JOC Article
pubs.acs.org/joc

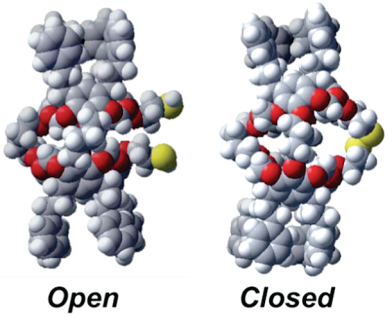
Controlled Gating of a Hemicarcerand by Disulfide−Dithiol Interchange

Roger C. Helgeson, Amy E. Hayden, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive, Los Angeles, California 90095-1569

houk@chem.ucla.edu

Received June 11, 2009



Introduction of a disulfide unit into the linker of a hemicarcerand creates a new way to control the entry and exit of guests. When the disulfide bond is reduced to two thiols, the "gate" opens, and guests can freely enter the hydrophobic core of the hemicarcerand. However, when the gate is closed, the host must be heated in the presense of excess guest in order for complexation to result. Several novel hemicarceplexes of this type have been synthesized. Molecular mechanics calculations are employed to explore the differing stabilities and ease of complexation of these host−guest complexes.

Introduction

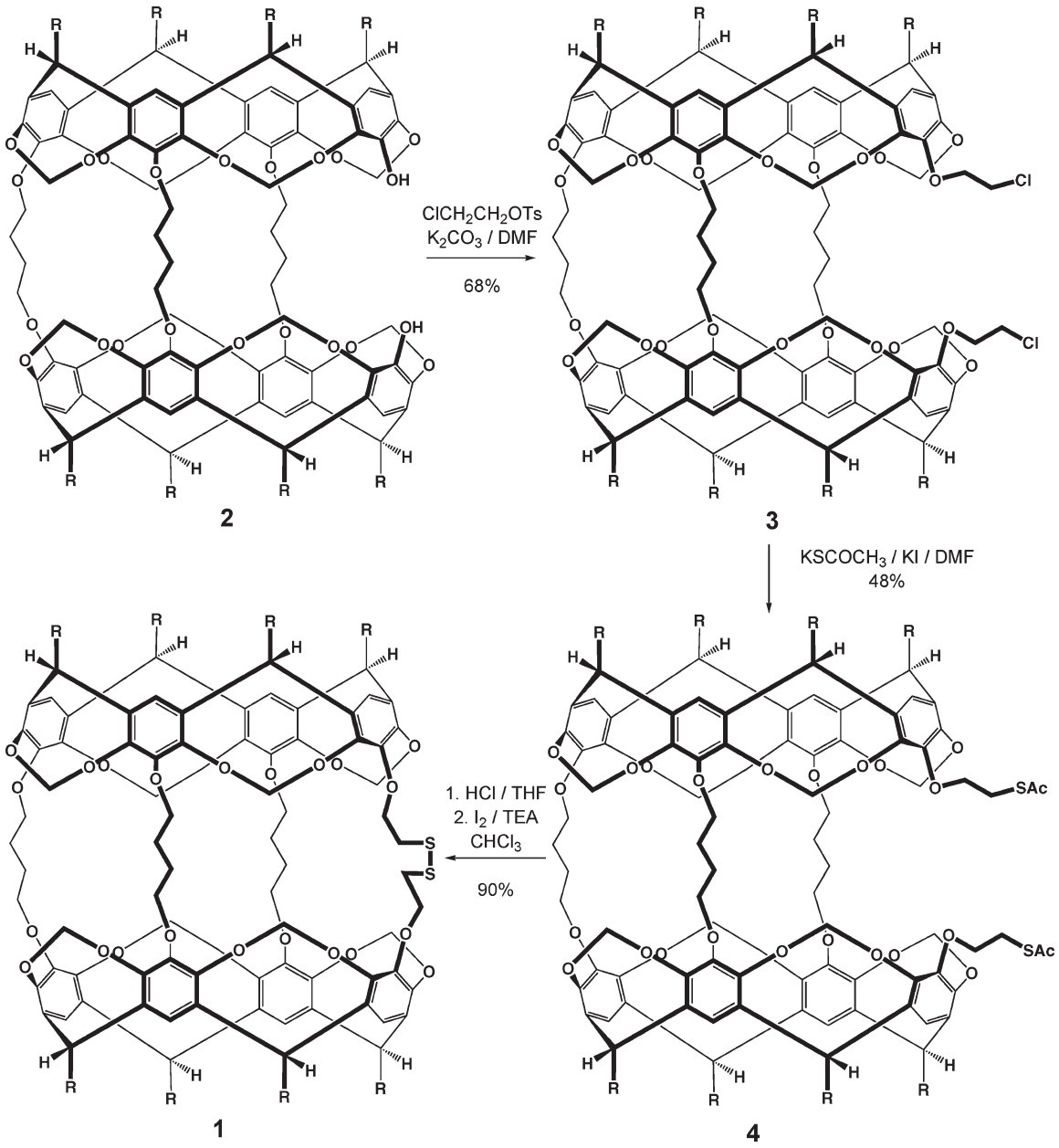
Cram's pioneering work on container molecules and constrictive binding was based upon modeling with CPK models.[1] Our group[2,3] subsequently discovered that guest molecules frequently enter and exit hemicarceplexes by conformational processes that we named "gating." In this context, gating involves a thermally induced conformational change that opens a portal so that guests can easily enter or exit.[4,5a] Such a process has been observed in other host molecules, such as Rebek's sportsball molecules.[6,7] A molecular mechanics study by our group revealed the gating mechanisms involved.[8] Badjic and co-workers[9] have reported a molecular basket with a conformationally controlled lid. Klärner's molecular tweezers[10] also undergo thermal conformational changes in order to accommodate guests. In host−guest systems, there are two energetic quantities associated with guest binding—constrictive and intrinsic binding. The constrictive binding[11,12] is the activation energy required for a guest to enter the host, while intrinsic binding is the change in energy upon formation of the host−guest complex from free host and guest. Intrinsic binding energy determines the equilibrium constant for binding; the intrinsic binding energy plus the constrictive binding energy determines the kinetic barrier to decomplexation.[12]

We conceived of chemically controlled gating and have undertaken the theoretical design and synthesis of a hemicarcerand with gating controlled by redox processes, namely, by installing a linker with a disulfide bond. Disulfide bonds are normally reduced to thiols inside cells because there is a

(1) Cram, D. J. *Nature* **1992**, *356*, 29–36.
(2) Nakamura, K.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1853–1854.
(3) Houk, K. N.; Nakamura, K.; Sheu, C.; Keating, A. E. *Science* **1996**, *273*, 627–629.
(4) Sheu, C.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 8056–8070.
(5) (a) Yoon, J.; Sheu, C.; Houk, K. N.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1996**, *61*, 9323–9339. (b) Warmuth, R.; Marvel, M. A. *Chem.—Eur. J.* **2001**, *7*, 1209–1220.
(6) Branda, N.; Grotzfield, R. M.; Valdés, C.; Rebek, J. *J. Am. Chem. Soc.* **1995**, *117*, 85–88.
(7) Kang, J.; Rebek, J. *Nature* **1996**, *382*, 239–241.
(8) Wang, X.; Houk, K. N. *Org. Lett.* **1999**, *1*, 591–594.
(9) Maslak, V.; Yan, Z.; Xia, S.; Gallucci, J.; Hadad, C. M.; Badjic, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 5887–5894.
(10) Lobert, M.; Bandmann, H.; Burkert, U.; Büchele; Podsadlowski, V.; Klärner, F.-G. *Chem.—Eur. J.* **2006**, *12*, 1629–1641.
(11) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717–7727.
(12) (a) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95–105. (b) Holman, K. T. *Encyclopedia of Supramolecular Chemistry* **2004**, *1*, 340–348.

Published on Web 12/29/2009 DOI: 10.1021/jo9012496

SCHEME 1. Preparation of a Hemicarcerand with a Disulfide Gate (R = Pentyl)



reducing environment inside the cell; there are exceptions, as in thermophilic bacteria.[13a] Therefore, a molecule with a disulfide gate could have applications in drug delivery, by turning off constrictive binding and releasing a guest upon transformation of the disulfide to the dithiol. Sanders, Otto, and co-workers have utilized thiol−disulfide equilibrations for the creation of dynamic combinatorial libraries in receptor−substrate studies.[14a] The photochemical cleavage of a linker in a hemicarceplex and guest egress has been reported.[13b] There are other examples of the utilization of disulfide connections in supramolecular systems including the formation of dimeric tris(disulfides) from the monomeric tris(thiol),[14b] the synthesis of a [5]carceplex with five disulfide linkages by Sherman and co-workers,[15] and most recently, the development of a biocleavable cyclodextrin-based polyrotaxane by Yui et al.[16] In our system, reduction of the disulfide link results in the opening of only one of the four linkers. The rest of the molecule remains intact and covalently linked. The reversible nature of this reaction provides a mechanism for loading the host with guest.

(13) (a) Beeby, M.; O'Connor, B. D.; Ryttersgaard, C.; Boutz, D. R.; Perry, L. J.; Yeates, T. O. *PLOS Biol.* **2005**, *3*, 1549–1558. (b) Piatnitski, E. L.; Deshayes, K. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 970–972.

(14) (a) Corbett, P. T.; Sanders, J. K. M.; Otto, S. *J. Am. Chem. Soc.* **2005**, *127*, 9390–9392. (b) Tam-Chang, S.-W.; Stehouwer, J. S.; Han, J. *J. Org. Chem.* **1999**, *64*, 334–335. (c) Horng, Y. Y.; Lin, K. L.; Tu, C. Y.; Sung, T. J.; Hsieh, C. C.; Hu, C. H.; Lee, H. M.; Kuo, T. S. *Eur. J. Org. Chem.* **2009**, 1511–1514.

(15) Naumann, C.; Place, S.; Sherman, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 16–17.

(16) Ooya, T.; Choi, S.; Yamashita, A.; Yui, N.; Sugaya, Y.; Kano, A.; Maruyama, A.; Akita, H.; Ito, R.; Kogure, K.; Harashima, H. *J. Am. Chem. Soc.* **2006**, *128*, 3852–3853.

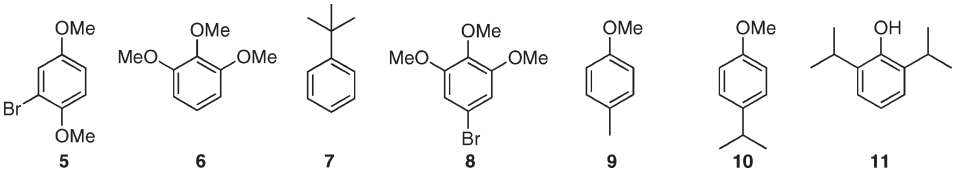


FIGURE 1. Small aromatic guests used in experiments and computations.

TABLE 1. Chemical Shifts (ppm) and Changes in Chemical Shifts ($\Delta\delta$) of Substituents on Benzene Guests Resulting from Complexation with 1 (R = Pentyl)

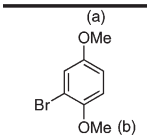
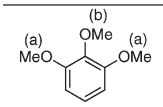
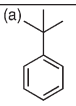
	Free Guest δ		*Complexed Guest δ*		*Complexed Guest Δδ*	
Guest Structure	^{a}H	^{b}H	^{a}H	^{b}H	^{a}H	^{b}H
 5	3.76	3.85	−0.41	−0.39	4.17	4.24
 6	3.85	3.86	−0.50	3.34	4.35	0.52
 7	1.34		0.18		1.16	

TABLE 2. Conditions for Decomplexation of 1⊗5, 1⊗6, and 1⊗7

entry	complex	base	equiv of base	thiol	equiv of thiol	time	% decomplexation
1[a]	**1⊗6**	DBU	10	$HS(CH_2)_4SH$	10	20 min	100
2	**1⊗6**	DBU	1	DTT	1	2 h	100
3	**1⊗6**	DBU	0.1	DTT	0.1	2 days	~10
4	**1⊗6**	DBU	1	DTT	0.1	2 days	~19
5	**1⊗5**	DBU	10	$HS(CH_2)_4SH$	10	25 min	100
6	**1⊗7**	DBU	10	$HS(CH_2)_4SH$	10	35 min	100

[a]This method was previously used to reduce crown ether disulfides to dithiols.[18]

Results and Discussion

Synthesis and Hemicarceplex Formation. The synthesis of disulfide-containing hemicarcerand **1** (R = pentyl) is outlined in Scheme 1 beginning with known compound **2**.[5a] O-Alkylation with 2-chloroethyl *p*-toluenesulfonate in DMF in the presence of K_2CO_3 at 55 °C for 4 days provides **3**. Subsequent reaction with potassium thioacetate in DMF at 60 °C in the presence of KI affords dithioacetate **4**. Deprotection with HCl in THF followed by oxidation to the disulfide was achieved with I_2 in the presence of TEA in $CHCl_3$ to give target compound **1**. The formation of disulfide hemicarceplexes was completed by heating hemicarcerand **1** in the guest of choice (Figure 1) for several days. The complex was isolated by cooling and subsequent precipitation with methanol.

The bulky substituted benzenes, 3-bromo-4-methoxyanisole (**5**), 1,2,3-trimethoxybenzene (**6**), and *tert*-butylbenzene (**7**), form hemicarceplexes upon heating a mixture of host and guest in solution at 130 °C. Guest **7** forms a hemicarceplex more sluggishly and requires heating for 6 days rather than the 3 days for **5** and **6**. The ^{1}H NMR chemical shifts of the substituents on the benzene rings of **5**, **6**, and **7** before and after complexation ($\Delta\delta = \delta_{free} - \delta_{complex}$) are shown in Table 1. The magnitude of the upfield shifts of the protons are similar to those of related hemicarceplexes in the literature.[17] The decomplexation of **1⊗6** in $CDCl_3$ at 25 °C was neglible after 1 month. In addition, 5-bromo-1,2,3-trimethoxybenzene (**8**), 4-isopropylanisole (**10**), 2,6-diisopropylphenol (propofol), and 4-methylanisole (**9**) do not form complexes with **1** at all under these conditions. The former three compounds are too large to form stable complexes at 130 °C, and the latter is too small to form a stable complex at 25 °C.

Guest Exchange under Redox Conditions. In order to demonstrate the utility of the redox-controlled gate, the hemicarceplexes **1⊗5**, **1⊗6**, and **1⊗7** were exposed to conditions that cause disulfide exchange—addition of the base DBU and a dithiol, either butane-1,4-dithiol or dithiothreitol (DTT). Complex and free host and guest were observed since the gate was opened as a result of reaction of the deprotonated dithiol with the disulfide linkage that leads to disulfide−dithiol interchange. Table 2 illustrates the conditions employed for disulfide−dithiol exchange and decom-

(17) Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 3229–3244.

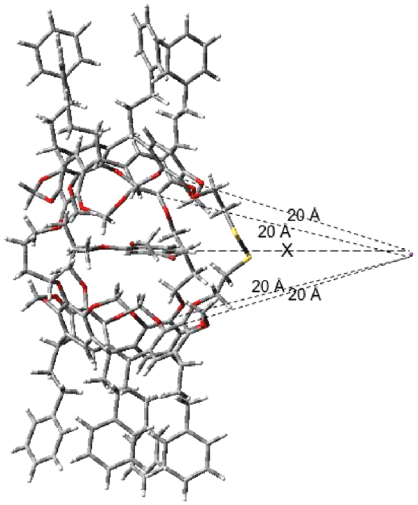


FIGURE 2. Hemicarceplex **1⊗5** (R = phenethyl). Dummy atom (pink) is 20 Å away from four points on the molecule. Distance *X* was varied in angstrom increments over the course of the dynamics calculations (MM3*, GB/SA $CHCl_3$).

plexation of **1⊗5**, **1⊗6**, and **1⊗7**. The ratio of $CDCl_3$/guest ≅ 5500 after decomplexation, so that the gate-opened hemicarcerand is almost exclusively filled with $CDCl_3$. The absence upfield of any signal for the complexed guest is consistent with the gate-opened hemicarcerand.

Computational Modeling. Molecular modeling was performed using the MM3* force field and a GB/SA solvation model for $CHCl_3$ in Macromodel.[19] The force field and methodology followed that described in ref 4. Each guest was examined with the gate closed (disulfide) and open (dithiol). In the computational modeling, phenethyl R groups were employed, but similar results would be expected with pentyl groups, as the R groups do not play a role in the gating. Both phenethyl and pentyl R groups (feet) have been used in related hemicarceplex formation, and CPK models indicate the R groups have little effect on the cavities and portals of the host.[20] When the gate is closed, the guest must enter and exit the inner cavity through a portal, the open region on the side of the host molecule. This was previously demonstrated to occur when the portal has both intrahemispheric bridges in the boat conformation.[4] A dummy atom was placed at a fixed distance from four points on the host (Figure 2). The guests were removed from the host by decreasing the distance *X* from the guest to the dummy atom in angstrom increments, with 100 ps of stochastic dynamics (time step = 1.0 fs) performed at each increment to ensure the host was relaxed into a low energy conformation. These computations give the activation energy of dissociation of each guest as well as the intrinsic and constrictive binding energies (Table 3). The intrinsic binding energies are for standard states and are the differece in MM3*/GBSA energies of complexes and of empty hemicarcerand plus guest. The dissociation energy is computed as the maximum along the reaction coordinate, *X*, compared to the complex energy. The constrictive binding energy is the difference between the dissociation energy (activation energy for dissociation) and the intrinsic binding energy.

TABLE 3. Computed Energetics of Complexation (kcal/mol, MM3*, GB/SA $CHCl_3$)

	intrinsic binding		dissociation energy		constrictive binding	
	open	closed	open	closed	open	closed
5	−9	−9	9	16	0	7
6	−9	−14	9	22	0	8
7	−13	−6	21	24	8	18
8	−17	−8	27	29	10	21
9	−11	−11	11	14	0	3
10	−8	−15	8	40	0	25
11	−10	25				

Guests **5**−**10** exhibit significant intrinsic binding with the host with the gate open or closed. Intrinsic binding is defined as the free energy of complexation. Some guests have a more negative intrinsic binding, indicative of more favorable interactions when the gate is open and others when the gate is closed. This results from the fact that some guests experience unfavorable steric interactions with the host when the gate is closed, and others do not. Guests **5** and **9** have the same intrinsic binding regardless of whether the gate is open or closed. For guest **5**, one methoxy group can jut out of a portal, while the other methoxy group as well as the bromine is able to comfortably occupy the space of the cavity. Guest **9** resides fully inside the cavity, whether the gate is open or closed.

Guests **6** and **10** experience more favorable intrinsic binding when the gate is closed, due to the favorable interactions introduced upon disulfide formation. For guest **6**, two of the methoxy groups extend out of two different portals while the third fits within the cavity. Again, with guest **10**, the methoxy group protrudes through a portal, while the isopropyl group fills the cavity.

Some guests, such as **7** and **8**, experience a less favorable binding energy when the gate is closed. The *tert*-butyl group of **7** is too large to comfortably protrude from a portal. Guest **8** has a similar conformation as **6**, which causes the bromine to be pointed toward one of the linkers, resulting in a steric interaction. Propofol (**11**), an anesthetic, is predicted to bind with the dithiol, but there is a positive intrinsic binding energy with the disulfide gate closed due to the steric bulk of the guest. One of the isopropyl groups juts out of a portal, making the other perfectly aligned to collide with a linker. The experiment with **11** failed to give a complex upon heating of **1** and propofol at 130 °C. The dissociation energies for guest **11** were not computed.

The barrier to complexation is the constrictive binding, while the barrier to decomplexation is the sum of both constrictive and intrinsic binding. Guests **5** and **6** are predicted to have a relatively low constrictive binding (7 and 8 kcal/mol, respectively) because they can manuever through the portal with relative ease, explaining the observed facile formation of these hemicarceplexes. However, the less bulky **9** demonstrates an even lower constrictive binding (3 kcal/mol) and modest instrinsic binding, which explains why **1⊗9** is not observed by NMR. Guest **7** forms a hemicarceplex more sluggishly due to a constrictive binding of 18 kcal/mol,

(18) Shinkai, S.; Inuzaka, K.; Migazaki, O.; Manabe, O. *J. Am. Chem. Soc.* **1985**, *107*, 3950–3955.

(19) *Maestro*, version 5.1.016; *MMshare*, version 1.1.018; Schrödinger, LLC, **2003**.

(20) (a) Kurdistani, S. K.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 1659–1660. (b) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590–5604. (c) Cram, D. J.; Helgeson, R. C.; Knobler, C. B.; Maverick, E. F. *Tetrahedron Lett.* **2000**, *41*, 9465–9470.

presumably resulting from the bulky *tert*-butyl group. Even higher constrictive binding for **8** and **10** (21 and 25 kcal/mol, respectively) suggests why these quite bulky guests are incapable of forming a hemicarceplex with **1**.

When the disulfide is converted to dithiol, the resulting portal is much larger than the portal created by the chair-boat flip. Therefore, it would be expected that there would be a freer exchange of the guest with solvent molecules. This is what is observed experimentally as well as predicted computationally (Table 3). The constrictive binding is zero or significantly smaller for the dithiol than the disulfide for all guests.

Comparisons between Complexation by Gated Hemicarcerand, 1, and Related Hemicarcerands in the Literature. Disulfide **1** is a member of a group of hemicarcerands in which diphenol **2** is bridged with a linker containing one to six contiguous atoms.[5a] The most heavily investigated hemicarcerand in this group was the host containing four tetramethylene bridges with four portals consisting of 26-membered rings connecting the rims of the two cavitand bowls.[21] A series of 31 hemicarceplexes including 19 aromatic guests were isolated and characterized for this hemicarcerand. Guest **9**, *p*-methylanisole, is the only compound utilized in this work and also reported for the tetramethylene host. Disulfide **1**, which contains portals consisting of two 26- and 28-membered rings, would be expected to have a smaller steric barrier for ingress and egress of guests than the smaller tetramethylene host. Consistent with this prediction, host **1** does not form an isolable hemicarceplex with **9**, while the smaller portals of the tetrabridged tetramethylene host forms a hemicarceplex, which was isolated and characterized. Guest **9** undoubtedly enters the inner cavity of **1** during the heating of the mixture, but decomplexation occurs rapidly when the crude product is dissolved in $CDCl_3$. The ^{1}H NMR spectrum of the material shows only free host and guest. When the fourth bridge of diphenol **2** is capped with a hexamethylene linker (the same number of contiguous atoms as in **1**), it is also possible to isolate and characterize a hemicarceplex containing **9** as guest.[22] This result is consistent with an ethylene unit having a larger steric effect than the disulfide group in **1**. The computed small value of 3 kcal/mol for the constrictive binding of hemicarceplex **1**@**9** is also consistent with the small steric barrier to complexation and decomplexation.

Guest **6**, 1,2,3-trimethoxybenzene, forms an isolable hemicarceplex with **1** after heating for 3 days at 130 °C. The *m*-xylyl-capped analogue of diphenol **2** also produces an isolable hemicarceplex with **6** after heating at 170 °C for 6 days.[5a] The lower temperature for formation of **1**@**6** can partially be explained by the larger portal size (28 atoms) of **1**, compared to 27 atoms for the *m*-xylyl-bridged hemicarcerand. The computed value of 8 kcal/mol for the constrictive binding energy is consistent with the absence of decomposition of **1**@**6** over 1 month at 25 °C. The formation of **1**@**5** with 3-bromo-4-methoxyanisole represents the first example of this guest in a hemicarcerand. The calculated constrictive binding energy of 10 kcal/mol is similar to that of guest **6**. The isolation and characterization of **1**@**7** represents the only example of a hemicarceplex with *tert*-butylbenzene as guest in the family of bridged hemicarcerands from diphenol **2**. The calculated value of 18 kcal/mol for the constrictive binding energy of **1**@**7** reflects the larger steric requirements for the *tert*-butyl substituent on **7**.

Guests **8** (5-bromo-1,2,3-trimethoxybenzene) and **10** (*p*-isopropylanisole) fail to form isolable hemicarceplexes after heating host and guest at 130 °C for 3 days. The calculated constrictive binding energies of 21 kcal/mol for **1**@**8** and 25 kcal/mol for **1**@**10** indicate that a temperature significantly higher than 130 °C is necessary to overcome the steric effects and allow ingress of the guest.

Conclusions

A hemicarcerand with a redox-controlled gate has been synthesized, and various aromatic guests have been incorporated into the inner core of the molecule. Molecular mechanics calculations have aided in the explanation and support of several experimental observations. Certain guests readily form hemicarceplexes because their size and shape allow facile entry into the host molecule and because these guests have favorable intrinsic binding. Other guests are not able to form complexes as readily or at all due to having bulky substituents that result in steric clashes with the host molecule.

Experimental Section

8,9,10,11,39,40,41,42-Octahydro-1,18,26,28,53,55,63,74-octapentyl-34,47-(epoxybutanoxy)-20,24:57,61-dimethano-2,52:3,51:16,30:17,29-tetramethano-1*H*,18*H*,26*H*,28*H*,53*H*,55*H*-bis[1,3]benzodioxocino[9,8-*d*:9′,8′-*d*′]-bis[1,3]benzodioxocino[9′,10′:17,18;10″,9″:25,26][1,3,6,11,14,16,19,24]octaoxacyclohexacosino[4,5-*j*:13,12-*j*′]bis[1,3]-65,72-di-(2′-chloro)ethoxybenzodioxocin (3). To a solution of 0.3 g (0.16 mmol) of diol **2**[5] and 2.5 g (10.7 mmol) of chloroethyl *p*-toluenesulfonate in 40 mL of anhydrous DMF under Ar was added 3.0 g (21.7 mmol) of potassium carbonate. The suspension was heated at 50 °C for 48 h, cooled to 25 °C, filtered, and the DMF evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and 10% aqueous NaCl (200 mL of each), and the organic layer was dried ($MgSO_4$), concentrated to 10 mL, and flash chromatographed on silica gel (100 g) made up in 1:1 CH_2Cl_2/hexane. Elution of the column with 1:1 CH_2Cl_2/hexane gave unreacted tosylate, and further elution with CH_2Cl_2 gave 220 mg (68%) of **3** as a white solid: mp 310 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 0.92 (t, CH_3, 24H), 1.36−1.42 (m, $CH_2CH_2CH_2$, 48H), 1.90−2.21 (m, $CHCH_2$, OCH_2CH_2, 28H), 3.72−4.24 (m, OCH_2CH_2, OCH_2O (inner H), CH_2Cl, 28H), 4.64−4.70 (m, $CHCH_2$, 8H), 5.85−5.76 (m, OCH_2 (outer H), 8H), 6.70−6.80 (m, ArH, 8H); the ^{1}H NMR peak assignments were confirmed with a Cosy 2D experiment; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 148.6, 148.5, 148.1, 144.1, 143.1, 138.9, 138.7, 138.3, 113.8, 99.5, 99.3, 73.1, 72.8, 42.0, 36.8, 32.8, 32.0, 32.0, 29.7, 29.6, 27.5, 26.9, 22.6, 14.0; MALDI HRMS calcd for $C_{120}H_{152}O_{24}Cl_2Na$ 2069.994, found 2069.996 $[M + Na]^+$.

8,9,10,11,39,40,41,42-Octahydro-1,18,26,28,53,55,63,74-octapentyl-34,47-(epoxybutanoxy)-20,24:57,61-dimethano-2,52:3,51:16,30:17,29-tetramethano-1*H*,18*H*,26*H*,28*H*,53*H*,55*H*-bis[1,3]benzodioxocino[9,8-*d*:9′,8′-*d*′]-bis[1,3]benzodioxocino[9′,10′:17,18;10″,9″:25,26][1,3,6,11,14,16,19,24]octaoxacyclohexacosino[4,5-*j*:13,12-*j*′]bis[1,3]-65,72-di-(2′-ethanethioate)ethoxybenzodioxocin (4). A suspension of 0.8 g (0.39 mmol) of dichloride **3** in 70 mL of anhydrous DMF under Ar was heated to 50 °C. To the solution were added 1.2 g (8.8 mmol) of potassium thioacetate and 0.6 g (3.6 mmol) of potassium iodide. The mixture was

(21) Robbins, T. A.; Knobler, C. B.; Bellew, D. R.; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111–122.
(22) Yoon, J.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1505–1506.

heated at 60 °C for 18 h, cooled to 25 °C, and the DMF evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 and 10% aqueous NaCl (300 mL of each), and the organic layer was dried ($MgSO_4$). After filtration, the CH_2Cl_2 solution was concentrated to 15 mL and flash chromatographed on silica gel (100 g) made up in CH_2Cl_2. Elution of the column with 1% EtOAc/99% CH_2Cl_2 gave 400 mg (48%) of **4** as a white solid: mp 298 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 0.93 (t, CH_3, 24H), 1.28−1.42 (m, $CH_2CH_2CH_2$, 48H), 1.92−2.24 (m, CHCH_2, 28H), 2.38 (s, CH3COS, 6H), 3.16 (t, CH2S, 4H), 3.82−4.22 (m, OCH_2CH$_2$, OCH_2O (inner H), 24H), 4.64−4.70 (m, CHCH$_2$, 8H), 5.80−5.87 (m, OCH_2O (outer H), 8H), 6.76 (s, ArH, 8H); the ^{1}H NMR peak assignments were confirmed with a Cosy 2D experiment; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 148.6, 148.2, 144.1, 143.0, 138.8, 138.7, 138.6, 138.4, 113.9, 99.6, 99.3, 72.9, 72.0, 36.8, 32.0, 30.5, 29.7, 29.6, 28.6, 27.6, 27.5, 26.8, 22.6, 14.0; MALDI HRMS calcd for $C_{124}H_{158}O_{26}S_2Na$ 2150.03, found 2150.04 $[M + Na]^+$.

8,9,10,11,40,41,42,43-Octahydro-1,18,26,28,54,56,64,82-octapentyl-34,48-(epoxybutanoxy)-20,24:57,61-dimethano-2,52:17,29-dimethano-3,52,16,30-(methynoxy-3,4-dithiahexoxymethyno)-1*H*,18*H*,26*H*,28*H*,39*H*,54H,56*H*-bis[1,3]benzodioxocino[9,8-*d*:9′,8′-*d*′]-bis[1,3]benzodioxocino[9′,10′:4,5;10″,9″:12,13][1,3,6,11,14,16,19,25]octaoxacyclohexacosino[17,18-*j*:27,26-*j*′]bis[1,3]-benzodioxocin (1). A solution of 150 mg (0.07 mmol) of bisthioacetate **4** in 150 mL of THF was heated to 65 °C, and 27 mL of 12 N hydrochloric acid was added in 1 mL portions. The mixture was refluxed for 48 h, cooled to 25 °C, and the THF evaporated. The residue was partitioned between CH_2Cl_2 and 10% aqueous NaCl (300 mL of each). The organic layer was extracted with H_2O (100 mL) and 10% aqueous NaCl (100 mL), dried ($MgSO_4$), and evaporated to give 140 mg of crude dithiol. The ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of the dithiol consisted of absorptions at δ 0.95 (t, CH_3, 24H), 1.30−1.53 (m, $CH_2CH_3CH_2$, 48H), 1.98−2.21 (m, CHCH_2, OCH$_2$CH_2), 2.83 (m, CH_2S, 4H), 3.86−4.27 (m, OCH_2CH$_2$, OCH_2O (inner H), 24H), 4.68−4.75 (m, CHCH_2, 8H), 5.85−5.88 (M, OCH_2O (outer H), 8H), and 6.81 (m, ArH, 8H). The crude product was dissolved in 600 mL of $CHCl_3$ under Ar. A 90 μL portion of Et_3N followed by dropwise addition of I_2 (prepared from 0.63 g of I_2 dissolved in 150 mL of $CHCl_3$). When a yellow color persisted, a sodium thiosulfate solution (4 g in 500 mL of H_2O) was added until the solution became colorless. A 100 mL portion of 10% aqueous NaCl was added, the layers were separated, and the organic layer was dried ($MgSO_4$). The $CHCl_3$ solution was concentrated to 10 mL and flash chromatographed on 100 g of silica gel made up in 1:1 CH_2Cl_2/hexane. The disulfide was eluted from the column with CH_2Cl_2 to give 130 mg (90%) of a white solid: mp 305 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 0.92 (t, CH_3, 24H), 1.28−1.45 (m, $CH_2CH_2CH_2$, 48H), 1.90−2.22 (m, CHCH_2, OCH$_2$CH_2, 28H), 3.00 (t, CH_2S, 4H), 3.84−4.28 (m, OCH_2CH$_2$, OCH_2O (inner H), 24H), 4.65−4.70 (m, CHCH$_2$, 8H), 5.80−5.82 (m, OCH_2O (outer H), 8H), 6.75−6.77 (m, ArH, 8H); the ^{1}H NMR peak assignments were confirmed with a Cosy 2D experiment; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 148.6, 148.5, 148.0, 144.2, 143.9, 138.8, 138.7, 138.4, 113.8, 99.3, 72.2, 36.8, 32.0, 29.6, 27.6, 27.2, 22.6, 14.0; MALDI HRMS calcd for $C_{120}H_{152}O_{24}S_2Na$ 2064.001, found 2063.993 $[M + Na]^+$.

1⊗1-Bromo-2,5-dimethoxybenzene (5) (Procedure A): To a pyrex test tube equipped with an inert gas inlet (Ar) were added 20 mg (0.009 mmol) of **1** and 2.0 g (9.2 mmol) of **5**. The mixture was heated at 130 °C with magnetic stirring for 3 days, cooled to ~50 °C, and poured into 50 mL of CH_3OH. The product was collected on a fine-mesh sintered glass funnel and dried under vacuum (25 °C) for 24 h to give 14 mg (63%) of the complex as a white solid: mp 306 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ −0.41 (s, OCH_3, 3H), −0.39 (s, OCH_3, 3H), 0.92 (t, CH_3, 24H), 1.25−1.65 (m, $CH_2CH_2CH_2$, 48H), 1.92−2.25 (m, CHCH_2, OCH$_2$CH_2, 28H), 3.00−4.80 (m, CH_2S, CHCH$_2$, OCH_2CH$_2$, OCH_2O (inner H), 36H), 5.55−5.94 (m, ArH guest, OCH_2O (outer H), 9H), 6.48 (m, ArH guest, 1H), 6.66 (s, ArH guest, 1H), 6.80−6.94 (m, ArH, 8H); MALDI HRMS calcd for $C_{128}H_{162}BrO_{26}S_2$ 2258.00, found 2258.03 $[M + H]^+$.

1⊗1,2,3-Trimethoxybenzene (6). A mixture of 20 mg (0.009 mmol) of **1** and 2.0 g (11.9 mmol) of **6** was heated at 130 °C for 3 days. Application of Procedure A gave 17 mg (77%) of the complex as a white solid: mp 306 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ −0.5 (s, OCH_3, 6H), 0.92 (t, CH_3, 24H), 1.24−1.60 (m, $CH_2CH_2CH_2$, 48H), 1.90−2.27 (m, CHCH_2, OCH$_2$CH_2, 28H), 2.99−3.05 (m, CH_2S, 4H), 3.38−4.45 (m, OCH_2CH$_2$, OCH_2O (inner H), OCH_3, 27H), 4.65−4.82 (m, CHCH$_2$, 8H), 4.95 (m, ArH guest, 1H), 5.63−5.88 (m, OCH_2O (outer H), 8H), 6.68 (m, ArH guest, 2H), 6.76−6.85 (m, ArH, 8H); MALDI HRMS calcd for $C_{129}H_{164}O_{27}S_2Na$ 2232.079, found 2232.090 $[M + Na]^+$.

1⊗*tert*-Butylbenzene (7). A mixture of 20 mg (0.009 mmol) of **1** and 2.0 g (14.9 mmol) of **7** was heated at 130 °C for 6 days. Application of Procedure A gave 16 mg (74%) of the complex as a white solid: mp 306 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 0.18 (s, CH_3 guest, 9H), 0.93 (t, CH_3, 24H), 1.25−1.65 (m, $CH_2CH_2CH_2$, 48H), 1.90−2.28 (m, CHCH$_2$, OCH$_2$CH_2, 28H), 3.00−3.28 (m, CH_2S, ArH guest, 5H), 3.45−4.43 (m, OCH_2CH$_2$, OCH_2O (inner H), 24H), 4.62−4.80 (m, CHCH$_2$, 8H), 5.05 (t, ArH guest, 2H), 5.63−5.84 (m, OCH_2 (outer H), 8H), 6.13 (d, ArH guest, 2H), 6.68−6.85 (m, ArH, 8H); MALDI HRMS calcd for $C_{130}H_{166}O_{24}S_2Na$ 2198.110, found 2198.111 $[M + Na]^+$.

Decomplexation of 1⊗5, 1⊗6, and 1⊗7: Solutions of 3 mg of the complex in $CDCl_3$ were placed in NMR tubes followed by portions of base and dithiol in $CDCl_3$ from stock solutions. The decomplexation was monitored by following the decrease of the intensity of the singlet at −0.5 (**1⊗6**), −0.39 and −0.41 (**1⊗5**), and 0.18 (**1⊗7**), in the ^{1}H NMR spectrum.

Method A: To the host solution (3 mg/0.5 mL) was added 100 μL portions of $HS(CH_2)_4SH$ and DBU from stock solutions of 18.3 mg $HS(CH_2)_4SH$ in 1.0 mL of $CDCl_3$ and 22.8 mg of DBU in 1.0 mL of $CDCl_3$. The ^{1}H NMR was monitored at 5 min intervals.

Method B: A similar procedure was used in which 10 and 100 μL aliquots were taken from stock solutions of 22.8 mg of DBU in 10 mL of $CDCl_3$ and 23.1 mg of dithiothreitol in 10 mL of $CDCl_3$.

Observation of Complex 1⊗6 in $CDCl_3$: A 3 mg sample of complex in 0.5 mL of $CDCl_3$ at 25 °C was followed by ^{1}H NMR for 1 month, and the spectrum was unchanged.

Acknowledgment. We are grateful to the National Science Foundation for financial support. A.E.H. acknowledges a traineeship (NSF IGERT: Materials Creation Training Program) and the UCLA Dissertation Year Fellowship.

Supporting Information Available: Experimental procedures, NMR spectra, and Cartesian coordinates of computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.