Communication

Dissymmetric Hemicarcerands and Reactions inside Chiral Hemicarcerands

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Most earlier hemicarcerands were assembled from four identical bridging groups and two identical bowl-shaped cavitands.[1] The lengths of the bridges and the sizes of the guests controlled complex formation and stability in solution. In 1995, Cram and his coworkers reported diol host **2** containing three $(CH_2)_4$ bridging groups and two available phenol groups.[2] Accordingly **2** provided new host systems, in which the fourth bridge differs from the three $(CH_2)_4$ bridges. For example, **3** complexes potassium picrate, with picrate ion in the host cavity and K^+ ligated by the six oxygens of the fourth bridge. Less symmetrical hemicarcerands which have a various unique four bridge were synthesized and those complexes with different guests were reported, recently.[2-8] Here we report the syntheses and study of new host system **4** and **5** from diol **2** as well as methyl lithium reaction inside chiral hosts **6**, **7**.

Prior report represented the synthesis of diol **2** in 40% yield from **1** and 3 equiv of $MsO(CH_2)_4OMs$ in a mixture of Cs_2CO_3 and *N*-methylpyrrolidinone (NMP) at 25 °C for 18 h.[2,3] This material served as a starting material for the syntheses of the new host systems in which the fourth bridge differs from the three $(CH_2)_4$ bridges of **2**. Treatment of this readily available diol **2** with excess phosphorous oxychloride in Et_3N-THF at 60 °C followed by chromatographic purification of the product with $CHCl_3$ as the mobile phase gave **4** □ THF (55%). In NMP as solvent and as Cs_2CO_3 base, at temperatures of 50 °C, diol **2** reacted with 1-azido-2,6-bis(bromomethyl)benzene[9] to give after chromatographic purification (thick layer plate, $CHCl_3$/silica gel), **5**□$CHCl_3$ (65%). The fact that **5** was isolated as its complex with $CHCl_3$ rather than with NMP inside indicates either that the final bond-making process occurred in an empty cavity, or that guest exchange, host□NMP + $CHCl_3$ → host/$CHCl_3$ + NMP, took place during the chromatographic purification

conducted at 25 °C. In contrast, originally formed sealed in complex involving **4** survived its isolation in the presence of $CHCl_3$ during chromatography. When **5**□$CHCl_3$ was heated in Ph_2O and naphthalene at 150 °C for 2 days, **5** □ naphthalene was formed in 90% yield. In this case, guest-to-host molar ratio of 100 was employed. Ph_2O whose molecular volume is too large to occupy the inner phase of the host **5** was used for solubility reason.

Table 1 lists the changes in chemical shifts of incarcerated and free host protons in ^{1}H NMR spectra. In all cases the δ values moved upfield upon incarceration, due to the shielding effects of the faces of the eight aryl groups that line much of the surface of the inner phase. At the extremes, the β protons of **5** □ naphthalene give a $\Delta\delta$ value of 3.94, whereas the α protons give 0.61 ppm. This result suggests that the β protons of naphthalene is placed in the highly shielding polar caps of **5**, and the α protons of naphthalene is placed in the much lower shielding, bridge region of the inner phase of **5**.

The conformation of this system was explored with force field calculations using Merck molecular force field (MMFF94)[10] in the program MacroModel.[11] This force field has parameters for wider variety of chemical systems and is well parameterized. Some comparisons of calculated result with AMBER* force field[12] which we used in previous studies,[13,14] were made to justify the usage of the MMFF to our system. For computational simplification, the eight $CH_2CH_2C_6H_5$ groups (feet) were replaced with CH_3 groups to provide **4-Me** and **5-Me**.

Figure 2 shows the optimized lowest energy structures of **4-Me** □ THF and **5-Me** □ naphthalene complexes found. With the smaller guest molecule, **4-Me** □ THF has rather compact host conformation where two bowls faced to each other are closer and staggered. **5-Me** □ naphthalene, on the

R = CH$_2$CH$_2$Ph

1

R = CH$_2$CH$_2$C$_6$H$_5$

2, A = H　　H;

3, A = CH$_2$CH$_2$(OCH$_2$CH$_2$)$_3$OCH$_2$CH$_2$;

4, A = P(O)Cl ; **5**, A = N$_3$-◯;

6, A = ◯ s ; **7**, A = CH$_2$,,,O–CH$_3$ / CH$_2$–O–CH$_3$
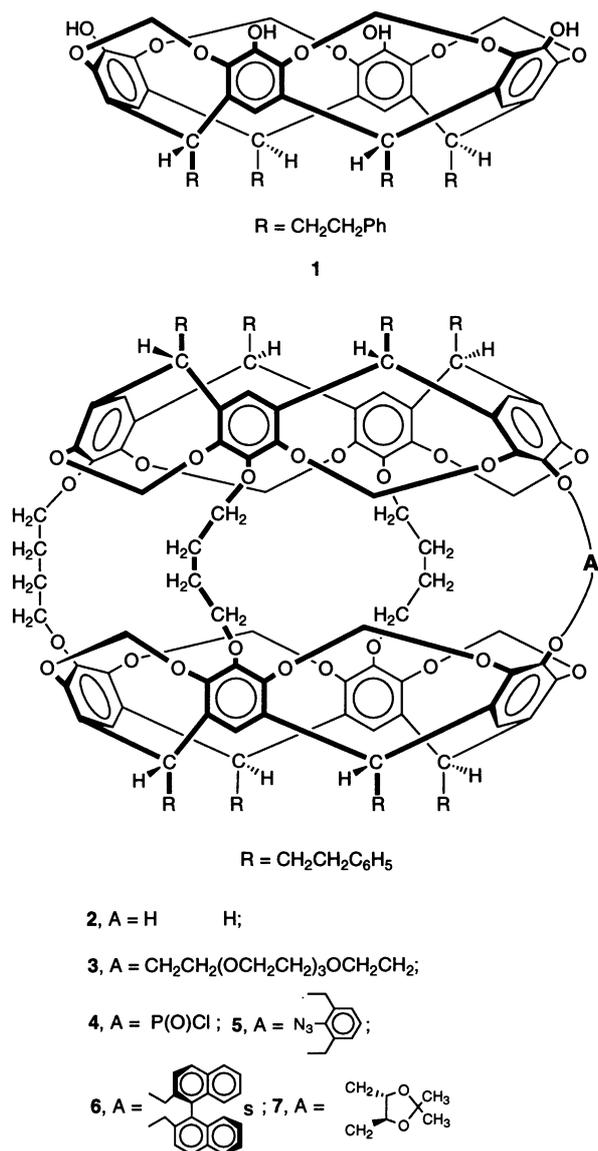
Figure 1. Structures of compounds **1**-**7**.

Table 1. Effect of Host Structure on 400 MHz ^{1}H NMR Spectra of Guests in CDCl$_3$ at 25 °C

host	guest	proton	δ (ppm)		Δδ^a (ppm)
			free	complexed	
4	(THF) H^a, H^b	H^a	1.85	-0.28	2.13
		H^b	3.75	1.04	2.71
5	CHCl$_3$		7.24	5.29	1.95
5	(naphthalene) H^a, H^b	H^a	7.66	7.05	0.61
		H^b	7.30	3.36	3.94

^{a}Δδ = δ$_{free\ guest}$ − δ$_{complexed}$, ppm.

other hand, has rather expanded host conformation with extended linkers. An interesting feature of this structure is the conformation of the azide moiety. With MMFF, azide group takes perpendicular orientation to the phenyl group even with simple phenylazide (PhN$_3$). On the contrary, in

4-Me⊙THF　　　　**5-Me⊙naphthalene**
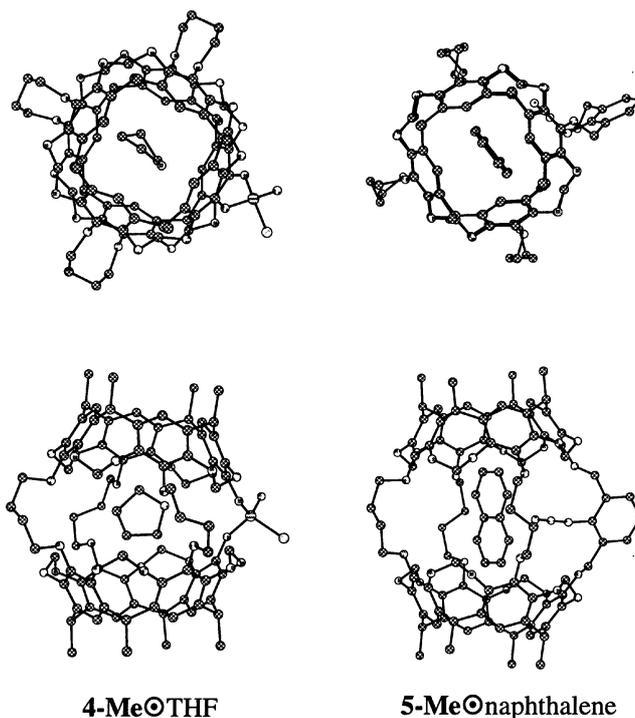
Figure 2. Optimized lowest energy structures of **4-Me** □ THF and **5-Me**□naphthalene.

both crystal structures and semiempirical/*ab initio* MO calculations,[15] phenylazide has azide group almost in the same plane as the aromatic group. However, the two ortho substituents make perpendicular conformation more favorable. We optimized 2,6-dimethyl-phenylazide at RHF/6-31G**[16] and found azide-phenyl torsion angle as 60°. The energy difference to the structure with 90° azide-phenyl torsion angle was found to be less than 1 kcal/mol. Hence we assume the azide group in **5** is virtually taking the perpendicular conformation as shown in Figure 2, with or without the guest molecule.

There are a lot of low energy structures of the host molecule with slight difference in the flexible linker conformation. There are also several low energy structures with different guest orientations for each complex. For example, with **5-Me** □ naphthalene, naphthalene can be rotated 90° along polar axis to give different stable complex structure. Since several simulated annealing led to essentially same structures as shown in Figure 2, we believe they represent the average structure of the complex.

Recently, chiral recognitions of (S)-**6** and (SS)-**7** with various chiral guests have been reported.[7] Most dramatically, host (S)-**6**, in a mixture of racemic guest 4-MeC$_6$H$_4$S(O)Me (100 : 1 molar ratio of guest-to-host) and Ph$_2$O, formed exclusively (S)-**6** □ (R)-4-MeC$_6$H$_4$S(O)Me. The diastereomeric ratio must be > 20, since no complexed guest of the (S)-configuration was detected by ^{1}H NMR when the experiment was repeated with only (S)-guest, (S)-**6** and Ph$_2$O. Chiral hemicarceplexes, differing only in the configuration of the guest, could be separated by chromatography. Experimentally, hemicarceplex (S)-**6** □ (R)-PhS(O)Me was easily separated from (S)-**6** □ (S)-PhS(O)Me (R$_f$ = 0.41 and 0.27

respectively).

Next question would be whether there is any selectivity when asymmetric reaction occurs inside these chiral hemicarcerands. When (S)-**6** □ CHCl$_3$ and empty (SS)-**7** were heated in 3-hexanone as solvent at 150 °C for 2 days, (S)-**6** □ CH$_3$CH$_2$C(O)CH$_2$CH$_2$CH$_3$ and (SS)-**7** □ CH$_3$CH$_2$C(O) CH$_2$CH$_2$CH$_3$ were formed, respectively. After (SS)-7 □ CH$_3$CH$_2$C(O)CH$_2$CH$_2$CH$_3$ was reacted with MeLi in THF at 0 °C for 5 hours, (SS)-**7** □ (±)CH$_3$CH$_2$C(OH)(CH$_3$)CH$_2$-CH$_2$CH$_3$ was obtained in about 1 : 1.7 diastereomeric ratio. This diastereomeric ratio could be calculated from the integrations of two incarcerated methyl peaks (CH$_3$CH$_2$C (OH)(CH$_3$)CH$_2$CH$_2$**CH$_3$**) in its ^{1}H NMR around -3.0 ppm. When **7** □ NMP was reacted with methyl lithium, we could also observe the addition of methyl group to the carbonyl group of NMP by FAB mass spectrum (m/e 2437, M$^+$) as well as ^{1}H NMR. However, since this complex was not stable under work up and chromatographic purification step, empty host and the starting material were obtained instead. **6** □ CH$_3$CH$_2$C(O)CH$_2$CH$_2$CH$_3$ was converted to **6** □ (±) CH$_3$CH$_2$C(OH)(CH$_3$)CH$_2$CH$_2$CH$_3$ under similar reaction condition. Again, diastereomeric ratio was calculated as 1 : 1.6 from its ^{1}H NMR spectrum.

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