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LETTERS

Synthesis and Crystal Structures of Novel Macrocyclic Compounds and Their Inclusion Phenomenon

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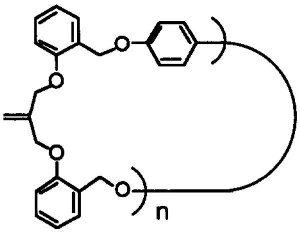
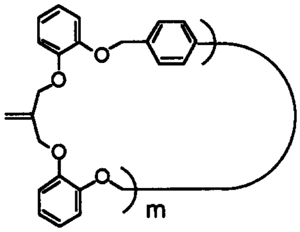
Abstract: Four kinds of macrocyclic polyethers containing isobutenyl group and aromatic rings were synthesized. X-ray analyses of crystal structure revealed significant differences in conformation among the compounds studied, in spite of their similarity in chemical formula. One compound was found to capture a benzene molecule in crystalline phase, while the others did not.

Macrocyclic molecules[1] such as crownethers or calixarenes can form molecular complexes with specific ions or molecules. This property has been noted from the viewpoint of applications to molecular recognition, separation, catalysis, and so on. There are some requirements for a host molecule to effectively capture a guest molecule;[2-5] (1) host and guest molecules have moieties to specifically interact with each other (e.g., hydrogen bonds), (2) a guest molecule fits in the cavity of a host molecule, and (3) a host molecule adopts such a conformation that it effectively interacts with a guest molecule (so-called preorganization).

In the above regards, it seems difficult to design a molecule which could recognize nonsubstituted aromatic compounds that have no apparent polarity. Such a host molecule needs to have a rigid macrocyclic cavity, and to have some aromatic rings to interact with guest molecules through π–π interactions. Based on this idea, we synthesized four kinds of macrocyclic polyethers, $\mathbf{1}_n$ and $\mathbf{2}_m$ (n, m = 1, 2), containing isobutenyl group and aromatic rings (*p*-phenylene and *p*-xylylene groups, respectively). In this communication, we report on differences in crystal structure, ^{1}H NMR chemical shifts, and molecular inclusion behavior among these compounds.



n=1: $\mathbf{1}_1$, n=2: $\mathbf{1}_2$



m=1: $\mathbf{2}_1$, m=2: $\mathbf{2}_2$

According to Scheme 1, hydroquinone was allowed to react with 3-(2-chloromethylphenoxy)-2-(2-chloromethylphenoxymethyl)propene (**3**). The [1:1] adduct $\mathbf{1}_1$ was mainly obtained, together with an

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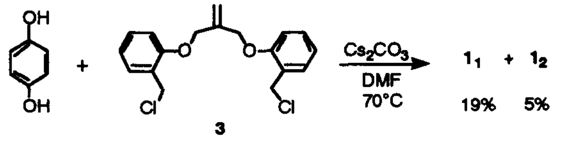
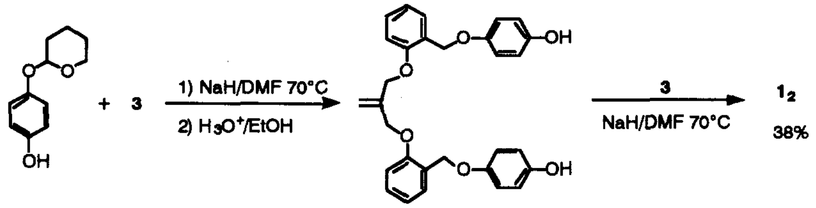
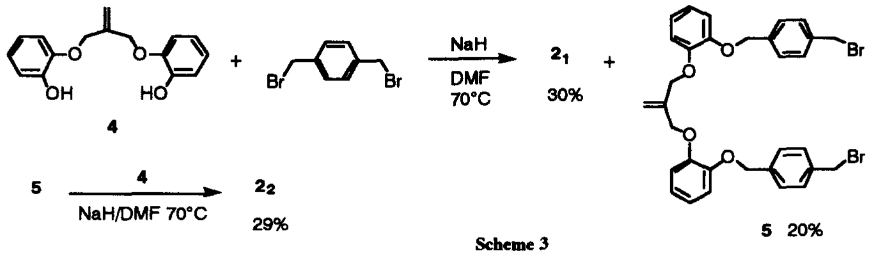
appreciable amount of the [2:2] adduct 1_2 (5 %). A two step reaction including the protection of hydroquinone (Scheme 2) afforded 1_2 in a better yield (38%). Macrocycles 1_1 and 1_2 were both recrystallized as colorless solids from benzene.[6] The reaction of 3-(2-hydroxyphenoxy)-2-(2-hydroxyphenoxymethyl)propene (**4**) and three equivalents of *p*-xylylenedibromide afforded two major products, the [1:1] adduct 2_1 (30 %) and dibromide **5** (20 %) (Scheme 3). Dibromide **5** was allowed to react with diol **4** under high dilution conditions, resulting in the [2:2] adduct 2_2 (29%). Macrocycles 2_1 and 2_2 were both recrystallized as colorless solids from dimethylformamide.[7] The formation of all these compounds was confirmed by ^{1}H NMR, mass spectroscopy, and X-ray crystal structure analysis.



Scheme 1



Scheme 2



Scheme 3

X-ray crystallographic analysis highlights a significant difference in conformation between 1_1 and 2_1, and 1_2 and 2_2, respectively.[8] In Figure 1, the most impressive feature is that 1_2 crystallizes with one benzene molecule within its cavity, while 2_2 does not. The benzene molecule is located at almost the center of the cavity, and its plane is almost perpendicular to those of the *p*-phenylene groups.

The results of DSC measurement for 1_2 showed two endothermic peak around 162 °C and 173 °C, and one broad exothermic peak around 234 °C. The peak at 173 °C corresponds to the melting point of 1_2, and that at 234 °C implies some thermal reactions such as rearrangement. Around 164 °C, TGA measurement found a sharp weight loss of 8.7%, comparable to the weight ratio of benzene/(1_2 + benzene) = 9.4 %. This temperature of benzene releasing indicates that the benzene molecule is strongly interacting with 1_2 in the solid state. Such a strong binding may originate not only from the cavity-size effect, but also from other specific interaction(s) with respect to π-electrons. The crystal structure shown in Figure 1 suggests that the factor stabilizing the complex is so-called C-H/π type interaction[9] rather than the π-π stacking type one. The shortest distance between H (p-C_6H_4) and C (benzene) atoms is 3.05 Å, and that between H (benzene) and C (o-C_6H_4) atoms is 2.96 Å, which are probable values for C-H/π bond.[9] On the other hand, ^{1}H NMR

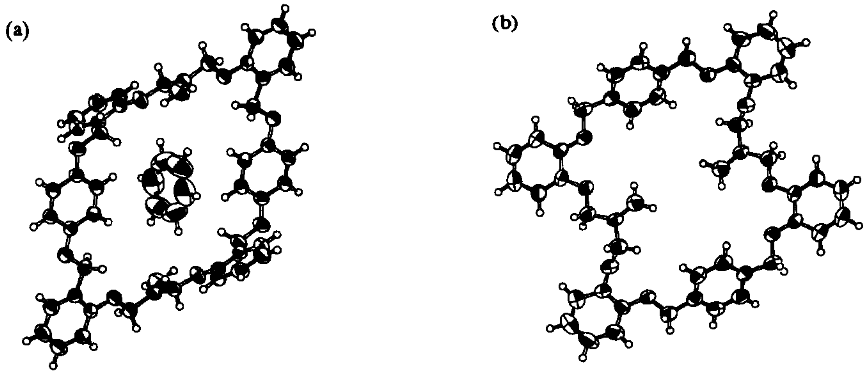


Figure 1: The X-ray crystal structures of [2:2] cyclic compounds, $\mathbf{1_2}$ (a) and $\mathbf{2_2}$ (b).

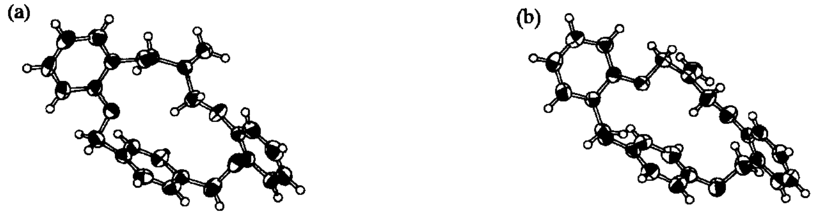


Figure 2: The X-ray crystal structures of [1:1] cyclic compounds, $\mathbf{1_1}$ (a) and $\mathbf{2_1}$ (b).

spectrum (in $CDCl_3$) showed that the chemical shift of benzene is almost identical to that of free benzene, implying that $\mathbf{1_2}$ and benzene are present separately in solution. In general, it has been reported that such two dimensional cyclophane[10] and even three dimensional cage molecule[11] hardly hold benzene molecule inside the cavity in solution. In the crystal, the CH/π interaction seems to cramp the tightly held benzene molecule in the center of the cavity.

As for $\mathbf{2_2}$ recrystallized from benzene, DSC measurement showed no weight change corresponding to the loss of solvent molecules. The crystal structure was solved for a single crystal further recrystallized from DMF solution. As shown in Figure 1(b), in contrast to $\mathbf{1_2}$, $\mathbf{2_2}$ does not have enough space to accommodate a molecule such as benzene, for two isobutenyl groups are directed toward the inside of the cavity. These results indicate that $\mathbf{2_2}$ cannot form a molecular complex with benzene. This difference in inclusion behavior between $\mathbf{1_2}$ and $\mathbf{2_2}$ may arise from the conformational stability with respect to Ar-CH_2-O-Ar unit: in the former two *trans* (φ = 175.3°, where φ is the dihedral angle of Ar-CH_2-O-Ar) and two *gauche* (φ = 75.3°) forms are found, while in the latter only *trans* (φ = 179.7°, 175.0°) form is found.

For both [1:1] adducts ($\mathbf{1_1}$ and $\mathbf{2_1}$), the unit molecule is asymmetric in crystal, and one of the methylene hydrogens of isobutenyl group is located very close to the benzene ring of *p*-phenylene group (Figure 2). For example, the shortest distance between H (O-CH_2-C=CH_2) and C (*p*-C_6H_4) atoms of $\mathbf{2_1}$ is 2.93 Å. This again implies the exertion of C-H/π interaction. This feature in structure is reflected in ^1H NMR spectra: by comparison with the corresponding [2:2] compounds, the chemical shifts of the methylene protons of $\mathbf{1_1}$ and $\mathbf{2_1}$ are shifted upfield by ~0.6 ppm, which can be attributed to so-called ring-current effects of the aromatic ring. This indicates that the methylene proton is located in the upright direction of the benzene ring with high probability, even in solution. Consequently, both $\mathbf{1_1}$ and $\mathbf{2_1}$ have no space enough to accommodate any guest molecules inside their cavity.

In conclusion, in all the compounds studied, only $\mathbf{1_2}$ has the ability to capture a benzene molecule.

The driving force of the complexation is interpreted in terms of the cavity-size effect, conformational stability and C-H/π interaction. This result exemplifies a drastic change in function due to a small change in atomic sequence in a molecule.

References and Notes

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6 $\mathbf{1}_1$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, -O-C*H*$_2$-C(=CH$_2$)-), 5.06 (s, -O-C*H*$_2$-Ar), 5.30 (s, -C(=C*H*$_2$)-), 6.66 (s, -O-*Ar*-O-), 6.8-7.5 (m, -O-*Ar*-CH$_2$-). FT-IR 1660, 1603, 1589 cm^{-1}. Precise MS calcd. for $C_{24}H_{22}O_4$ 374.1517, found 374.1524

$\mathbf{1}_2$: ^{1}H NMR (300 MHz, $CDCl_3$) d 4.67 (s, -O-C*H*$_2$-C(=CH$_2$)-), 5.02 (s, -O-C*H*$_2$-Ar), 5.38 (s, -C(=C*H*$_2$)-), 6.79 (s, -O-*Ar*-O-), 6.8-7.5 (m, -O-*Ar*-CH$_2$-). FT-IR 1663, 1604, 1592 cm^{-1}. FAB MS (positive mode) m/z 748

7 $\mathbf{2}_1$: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, -O-C*H*$_2$-C(=CH$_2$)-), 5.03 (s, -O-C*H*$_2$-Ar), 5.28 (s, -C(=C*H*$_2$)-), 6.8-7.3 (m, -O-*Ar*-O-), 7.16 (s, -CH$_2$-*Ar*-CH$_2$-). FT-IR 1594, 1257 cm^{-1}. Precise MS calcd. for $C_{24}H_{22}O_4$ 374.1517, found 374.1583

$\mathbf{2}_2$: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.63 (s, -O-C*H*$_2$-C(=CH$_2$)-), 5.03 (s, -O-C*H*$_2$-Ar), 5.28 (s, -C(=C*H*$_2$)-), 6.8-7.3 (s,-O-*Ar*-O-), 7.35 (s, -CH$_2$-*Ar*-CH$_2$-). FT-IR 1661, 1591, 1261 cm^{-1}. FAB MS (positive mode) m/z 747. Elemental analysis calculated for $C_{48}H_{44}O_8$: C, 76.98; H, 5.92; O, 17.09; found: C, 76.53; H, 5.87; O, 17.43.

8 Crystal data for 1:1 complex of $\mathbf{1}_2$ with benzene: $C_{54}H_{50}O_8$, Mw=826.98, crystal size 0.4 X 0.3 X 0.2 mm, crystal system=triclinic, space group $P\bar{1}$ (#2), a=9.099(3), b=10.351(4), c=13.382(6) Å, α=112.51(2)°, β=104.92(2)°, γ=94.89(2)°, V=1101.0(8) Å^3, D_{calcd}=1.247 g/cm^3. The data were collected on an mxc18k diffractometer, λ(Mo-Kα)=0.7107 Å, ω-2θ scan, μ=0.83 /cm, 4188 measured and 3880 unique reflections ($2\theta_{max}$=50.0°, R_{int}=0.009). The structure was solved by direct method methods (SIR92: A. Altomare, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi, G. Polidori, *J. Appl. Cryst.* 1994, **27**, 435) and expanded using Fourier techniques. The non-hydrogen atoms were refined automatically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least sqare refinment was based on 2588 observed refrections ($I>2.00\sigma(I)$) and 280 variable parameters and converged (largest parameter shift was 0.15 times its esd) with unweighted and weighted agreement factors of: R=0.045, R_w=0.055.

Crystal data for $\mathbf{1}_1$: $C_{24}H_{22}O_4$, Mw=374.44, crystal system=monoclinic, space group $P2_1/n$(#14), a=17.007, b=14.825, c=7.817 Å, β=90.712°,V=1953.1 Å^3, D_{calcd}=1.273 g/cm^3. unweighted and weighted agreement factors of: R=0.046, R_w=0.049.

Crystal data for $\mathbf{2}_2$: $C_{48}H_{44}O_8$, Mw=748.87, crystal system=monoclinic, space group $P2_1/c$(#14), a=17.378(6), b=15.774(5), c=7.335(3) Å, β=96.82(2)°,V=1996(1) Å^3, D_{calcd}=1.246 g/cm^3. unweighted and weighted agreement factors of: R=0.050, R_w=0.055.

Crystal data for $\mathbf{2}_1$: $C_{24}H_{22}O_4$, Mw=374.44, crystal system=triclinic, space group $P\bar{1}$ (#2), a=7.920(3), b=11.130(2), c=11.513(4) Å, α=73.31(2)°, β=85.92(2)°, γ=85.24(2)°,V=967.6(5) Å^3, D_{calcd}=1.285 g/cm^3. unweighted and weighted agreement factors of: R=0.049, R_w=0.068.

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