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Chiral Biscavitand Propellers: Synthesis, Conformations and Multiple Guest Binding

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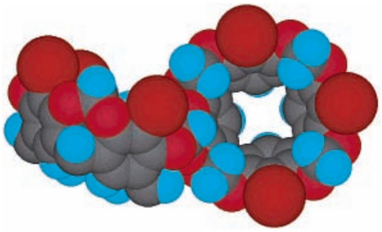
ABSTRACT



The synthesis and properties of molecules containing two cavitand bowls, with interbowl linkages comprising one carbon atom at various oxidation levels, are reported. A carbonyl-bridged biscavitand binds three CH_2Cl_2 molecules in the solid state through a helical conformation. Evidence for the same chiral conformation in the solution phase is presented.

In the development of new hosts with novel functions, binding and recognition groups must be positioned and oriented in well-defined ways. Cavitand bowls are conformationally rigid cavity molecules derived from resorcinarenes, which bind neutral guest molecules weakly in their cavity through van der Waals interactions.[1] When two such cavities are made to operate in unison, however, very strong guest binding can result. The first such dimeric cavitand-based hosts were synthesized by uniting a pair of bowls in a rim-to-rim fashion. Studies into these fully encapsulating biscavitands, carcerands and hemicarcerands, in which the two bowl rims are linked by covalent bonds at two or more locations on each bowl rim, have led to many important discoveries and new theories.[1,2]

This paper describes the preparation of a new class of *nonencapsulating* biscavitand bowl hosts. We show that the pair of bowl moieties in these new hosts can act cooperatively by templating the assembly of three solvent molecules in the solid phase. We also demonstrate that biscavitand compounds linked at only one position on each bowl exhibit varied and tunable conformational properties about their two-bond linkers in the solution phase.

Since cavitand bowls are such rigid moieties and the four evenly spaced, derivatizable rim carbons are sterically encumbered, we reasoned that a sufficiently short connecting chain between two such aromatic carbons on different cavitands might lead to a conformationally restricted system capable of guest complexation.[3] Our approach to one-carbon-linked biscavitands **2a**−**c** takes advantage of the selective lithium−bromine exchange reaction of tetrabromocavitands (Scheme 1).[4] Thus, addition of 1.1 equiv of *n*-BuLi to a dry THF solution of tetrabromide **1** at low temperature followed by 0.5 equiv of methyl formate furnishes **2a** in 33% yield (undecyl feet) and 35% yield (pentyl feet).[5] Deoxygenation

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[†] To whom correspondence should be addressed regarding the crystal structure.

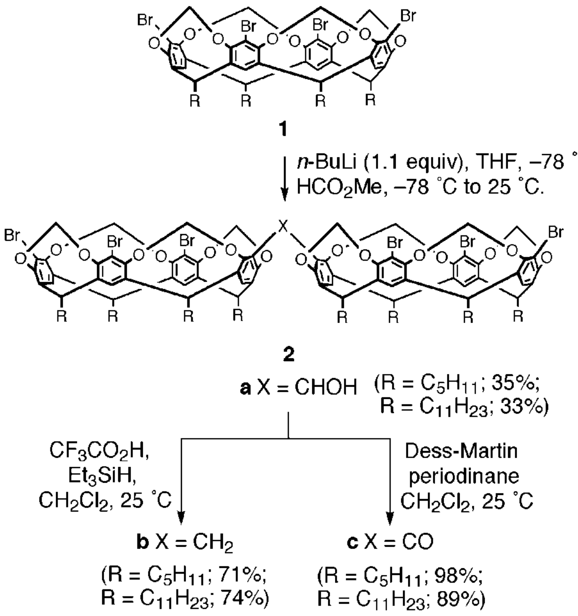
(1) (a) Cram, D. J. *Science* **1983**, *219*, 1177−1183. (b) Cram, D. J.; Cram, J. M. *Container Molecules and their Guests*, Monographs in Supramolecular Chemistry, Vol. 4; Stoddart, J. F., Ed., Royal Society of Chemistry: Cambridge, 1994. (c) Verboom, W. in *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; pp 181−198.

(2) (a) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (b) Warmuth R. *J. Inclusion Phenom. Mol. Recognit. Chem.* **2000**, *37*, 1−38. (c) Naumann, C.; Sherman, J. C. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; pp 199−218. (d) Warmuth, R. *Eur. J. Org. Chem.* **2001**, 423−437. (e) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95−105.

(3) To the best of our knowledge, there are no reports of bisbowl molecules with connecting chains of less than three atoms.

10.1021/ol025704n CCC: $22.00

Scheme 1. Synthesis of New Biscavitand Bowl Hosts **2a−c**



of alcohol **2a** was readily accomplished with Et_3SiH/CF_3CO_2H, the methylene-linked bisbowl **2b** being isolated in good yield. Dess−Martin periodinane-mediated oxidation of secondary alcohol **2a** to ketone **2c** also proceeded in high yield.

The crystal structure of ketone **2c** (pentyl feet) reveals a chiral solid state propeller conformation in which the two bowls are essentially orthogonal to one another (Figure 1).[6,7] The molecular structure has a C_2 symmetry axis about the C═O bond, and the carbonyl group lies at an angle of 44.4° to the aromatic rings to which it is attached. The bisbowl complexes three molecules of CH_2Cl_2, one being contained in each of the two bowls (each with deeply penetrating Cl atoms[8]), the third positioned between the other two, with its carbon located along an axis described by the interbowl C═O bond and its Cl atoms pointing toward Cl atoms of the other CH_2Cl_2 molecules. The three guests thus cover the solvent-accessible concave surface of the biscavitand by adopting a helical arrangement that is complimentary to that of the host. This unique chiral arrangement of CH_2Cl_2 molecules is not seen in the crystal structure of the neat solvent.[9]

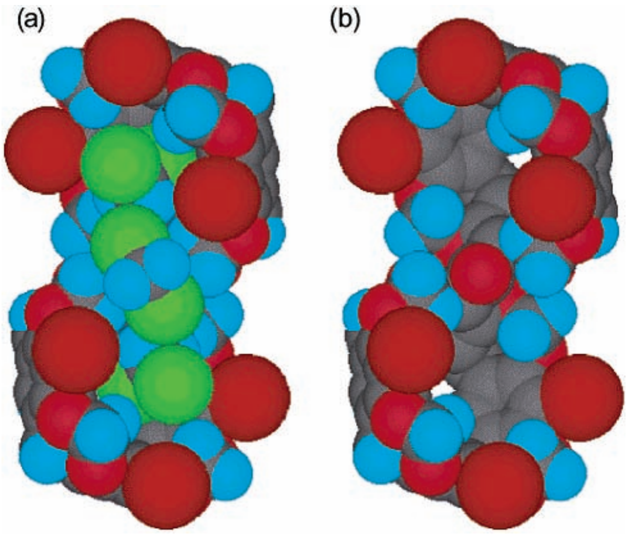


Figure 1. CS Chem 3D renderings of the molecular structure of caviplex **2c**·$3CH_2Cl_2$. Coordinates were obtained from single-crystal X-ray analysis of a sample of biscavitand ketone **2c**. The crystals were grown by slow evaporation of a solution of **2c** in CH_2Cl_2/EtOH. Pentyl feet are omitted for clarity. (a) View down the O═C bond of the space filling model of **2c** with bound CH_2Cl_2 molecules. (b) Same orientation minus the guests.

Cavitands with an X_3Y-type rim substitution pattern generally exhibit a maximum of six signals due to their nonaromatic bowl protons in ^1H NMR spectra.[4d] These signals arise as a result of the presence of two methine proton environments (H_{foot}, triplet), two “inside” methylene proton environments (H_{in}, doublet), and two “outside” methylene proton environments (H_{out}, doublet). This region of the ^1H NMR spectrum of one such compound, methyl tribromocavitand **3**,[4d] is reproduced in Figure 2 along with spectra of each of the three bisbowls **2a**-**c**.

Whereas the room temperature spectra of -CH_2- and -CO-linked biscavitands display splitting patterns similar to those of X_3Y-substituted monocavitands (Figure 2, compare the spectra of **3**, **2b**, and **2c** at 27 °C), that of CHOH-bridged compound **2a** is more complex, displaying four methine (H_{foot}) environments, three “inside” methylene (H_{in}) environments, and four “outside” methylene (H_{out}) environments at 600 MHz. Within each bowl of alcohol **2a**, every H_{foot}, H_{in}, and H_{out} proton has intrinsic nonequivalence.[10,11]

^1H NMR spectra of ketone **2c** in $CDCl_3$, CD_2Cl_2, and CS_2 at 27 °C show signs of line broadening. Upon cooling of

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(4) (a) Larsen, M.; Jorgensen, M. *J. Org. Chem*. **1996**, *61*, 6651−6655. (b) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.* **2000**, *65*, 602−605. (c) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.* **2000**, *65*, 5846−5848. (d) Irwin, J. L.; Sherburn, M. S. *Org. Lett.* **2001**, *3*, 225−227. (e) Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem*. **2001**, *66*, 8227−8229.

(5) **2a** is best prepared in this way, by generating the (readily oxidized) aldehyde in situ. Attempts to construct bisbowl ketones **2c** directly by adding lithiocavitands to cavitands with a CO_2Me group at the rim[4d] were unsuccessful, the bowl-appended monoesters being recovered unchanged. Cavitand monoesters were similarly unreactive towards 2,6-dimethoxy-1-lithiobenzene.

(6) Taking the average planes of the bowls as those described by the positions of the eight acetal oxygens, the angle between the two cavitand moieties is 87.5°.

(7) The propeller structure for diaryl ketones in the solid state is well-known: Rapoport, Z.; Biali, S. E.; Kaftory, M. *J. Am. Chem. Soc*. **1990**, *112*, 7742−7748.

(8) Caviplexes with dichloromethane residing inside the bowl have been witnessed previously. (a) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.l Helgeson, R. C. *J. Am. Chem. Soc*. **1988**, *110*, 2229−2237. (b) Beer, P. D.; Tite, E. L.; Drew, M. G. B.; Ibbotson, A. *J. Chem. Soc., Dalton Trans*. **1990**, 2543−2550. (c) Berridge, T. E.; Chen, H.; Hamor, T. A.; Jones, C. J. *Polyhedron* **1997**, *16*, 2329−2333. (d) Sebo, L.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta*. **2000**, *83*, 93−113.

(9) Kawaguchi, T.; Tanaka, K.; Takeuchi, T.; Watanabe, T. *Bull. Chem. Soc. Jpn*. **1973**, *46*, 62−66.

(10) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Braunschweig, 1969; Chapter 5-2, pp 368−379.

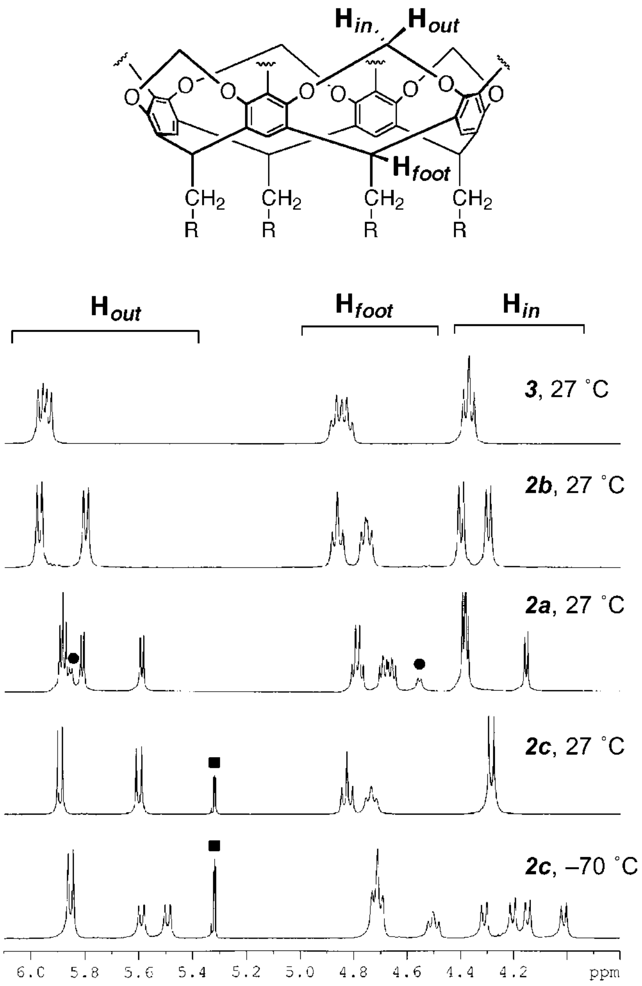

Figure 2. ^1H NMR spectra of cavitands **3** and **2a**−**c**. Spectra of **2b** and **2a** were recorded in $CDCl_3$, and those of **2c** were run in CS_2/CD_2Cl_2 (4:1). The 600 MHz spectrum of **2a** is reproduced; the others were recorded at 400 MHz. Resonances due to C*H*-O*H* protons of **2a** are labeled with solid circles; the squares denote peaks due to $CHDCl_2$.

solutions of ketone **2c** from 27 to −70 °C, ^1H NMR signals progressively decoalesce to provide a more complex spectrum.[12] Thus, at −70 °C, four distinct "inside" methylene (H_{in}) environments are in evidence and multiple overlapping H_{foot} and H_{out} environments are visible.[13] In this case, the four aliphatic bowl protons display nonequivalence due to unequal conformer population.[10]

It is clear, therefore, that there is restricted rotation in bisbowl ketone **2c**. The question is: what is the preferred conformation of **2c** in solution? Since the cavitand moieties are conformationally inflexible, the conformational interchange must be occurring about the two sp^2−sp^2 single bonds to the carbonyl carbon. Furthermore, the presence of four H_{in} environments in the molecule is consistent with conformations of ketone **2c** in which the proton environments of one bowl are mirrored in the second.

Simple diaryl ketones are known to prefer the propeller conformation (Figure 3, boxed structure) in both the solid state[7] and solution.[14] However, whereas reported symmetrical diaryl ketones can adopt only two such helical enantiomeric conformations, the situation with biscavitand ketone **2c** is more complex as the two faces of each aromatic ring that make up the benzophenone moiety are diastereotopic.[15] In fact, *three* pairs of twisted enantiomeric conformations are identifiable for **2c**, which can be classified according to the location of the carbonyl O with respect to each bowl (i.e. *in* or *out*) (Figure 3).

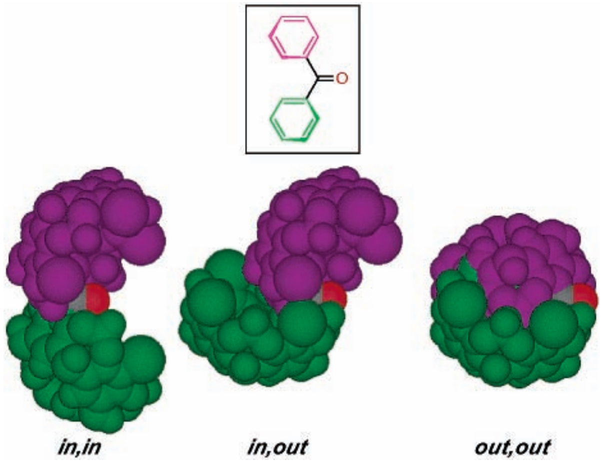

Figure 3. The three possible conformations of bisbowl ketone **2c**. One set of enantiomers is depicted, and these correspond to the benzophenone propeller conformation shown in the box. The two cavitands are colored to assist viewing. Terms *in* and *out* refer to the carbonyl oxygen and its orientation with respect to the concave and convex surfaces of the two bowls. A 180° rotation about one of the two interbowl C−C bonds interconverts two forms. Note the large number of very close contacts in the *out,out*-conformation.

The *in,out*-conformation is clearly not populated to any significant extent at −70 °C since every proton in this structure is diastereotopic: eight signals would thus be expected for each of the H_{foot}, H_{in}, and H_{out} sets. Both *in,in*- and *out,out*-conformers possess the C_2 symmetry that correlates with the low-temperature NMR spectrum. We discount the *out,out*-conformation, however, since it is severely strained.[16] We conclude that the preferred conformation of **2c** in solution must be the C═O *in,in*-twisted conformer, which is the structure observed in the solid state. Computer

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[11] Intrinsic nonequivalence in this system arises as a result of the conformationally rigid nature of each cavitand bowl: the two faces of each aromatic residue contained therein is thus differentiated.

[12] See Supporting Information for full details.

[13] The compound crystallizes from solution below this temperature, precluding further study.

[14] Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* **2001**, *66*, 488−495.

[15] For studies with bis(tricarbonylchromium) complexes of diaryl ketones, see: Weissensteiner, W.; Scharf, J.; Schlögl, *J. Org. Chem.* **1987**, *52*, 1210−1215.

[16] Both *in,out*- and *out,out*-conformers have close contacts between the bowls involving acetal bridge protons adjacent to the benzophenone moiety, and in the latter case this strain is severe.

simulations of H_{in}/H_{out} signals give rate constants of 3 000 s^{-1} at 27 °C and 9 s^{-1} at −70 °C, from which a free energy of activation ($\Delta G^{\ddagger}$) of 47.5 kJ mol^{-1} for the interconversion between the two enantiomeric *in*,*in*-conformers of ketone **2c** was obtained. This energy barrier is significantly higher than that recently obtained for bis(2,4,6-trimethylphenyl)ketone ($\Delta G^{\ddagger}$=19 kJ mol^{-1}).[14,17]

Whereas ketone **2c** exhibits temperature-dependent NMR behavior, ^{1}H NMR spectra of -CH_2- and -CHOH-linked bisbowls **2a** and **2b** remain unchanged from 27 to −70 °C. These compounds are evidently more conformationally flexible than the corresponding ketone. A group of conformations similar to those depicted in Figure 3 are accessible to bisbowl methane **2a** and alcohol **2b**.[18] Models of the *out*,*out*-conformer are more strained in these compounds, however, since the cavitand rims are in closer proximity as a result of the smaller bond angle at the linking carbon.

It is noteworthy that whereas there have been no previous reports of one-atom-linked biscavitands, several calix[4]arene analogues have been reported.[19] While no detailed studies into their conformational preferences have been reported, these biscalix[4]arenes have been shown to bind tetraalkylammonium cations and alkylpyridinium cations through a closed shell, hemicarcerand-like conformation.[19,20] Solutions of bisbowls **2a**−**c** do not complex tetramethylammonium or methylpyridinium ions under the same conditions, a result that offers further evidence for a high energetic penalty for **2a**−**c** to adopt a closed shell conformation. This marked difference in conformational preference between calix[4]arene- and cavitand-based systems presumably arises as a result of both the buttressing effect of substituents ortho to the intercavity linker and the conformational rigidity of the cavitand moieties in the present series.

For hosts akin to **2a**−**c** to be useful in enantioselective processes, atropisomers must be isolable at ambient teperature. The preparation of analogues of these unique double-cavity molecules with higher enantiomerization barriers is underway.

Acknowledgment. We thank Prof. Sev Sternhell (University of Sydney) for helpful discussions, Dr. Ian Luck (University of Sydney) for assistance with NMR, and the Australian Research Council and the University of Sydney for funding.

Supporting Information Available: X-ray crystallographic details for **2c**·$3CH_2Cl_2$; experimental and simulated ^{1}H NMR spectra of **2c** at key points from −70 and 27 °C, and accompanying rate constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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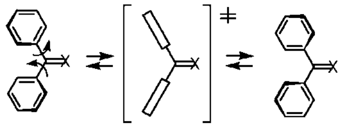
(17) In bis(2,4,6-trimethylphenyl)ketone a disrotatory one-ring flip mechanism is proposed.[12] Models of **2c** undergo a conrotatory two-ring flip pathway more readily. For a discussion of molecular rotors, see: Balzani, V.; Cedi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391.

(18) Computational and experimental data point to a similar preferred twisted conformation in diaryl methanes: Strassner, T. *Can. J. Chem.* **1997**, *75*, 1011−1022.

(19) Head-head, methylene-linked biscalix[4]arenes: (a) Böhmer, V.; Goldmann, H.; Vogt, W.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, *30*, 1391−1394. (b) Araki, K.; Hisaichi, K.; Kanai, T.; Shinkai, S. *Chem. Lett.* **1995**, 569−570. (c) Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325−2334.

(20) The closed shell (hemicarcerand-like) structure of one-atom-linked biscalix[4]arenes and bisbowls requires a conformation about the two-bond linker that corresponds to the transition state for enantiomerization (***ii***):



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