

Chiral and somewhat hydrophilic hemicarceplexes

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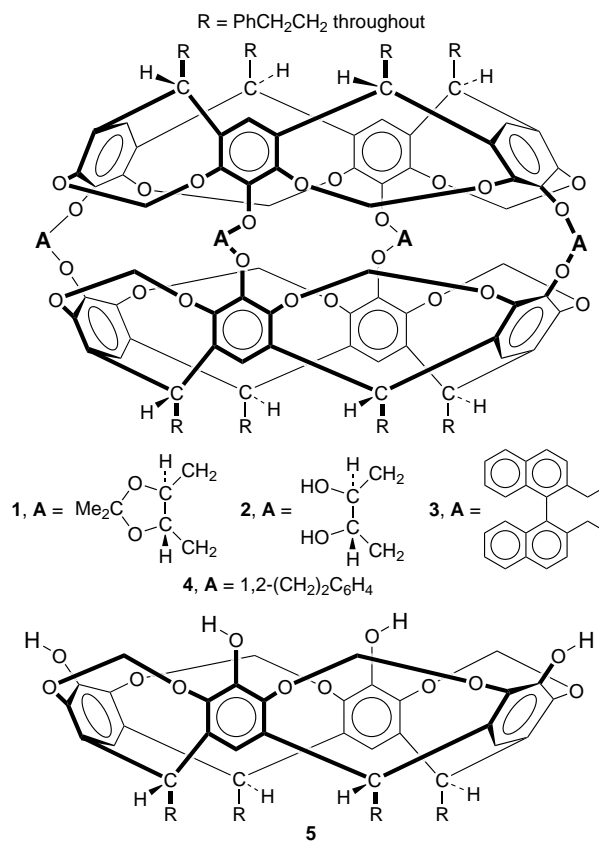
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Five new hemicarceplexes involving chiral hosts **1** and **2** have been synthesized and characterized, two by crystal structure determinations; chiral recognition by one host in complexing butan-2-ol is described.

This research had two objectives: to prepare chiral hemicarcerands for chiral recognition of guests in complexation studies, and to obtain hemicarcerands soluble in hydroxylic solvents for examination of solvent effects on complexation. Previously, we found that diastereomers of $3\text{OEtCHBrCH}_2\text{Br}$ decomplexed at rates that differed by a factor of 9 in CDCl_3 at 23 °C.¹ In the present work we report the syntheses and characterizations of complexes of **1** and **2** from tetrol **5** and (*S,S*)-(-)-1,4-di-*O*-tosyl-2,3-isopropylidene-L-threitol.² The shell closures were conducted in Me_2SO to give 16% of $1\text{OMe}_2\text{SO}$,[†] in Me_2NCOME to give 22% of $1\text{OMe}_2\text{NCOME}$,[†] and in Me_2NCHO to provide 20% of $1\text{OMe}_2\text{NCHO}$.[†] Products were separated chromatographically from substantial amounts of diol containing only three bridges, which suggests the rates of introducing the fourth bridge were substantially slower than for the first three bridges, probably for steric reasons. Complex $1\text{OMe}_2\text{SO}$ required heating at 230 °C in Ph_2O for two days to decomplex, but considerable host decomposition accompanied decomplexation. Clean decomplexation occurred with $1\text{OMe}_2\text{NCOME}$ in Ph_2O or 1,2,4- $\text{Cl}_3\text{C}_6\text{H}_3$ (214 °C, 8 h) or $1\text{OMe}_2\text{NCHO}$ in either solvent (150–160 °C, 3 d) to give empty **1**[†] (80–90%). The acetonide protecting groups were removed (80–90%) from $1\text{OMe}_2\text{NCOME}$ without decomplexation by heating its solution at reflux in $(\text{CH}_2)_4\text{O}$ containing 10 drops of concentrated aqueous HCl for 2 h to provide $2\text{OMe}_2\text{NCOME}$ (80%).^{†,‡} Similar treatment of $1\text{OMe}_2\text{SO}$ and $1\text{OMe}_2\text{NCHO}$ gave $2\text{O}(\text{CH}_2)_4\text{O}$.[†] Thus decomplexation accompanied deprotection. We suggest that $1\text{OMe}_2\text{SOH}^+$ and $1\text{OMe}_2\text{NCHOH}^+$ are respective intermediates in these decomplexations, and that these cations decomplex much more rapidly than does the neutral starting material. In a different host, $\text{hostOEt}_2\text{NH}_2^+$ decomplexed instantaneously under conditions such that $\text{hostOEt}_2\text{NH}$ was stable.³

In $\text{CDCl}_2\text{CDCl}_2$ as solvent at 150 °C the appearance of free guest ¹H NMR signals showed half lives for decomplexation of $1\text{OMe}_2\text{NCOME}$ and $2\text{OMe}_2\text{NCOME}$ to be ~113 and ~4.5 h, respectively. The rigidity of the acetonide bridges of **1** appears to inhibit the loss of Me_2NCOME from the inner phase of **1** more than does the more flexible acyclic bridge system of **2**. The decomplexation half-life of $1\text{OMe}_2\text{NCHO}$ at 138 °C in $\text{CDCl}_2\text{CDCl}_2$ was ~1.5 h, reflecting the smaller size of Me_2NCHO compared to Me_2NCOME .

Crystal structures of $1\text{OMe}_2\text{SO}$ and $2\text{OMe}_2\text{NCOME}$ show the disposition of the chiral bridges.[§] Side and top stereoviews are portrayed in Fig. 1, the latter including only the guest and bridges connecting the two hemispheres, whose four oxygens are each joined by lines to form two near squares. Notice the unshared electron pairs of the bridge oxygens invariably face inward toward the cavity, which orients the other atoms outward away from the cavity. The two squares are within 1–2° of occupying parallel planes, and are rotated with respect to each other about their long normal axis by 15° in $1\text{OMe}_2\text{SO}$ and by 13° in $2\text{OMe}_2\text{NCOME}$. The average distances between oxygen planes are 3.27 and 3.67 Å, respectively. The crystals are



somewhat disordered in the regions of the feet and solvent and with respect to the guests' locations relative to their hosts. In the disorder model for $1\text{OMe}_2\text{SO}$, two Me_2SO guest locations are equally likely, either with one Me in the upper bowl (as in the drawing) or with one Me in the lower bowl of **1**. This model is in agreement with ¹H NMR evidence and with crystal structures of similar complexes. The plane of the Me_2NCOME guest in either of its orientations in $2\text{OMe}_2\text{NCOME}$ lies nearly along one of the diagonals of the O₄ squares, and its long MeNCMe axis is essentially aligned with the host's long axis. The twisting of the two hemispheres of the hosts with respect to one another is less than the 24° observed in the crystal structure of $4\text{OMe}_2\text{NCOME}$.⁴

The 500 MHz ¹H NMR spectrum of $1\text{OMe}_2\text{SO}$ in CDCl_3 gave two CH₃ singlets at δ -0.91 and -1.03 and thus Δδ = 0.12 ppm. Variable-temperature ¹H NMR spectra of $1\text{OMe}_2\text{SO}$ in $\text{CDCl}_2\text{CDCl}_2$ from -80 to 180 °C showed no sign of either splitting or coalescence of these signals, and the whole spectrum showed little temperature dependence. Thus the two guest methyl signals reflect their enantiotopic character in the asymmetric environment of the chiral host. Separately, **1** was heated in 4:1 (v/v) $\text{Pr}^i\text{OH}-\text{Ph}_2\text{O}$ to 80 °C for 4 d to form $1\text{OPr}^i\text{OH}$,[¶] which in CDCl_3 similarly exhibited 500 MHz ¹H NMR signals (two sets) for two enantiotopically related Me groups at δ -2.03 and -2.18 to give a Δδ = 0.15 ppm.

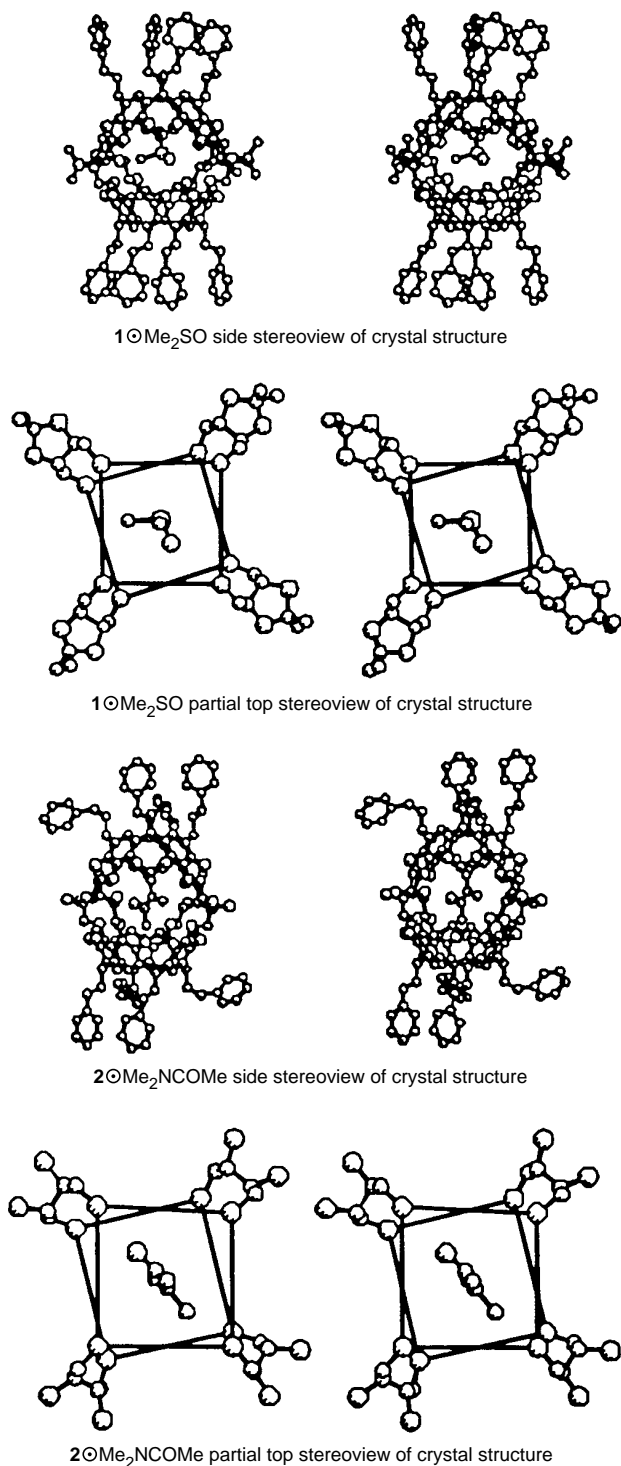


Fig. 1

In an exploratory chiral recognition experiment, (*S,S*)-**1** was heated in a mixture of 1:4 (v/v) Ph₂O–Bu^sOH (racemic) for three days at 95–100 °C, and the complex was precipitated with MeOH and submitted to TLC on silica gel plates with 20:1 (v/v) CHCl₃–EtOAc to provide a 2:1 ratio of diastereomeric complexes[¶] (¹H NMR guest measurements), *R_f* = 0.8 major product, and *R_f* = 0.5 minor product. This result shows a

surprisingly large sensitivity of the surface-absorption properties of the (*S,S*)-**1** host to the *configuration* of an incarcerated and largely inner-phase-mobile guest separated from the surface of the complex by the host's multi-Ångström-thick shell. Further chiral recognition studies involving **1** and **2** should provide interesting results. The fact that 2 \ominus guests are soluble in EtOH and higher alkanols suggests that if the eight PhCH₂CH₂ groups of **2** are replaced by Me groups, the host might be water soluble. We are investigating this possibility.

Footnotes and References

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† Elemental analyses including N and S of guests were within 0.30 of theory, FAB MS gave host \ominus guest signals as the parent ion, and the expected ¹H NMR spectra were found in CDCl₃.

‡ The following experiments are illustrative. To a stirred suspension under argon of Rb₂CO₃ (2.5 g) in dry Me₂NCHO (50 ml) at 70 °C was added tetrol **5** (0.50 g, 0.50 mmol) and (*S,S*)-(-)-1,4-ditosyl-2,3-isopropylidene-L-threitol (1.16 g, 2.50 mmol) dissolved in Me₂NCHO (50 ml) over a period of 12 h. The mixture was stirred 1 d at 70 °C, 1.16 g of additional ditosylate was added, and the mixture stirred at 70 °C for 2 d and at 100 °C for 1 d. The mixture was filtered, and the filtrate was evaporated under vacuum to a solid, which was extracted with CHCl₃ and filtered. The solvent was evaporated and the product chromatographed on silica gel with 20:1 CHCl₃–EtOAc (v/v) to give 0.128 g (20%) of 1 \ominus Me₂NCHO.† Deprotection of 1 \ominus Me₂NCOME was accomplished by heating 31 mg of the acetone in 5 ml of (CH₂)₄O and 10 drops of concentrated aqueous HCl at reflux for 2 h. The organic layer was dried (MgSO₄) and evaporated, and the resulting solid was chromatographed [silica gel, 10% MeOH in CH₂Cl₂ (v/v)] to give 27 mg (87%) of 2 \ominus Me₂NCOME.† Decomplexation of 1 \ominus Me₂NCHO was accomplished by heating 30 mg of the complex in 2 ml of Ph₂O at 150 °C for 3 d. The product was precipitated with MeOH to give 25 mg of **1**.† Complexation of **1** with racemic Bu^sOH involved heating 20 mg of **1** in a mixture of 1 ml of Ph₂O and 4 ml of Bu^sOH for 3 d under argon at 95 °C. The solution was cooled and 1 \ominus Bu^sOH was precipitated with excess MeOH and purified by preparative silica gel TLC [20:1 CHCl₃:EtOAc (v/v)] to give 15 mg of 1 \ominus Bu^sOH.†

§ *Crystal data*: the crystal structures of 1 \ominus Me₂SO and 2 \ominus Me₂NCOME were each determined at 25 °C from cut colorless crystals in capillaries mounted on a Syntex P1 diffractometer with Cu-K α radiation, maximum $2\theta = 100^\circ$. The structure of 1 \ominus Me₂SO (crystallized from CH₂Cl₂–EtOH–EtOAc) belongs to the monoclinic space group *P*2₁, *a* = 17.7483(7), *b* = 19.5425(7), *c* = 26.231(1) Å, $\beta = 107.200(1)^\circ$, *V* = 8691 Å³, *Z* = 2, 10080 unique reflections, 5081 > 4 σ (*F*), was solved by direct methods (SHELXS90)^{5a} and was refined to *R* = 0.14. Disordered or low-occupancy solvent molecules, some EtOAc and some unidentified fragments, were found in 12 regions of the unit cell.

The structure of 2 \ominus Me₂NCOME (crystallized from CHCl₃–PrⁿOH) belongs to the triclinic space group *P*1, *a* = 13.811(7), *b* = 16.239(9), *c* = 20.785(11) Å, $\alpha = 111.38(1)$, $\beta = 95.13(1)$, $\gamma = 110.90(1)^\circ$, *V* = 3924 Å³, *Z* = 1, 8059 unique reflections, 4566 > 4 σ (*F*), was solved by direct methods (SHELX86)^{5a} and was refined to *R* = 0.14. The solvent content is uncertain; the final model includes 2 CHCl₃, 1 PrⁿOH and 3 other solvent fragments. For both structures, final refinements were performed with SHELXL93^{5b} with isotropic displacement parameters and hydrogen atoms in calculated positions. CCDC 182/647.

¶ FAB MS gave host \ominus guest or host signals as parent ion and the expected ¹H NMR spectra were found in CDCl₃.

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