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Heterodimerization Studies of Calix[4]arene Derivatives in Polar Solvents

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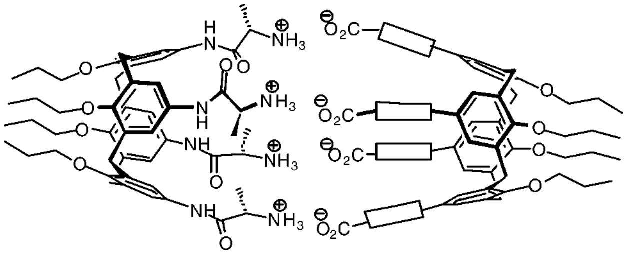
ABSTRACT



Several calix[4]arene derivatives propylated on the lower rim and substituted on the upper rim with amino or carboxyl groups have been synthesized. Examples include calixarenes substituted with alanino (C- and N-linked), amino, carboxy, carboxyphenyl, and amidino groups. The self-assembly of these derivatized calixarenes into heterodimers has been studied by NMR in DMSO-d_6 or CD_3OD with 5% aqueous phosphate buffer.

Molecular recognition is a rapidly growing field centered around the synthesis and study of molecules capable of recognizing and binding one another through intermolecular interactions such as hydrogen bonds, π-stacking, hydrophobic interactions, electrostatic interactions, and van der Waals interactions. These molecules have a wide variety of applications, including catalysis, drug delivery, chiral separation, biocatalysis, and supramolecular assembly. One particular area that has received considerable attention is the design and synthesis of self-assembling capsules. A self-assembling capsule is a supramolecular structure made up of two or more molecules that come together through noncovalent, reversible interactions to form an enclosed cavity. If an appropriate guest molecule is mixed in with the monomers, the guest will be encapsulated within the cavity.

To utilize capsules and complexes for biological applications, they must self-assemble and be soluble in polar, protic solvents. Although there are many examples of self-assembling dimers in nonpolar solvent, these compounds utilize hydrogen bonding[1] and the addition of small amounts of polar solvent often disrupts the complex. Recently, the synthesis of dimers that assemble through ionic interactions in polar solvents has been reported.[2] In these cases, the dimerization is favored by the increased bond strength of ionic bonds over hydrogen bonds. Here, we report the synthesis of calixarene derivatives that utilize ionic interactions to form heterodimers in polar solvent.

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[1] For dimers formed through hydrogen bonds in nonpolar solvents, see: (a) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12670−12672. (b) Castellano, R. K.; Nickolls, C.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 11156−11163. (c) Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 10002−10003. (d) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489−8496. (e) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712. (f) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426. (g) Rincón, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **2001**, *123*, 3493−3498. (h) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643. (i) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407. (j) Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568−4579. (k) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264−1266. For dimers formed through hydrogen bonds in polar solvents, see: (l) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376−2377. (m) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, 2374−2375. (n) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Chem. Commun.* **2001**, 1890−1891.

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We have prepared a number of calix[4]arene derivatives substituted on the upper rim with amino or carboxyl groups, including C-linked alaninocalix[4]arene **1**,[3] N-linked alaninocalix[4]arene **2**, anilinocalix[4]arene **3**,[4] carboxycalix[4]arene **4**, carboxyphenylcalix[4]arene **5**, and amidinocalix[4]arene **11**. Calix[4]arene derivatives **1** and **3** are shown in Figure 1. The syntheses of **2**, **4**, **5**, and **11** are shown in Schemes 1−3.

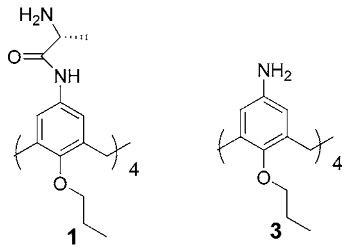
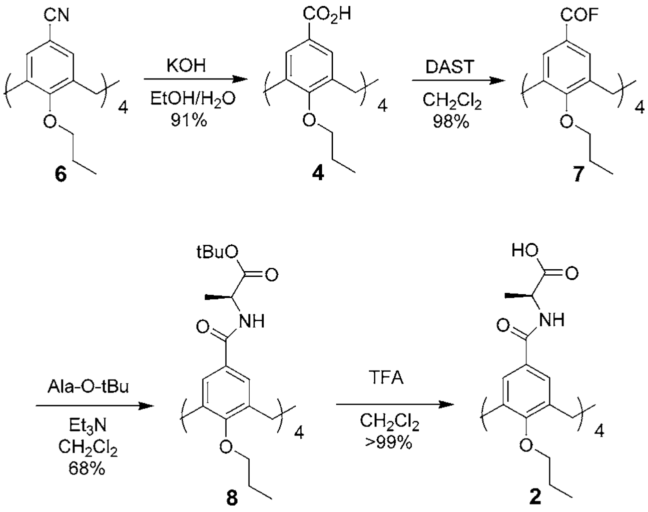


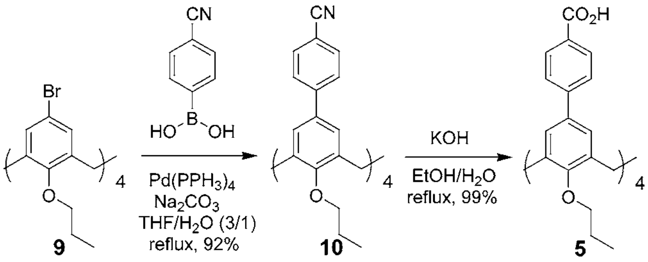
Figure 1. Previously synthesized calix[4]arene derivatives.

N-Linked alaninocalix[4]arene was synthesized in four steps from nitrilocalix[4]arene **6** (Scheme 1), which was prepared following the procedure from Pinkhassik et al.[5] The nitrile was hydrolyzed with potassium hydroxide in EtOH/water to form carboxycalix[4]arene **4**. The acid derivative **4** was then converted to the acid fluoride **7** using diethylaminosulfur trifluoride (DAST) in methylene chloride. *tert*-Butyl protected alanine was coupled to **7** using triethylamine in methylene chloride to afford the protected alaninocalix[4]arene **8**. Deprotection of **8** with trifluoroacetic acid (TFA) in methylene chloride yielded the desired product, N-linked alaninocalix[4]arene **2**.

Scheme 1. Synthesis of Alaninocalix[4]arene **2** and Carboxycalix[4]arene **4**

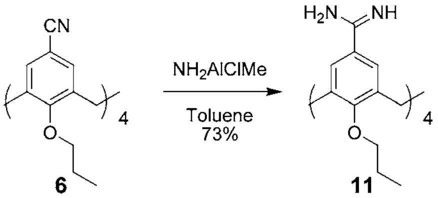


Scheme 2. Synthesis of Carboxyphenylcalix[4]arene **5**



Carboxyphenylcalix[4]arene **5** was prepared in two steps from bromocalix[4]arene **9**[6] (Scheme 2). Suzuki coupling of **9** with *p*-cyanophenylboronic acid was accomplished in THF/water using palladium tetrakis(triphenylphosphine) and sodium carbonate. Hydrolysis of the resulting nitrilophenylcalix[4]arene **10** with potassium hydroxide in EtOH/water affords compound **5** in excellent yield.

Scheme 3. Synthesis of Amidinocalix[4]arene **11**



Amidinocalix[4]arene **11** was synthesized from nitrilocalix[4]arene in one step using an alkylchloroaluminum amide[6] (Scheme 3). The aluminum reagent was prepared in situ from trimethyl aluminum and ammonium chloride in dichloroethane.[7]

The self-assembly of these derivatized calixarenes into heterodimers was studied by NMR in DMSO-d_6 or CD_3OD with 5% aqueous phosphate buffer. Anilinocalix[4]arene **3** does not dimerize with either **2** or **4** in the DMSO/buffer, pH 4.3 mixture. In contrast, C-linked alaninocalix[4]arene **1** does form a complex with **2**, **4**, and **5** in DMSO/buffer, pH 6.5 (Figure 2).

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(2) For dimers formed through ionic interactions in polar solvents, see: (a) Corbellini, F.; Di Costanzo, L.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946−9947. (b) Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569−6575. (c) Grawe, T.; Schrader, T.; Gurrath, M.; Kraft, A.; Osterod, F. *J. Phys. Org. Chem.* **2000**, *13*, 670−673. (d) Hamelin, B.; Jullien, L.; Derouet, C.; du Penhoat, C. H.; Berthault, P. *J. Am. Chem. Soc.* **1998**, *120*, 8428−8447. (e) Lee, S. B.; Hong, J.-I. *Terahedron Lett.* **1996**, *37*, 8501−8504. (f) Zadmard, R.; Schrader, T.; Grawe, T.; Kraft, A. *Org. Lett.* **2002**, *4*, 1687−1690.

(3) Brewster, R. E.; Shuker, S. B. *J. Am. Chem. Soc.* **2002**, *124*, 7902−7903.

(4) Matthews, S. E.; Saadioui, M.; Böhmer, V. *J. Prakt. Chem.* **1999**, *341*, 264−273.

(5) Pinkhassik, E.; Sidorov, V.; Stibor, I. *J. Org. Chem.* **1998**, *63*, 9644−9651.

(6) Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569−6575.

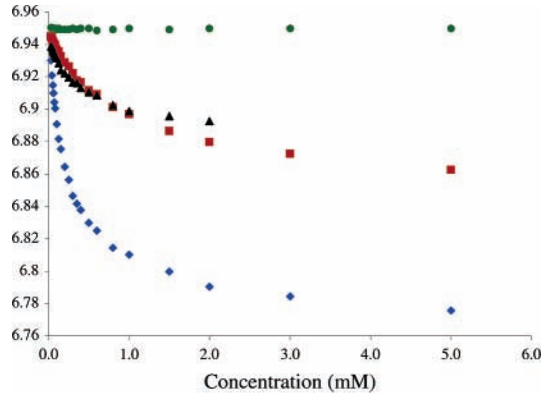

Figure 2. NMR dilution studies of C-linked alaninocalix[4]arene **1** with N-linked alaninocalix[4]arene **2**, carboxycalix[4]arene **4**, and carboxyphenylcalix[4]arene **5** in DMSO-d_6/5% phosphate buffer at pH 6.5.

Table 1. Heterodimer Association Constants

heterodimers	K_a (M^{-1})	solvent
1 + **2**	5040	DMSO-d_6/5% buffer, pH 6.5
1 + **5**	4410	DMSO-d_6/5% buffer, pH 6.5
1 + **4**	1200	DMSO-d_6/5% buffer, pH 6.5
3 + **2**	[a]	DMSO-d_6/5% buffer, pH 4.3
3 + **4**	[a]	DMSO-d_6/5% buffer, pH 4.3
11 + **2**	[a]	CD_3OD/5% buffer, pH 8.8
11 + **4**	[a]	DMSO-d_6/5% buffer, pH 8.8

[a] No dimerization observed.

The dimerization of these derivatives is attributed to the larger difference in pK_a's of protonated **1** (pK_a ~ 9) and **2**, **4**, and **5** (pK_a ~ 5) compared to that of **3** (pK_a ~ 4.7) and **2**, **4**, and **5**. The monomers with the largest pK_a difference, N-linked and C-linked alaninocalix[4]arene, form the tightest binding heterodimer ($K_a = 5040$ M^{-1}).[2] Carboxyphenylcalix[4]arene also forms a strong heterodimer with **1** ($K_a = 4410$ M^{-1}),[8] followed by carboxycalix[4]arene ($K_a = 1200$ M^{-1}).[8] It is interesting to note that addition of the phenyl spacers to the calix[4]arene scaffold increases the size of the heterodimer with little effect on its ability to dimerize (Table 1).

No dimerization was observed between amidinocalix[4]arene **11** and carboxycalix[4]arene **4** or N-linked alaninocalix[4]arene **2** (Table 1).

All of the heterodimers were analyzed using Job plots, and a representative plot of **1** and **2** is shown in Figure 3.

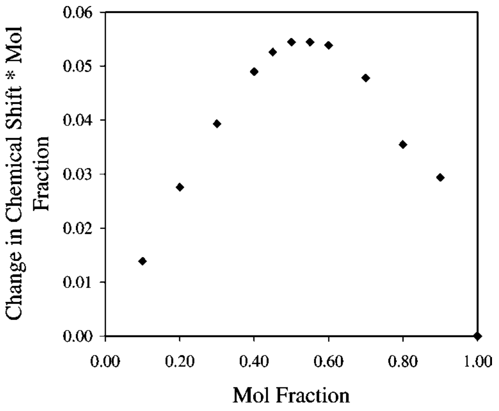

Figure 3. Job plot of the aryl protons of C-linked alaninocalix[4]arene **1** with N-linked alaninocalix[4]arene **2** in DMSO-d_6/5% phosphate buffer at pH 6.5.

All of the Job plots have a maximum at approximately 0.5, indicating the assembly of a supramolecular structure with a 1:1 monomer ratio. The NMR spectra from both the Job plots and the dilution studies have sharp peaks that are consistent with the formation of heterodimers rather than larger assemblies, which would be expected to have broader peaks in the NMR spectra.

In summary, this paper describes the ability of calix[4]arene derivatives to self-assemble into heterodimers in polar solvents with association constants of 5000−1000 M^{-1}. Although the calix[4]arene derivatives are water soluble as monomers, the heterodimers are not. We are currently synthesizing calix[4]arene derivatives with alcohols on the lower rim to increase the water solubility.

Acknowledgment. We thank NSF (0316801) and the Georgia Institute of Technology for financial support.

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

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(7) Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969−1972.

(8) All of the association constants were calculated using the method described in: Nakano, M.; Nakano, N. I.; Higuchi, T. *J. Phys. Chem.* **1967**, *71*, 3954−3959.