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SYNTHESES AND STRUCTURE OF STILBENE CROWNS.[1]

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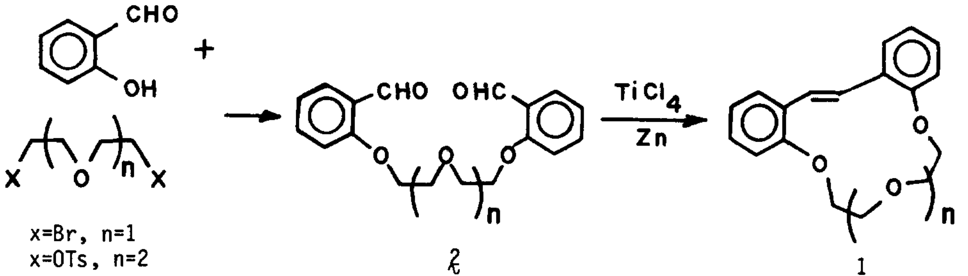
Summary: Syntheses of E- and Z-[a,e]-dibenzo-7,10,13-trioxacyclotrideca-1,3,5-triene, 1 (n=1) and E- and Z-[a,e]-dibenzo-7,10,13,16-tetraoxacyclohexadeca-1,3,5-triene, 1 (n=2) are described and the X-ray structure of E-1 (n=1) is reported.

As part of a program to develop new chemical models for enzymatic catalysis, stilbene molecules in which the aromatic rings are restricted from rotating are desired. This restriction should be readily accomplished by linking the 2,2' positions with an appropriate bridging moiety. Recent advances in synthetic methods for polyether podands[2] and for cycloalkenes[3] have suggested a straightforward approach to the desired molecules. This letter reports the facile two-step syntheses of a mixture of double bond isomers of stilbene crown ethers 1 (n=1,2) viz., E- and Z-[a,e]-dibenzo-7,10,13-trioxacyclotrideca-1,3,5-triene and E- and Z-[a,e]-dibenzo-7,10,13,16-tetraoxacyclohexadeca-1,3,5-triene.



Compound 1 (n=1) was made in 60% overall yield from salicylaldehyde via bis[2-(2-formylphenoxy)-ethyl] ether, 2 (n=1). Salicylaldehyde was treated with sodium hydroxide in dioxane: HMPA (2:1, V/V)[4] followed by addition of bis(2-bromoethyl) ether to produce 2 (n=1) in 73% yield.[5] Addition of 2 (n=1) to $TiCl_4$-Zn in dioxane[6] gave the desired compound, 1 (n=1) (83% yield) as a mixture of E- and Z-isomers (60/40:E/Z by ^1H NMR). The E-isomer separated readily by recrystallization[7] from cyclohexane, while the Z-isomer[8] was purified by preparative TLC.

Compound 1 (n=2) was prepared in 31% overall yield from salicylaldehyde via 1,2-bis[2-(2-formylphenoxy)—ethoxy]-ethane, 2 (n=2). Salicylaldehyde was treated with sodium hydroxide in THF:HMPA (2:1,V/V) followed by addition of triethylene glycol ditosylate to produce 2 (n=2) in 72% yield![10] Addition of 2 (n=2) to $TiCl_4$-Zn in dioxane gave the desired compound 1 (n=2) in 43% yield as a mixture of *E*- and *Z*-isomers (48/52:*E*/*Z* by ^{1}H NMR). The *E*-isomer[11] was separated from this mixture by chromatographic methods.[12]

The structure of the *E*-**1** (n=1), determined by X-ray diffraction analysis[13], is shown in Fig. 1. Structural parameters for the macrocyclic ring are given in Table 1. Of note are the values for the polyether bridge. On one side the bridge is attached orthogonal (C12-013-C1-C2) to the ring while on the other side the bridge and ring are nearly coplanar (C5-C6-07-C8). Significant differences also appear in the bond angles about the two aryl ether oxygens, 07 and 013. The conformation along the polyether bridge (07-C8-C9-010-C11-C12-013) is approximately t-g-t-g-g-t, although the dihedral about 010-C11 is 90°. The angle between the planes formed by the two aromatic rings is 22.8°. These structural data indicate a lack of symmetry between the aromatic rings and a non-equivlence of the vinylic protons.

This lack of symmetry in the crystal structure was not observed in the NMR (^{1}H and ^{13}C) spectra, which indicated C_2 symmetry in the molecule.[16] Since the only way to explain both the NMR and X-ray data was by a rapid conformational equilibration in solution among the rotamers (synchronous rotation about the C2-C3 and C4-C5 bonds), low temperature ^{1}H NMR studies were conducted. No appreciable changes in the aromatic or vinylic signals were noticed on reducing the temperature from 300 to 200 K, indicating that the barrier to interconversion among the rotamers is lower than 10 kcal/mole.

There is one notable difference in the ^{1}H NMR spectra of *E*-**1** (n=1,2). The vinylic protons in *E*-**1** (n=1) are at 7.838 δ, while in *E*-**1** (n=2) they are at 7.560 δ. A possible explanation is that the larger macroring allows the double bond to be closer to coplanarity with the aromatic rings.

The synthesis of **1** represents a novel entry into polyether macrocycles. This synthesis serves as a model for a crucial step in proposed syntheses of ring-substituted derivatives of **1**. It is especially useful to note that such high yields are obtained in the bridging step without protection of the aldehyde. The good yields, simple experimental procedures, and ease of separation of *E*- and *Z*-isomers make this approach an attractive entry into some potentially interesting compounds.

Investigations into the chemistry of the isomers of **1** and syntheses of analogs are currently in progress.

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References and Notes

1. This work is supported by a grant from the National Institute of Health, GM 29128-01. J.T.-R. acknowledges the CONACYT of Mexico for financial support.

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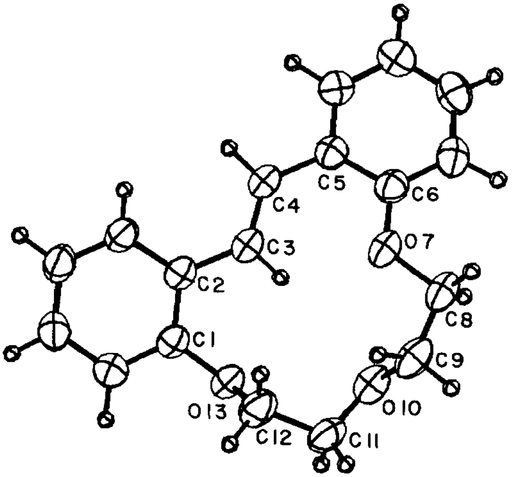

Figure 1. Ortep drawing of crystal structure of E-**1** (n-1).

Table 1. Selected structural parameters for _E_-[a,e]-dibenzo-7,10,13-trioxacyclotrideca-1,3,5-triene.[a,b]

Atoms	Bond Length (Å)	Atoms	Bond Angle (°)	Atoms	Dihedral Angle (°)
C1-C2	1.397(2)	C1-C2-C3	119.35(11)	C1-C2-C3-C4	171.8
C2-C3	1.461(2)	C2-C3-C4	127.32(12)	C2-C3-C4-C5	-176.4
C3-C4	1.326(2)	C3-C4-C5	128.17(12)	C3-C4-C5-C6	- 17.0
C4-C5	1.471(2)	C4-C5-C6	124.18(11)	C4-C5-C6-07	- 5.0
C5-C6	1.410(2)	C5-C6-07	115.31(11)	C5-C6-07-C8	177.0
C6-07	1.361(2)	C6-07-C8	121.68(11)	C6-07-C8-C9	-176.3
07-C8	1.421(2)	07-C8-C9	104.98(12)	07-C8-C9-010	63.5
C8-C9	1.482(2)	C8-C9-010	109.82(13)	C8-C9-010-C11	-161.9
C9-C10	1.422(2)	C9-010-C11	113.97(13)	C9-010-C11-C12	90.1
010-C11	1.412(2)	010-C11-C12	113.38(14)	010-C11-C12-013	68.5
C11-C12	1.509(2)	C11-C12-013	107.77(13)	C11-C12-013-C1	-165.4
C12-C13	1.437(2)	C12-013-C1	114.65(10)	C12-013-C1-C2	89.7
013-C1	1.390(1)	013-C1-C2	119.68(11)	013-C1-C2-C3	- 1.4

[a] Standard deviations are given in parentheses.

[b] All aromatic bond lengths are between 1.370 and 1.410 Å. All aromatic bond angles are between 116.51 and 122.35°.

4. When this reaction was done in 1-butanol, the reported[2b] solvent of choice, a much lower yield (34%) was obtained. Use of this solvent mixture allowed for higher yields and easier isolation of **2**.

5. Yellowish powder, mp. 66-7°C uncorr. ^{1}H NMR (200 MHz, $(CD_3)_2CO$): δ 10.507 (s, O=C-H, 2H); Aromatic protons: 7.844 (dd, J_1 = 7.681 Hz, J_2 = 1.868 Hz, 2H), 7.550 (ddd, J_1 = 8.408 Hz, J_2 = 7.369 Hz, J_3 = 2.076 Hz, 2H), 7.094-6.986 (m, 4H); 4.297-3.911 (A_2B_2 m, $ArOCH_2CH_2$, 4H). IR (KBr): 2940, 2780, 1670, 1590, 1390, 1050, 750 cm^{-1}. UV (MeOH) λ_{max} (ε): 214 nm (145,982), 252 (76,434), 318 (61,974). MS: m/e = 314 (5.9%) M$^+$, 315 (1.3) M+1, 316 (0.3) M+2, 286 (1.0), 165 (5.6), 149 (42.0), 121 (100).

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7. MP = 149.5-150.5°C uncorr. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.838 (s, 2H, =C-H); aromatic protons: 7.526 (dd, J_1 = 2.568 Hz, J_2 = 1.465 Hz, 2H), 7.219 (td, J_1 = 7.629 Hz, J_2 = 1.465 Hz, 2H), 7.096-6.874 (m, 4H); 4.117-3.787 (A_2B_2m, 8H, $ArOCH_2CH_2$). ^{13}C NMR[9] (50.3 MHz, $CDCl_3$) δ 126.466 (d, ^1J = 157.212 Hz, C3 + C4), 157.227 (s, C1 + C6), 129.296 (s, C2 + C5); Aromatic carbons: 127.863 (dd, ^1J = 160.911 Hz, ^3J = 7.398 Hz), 127.385 (dd, ^1J = 160.911 Hz, ^3J = 7.398 Hz), 122.497 (dd, ^1J = 159.986 Hz, ^3J = 8.323 Hz), 117.242 (dd, ^1J = 158.136 Hz, ^3J = 8.323 Hz); 70.752 (t, ^1J = 142.420 Hz, C9 + C11), 70.091 (t, ^1J = 143.240 Hz, C8 + C12); IR (KBr): 3020, 1640, 1590, 1470, 1445, 1250, 1030, 990 cm^{-1}; UV (MeOH) λ_{max} (ε): 207 nm (24,900, 232 (14,550), 237 sh (14,100), 289 (15,300), 300 (15,600), 320 (19,050), 334 sh (13,800); MS: m/e = 282 (100%) M^+, 283 (15.0) M+1, 284 (3.1) M+2, 223 (15.5), 131 (14.7), 165 (9.6), 181 (10.5).

8. Oil, B.P. ∿ 250°C (1 torr). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.144-6.666 (m, Ar-H, 8H), 6.656 (s, =C-H, 2H), 4.035-3.743 (m, $ArOCH_2CH_2$, 8H). ^{13}C NMR[9] (50.3 MHz, $CDCl_3$): δ 127.398 (d, ^1J = 160.91 Hz, C3 + C4), 155.45 (s, C1 + C6), 132.273 (s, C2 + C5); aromatic carbons: 129.972 (dd, ^1J = 140.567 Hz, ^3J = 9.247 Hz), 127.784 (dd, ^1J = 160.911 Hz, ^3J = 9.248 Hz), 115.117 (dd, ^1J = 157.212 Hz, ^3J = 7.398), 113.683 (dd, ^1J = 157.212 Hz, ^3J = 7.398 Hz); 70.752 (t, ^1J = 142.416 Hz, C9), 68.914 (t, ^1J = 135.017 Hz, C8); UV (MeOH) λ_{max} (ε): 216 nm sh (26,789), 272 (6,697), 279 (6.697); IR (nujol mull): 2860, 1600, 1490, 1250, 1150, 1055, 950 cm^{-1}; MS: m/e = 282 (100%) M^+, 283 (18.0) M+1, 223 (25.2).

9. Assignments were made in the basis of off-resonance broad band, gated, and single-frequency c.w. heteronuclear decoupling spectra.

10. When dioxane was used a lower yield was obtained, presumably due to decomposition of the ditosylate.

11. Semisolid, mp <25°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.560 (s, 2H, =C-H); aromatic protons: 7.440 (dd, J_1 = 1.9 Hz, J_2 = 7.5 Hz, 2H), 7.5-6.7 (m, 6H); 4.20-3.50 (m, 12H).

12. This isomer was separated by column chromatography on silica gel by elution with CH_2Cl_2 and then purified by preparative TLC.

13. Crystal Data: $C_{18}H_{18}O_3$, orthorhombic space group Pbca, a = 21.914(4), b = 18.720(4), c = 7.164(1) Å, Z = 8, d = 1.276 gcm^{-3}, R = 0.041 for 1841 observed data having $2° \le \theta \le 70°$, λ = 1.54184 Å for CuKα radiation. Intensity data were collected by the θ-2θ scan method on an Enfaf-Nonius CAD4 diffractometer. Scan rates varied from 0.36 to 10.0 deg. min^{-1} in order to measure all significant data with $I \sim 50\sigma(I)$. Corrections for background, Lorentz, polarization, and absorption (μ = 7.02 cm^{-1}) effects were applied. The structure was solved by direct methods (MULTAN 78)[14] and refined by least squares techniques (Enraf-Nonius SDP).[15] Nonhydrogen atoms were treated anisotropically, and hydrogen atoms were refined isotropically.

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16. The vinylic protons appear as one sharp singlet and only one set of signals due to aromatic protons is observed in the ^{1}H NMR. Only 9 peaks are observed in the ^{13}C NMR.

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