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An Efficient (One-Pot) Synthesis of a New Class of Cyclophanes

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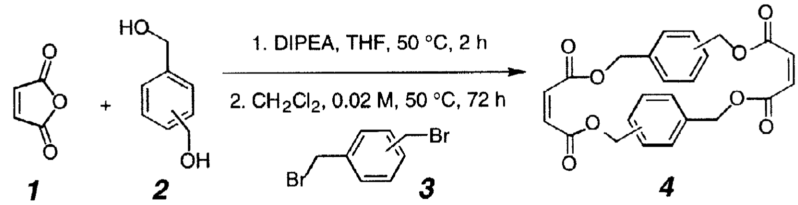
Abstract: *A new method for the synthesis of maleate(and phthalate)-bridged cyclophanes is described. For example, cyclophanes* **4** *(or* **5***) were obtained in 37-55 % yields by treating maleic (or phthalic) anhydride with various benzene dimethanols and reacting the resulting bis-carboxylate salts with various α,α'-dibromoxylenes. A cyclophane containing copolymer of* **4** *with 1,3-propanedithiol was prepared.*

Cyclophanes have long been targeted for chemical synthesis because of their often unique rigid, cyclic structure making them potentially interesting hosts for small molecules or metals.[1] Indeed, numerous syntheses of cyclophanes have been described, but are often non-trivial.[2] There has also been recent interest in incorporating cyclophanes into polymers.[3] Materials of this type may have practical applications (e.g. wastewater purification) if the incorporated cyclophane can selectively bind organic substrates (e.g. benzene, toluene, chloroform, methylene chloride).[4] Here we report a very efficient method for the one-pot synthesis cyclophanes that contain two (or three) maleate (or phthalate) bridges and the copolymerization of cyclophane **4pp** with a dithiol.

While developing a general strategy for the synthesis of unsymmetrical maleates for use as trapping agents for living polymer anions,[5] we discovered that this methodology was also useful for the synthesis of cyclophanes. Specifically, two equivalents of maleic anhydride (**1**) were reacted with a benzene dimethanol (**2**) in the presence of *N,N*-diisopropylethylamine in THF. The resulting bis-carboxylate salt was made homogeneous by the addition of anhydrous CH_2Cl_2 and then reacted with an α,α'-dibromoxylene (**3**) to give moderate yields of cyclophane **4**. Each of the six constitutional isomers of **4** was prepared (in similar yield) by systematically varying the substitution pattern of the starting diols and dibromides (Table 1). Compounds **5** and **6**, arising from the use of phthalic anhydride or mesitylene derivatives, respectively, demonstrate some additional versatility that is accommodated by this strategy.



All of these cyclophanes are highly crystalline materials. The melting points of the symmetrical isomers of **4** are higher than those of the unsymmetrical. The ORTEP drawing of the single crystal X-ray structure (determined at 298 K) of the *para,para*-isomer **4pp** is shown in Figure 1. The phenyl rings are

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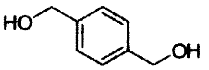
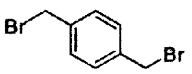
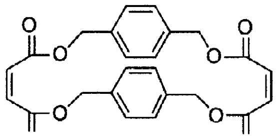
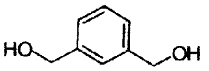
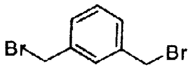
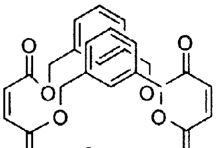
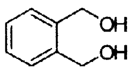
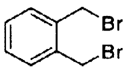
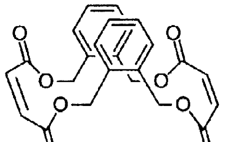
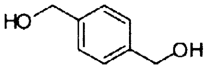
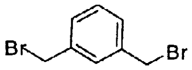
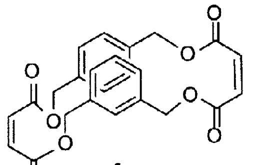
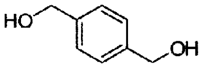
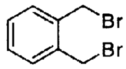
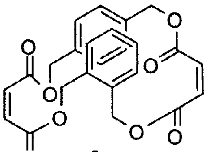
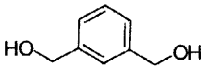
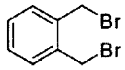
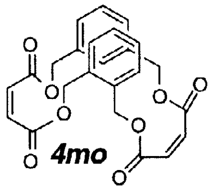
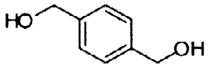
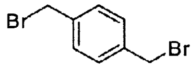
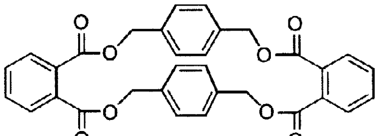
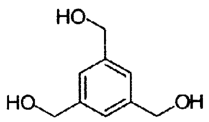
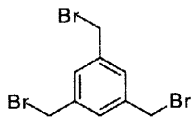
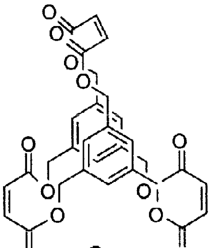
Table 1. Preparation of bis-maleate-bridged (all isomers of **4**), bis-phthalate-bridged (**5**), and tris-maleate-bridged (**6**) cyclophanes.

Alcohol	Bromide	Product	Yield (%)	mp (°C)
		 **4pp**	48	208-211
		 **4mm**	37	170-174
		 **4oo**	55	190-193
		 **4pm**	40	125-127
		 **4po**	46	139-141
		 **4mo**	51	164-166
		 **5**[a]	22	> 240
		 **6**	2	> 240

[a] Phthalic rather than maleic anhydride was used for the preparation of compound **5**.

disordered; 60% lie in the rough plane of the macrocycle and the remainder are ~50° out of plane. Interestingly, when the crystal was cooled in a stream of liquid nitrogen, an irreversible phase change was observed--the crystal burst.

The difunctional nature of cyclophanes **4** suggested their use as monomers for step-growth polymerization. A low molecular weight cyclophane-containing polymer was obtained by reaction of cyclophane **4pp** with 1,3-propanedithiol (TEA in THF, 80 °C). The gel permeation chromatogram (GPC) for the resulting material (Figure 2) shows a distribution of oligomers having an M_n of 2.5 kg/mol and a polydispersity index (PDI) of 1.69, typical for a step-growth polymerization. In contrast to the monomeric cyclophanes this polymer was freely soluble in a wide variety of organic solvents including THF and acetone.

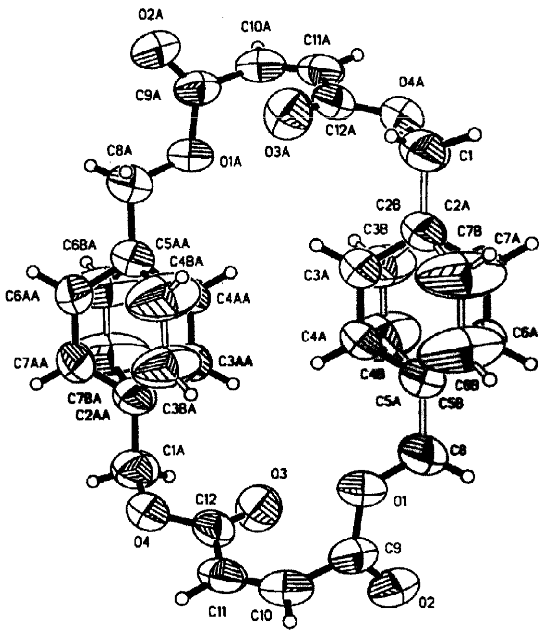
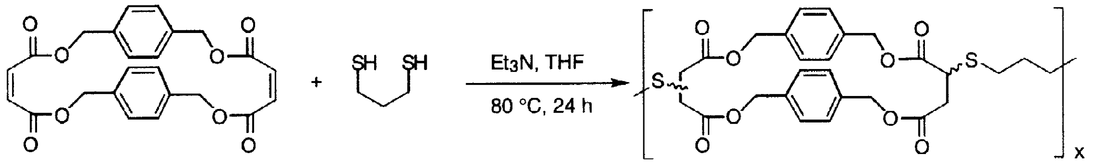


Figure 1. ORTEP drawing of X-ray crystal structure for cyclophane **4pp**.



4pp

7 x ~7

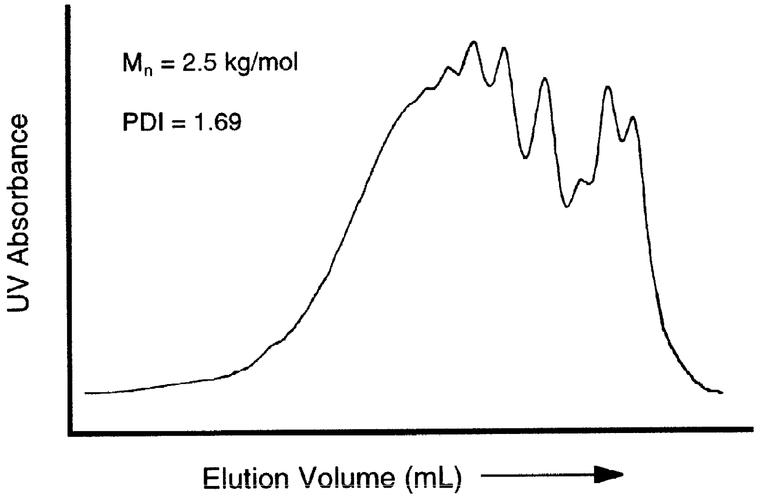


Figure 2. Gel permeation chromatogram of cyclophane-containing oligomer **7**.

Representative Experimental Procedure

Benzene dimethanols (4 mmol) and maleic anhydride (8 mmol) were dissolved in THF (5 mL) in a 50 mL culture tube fitted with a Teflon-lined cap. The solution was purged with argon for 5 min and *N,N*-diisopropylethyl amine (DIPEA, 8.8 mmol) was added slowly dropwise (5-10 min) into the solution via syringe. Following the mildly exothermic initial reaction, the solution was capped and stirred at 50 °C for 2 h. The resulting slurry was transferred to a 500 mL round-bottomed flask fitted with a drying tube and diluted with CH_2Cl_2 (200 mL) to make the solution homogenous. The α,α'-dibromoxylene was added (4 mmol), and the solution was stirred at 50 °C for 72 h. The resulting solution was washed with brine (2 x 75 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was then flashed through silica gel using chloroform as the eluent (the product band was visible) to give cyclophanes **4** as white crystalline solids. The observed high resolution (FAB) mass spectral data for the new cyclophanes was within 8 ppm of the calculated value, indicating that all were monomeric compounds. Infrared and ^1H and ^{13}C (DEPT) NMR spectra were also consistent with the assigned structures and indicated a high level of purity for each.

^{1}H NMR data ($CDCl_3$) for cyclophanes 4-6.

4pp: δ 7.24 (s, 8 H, Ar-$\underline{H}$), 6.24 (s, 4 H, $CO_2C\underline{H}=C\underline{H}CO_2$), and 5.19 (s, 8 H, $OC\underline{H}_2Ph$).

4mm: δ 7.34 (m, 8 H, Ar-$\underline{H}$), 6.34 (s, 4 H, $CO_2C\underline{H}=C\underline{H}CO_2$), and 4.95 (s, 8 H, $OC\underline{H}_2Ph$).

4oo: δ 7.37 (m, 8 H, Ar-$\underline{H}$), 6.29 (s, 4 H, $CO_2C\underline{H}=C\underline{H}CO_2$), and 5.27 (s, 8 H, $OC\underline{H}_2Ph$).

4pm: δ 7.34 (m, 7 H, Ar-$\underline{H}$), 6.81 (s, 1 H, Ar-$\underline{H}$), 6.37 (d, 2 H, J = 12.0 Hz, $CO_2C\underline{H}=CH'CO_2$), 6.27 (d, 2 H, J = 12.0 Hz, $CO_2CH=C\underline{H}'CO_2$), 5.15 (s, 4 H, $OC\underline{H}_2Ph$), and 4.97 (s, 4 H, $OC\underline{H}_2Ph'$).

4po: δ 7.37 (s, 4 H, Ar-$\underline{H}$), 7.31 (s, 4 H, Ar-$\underline{H}$), 6.30 (d, 2 H, J = 12.0 Hz, $CO_2C\underline{H}=CH'CO_2$), 6.22 (d, 2 H, J = 12.0 Hz, $CO_2CH=C\underline{H}'CO_2$), 5.16 (s, 4 H, $OC\underline{H}_2Ph$), and 4.88 (s, 4 H, $OC\underline{H}_2Ph'$).

4mo: δ 7.35 (m, 8 H, Ar-$\underline{H}$), 6.30 (d, 2 H, J = 12.0 Hz, $CO_2C\underline{H}=CH'CO_2$), 6.26 (d, 2 H, J = 12.0 Hz, $CO_2CH=C\underline{H}'CO_2$), 5.15 (s, 4 H, $OC\underline{H}_2Ph$), and 5.02 (s, 4 H, $OC\underline{H}_2Ph'$).

5: δ 7.78 (m, 4 H, Ar-$\underline{H}$), 7.56 (m, 4 H, Ar-$\underline{H}$), 7.18 (s, 8 H, Ar'-$\underline{H}$), and 5.27 (s, 8 H, $OC\underline{H}_2Ph$).

6: δ 6.91 (s, 6 H, Ar-$\underline{H}$), 6.41 (s, 6 H, $CO_2C\underline{H}=CHCO_2$), and 5.00 (s, 12 H, $OC\underline{H}_2Ph$).

Acknowledgments

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[3] For example see: Huber, J.; Scherf, U. *Macromolecular Rapid Communications* **1994**, *11*, 897.

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