

Crown Ether-Type Cyclophanes: Efficient Synthesis via Quadruple or Double Cycloadditions and Molecular Recognition Study

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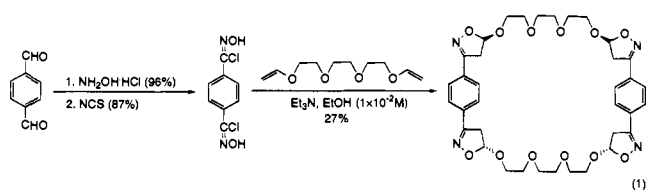
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Macrocycles constitute a large spectrum of compounds involving both artificial substances and natural products such as crown ethers, cryptands, cyclophanes, porphyrins, and macrolides. These compounds initiated the exciting area of host–guest supramolecular chemistry,¹ which has developed enormously. There are several strategies for obtaining macrocycles, including cyclization, capping, and condensation.² We report here a very efficient method for the preparation of macrocycles by using quadruple or double cycloadditions. To our knowledge, there is no precedent for the generation of macrocycles by using quadruple cycloadditions as cornerstones.³

Our synthetic strategy for novel crown ether-type cyclophanes is based on the multiple cycloadditions between bifunctional dipoles and bifunctional dipolarophiles (Scheme 1). The bifunctional dipoles were generated from the corresponding dialdehyde (isophthalaldehyde, terephthalaldehyde, and 2,6-pyridinedicarboxaldehyde⁴) by Huisgen's method,⁵ and for the bifunctional dipolarophiles, divinyl ethers and diacrylates⁶ were selected. With appropriate combination of bifunctional dipoles and bifunctional dipolarophiles, the ring size of crown ether-type cyclophanes could be controlled through either 2 + 2 quadruple cycloadditions or 1 + 1 double cycloadditions.

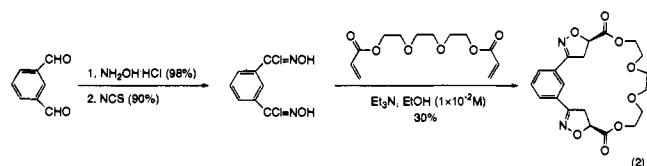
Divinyl ether (diethylene glycol and triethylene glycol) dipolarophiles were cycloadded with bifunctional dipoles. In all cases, macrocycles formed as major products were via 2 + 2 quadruple cycloadditions. Synthesis of the 40-membered macrocycle **1** is representative (eq 1).⁷ The isolated yield of the final quadruple cycloadduct **1** was 27%, which corresponds to 72% yield per cycloaddition. Furthermore, dihydroximoyl chlorides (the precursors of dinitrile oxide dipoles) could be efficiently prepared from the corresponding dialdehydes in just two steps with high yields. Thus, this quadruple cycloadditive macrocycle formation constitutes a novel, efficient synthetic method for making various crown ether-type cyclophanes.

Figure 1 summarizes the structures and isolated yields (final quadruple cycloadditions) of major macrocyclic products. The structure of macrocycle **1** was confirmed by X-ray crystal-



lography, and the configurations of the other macrocycles were tentatively assigned by analogy. The structures of 2 + 2 quadruple cycloadditive macrocycles were identified by elemental analysis, gel permeation chromatography, mass spectroscopy, IR, ¹H NMR, and ¹³C NMR.⁸

Diacrylate dipolarophiles provided either 2 + 2 quadruple cycloadducts or 1 + 1 double cycloadducts as major products depending on the geometry of the bifunctional dipoles and the chain length of the dipolarophiles. With meta-related bifunctional dipoles (isophthaldinitrile oxide and 2,6-pyridinedinitrile oxide), 1 + 1 double cycloadducts were formed in good yields. A typical synthesis of 21-membered macrocycle **8** is shown in eq 2.



In reactions with a para-related bifunctional dipole (terephthaldinitrile oxide⁹), both diethylene glycol diacrylates and triethylene glycol diacrylates afforded 2 + 2 quadruple cycloadducts. However, in the case of tetraethylene glycol diacrylate, the chain length was long enough to react with terephthaldinitrile oxide in 1 + 1 fashion and the 1 + 1 double cycloadduct **15** was formed as the major product. Figure 2 shows the structures and isolated yields of macrocycles formed from diacrylate dipolarophiles. The chemical structures of macrocycles **8** and **11** were confirmed by X-ray crystallography, and the configurations of the other macrocycles were tentatively assigned by analogy. The structures of macrocycles were also fully characterized.⁸

Figure 3 shows the X-ray crystal structures of macrocycles **1**, **8**, and **11**. The crystal structures clearly indicate that the 2 + 2 quadruple cycloadduct **1** has a good-sized (ca. 18.8 Å × 3.8 Å) cavity for host–guest complexation with neutral organic guest molecules and the 1 + 1 double cycloadducts **8** and **11** may be used as host molecules for complexation with ionic species.

(7) A typical reaction procedure follows. To a mixture of terephthaldihydroximoyl chloride (500 mg, 2.15 mmol) and triethylene glycol divinyl ether (440 μL, 2.15 m.mol) in EtOH (250 mL) was added dropwise triethylamine (690 μL, 4.95 mmol) in EtOH (10 mL) using a syringe pump (time of addition: 10 h). The reaction mixture was stirred at ambient temperature for 14 h. Evaporation of solvent followed by flash chromatography (SiO₂, 2:1 CH₂Cl₂/EtOAc) afforded 229 mg (27%) of macrocycle **1** as a white solid: mp 132.3–132.7 °C; ¹H NMR (CDCl₃) δ 7.57 (s, 8H), 5.83–5.80 (m, 4H), 3.96–3.89 (m, 4H), 3.85–3.73 (m, 4H), 3.71–3.61 (m, 16H), 3.41–3.16 (m, 8H); ¹³C NMR (CDCl₃) δ 157.2, 131.4, 127.8, 104.5, 71.5, 71.3, 68.4, 42.0; IR (CHCl₃, cm⁻¹) 3021, 2401, 1521, 1425, 1216, 929, 758, 670. Anal. Calcd for C₃₆H₄₄N₄O₁₂: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.52; H, 6.42; N, 7.61. MS. FAB⁺: calcd for C₃₆H₄₄N₄O₁₂ 725, found 726 (M⁺ + H). GPC (Shodex KF80M column): V_r (CHCl₃, mL) 16.307.

(8) All characterization data are included as supplementary material.

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(6) Diethylene glycol diacrylate and triethylene glycol diacrylate were prepared from the corresponding diethylene glycol and triethylene glycol in almost quantitative yields.

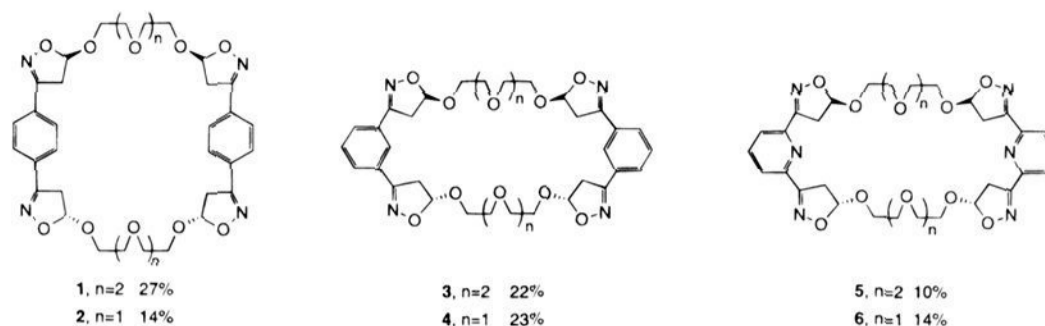


Figure 1. The structures and isolated yields of 2 + 2 quadruple cycloadditive macrocycles from divinyl ether dipolarophiles.

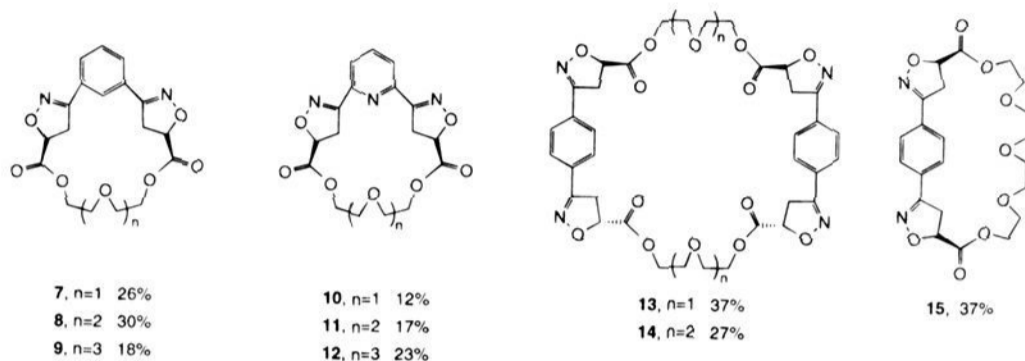
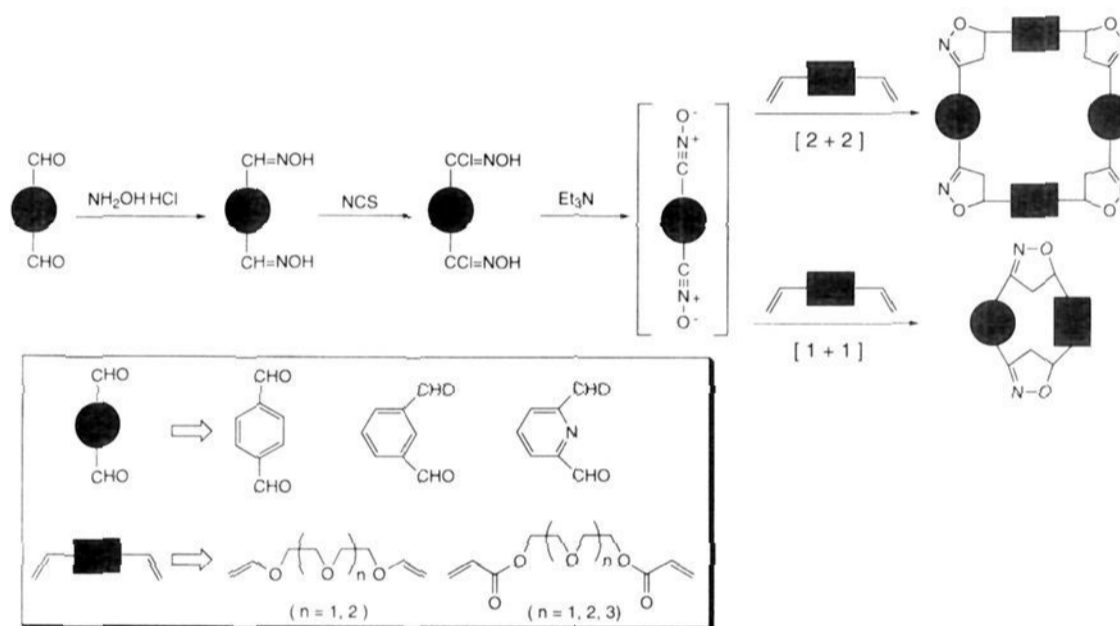


Figure 2. The structures and isolated yields of macrocycles formed from diacrylate dipolarophiles.

Scheme 1



To show the utility of these products, we have studied the molecular interactions between two macrocycles (**1** and **14**) and L-ascorbic acid by UV spectroscopy.¹⁰ Upon mixing host **1** or

14 and the guest (L-ascorbic acid) in $\text{CHCl}_3/\text{EtOH}$ (3:1) solution at 25 °C, we observed the change of absorbances at 250 nm (λ_{max} of L-ascorbic acid). Significant binding of L-ascorbic acid with macrocycle **1** or **14** was observed.

In conclusion, we have developed an efficient synthetic method for crown ether-type cyclophanes by using quadruple or double cycloadditions as cornerstones, and these macrocycles should be useful as host compounds in molecular recognition studies with various biologically interesting guest molecules.

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Supplementary Material Available: Characterization data for all macrocycles and X-ray data of macrocycles **1**, **8**, and **11** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

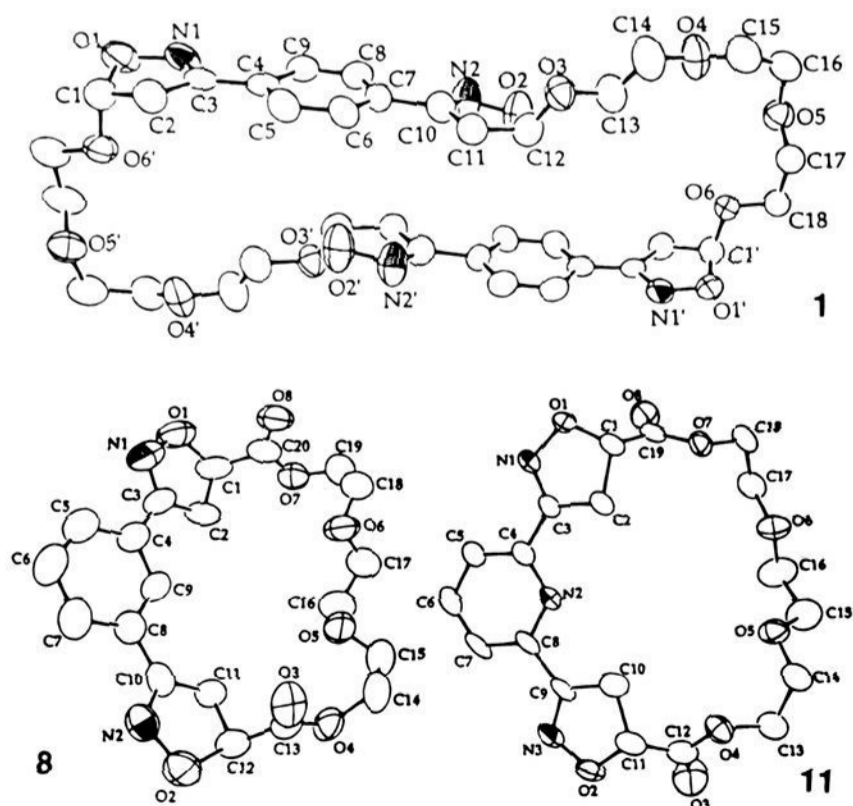


Figure 3. X-ray crystal structures of macrocycles **1**, **8**, and **11**.