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1,8,15,22,30,34-HEXAOXA-29,35-DIOXO[8.8.7](1,4,2)CYCLOPHA-3,5,17,19-TETRAYNE AND 1,8,15,22,30,34-HEXAOXA-29,35-DIOXO[8.8.7](1,4,2)CYCLOPHANE, MODELS FOR CONFORMATIONALLY-DEFINED HOSTS

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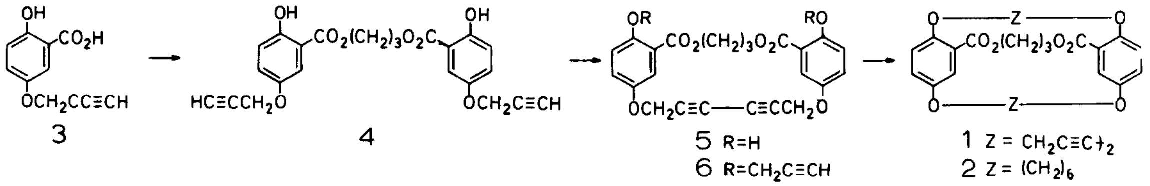
Abstract: The title molecules exhibit minimum barriers of 24-26 kcal mol^{-1} to ring inversion; an X-ray crystal structure of the saturated phane shows the aromatic rings to lie in contact and stacked.

We are interested in stereochemically-defined host molecules.[1] The title molecules (1 and 2, Scheme 1) test the effect of tethering together the arenes of the parent [8.8]paracyclophanes.[2] Previous work in this laboratory has shown that $\Delta G^{\ddagger}$ for passage of fused arenes[3] or simple alkoxycarbonyl groups[3,4] through the cavities of these systems is 12-13 kcal/mol We now report that the short diester bridges of 1 and 2 impose inversion barriers above ca. 25 kcal/mol.[5] An X-ray crystal structure of saturated 2 reveals that the arenes lie in contact and stacked, the first three atoms of three of the four alkoxy fragments are essentially coplanar with the attached arenes.

Scheme 1 outlines the preparation of 1 and 2. Reaction of 1,3-dibromopropane with acid 3[6] (Et_3N, DMF, 60°, 24 h)[7] gave diester 4[8] in 69% yield, oxidative cyclization of 4



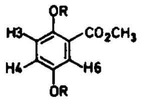
Scheme 1. Preparation of 1 and 2.

[$Cu(OAc)_2 \cdot H_2O$, pyridine, 44°, 2 h][9] provided dihydroxymetacyclophane 5 (57%).[8] Propargylation of 3 ($HC\equiv CCH_2Br$, K_2CO_3, DMF, room temp., 20 h)[10] furnished metacyclophane diether 6 (93%).[8] Oxidative cyclization of 6 [$Cu(OAc)_2 \cdot H_2O$, pyridine, 42°, 10 min][9] afforded the difficultly soluble 1[8] in 40% yield (18% isolated yield after extensive chromatography). Reduction of 1 [H_2

(1 atm), 5% Rh/Al_2O_3, EtOAc, room temp] gave 2 (81%).[8] Mass spectra of 1 contained no molecular ion, but the M^+ peak of 2 [m/e· 512.2412, calc. ($C_{29}H_{36}O_8$) 512.2400] showed 1 and 2 to be cyclic monomers.

Table 1 shows the cyclization shifts ($\Delta\delta = \delta_{phane} - \delta_{model}$)[2] of 1 and 2,[11] upfield shifts are negative.[2] Stiff 1 shows cyclization shifts near zero, while flexible 2 shows substantial upfield shifts, the cyclization shifts of 1 and 2 closely resemble those of earlier similarly-bridged phanes.[2-4] Thus, the arenes of 1 are held apart, while 2 lies collapsed.[2]

Phane	Model	Solvent	$\Delta\delta_{H-3}$	$\Delta\delta_{H-4}$	$\Delta\delta_{H-6}$
1	7[2]	DMSO-d_6	+0.114	-0.100	-0.036
2	8[6]	$CDCl_3$	-0.27	-0.30	-0.34



7 R = $CH_2C{\equiv}CH$
8 R = $CH_2CH_2CH_3$

Table 1. Cyclization shifts of 1 and 2, in ppm, model compounds appear at the right.

The CO_2CH_2 AB patterns (from irradiation of $CO_2CH_2CH_2$) of 1 and 2 do not broaden significantly on heating, minimum inversion barriers were set by bandshape analysis.[3] For 1 at 167°C in DMSO-d_6, $t \geq 0.14$ s, $k \leq 7.1\ s^{-1}$, $\Delta G^{\ddagger}_{440} \geq 24$ kcal/mol; for 2 at 181°C in bromobenzene-d_5, $t \geq 0.24$ s, $k \leq 2.4\ s^{-1}$, $\Delta G^{\ddagger}_{454} \geq 26$ kcal/mol. Here t is the average lifetime, k the unimolecular rate constant, and $\Delta G^{\ddagger}_T$ the free energy of activation at T° K; the dynamic NMR studies were performed at 200 MHz.

These barriers are much higher than those imposed by fused arenes[3] or monodentate alkoxycarbonyl groups.[3,4] Dreiding models suggest that ring inversion of 1 demands somewhat synchronous rotation of the two arenes; this condition may produce the higher barrier of 1, but seems unlikely to enforce that of 2.

Crystal data of 2· $C_{29}H_{36}O_8$; monoclinic; space group $P2_1/c$, a = 14.899(3), b = 10.144(3), c = 17.037(3) Å; β=100.20(2)°, Z = 4, $d_{calc.}$ = 1.34 g/cm^3. The structure was solved by direct methods,[12] and refined [based on the 4595 reflections with $F_0^2 > 3\sigma(F_0)^2$ and sine $\theta/\lambda \leq$ 0.649 $Å^{-1}$] anisotropically for C and O atoms and isotropically for hydrogens to a final R_1 value of 4.2%. Figure 1 shows the structure.[13]

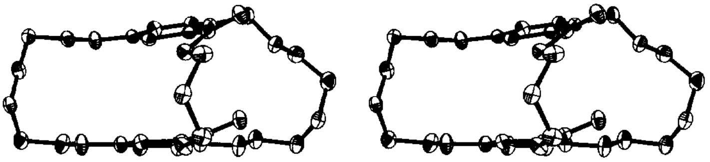


Figure 1. Stereoview of 2, viewed parallel to the lower [C(23)-C(28)] arene, hydrogens omitted for clarity.[18]

The arenes lie 3.5-4.5 Å apart, roughly the contact distance. The dihedral angles of the two longer bridges appear in Table 2. The O(15)-O(22) bridge has an approximate local C_2 axis and a torsional-angle sequence of $aag^+g^+ag^+g^+aa$, similar fragments are found in cyclotetradecanes[14] and 14-crown-4.[15] Local C_2 symmetry for the O(1)-O(8) bridge would drive C(7) into a carbonyl oxygen, O(36); instead, C(7) twists toward the opposite arene.

C(27)-C(26)-O(1)-C(2)	16.3°	C(11)-C(12)-C(15)-C(16)	15.0°
C(26)-O(1)-C(2)-C(3)	178.5°	C(12)-O(15)-C(16)-C(17)	169.3°
O(1)-C(2)-C(3)-C(4)	56.0°	O(15)-C(16)-C(17)-C(18)	65.5°
C(2)-C(3)-C(4)-C(5)	83.8°	C(16)-C(17)-C(18)-C(19)	69.9°
C(3)-C(4)-C(5)-C(6)	109.9°	C(17)-C(18)-C(19)-C(20)	148.5°
C(4)-C(5)-C(6)-C(7)	62.4°	C(18)-C(19)-C(20)-C(21)	65.6°
C(5)-C(6)-C(7)-O(8)	173.8°	C(19)-C(20)-C(21)-O(22)	59.4°
C(6)-C(7)-O(8)-C(9)	134.9°	C(20)-C(21)-O(22)-C(23)	174.8°
C(7)-O(8)-C(9)-C(10)	62.3°	C(21)-O(22)-C(23)-C(28)	5.0°

Table 2. Dihedral angles of the O(15)-O(22) and O(1)-O(8) bridges of 2.

Thus, collapse of 2 requires considerable kinking of the hexamethylene spacer.[16] The crystal conformation of 2, which is consistent with the solution cyclization shifts, may be dictated by any or all of 1) arene stacking, 2) alicyclic conformational preferences,[14-16] 3) conjugation of the carbonyl and arene pi systems, and 4) similar conjugation of the $ArOCH_2$ lone pairs.[17] The close similarity of the cyclization shifts of 2 to those of related "monocyclic" phanes[2-4] suggests that those phanes adopt similar conformations.

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11. a) 1 (DMSO-d_6): 7.300 ppm (d, J = 9.0 Hz, 2H, H-3), 7.220 (d, J = 3.0, 2H, H-6), 7.093 (dd, J = 9.0, 3.0 Hz, 2H, H-4), 5.03 ($\underline{A}B$, J = 18 Hz, 2H, 2-$ArOCH_2$), 5.03 ($A\underline{B}$, J = 18 Hz, 2H, 2-$ArOCH_2$), 4.98 ($\underline{A}B$, J = 17.2 Hz, 2H, 5-$ArOCH_2$), 4.95 ($A\underline{B}$, J = 17.2 Hz, 2H, 5-$ArOCH_2$), 4.537 [$A_2\underline{B_2}XY$, J = (-)11.?, 7.0, 4.45 Hz, 2H, endo-$CO_2\underline{CH_2}$], 4.281 [$\underline{A_2}B_2XY$, J = (-)11.2, 7.3, 4.2 Hz, 2H, exo-CO_2CH_2], 2.193 [$A_2B_2X\underline{Y}$ = (-) 15.4, 7.3, 4.45 Hz, 1H, endo-$CO_2CH_2\underline{CH_2}$], 2,106 [$A_2B_2\underline{XY}$, J = (-)15.4, 7.0, 4.2 Hz, 1H, exo-$CO_2CH_2\underline{CH_2}$].
    b) 2 ($CDCl_3$)· 7.080 (d, J = 3.0 Hz, 2H, H-6), 6.717 (dd, J = 8.8, 3.2 Hz, 2H, H-4), 6.615 (d, J = 9.0 Hz, 2H, H-3), 4.574 [$\underline{A_2}B_2XY$, J = (-)11.2, 8, 3 Hz, 2H, CO_2CH_2], 4.528 [$A_2\underline{B_2}XY$, J = (-)11.2, 7, 2 Hz, 2H, CO_2CH_2), 3.92-3.81 (m, 8H, $ArOCH_2$), 2.214 ($A_2B_2\underline{XY}$, 2H, $CO_2CH_2\underline{CH_2}$), 2.2-1.4 (m, 16H, chains).
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18. Figure 2 shows the systematic numbering of 2. In the stereoview above (Fig. 1), the O(1)-O(8) bridge is at the right, the O(15)-O(22) bridge at the left, and the C(9)-C(14) arene at the top.

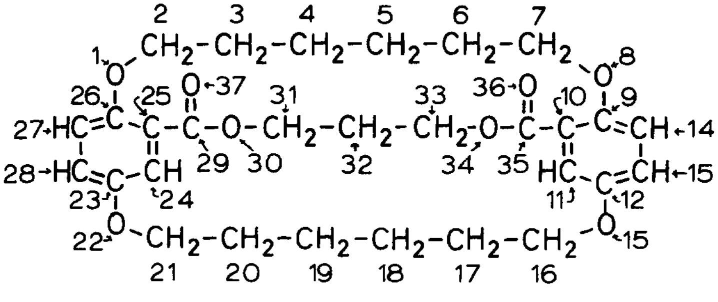

Figure 2. Systematic numbering of 2.

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