari, K.; Flood, A. H. *Chem.—Eur. J.* **2011**, *17*, 312. (d) Berryman, O. B.; Sather, A. C.; Hay, B. P.; Meisner, J. S.; Johnson, D. W. *J. Am. Chem. Soc.* **2008**, *130*, 10895. (e) Bardelang, D.; Udachin, K. A.; Leek, D. M.; Margeson, J. C.; Chan, G.; Ratcliffe, C. I.; Ripmeester, J. A. *Cryst. Growth Des.* **2011**, *11*, 5598.

(4) (a) Hay, B. P.; Bryantsev, V. S. *Chem. Commun.* **2008**, *21*, 2417. (b) Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2005**, *127*, 8282. (c) Pedzisa, L.; Hay, B. P. *J. Org. Chem.* **2009**, *74*, 2554. (d) Li, W.; Xu, Q.; Li, Y.; Zhu, W.; Cui, J.; Ju, Y.; Li, G. *Tetrahedron Lett.* **2013**, *54*, 3868.

(5) Farnham, W. B.; Roe, D. C.; Dixon, D. A.; Calabrese, J. C.; Harlow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7707.

(6) Zhu, S. S.; Staats, H.; Brandhorst, K.; Grunenberg, J.; Gruppi, F.; Dalcanale, E.; Lutzen, A.; Rissanen, K.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 788.

(7) (a) Bedford, R. B.; Betham, M.; Butts, C. P.; Coles, S. J.; Hursthouse, M. B.; Scully, P. N.; Tucker, J. H.; Wilkie, J.; Willener, Y. *Chem. Commun.* **2008**, 2429. (b) Morales, D.; Puerto, M.; Rio, I.; Perez, J.; Lopez, R. *Chem.—Eur. J.* **2012**, *18*, 16186.

(8) For cation recognition: (a) Cho, S. J.; Hwang, H. S.; Park, J. M.; Oh, K. S.; Kim, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 485. (b) Lee, W. Y.; Park, C. H.; Kim, S. *J. Am. Chem. Soc.* **1993**, *115*, 1184. (c) Chunzhi, C.; Cho, S. J.; Kim, K. S. *J. Phys. Chem. A* **1998**, *102*, 1119.

(9) http://ambermd.org/doc12/Amber12.pdf.

(10) http://www.gaussian.com/g_tech/g_ur/m_citation.htm.

(11) Wakasugi, T.; Miyakawa, T.; Suzuki, F.; Itsuno, S.; Ito, K. *Synth. Commun.* **1993**, *23*, 1289.

## ■ NOTE ADDED AFTER ASAP PUBLICATION

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