

C_{4v} -Symmetric Tetrathiahemicarcerand II: Equilibrium Shift of Carceplexes by Bottleneck Effect of Four Thia Groups

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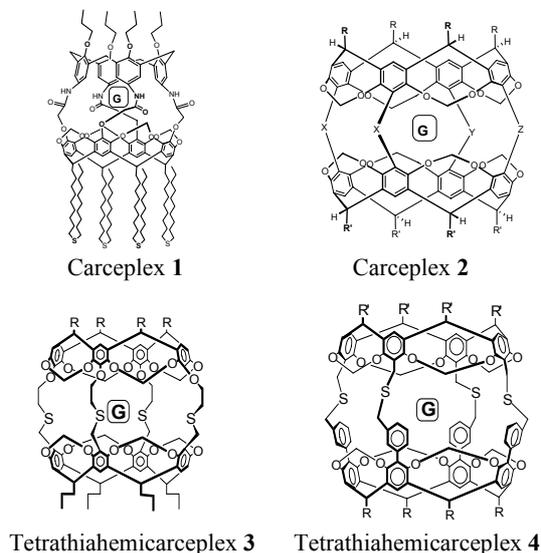
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The different spacial orientations between container molecule or molecular capsule and encapsulated guest result in new types of stereoisomerisms, the so-called carceroisomers¹ or orientational isomers.² These new types of stereoisomerisms are fascinating research fields due to their potentials as a molecular spin for data storage devices or molecular electronics,³ and a molecular reactor for stereoselective reactions.⁴

Reinhoudt reported a carceplex DMF@**1** in which the two kinds of guest's orientation were observed at $-40\text{ }^{\circ}\text{C}$ by ^1H NMR spectroscopy due to the restricted tumbling of a unsymmetrical molecule (DMF).¹ Sherman *et al.* reported C_{4v} carceplex **G@2** ($X = Y = Z = \text{OCH}_2\text{O}$) which showed twistomers due to the twisting of carceplex through C_4 axis to maximize their van der Waals interactions.⁵ Tetrathiahemicarceplex **G@3** showed twistomers as well as carceroisomers on ^1H NMR spectrum depending on the guest and temperature.⁶

The equilibrium between carceroisomers or twistomers is usually very fast at ambient temperature and these isomers have been observed by ^1H NMR only at low temperature. To obtain carceroisomers stable at higher temperature multiple noncovalent interactions between host and guest as well as between guests should operate cooperatively. Here the equilibrium shift between C_{4v} tetrathiahemicarceplexes **G@4** by the bottleneck effect of the four thia groups of hemicarcerand **4** was reported.

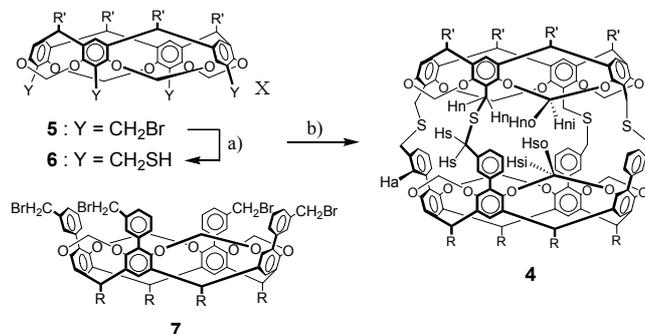
Cavitands **5** and **7** were obtained by the known procedures.³



Tetrathiol **6** was obtained from cavitand **5** by treatment with thiourea in *N,N*-dimethylformamide and basic hydrolysis in 60% yield.⁷ The shell closing reaction in DMA between tetrathiol **6** and bromomethylcavitand **7** gave tetrathiahemicarcerand **4** in 17% yield.

The energy minimized structures of two carceplexes **A** and **B** of 4-iodotoluene@**4** by Spartan[®] (MM+Force Field) were shown in Figure 1. The inner cavity of northern hemisphere is smaller than that of southern hemisphere because of four thia groups of northern hemisphere. The iodine atom of 4-iodotoluene has complementary size to nest suitably into the cavity of southern hemisphere, which may make carceplex **A** a kinetic carceplex. On the other hand I-C bond of carceplex **B** is squeezed by the four thia groups imposing "the bottleneck effect", which may make carceplex **B** a thermodynamic carceplex.

Figure 2 shows ^1H NMR spectra of hemicarcerand **4** (a) and hemicarceplexes **G@4** (b ~ e) formed by heating the solution of hemicarcerand **4** ($[\mathbf{4}] = 4.4\text{ mmol}$) and 3 equiv. 4-X-toluene



Scheme 1. Synthesis of Hemicarcerand **4** ($R = (\text{CH}_2)_6\text{CH}_3$, $R' = (\text{CH}_2)_4\text{CH}_3$). Reagents: a) 1. Thiourea, 2. 3 N NaOH, 60%, (b) DMA, Cs_2CO_3 , 17%.

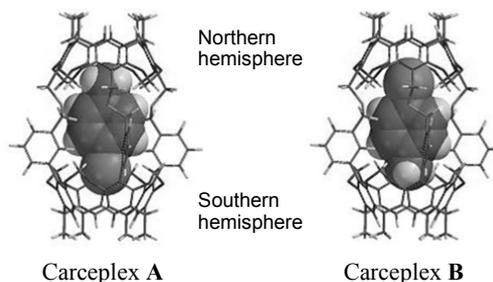


Figure 1. Energy minimized structure of two carceplexes **A** and **B** of 4-iodotoluene@**4** by Spartan[®] (MM+ Force Field, The feet were substituted by methyl for clarity).

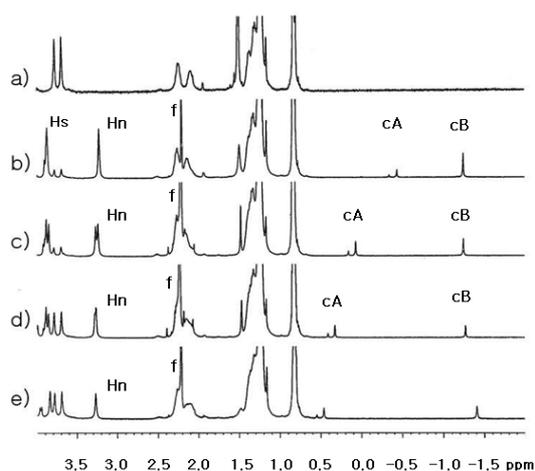


Figure 2. The partial ^1H NMR spectra (400 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) of hemicarcerand **4** and hemicarceplexes **G@4**: a) hemicarcerand **4**, ($[\text{4}] = 4.4 \text{ mM}$), b) 4-iodotoluene@**4**, c) 4-bromotoluene@**4**, d) 4-chlorotoluene@**4**, e) *p*-xylene@**4**, f: Me of free guest, cA: Guest's Me of conformer A, cB: Guest's Me of conformer B.

in $\text{C}_2\text{D}_2\text{Cl}_4$ at 65°C for 2 days and the selected chemical shifts were summarized in Table 1. There are two distinct chemical shift changes indicating complexation, the large upfield shifts of CH_2SCH_2 peaks ($\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}} = -0.12 \sim 0.47 \text{ ppm}$) and the appearance of methyl peak of complexed 4-substituted toluene which are shifted upfield ($\Delta\delta = 1.75 \sim 3.62 \text{ ppm}$) according to the proximity of methyl to the magnetic shielding zone of resorcin[4]arene unit.

Two carceroisomers appeared in different ratios. Guest's CH_3 peak of hemicarceplex 4-iodotoluene@**4** appeared at -1.24 ppm ($\Delta\delta = 3.44 \text{ ppm}$) and -0.44 ppm ($\Delta\delta = 2.64 \text{ ppm}$) and the ratio of two isomers ($[\text{A}] : [\text{B}]$) changes from 1:0.6 (taken in 10 min at 65°C in $\text{C}_2\text{D}_2\text{Cl}_4$) to 1.00 : 2.76 (taken after 2 days at 65°C in $\text{C}_2\text{D}_2\text{Cl}_4$), which suggests that one is a kinetic carceplex (Carceplex A) and the other is a thermodynamic carceplex (Carceplex B). In case of 4-bromotoluene@**4** and 4-chlorotoluene@**4** the methyl peaks appeared at -1.25 ($\Delta\delta = 3.44$) and 0.07 ($\Delta\delta = 2.14$), -1.27 ($\Delta\delta = 3.44$) and 0.33 ($\Delta\delta = 1.90$), respectively. Ratios of carceroisomers of 4-bromotoluene@**10** and 4-chlorotoluene@**10** are 1.00 : 1.05 and 1.00 : 0.78, respectively, which don't change significantly due to their fast thermodynamic equilibrium. For *p*-xylene@**4** the methyl peaks appeared at -1.41 ($\Delta\delta = 3.62$) and 0.46 ($\Delta\delta = 1.75$) ppm approximately in 1:1 ratio. As the 4-substituent becomes larger⁸ in the order of Cl, CH_3 , Br, and I, the ratio of carceplex B : A becomes larger, 0.78, 1.00, 1.05, and 2.76, respectively.

The spacial arrangements of guest in hemicarcerand **4** were confirmed by NOESY measurements (600 MHz, CDCl_3 , 25°C). The hemicarceplex 4-iodotoluene@**4** with approximately 1:1 ratio of carceplexes was obtained by heating the $\text{C}_2\text{H}_2\text{Cl}_4$ solution of hemicarcerand **4** and 5 equiv 4-iodotoluene at 65°C for 3 hrs. The partial 2D NOESY spectrum of hemicarceplex 4-iodotoluene@**4** (Figure 3, The protons are labeled in hemicarcerand **4** on Scheme 1) shows that correlations exist between guest's CH_3 peak at -0.23 ppm and those of H_{no} , H_{ni} , or H_{n} of the northern hemisphere, and between guest's CH_3 peak at -1.09 ppm and those of H_{a} , H_{so} , or H_{si} of the southern

Table 1. The distinct chemical shifts in ^1H NMR spectra (400 MHz) of two carceplexes 4-X-toluene@**4** after 2 days at 65°C in $\text{C}_2\text{D}_2\text{Cl}_4$ and the Ratios of carceplexes.

X	δ (ppm)				Carceplex Ratio (A : B)	van der Waals Volume of X^8 (cm^3/mole)
	CH_2SCH_2		Guest's CH_3			
	H_s	H_n	A	B		
No Guest	3.77	3.69	-	-	-	-
I	3.87	3.22	-0.44	-1.24	1.0 : 2.76	19.64
Br	3.89	3.25	0.07	-1.25	1.0 : 1.05	15.12
Cl	3.87	3.27	0.33	-1.27	1.0 : 0.78	12.00
CH_3	3.84	3.27	0.46, -1.41		1.0 : 1.0	13.67

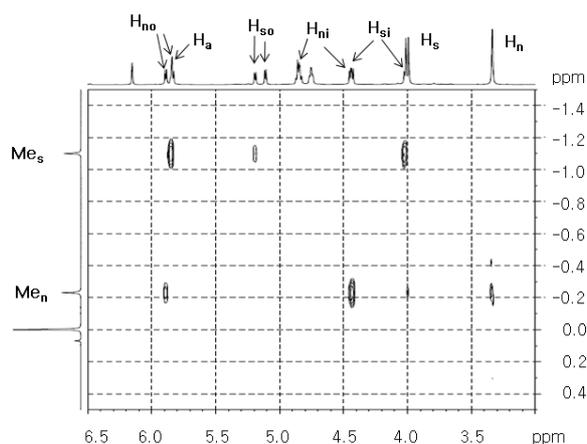


Figure 3. Partial 2D NOESY spectrum (600 MHz) of 4-iodotoluene@**4** in CDCl_3 at 25°C . The abbreviations a, n, s, o, and i stand for aryl, northern, southern, outer, and inner, respectively.

hemisphere, which correspond to those of carceplex A and B, the kinetic and the thermodynamic carceplex, respectively.

In conclusion, kinetic and thermodynamic carceplexes of **G@4** were observed and their orientations of guest were characterized. The ratio of thermodynamic vs. kinetic carceplex **G@4** at 65°C increased as the size of 4-substituent increases due to the "Bottleneck effect" of four thia groups of tetrathia-hemicarcerand **4**.

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