C₄ᵥ-Symmetric Tetrathiahemicarcerand II: Equilibrium Shift of Carceplexes by Bottleneck Effect of Four Thia Groups

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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 carceroisomers or orientational isomers. These new types of stereoisomerisms are fascinating research fields due to their potentials as a molecular spin for data storage devices or molecular electronics, and a molecular reactor for stereoselective reactions.

Reinhoudt reported a carceplex DMF@1 in which the two kinds of guest's orientation were observed at -40 °C by ¹H NMR spectroscopy due to the restricted tumbling of an unsymmetrical molecule (DMF). Sherman et al. reported C₄ᵥ carceplex G@2 (X = Y = Z = OCH₂O) which showed twistomers due to the twisting of carceplex through C₄ᵥ axis to maximize their van der Waals interactions. Tetrathiahemicarcerex showing twistomers as well as carceroisomers on ¹H NMR spectrum depending on the guest and temperature.

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 isomers due to the twisting of carceplex through C₄ᵥ axis to maximize their van der Waals interactions. These new types of stereoisomerisms, the so-called carceroisomers, may make carceplex B a thermodynamic 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 hemicarcerexes G@4 (b ~ e) formed by heating the solution of hemicarcerand 4 ([4] = 4.4 mmol) and 3 equiv. 4-X-toluene.

Tetrathioll 6 was obtained from cavittand 5 by treatment with thiourea in N,N-dimethylformamide and basic hydrolysis in 60% yield. The shell closing reaction in DMA between tetrathioll 6 and bromomethylcavittand 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 hemicarcerexes G@4 (b ~ e) formed by heating the solution of hemicarcerand 4 ([4] = 4.4 mmol) and 3 equiv. 4-X-toluene.

Scheme 1. Synthesis of Hemicarcerand 4 (R = (CH₂)₆CH₃, R' = (CH₂)₆CH₃). Reagents: a) 1. Thiourea, 2. 3 N NaOH, 60%, (b) DMA, Cs₂CO₃, 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).
in C2D2Cl4 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 CH2SCH2 guest’s CH3 peak of hemicarceplex 4-iodotoluene@4 which are shifted upfield (Δδ = 1.75 ~ 3.62 ppm) according to the proximity of methyl to the magnetic shielding zone of resorcin[4]arene unit.

Two carceplexomers appeared in different ratios. Guest’s CH1 peak of hemicarceplex 4-iodotoluene@4 appeared at -1.24 ppm (Δδ = 3.44 ppm) and -0.44 ppm (Δδ = 2.64 ppm) and the ratio of two isomers ([A] : [B]) changes from 1:0.6 (taken in 10 min at 65 °C in C2D2Cl4) to 1.00 : 2.76 (taken after 2 days at 65 °C in C2D2Cl4), 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 (Δδ = 3.44) and 0.07 (Δδ = 2.14), -1.27 (Δδ = 3.44) and 0.33 (Δδ = 1.90), respectively. Ratios of carceplexomers 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 (Δδ = 3.62) and 0.46 (Δδ = 1.75) ppm approximately in 1:1 ratio. As the 4-substituent becomes larger in the order of Cl, CH3, 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, CDCl3, 25 °C). The hemicarceplex 4-iodotoluene@4 with approximately 1:1 ratio of carceplexes was obtained by heating the C2H2Cl4 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 CH2 peak at -0.23 ppm and those of Ha, Hα, or Hs of the northern hemisphere, and between guest’s CH3 peak at -1.09 ppm and those of Hn, Hα, or Hs of the southern 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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References


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 C2D2Cl4 and the Ratios of carceplexes.

<table>
<thead>
<tr>
<th>X</th>
<th>CH2SCH2</th>
<th>Guest’s CH3</th>
<th>Carceplex Ratio (A : B)</th>
<th>van der Waals Volume of X (cm3/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Guest</td>
<td>3.77</td>
<td>3.69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>3.87</td>
<td>3.22</td>
<td>-0.44 : -1.24</td>
<td>1.0 : 2.76</td>
</tr>
<tr>
<td>Br</td>
<td>3.89</td>
<td>3.25</td>
<td>0.07 : -1.25</td>
<td>1.0 : 1.05</td>
</tr>
<tr>
<td>Cl</td>
<td>3.87</td>
<td>3.27</td>
<td>0.33 : -1.27</td>
<td>1.0 : 0.78</td>
</tr>
<tr>
<td>CH3</td>
<td>3.84</td>
<td>3.27</td>
<td>0.46 : -1.41</td>
<td>1.0 : 1.0</td>
</tr>
</tbody>
</table>

Figure 2. The partial 1H NMR spectra (400 MHz, C2D2Cl4) of hemicarcerand 4 and hemicarceplexes G@4: a) hemicarcerand 4, (4|4| = 4.4 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.

Figure 3. Partial 2D NOESY spectrum (600 MHz) of 4-iodotoluene@4 in CDCl3 at 25 °C. The abbreviations a, n, s, o, and i stand for aryl, northern, southern, outer, and inner, respectively.