Syntheses of Novel Cyclic Polyethers and Their Complexation with Benzene Derivatives

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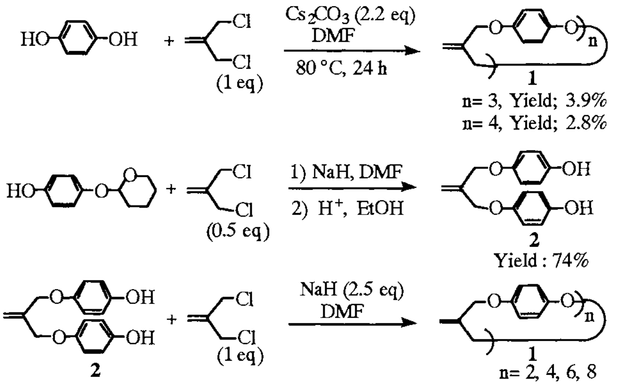
Cyclic polyethers have been synthesized from the hydroquinone and methallyl (isobutenyl) dichloride. Of these, only the tetramer forms 1:1 complexes with benzene derivatives.

To date, much attention has been paid to the functionalization of certain host skeletons such as bowl- or capsule-shaped molecules, because of their specific and unique features for guest compounds.[1] Recently, we have reported that cyclic polyethers bearing methallyl diphenyl ether groups can be converted to the corresponding calixarene analogues[2] and crownophanes[3] *via* tandem (double) Claisen rearrangement. Since then, the tandem Claisen rearrangement has been extended to the synthesis of bis-calix[n]arenes,[4] while the functional methallyl group has been applied to the synthesis of dendrimers.[5]

In this paper we report the syntheses of novel cyclic polyethers from the reaction between hydroquinone and methallyl dichloride as well as their complexation with certain benzene derivatives. The direct cyclization reaction of hydroquinone with methallyl dichloride mainly resulted in the formation of oligomers, and low yields of cyclic polyethers (**1**), as shown in Scheme 1. On the other hand, the indirect reaction involving the adduct (**2**) proved to be a better method for preparing the cyclic polyethers in greater yield. Compound **2** was easily obtained in 74% overall yield, as shown in Scheme 1.[6]

Scheme 1.



The cyclization reaction between **2** and methallyl dichloride gave **1** (n= 2, 4, 6, and 8), as summarized in Scheme 1 and Table 1. The structures of **1** were confirmed by ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy.[7]

The tetramer (n=4) and hexamer (n=6) were obtained as main products under all of the reaction conditions. The selectivity of the tetramer can be increased with using highly dilute solvent conditions. This indicates that the cyclization step to produce the dimer (n=2) is hindered by the ring size being too small. In the ^{1}H-NMR spectra, the aromatic protons of **1** show a tendency to shift downfield as the ring size of **1** is increased.

Table 1. The reaction between **2** and methallyl dichloride

Base	M of DMF	Temp. /°C	Time[a] /h	Yield of cyclic polyether[b] /%			
				n=2	n=4	n=6	n=8
NaH	0.05	65	2	0	13	10	5
NaH	0.025	rt	5	0	16	9	4
NaH	0.025	65	5	0	24	14	4
NaH	0.013	65	24	1	24	4	4
Cs_2CO_3	0.025	65	24	5	23	13	6

Base; 1.25 eq vs. OH. [a] Addition time of methallyl dichloride. [b] Estimated by ^{1}H-NMR.

In addition, the capacity for **1** to complex guest molecules has been studied. It was found that only the tetramer **1** (n=4) forms complexes with benzene derivatives in the solid state. The host-guest ratios for each of the complexes have been determined by ^{1}H-NMR and thermal analysis, as summarized in Table 2.[8]

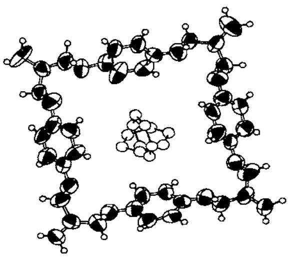
Table 2. The complexation properties of **1** (n= 4) with benzene derivatives

Guest.	Peak Intensity Ratios[a] Tetramer : Guest	TGA Temp, /°C	weight /%
Benzene	1 : 0.88	124.1,	-10.3
Toluene	1 : 0.88	112.5,	-11.6
p-Xylene	1 : 0.83	120.8,	-11.7
Chlorobenzene	1 : 0.89	123.9,	-13.9

[a] Estimated by ^{1}H-NMR.

The NMR intensity ratio for the guest molecules is slightly lower than that of the host **1** (0.83-0.89 : 1, respectively), while the signals for the benzene derivatives occur in exactly the same positions as those for the pure components in $CDCl_3$. This implies that the guest molecules exist freely in $CDCl_3$. The weight change temperature and weight change of complexes ranged between 112.5-124.1 °C and -10.3-13.9%, respectively, as determined by thermogravimetric analysis (TGA). These experimental results clearly demonstrate that the tetramer is able to form 1:1 complexes with certain benzene derivatives. However, attempts to complex the tetramer with larger aromatic molecules such as naphthalene and biphenyl, failed on account of the greater size of the guests.

The crystalline 1:1 host-guest complex suitable for an X-ray analysis was obtained from recrystallizaton of tetramer **1** in the mixture of benzene and $CHCl_3$.[9]



The crystal structure shows the four benzene rings directed toward the center of the ring, while the four exo-methylenes are directed away from the cavity. The benzene guest molecule adapts a face-to-face conformation with each of the four benzene rings, almost perpendicular to the least square plane of the host. The shortest non-bonded C-C contact between the benzene rings of the host and guest is observed to be 3.33 Å. However, the benzene ring is statistically disordered on the two-fold axis.

In conclusion, novel cyclic polyethers can be synthesized from hydroquinone and methallyl dichloride. Of these, only the tetramer has been shown to form 1:1 complexes with certain benzene derivatives. Furthermore, those cyclic polyethers bearing functional methallyl hydroquinone diether subunits could prove to be useful as precursors, applied not only to the synthesis of novel cyclophanes by tandem Claisen rearrangement, but also to the functionalization of their skeletons.

References and Notes

1 For a review, see: a) K. Goto and R. Okazaki, *Liebigs Ann./ Recueil.*, **1997**, 2393. b) A. Ikeda and S. Shinkai, *Chem. Rev.*, **97**, 1713 (1997).

2 K. Hiratani, K. Kasuga, M. Goto, and H. Uzawa, *J. Am. Chem. Soc.*, **119**, 12677 (1997).

3 K. Hiratani, H. Uzawa, K. Kasuga, and H. Kambayashi, *Tetrahedron Lett.*, **38**, 8993 (1997).

4 J. Wang and C. D Gutsche, *J. Am. Chem. Soc.*, **120**, 12226 (1998).

5 M. Jayaraman and J. M. J. Frechet, *J. Am. Chem. Soc.*, **120**, 12996 (1998).

6 Adduct (**2**): ^{1}H-NMR (300 MHz, DMSO-d_6) $\delta = 4.49$ (s, 4H, OCH_2), 5.27 (s, 2H, exo-CH_2), 6.65 and 6.74 (dd, J= 6.6, 8H, Ph), 8.91 (s, 2H, OH) ppm.

7 Synthesis of cyclic polyethers (**1**): typical procedure: To a solution of **2** (1 mmol) in dry dimethylformamide (DMF, 0.013 M) was added sodium hydride (2.5 mmol) under a nitrogen atmosphere. After 30 min of stirring at room temperature, a solution of methallyl dichloride (1 mmol) in dry DMF (50 mL) was added over a period of 24 h at 65 °C into the reaction mixture with stirring. After DMF was removed from the reaction mixture under reduced pressure, the residue was extracted with $CHCl_3$ (200 mL), the $CHCl_3$ solution was washed with water two times, and dried over anhydrous magnesium sulfate. After the solvent was removed, the cyclic polyethers were isolated by preparative HPLC eluted with $CHCl_3$. **1** (n=2): ^{1}H-NMR (500 MHz, $CDCl_3$) $\delta = 4.57$ (s, 8H, OCH_2), 5.40 (s, 4H, exo-CH_2), 6.51 (s, 8H, Ph) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 69.54, 117.75, 117.25, 142.41, 152.73 ppm. Mass Calcd (found) for $C_{20}H_{20}O_4$: 324.136 (324.134). **1** (n=3): ^{1}H-NMR (500 MHz, $CDCl_3$) $\delta = 4.59$, 5.31, 6.74 ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 69.54, 115.74, 116.00, 141.65, 153.01 ppm. Mass Calcd. (found) for $C_{30}H_{30}O_6$: 486.56 (486). **1** (n=4): ^{1}H-NMR (500 MHz, $CDCl_3$) $\delta = 4.57$, 5.36, 6.79 ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 69.31, 115.72, 115.80, 141.13, 152.96 ppm. Mass Calcd. (found) for $C_{40}H_{40}O_8$: 648.272 (648.274). **1** (n=6): ^{1}H-NMR (500 MHz, $CDCl_3$) $\delta = 4.57$, 5.37, 6.83 ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 69.28, 115.58, 115.74, 140.87, 152.93 ppm. Mass Calcd. (found) for $C_{60}H_{60}O_{12}$: 972.40 (972). **1** (n=8): ^{1}H-NMR (500 MHz, $CDCl_3$) $\delta = 4.58$, 5.38, 6.85 ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) 69.28, 115.50, 115.73, 140.81, 152.96 ppm. Mass Calcd. (found) for $C_{80}H_{80}O_{16}$: 1296.54 (1295).

8 Complex preparation: the cyclic ethers were dissolved in the corresponding solvents by heating, then the precipitated complexes were dried in *vacuo* at 50 °C for 3 h after washing with *n*-hexane.

9 Crystal data for the 1:1 complex of tetramer **1** with benzene: $C_{40}H_{40}O_8$, Mw= 648.75, crystal size 0.4 X 0.4X 0.05 mm, crystal system= triclinic, space group P1(#1), a= 4.953 (2), b= 14.245 (4), c= 14.258 (4) Å, α = 88.35 (2)°, β = 80.12 (2)°, γ = 80.20 (2)°, V= 976.6 (6) Å^3, D_{calcd}= 1.103 h/cm^3. The data were collected on a Enraf-Nonius CAD4 diffractometer, λ(Cu Kα)= 1.54178 Å, ω-scan, μ=6.21 cm^{-1}, 2992 measured and 2863 unique reflections ($2\theta_{\mathrm{max}}$=119.9, R_{int}= (0.042). The structure was solved by direct methods (System90: Hou Yonggeng, Gao Min, Li Lipu, Hou Peixin, (1994). Acta Cryst. A50, pp 748-753) and expanded using Fourier techniques. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-square refinement was based on 1201 observed reflections (I> 3.00 σ (I)) and 447 variable parameters and converged (largest parameter shift 1.27 times its esd) with unweighted and weighted agreement factors of: R= 0.102, Rw= 0.125.