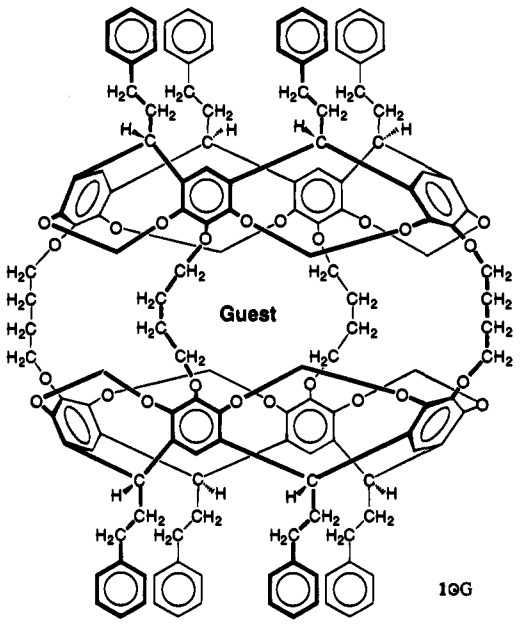
Stepwise Shell Closures Provide Hosts That Expose or Protect Guests[1] from Outer-Phase Reactants

Siavash K. Kurdistani, Roger C. Helgeson, and Donald J. Cram*

Department of Chemistry and Biochemistry, University of California at Los Angeles, Los Angeles, California 90024

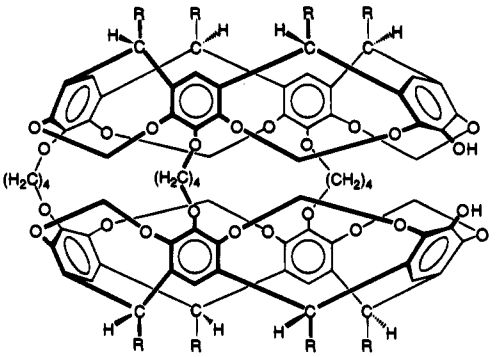
Received August 29, 1994

An earlier paper[2] reported the syntheses of hemicarcerand **1** and 30 hemicarceplexes of **1** (**1**⊙G) and crystal structures of seven of these complexes. We reported[3] that through-shell

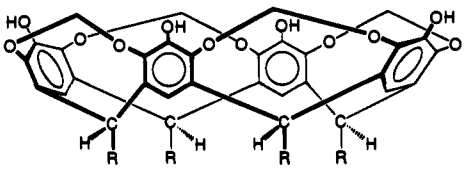


1⊙G

oxidation and reduction reactions occurred between guests in the inner phase of **1** and several respective oxidizing or reducing agents dissolved in the outer-phase common solvent (THF). Here we report the first examples of bimolecular (S_N2) reactions of inner-phase guests with outer-phase reactants, which occur with high regiospecificity for the guest and high selectivity among potential reactants in the entryway of the host's equatorially-located opening. We also report the syntheses of 14 new hemicarceplexes (**1**⊙G), some from diol **2**,[4] whose practical synthesis from 2 mol of tetrol **3**[2] depends on the first three bridges forming faster than the fourth. We previously encountered this phenomenon when the bridges were OCH_2O[5] instead of $O(CH_2)_4O$ of the present investigation. Diol **2** possesses an equatorially-located entryway large enough for guests with dimensions slightly smaller than the inner phase of the system to enter and depart that phase very rapidly (CPK model examination). The ready availability of **2** coupled with the probability that the hemicarcerand **1** synthesis at 25 °C involves **2** as an intermediate[2] suggests that **2** might act as a starting material for syntheses of (1) hemicarceplexes of **1** unavailable by heating empty **1** in guests or Ph_2O as solvent to 80−170 °C for long periods[2] and (2) new hemicarceplexes in which the fourth bridge differs from the other three.

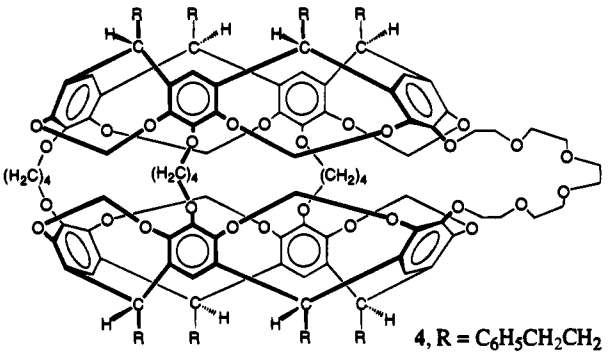


2, R = $C_6H_5CH_2CH_2$

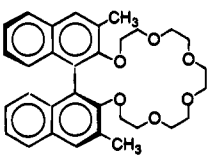


3, R = $C_6H_5CH_2CH_2$

Diol **2** was synthesized from tetrol **3**[4] using Sherman's templating procedure[6] (NMP−Cs_2CO_3−4 equiv of $MsO(CH_2)_4OMs$,[7] 25 °C, 13 h, 30−40%). Diol **2** when stirred for 48 h at 25 °C in HMPA[7]−Cs_2CO_3 containing excess $MsO(CH_2)_4OMs$ gave (60%) empty **1**.[6] HMPA[3] is too large for incarceration (CPK model inspection). With *N*-formylmorpholine as solvent, diol **2** gave (25 °C, 24 h, 85%) **1**⊙$O(CH_2CH_2)_2NCHO$.[4] In HMPA[7] as solvent containing 100 equiv of 1,4-benzoquinone, **2** gave (25 °C, 36 h, 5%) **1**⊙1,4-benzoquinone,[3] which cannot be prepared directly from empty **1**. In HMPA[7] containing 100 equiv of naphthalene (25 °C, 5 days), **1** gave (30%) **1**⊙naphthalene,[4] whose crystal structure showed it to be isostructural with four other complexes[2] of **1**.[8] In NMP[7] (25 °C, 48 h, 30%) or HMPA[7] (55 or 25 °C, 24 h, 30%) containing 100 equiv of $TsO(CH_2CH_2O)_5Ts$,[7] **2** gave **4**.[4]



4, R = $C_6H_5CH_2CH_2$



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Application of Sherman's template procedure[6] for shell closures with NMP as solvent and excess $MsO(CH_2)_4OMs$[7] as bridging agent gave **1**⊙NMP[4] (2 days, 25 °C, then 1 day, 60 °C, 55%), which when heated to 250 °C in Ph_2O (36 h) gave **1**

(1) We warmly thank the U.S. Public Health Services for supporting Grant GM-12640.

(2) Robbins, T. A.; Knobler, C. B.; Bellew, D. R.; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111−122.

(3) Robbins, T. A.; Cram, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 12199.

(4) All new compounds gave elemental analyses within 0.30% of theory except **2**, which analyzed for **2**⊙$5H_2O$, and **4**, which analyzed for **4**⊙H_2O. FAB MS and ^1H NMR spectra are consistent with their structures.

(5) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717−7727.

(6) Chapman, R. G.; Chopra, N.; Cochien, E. D.; Sherman, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 369−370.

(7) NMP is *N*-methylpyrrolidinone. Ms is CH_3SO_2. HMPA is hexamethylphosphoramide. Ts is *p*-$CH_3C_6H_4SO_2$.

(8) We thank Dr. C. B. Knobler for this determination. Details will be published elsewhere.

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(quantitative). This host, when heated at 135−200 °C (3−10 days) neat or in Ph_2O with at least 100 equiv of *o*-, *m*-, or *p*-cresol, *o*-, *m*-, or *p*-toluidine, naphthalene, resorcinol, phenyl allyl ether, or *o*-allylphenol, gave the corresponding 1⊙G[4] complexes in 80−100% yields.

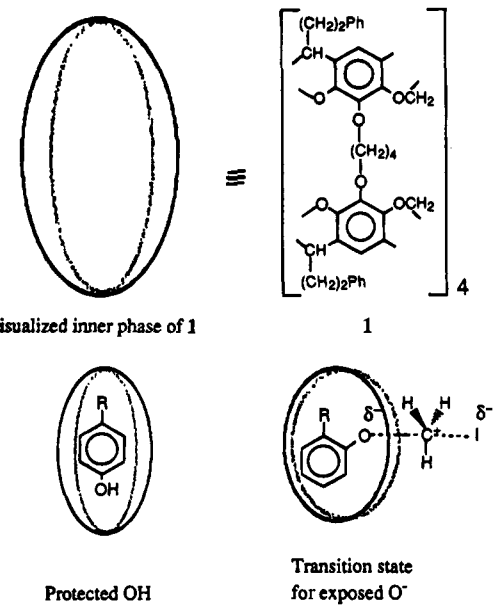
In D_2O-saturated $CHCl_3$ at 25−40 °C, no D-for-H exchange occurred on the hydroxyls of 1⊙G when G was 4-$HOC_6H_4CH_3$, 4-HOC_6H_4OH,[3] or 2-HOC_6H_4OH. In the same medium at 25 °C, 1⊙4-HOC_6H_4OH does, but 1⊙4-$HOC_6H_4CH_3$ does not exchange when diazobicyclo[5.4.0]undec-7-ene (DBU) is present. In THF−NaH at 25 °C, 1⊙G guest exchanges upon quenching with D_2O when G is 2-HOC_6H_4OH,[3] but not when G is 4-$HOC_6H_4CH_3$ or 4-HOC_6H_4OH.[3]

In a study of potential S_N2 reactions of guests of 1⊙G, the complexes were treated with THF−NaH−CH_3I (100 equiv of reactant to G) at 25 °C for 1−5 h. Guests 2-$HOC_6H_4CH_3$ and 3-$HOC_6H_4CH_3$ were methylated on oxygen without decomplexation, whereas 1⊙4-$HOC_6H_4CH_3$ was recovered unchanged. As guest, 3-HOC_6H_4OH was methylated on both oxygens; 2-HOC_6H_4OH gave a mixture of mono- and dimethylated carceplexes; 4-HOC_6H_4OH gave no reaction; and 2,5-$(HO)_2C_6H_3CH_3$[2] gave a mixture of the two possible monomethylated isomeric incarcerated guests. In the anion-activating solvent $[(CH_3)_3N]_3PO$ (45 °C, 4 h), guests 2-$HOC_6H_4OCH_3$ and 2,5-$(HO)_2C_6H_3CH_3$ were fully methylated in >95% yield, whereas 4-HOC_6H_4OH gave ~40% 4-$HOC_6H_4OCH_3$, starting material, and benzoquinone. Under the same conditions, 4-$HOC_6H_4OCH_3$ and 4-$HOC_6H_4CH_3$ gave only starting material.[9] Attempts to alkylate guest-resorcinol's phenolic hydroxyls with CH_3CH_2I, $CH_2{=}CHCH_2I$, or $PhCH_2Br$ failed. Control experiments demonstrated that the isotopic exchange and methylations could not have proceeded by dissociative-alkylation-reassociative mechanisms.[2]

These results are rationalized in terms of sterically enforced alignments of the long axes of the host and guest. Examinations of CPK models of 1⊙G where G is an ortho- or meta-disubstituted benzene suggest comfortable conformations in which one or the other of the two substituents can protrude from the host's cavity into the equatorially-located entryway that connects the inner and outer phases of dissolved 1⊙G. A crystal structure[2] of 1⊙2-BrC_6H_4OH showed that the guest's Br is located in the polar cap of the complex while the OH is located in the equatorial-entryway region. Both the isotopic exchange and alkylation reactions must occur in this entryway, the transition states involved being "solvated" largely by the $O(CH_2)_4O$ moieties of the host that line the channel. In contrast, model examinations and crystal structures of 1⊙1,4-$I_2C_6H_4$ and 1⊙1,4-$(CH_3)_2C_6H_4$ show that both substituents occupy the polar caps of the host. If one of these substituents is hydroxyl, it is protected from isotopic exchange or methylation by the polar caps of the host. Model examination also shows that, of the four alkylating agents studied, only CH_3I is small enough to bring its methyl carbon close enough to ArO^- to provide the linear transition state ($ArO^{\delta-}\cdots C^{\delta+}\cdots I^{\delta-}$) required for reaction. Thus the shell of the host can protect or expose functional groups to selected external reagents depending on sterically enforced host−guest geometrical relationships. Scheme 1 illustrates these interpretations. Effects such as these undoubtedly contribute to the high structural recognition that characterizes many enzyme-moderated reactions.

Molecular model examination of hemicarcerand−corand **4** suggests that the six oxygens of the fourth bridge can easily adopt a shallow helical conformation, allowing the oxygens' 12 unshared electron pairs to converge on large metal cations. When $CDCl_3$ solutions of **4** were shaken or sonicated (1 min) with 0.015 M aqueous solutions of sodium, potassium, or strontium picrates, substantial amounts of the colored picrate salts were extracted into the organic layer, indicating that the metal ions were bound and lipophilized by the fourth bridge to an extent roughly comparable to or greater than that of the lipophilic corands containing six oxygens (e.g., **5**).[10]

Scheme 1



The interesting question arises as to whether the picrate ions of the colored complexes in the $CDCl_3$ layers were incarcerated in the hemicarcerand portion of **4**. The FAB MS of the complex derived from potassium picrate gave substantial peaks[11] at *m/e* 2663.8 and 2437.9, corresponding to 4⊙K^+⊙(picrate anion) (2665.9) and 4⊙K^+ (2437.9), respectively, which indicates that at least *some* of the picrate anion was incarcerated. The FAB MS of the complex derived from sodium picrate gave a substantial peak at *m/e* 2422.0 corresponding to 4⊙Na^+ (2421.8), but none at 2650, where 4⊙Na^+⊙(picrate anion) should give a signal. In earlier work on complexes of Na^+ and K^+, it was found that only certain of the complexes with moderate to high binding free energies in solution gave FAB MS signals for the complexed ion.[12] We never before have observed FAB MS signals for complexes that include both guest anion and cation. Apparently both K^+ and picrate anion are bound by the binary host **4**, but if both Na^+ and picrate anion are bound by **4**, the binding free energies of the latter are not strong enough for the double complex to survive its passage into the gas phase. Molecular model (CPK) examinations of 4⊙M^+ indicate that, in its helical form, more of the six bridging oxygens of **4** can simultaneously ligate K^+ than Na^+, and that incarcerated picrate's phenolic O^- can ligate K^+ but not Na^+ centered in the helical, spanning $O(CH_2CH_2O)_5$ moiety.

These results demonstrate that the readily-prepared cavitand, diol **2**, is a potential starting material for making hemicarceplexes at 25 °C whose guests are too large or too thermally unstable to be heated into empty hemicarcerand. They also illustrate how the two free but highly preorganized hydroxyls of **2** can be covalently bonded to new bridging groups to build binary hosts with both anion- and cation-binding properties. In addition, the vastly increased solubility in hydroxylic solvents of **4** compared to **1** suggests that appropriate substitution of the hydroxyls of **2** might provide water-soluble hemicarceplexes.

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(9) The products were analyzed by 360 MHz ^1H NMR spectral comparisons with authentic spectra of characterized compounds, which were prepared by heating free **1** in the presence of large excesses of guests (neat or in Ph_2O) at elevated temperatures for extended periods.

(10) Cram, D. J. *Angew. Chem.* **1986**, *25*, 1039−1057.

(11) The $CDCl_3$ layers from the extractions were evaporated and the residues submitted to FAB MS analyses.

(12) Examples of hemispheraplexes or cryptahemispheraplexes that give strong FAB MS signals for M + Na^+ or M + K^+ are reported as follows: (a) Tucker, J. A.; Knobler, C. B.; Goldberg, I.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 5460−5482. (b) Helgeson, R. C.; Czech, B. P.; Chapoteau, E.; Gebauer, C. R.; Kumar, A.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6339−6350. (c) Bryant, J. A.; Helgeson, R. C.; Knobler, C. B.; deGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1990**, *55*, 4622−4634.