Synthesis and Characterization of 1,8,15,22-Tetraoxa[8.8]-paracyclophane-3,5,17,19-tetrayne-10,25-dicarboxylic Acid,[†] a Novel Water-Soluble and Donut-Shaped Molecule

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Abstract: Synthesis of the title molecule (**1**) along with an investigation of its conformation and ability to form inclusion-type stacking complexes with aromatic and aliphatic guests is described. It is shown that **1** possesses a geometry with the two aromatic rings well separated by the rigid dioxaoctadiyne spacers. Its perhydro derivative **7** in contrast exists in a collapsed conformation. Complexation of **1** with aromatic guests proceeds not via formation of an inclusion complex but is accompanied by a conformational flattening of **1** with consequent formation of a classical open-faced stacking complex.

Introduction

We are interested in the construction of molecules that (a) are water soluble and (b) possess hydrophobic cavities of well-defined dimensions. The principal interest in molecules of this type lies in the possibility of their showing a functional similarity to the hydrophobic cavities of enzymes. There is considerable current interest in the cyclodextrins as enzyme models of this general sort[1-18] and there is some current activity[19-25] in the construction of donut-like cyclophanes similar to those discussed here.

The particular structural type of interest to us is as follows (Figure 1), a cyclophane whose π-π (Ar-Ar (Figure 1)) distance of approximately 3.6 Å (i.e., ring-ring distance of 7.2 Å) permits insertion of an aromatic ring (Ar') into the hole in a flat orientation. The desired Ar-Ar inter-ring distance is to be defined by rigid spacers. Variation in the nature of the aromatic faces and the positioning and nature of the spacers on the aromatic rings all in principle permit one to define accurately the dimensions of the molecule's cavity. We have previously reported on our work on the molecular tweezers of this type wherein the Ar's of Figure 1 are caffeine rings joined by a single rigid spacer.[26]

The molecule of interest here is cyclophane (**1**). This was

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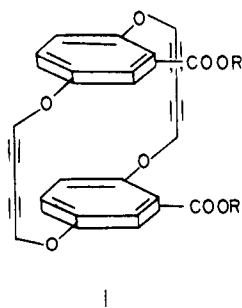
chosen as an initial goal in order to answer the following questions: (1) Can one close the 22-membered ring of **1** in a synthetically efficient manner by use of the cupric ion acetylene dimerization[27-31] reaction? (2) Molecular models suggest that the 1,6-hexadi-2,4-ynyl ether spacers of **1** should keep the two aromatic rings well separated from one another; is this correct? (3) Is **1** conformationally mobile? (4) Models suggest that **1** may be able to accommodate a benzene molecule within the cavity due to the lateral spacer-spacer distance. How does **1**

complex with aromatics? (5) Since water solubility is of paramount importance, will molecules of this sort exhibit water solubility to a sufficient extent ($\geq \sim 0.002$ M) to observe complexation by NMR techniques?

Synthesis

The syntheses of **1** are given in Figure 2 and are detailed in the Experimental Section. The following points are noteworthy. Alkylation of (e.g.) **2b** with propargyl bromide-potassium carbonate in acetone proceeds with acceptable positional selectivity,[32-34] although prolonged reaction smoothly produces the 2,5-dipropargyloxybenzoates **4a-e**.

Cyclization of **6a, 6c,** and **6d** to **1a, 1c,** and **1d,** respectively, proceeds in pyridine with cupric acetate at ~40 °C in remarkably high yields considering the size of the rings formed. We feel that the success of this reaction is due more to the few degrees of conformational freedom of **6,** with its plethora of rigid subassemblies, than to any type of complexation phenomenon. The cyclization reactions proceed smoothly enough at ordinary concentration (67% yield of **1b** by cyclization of 23 mM **6b**) that high-dilution conditions are not necessary. We have noted a similar ease of cyclization in the naphthalene series (e.g. 2,6-dipropargyloxynaphthalene[35]) and there is some literature precedent for this reaction's proceeding in good yield[28,30] at modest concentrations.

That the products of cyclization are the cyclic monomers (we refer to **1** as cyclic monomer) rather than dimers or higher follows from direct molecular weight measurements of **1b** and **1d** and on their hydrogenation to the saturated derivatives **7.** Mass spectral and solution (isopiestic method[36]) molecular weights for **1b, 7b,** and **7d** require the monomeric structures assigned. Examination of the mass spectrum of the mother liquors from the recrystallization of **7b** showed there to be some dimer present (mass ~1280) but it could not be isolated.

The principal synthetic difficulty encountered was in trying to effect the saponification of **1b.** It is an exceedingly insoluble material. Attempted saponification of it led to either no reaction, with recovered **1b,** or to a complex mixture of products arising (apparently) from a base-catalyzed acetylene to diene rearrangement process.[37,38] Construction of **1c,** with an eye toward employing the reductive cleavage of trichloroethyl esters,[39] was carried out. Zinc-acetic acid treatment of **5c,** however, reduced one diyne to an enyne without affecting the ester, while treatment of **1c** with zinc in acetic acid led either to no reaction or to a complex mixture of products. Hexyl ester **1d,** on the other hand, was, when prepared, conveniently soluble and low melting (mp 155 °C), and could be saponified smoothly to **1a.** This acid is conveniently purified by recrystallization of its sodium or potassium salt **1e** from water.

[†] Also named 2,9,14,21-tetraoxatricyclo[20.2.2.2^10,13]octacosa-10,12,22,24,25,27-hexaene-4,6,16,18-tetrayne-11,24-dicarboxylic acid.
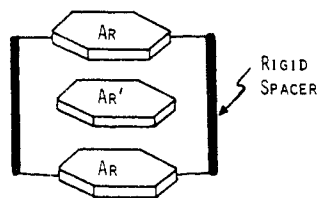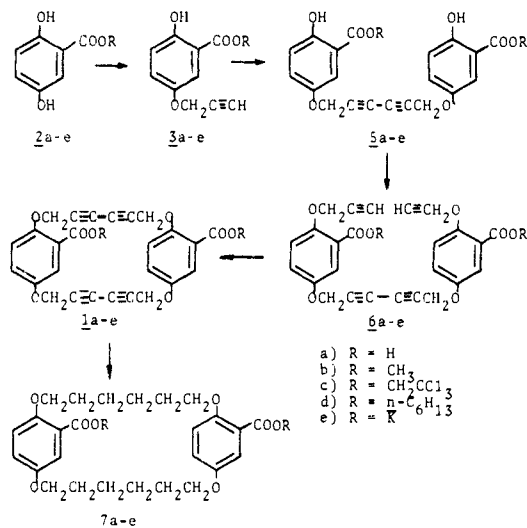
Figure 1.

Figure 2.

Figure 3. ^{1}H NMR (270 MHz) of **1e** in deuterium oxide. Curve a: experimental spectrum. Curve c: simulated spectrum: δ H3 7.09, δ H4 7.044, δ H6 7.041, J_{34} = 9.05 Hz, J_{36} = 0.72 Hz, J_{46} = 3.14 Hz. Curve b: Lorentzian plot, $\nu_{1/2}$ = 1 Hz, of curve c.

Conformation

For the purpose of considering the conformation of the **1** and **7** series of cyclophanes we define an NMR parameter, the *cyclization shift*, of the aromatic protons.[40] For a given proton this is the chemical shift (δ) of it in the **1** or **7** series less the chemical shift of the corresponding proton in the appropriate 2,5-dipropyloxybenzoate (**7** series) or 2,5-dipropargyloxybenzoate (**1** series) ester. A negative value corresponds to an upfield shift on formation of the cyclophane from its acyclic precursor. Cyclization shifts for various salts and esters of **1** and **7** are given in Table 1.

For the **1** series cyclization shifts are all less than 0.08 ppm (mean −0.023 ± 0.04). The immediate conclusion to be drawn from this is that to the extent that these shifts are interpretable the two rings in **1** are isolated from one another by the rigid diyne spacer. This is not true for **7** (see below). Whether there is a preferred limiting conformation of **1** as in Figure 4 cannot be said. One may estimate chemical shifts for the three limiting conformations of Figure 4, employing the tables of Haigh and Mallion.[41] Conformation F–F, with a ring-ring distance of ~7 Å. is predicted to have a cyclization shift of no more than −0.05 ppm. This is in agreement with experiment. The planar conformation which, due to the size of the diyne spacers. is equally available (but only with the carboxyl substituent "out") has a predicted cyclization shift of the internal protons of no more than +0.02 ppm. This also is in agreement with experiment. The E–F conformation, with a calculated cyclization shift for the internal protons of ca. −0.1 ppm, may be ruled out as the sole conformation of **1**. We conclude that there is most likely no strongly preferred conformation for the **1** series.

The situation is remarkably different for the **7** series. We first note that models suggest that **7** should assume an extended conformation wherein the ring-ring distance is ~7.2 Å, one that is close to that of **1**. Experiment does not agree with this, as substantial upfield cyclization shifts are observed for **7**.

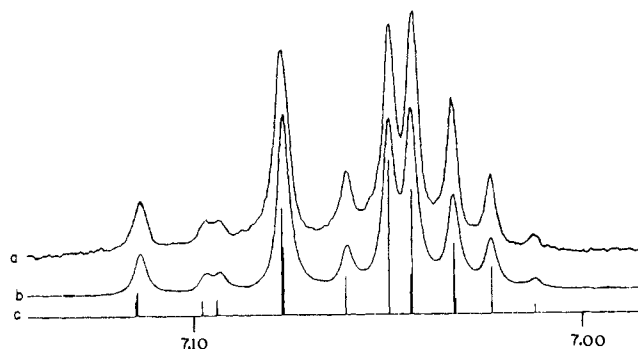The data (Table 1, entries 3, 3, and 6) support the idea that

in chloroform **7** and its salts assume an F–F conformation with a concomitant collapse to a ca. 4 Å ring–ring distance. In the solvents water and dimethyl sulfoxide, however, the signal for H6 is almost unaffected by cyclization (entries 1, 4, and 5). One can interpret this anomalous behavior of H6 as evidence for either a solvent-induced shift from an F–F toward an F–E conformation (Figure 4) or a skewing of an F–F arrangement in order to increase solvation of the functional group as pictured in Figure 5. We favor the latter as the simpler hypothesis. It is also consistent with the self-association of potassium 2,5-dipropyloxybenzoate (Table 1, entry 12) in water where H3 and H4 signals show larger upfield shifts on dimerization than does that of H6. Other than the observation "natura abhorret a vacuo", we have no satisfactory explanation for the apparent buckling of the hexamethylene chain in **7**, nor can we explain why the apparent movement of H6 away from the other ring is not accompanied by larger upfield shifts for H3 and H4. We suspect, though, that the latter is an artifact of the poor correlation between ring current effects and geometry in this type of highly substituted molecule.

Acid **7a** in methanol shows a 3.8% hypochromicity; salt **73** in water shows a 5.8% hypochromicity.

Tabushi et al.,[21] in studying a [2.2.2.2]cyclophane, observed large temperature-dependent chemical shifts which were interpreted in terms of (our terminology) an F–F ⇆ F–E type of conformational equilibrium. Neither **7b** in chloroform-*d* nor **7e** in deuterium oxide exhibited a perceptible temperature dependence of their NMR spectra. For **7b**, H3 goes from δ 7.164 at 80 °C to δ 7.115 at −38 °C, a change of 0.05 ppm. Similar shifts were observed for the other protons of **7b** and of **7e**. In light of Tabushi's results[21] **7** would appear to process a unique "best" conformation, presumably the F–F conformation.
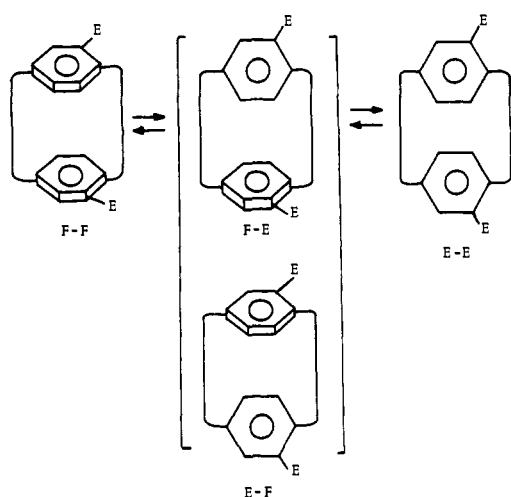
Complexation

The cavity of **1e** approximates a two-ended box ~4 Å on a side and as such should be capable of forming complexes with aliphatic molecules with insertion of an alkane tail into the cavity. With **1e** one expects association constants on the order of 5–15 M^{-1} for this process.[42–46] The interaction of **1e** with hexyltrimethylammonium bromide (**8**) was studied as a probe of this. Salt **8** was chosen as it is known[47] not to form micelles at modest concentrations. Variation of the chemical shift of protons of **8** as a function of the concentration of **1e** was analyzed via the equation[48–52] $1/\Delta_{obsd} = 1/K\Delta C + 1/\Delta$ where Δ_{obsd} is δ (uncomplexed) $- \delta_{obsd}$ at concentration C and Δ is δ (uncomplexed) $- \delta$ (complexed). As the assumption that the major component is in large excess was not met, C was calculated by an iterative procedure.[51,53] Considerable variation in Δ values and K_{assoc} was found depending on the resonance of **8** examined and the internal chemical shift standard employed.

Table I. Cyclization Shifts for **1** ("Rigid") and **7** ("Floppy") Cyclophanes[f]
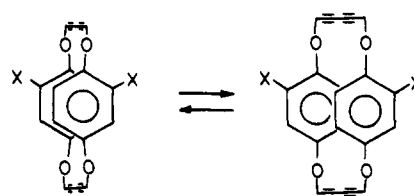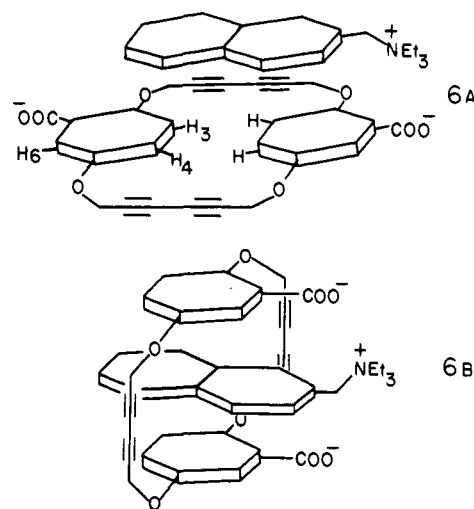
entry	spacer	subst	solvent	note	$\Delta\delta_{H3}$	$\Delta\delta_{H4}$	$\Delta\delta_{H6}$
1	floppy	COO⁻K⁺	D₂O	a	−0.203	−0.231	0
2	floppy	COOCH₃	CDCl₃		−0.297	−0.31	−0.169
3	floppy	COOH	CDCl₃	a	−0.25	−0.206	−0.25
4	floppy	COO⁻K⁺	D₂O–Me₂SO		−0.17	−0.23	+0.021
				e	(−0.23)	(−0.30)	
5	floppy	COOH	Me₂SO	a	−0.244	−0.291	−0.06
6	floppy	COO⁻⁺NR₄	CDCl₃		−0.128	−0.097	−0.105
7	rigid	COOCH₃	CDCl₃		−0.074	−0.03	−0.027
8	rigid	COOCH₃	CDCl₃	b	−0.079	+0.043	+0.015
9	rigid	COOC₆H₁₃	CDCl₃		−0.066	−0.002	−0.044
10	rigid	COOC₆H₁₃	CDCl₃	b	−0.069	+0.036	+0.003
11	rigid	COO⁻Na⁺	D₂O	c	−0.087	−0.026	−0.056
12		COO⁻K⁺	D₂O	a, d	−0.244	−0.291	−0.06

[a] Extrapolated to infinite dilution. [b] Relative to uncyclized precursor. [c] Chemical shifts derived from a LAOCOON III simulation of the three-spin system. See Figure 3. [d] Self-association shifts for autocomplexation of potassium 2,5-di(1'-propargyloxy)benzoate in deuterium oxide. [e] Calculated from "half-cyclized" **6e**. [f] The derivative studied (see Figure 2) is specified in column 3. Negative $\Delta\delta$ implies an upfield shift on cyclization.

Figure 4.

Figure 5.

PROTON	K_{ASSOC}(M⁻¹)	Δ
H3	51 ± 1	241.5 ± 2
H4	57.4 ± 1	248 ± 0.3
H6	168 ± 9.6	19.6
CH₂	83.8 ± 7.5	116 ± 4

Figure 6. Experimentally determined association constants for interaction of **9** with **1e**. Values calculated from chemical shift vs. concentration for each aromatic proton of **1e** are shown. Values labeled Δ are the calculated (upfield) shifts of the respective protons in the complex (**6A** or **6B**).

Association constants for complexation of **8** with **1e** (5.0 ± 2.8 M⁻¹) and with potassium 2,5-dipropargyloxybenzoate (1.6 ± 0.8 M⁻¹) were calculated. The Δ values were not accurate enough, however, to make a statement concerning the geometry of the complex. The interaction of **8** with **1e** is appreciably stronger than with the monomer, and the association constants are close to those calculated for insertion complexation. However, for the following reasons, we are hesitant to argue that these results should be construed as strong evidence for this hypotheses: the association constants computed are in fact quite small (this is of course a defect in the model). The assumptions built into the analysis employed, namely, 1:1 complexation, are clearly very crude. This is presumably responsible for the large errors in computed Δ values and their dependence on which proton was being considered. No effort was made to derive $\Delta H°$ and $\Delta S°$ for the putative equilibrium.

Models suggest that the cavity of **1** can, with but a slight amount of puckering, accommodate an aromatic ring. Complexation of **1e** with 2-naphthylmethyltriethylammonium chloride[53,54] (**9**) was studied, using the same techniques as above, as a probe for this interaction process with rather surprising results. From the NMR spectra of **1e** as a function of the concentration of added **9** (and vice versa) one may calculate association constants for the **1e**:**9** complex from each proton position and chemical shifts of each ring proton in the complex. These numbers are given in Figure 6 and may be summarized as follows. Monomer **4e** exhibits self-association with a K_{assoc} (assumed 1:1 complex) of approximately 1 M⁻¹.

This is consistent with other weak hydrophobic stacking interactions[51,55,57] and is not particularly noteworthy. The association of **4e** with **9** exhibits a similarly small association constant of ca. 2 M⁻¹. The interaction of **1e** with **9** (Figure 6), however, exhibits a much larger association constant of ca. 55 M⁻¹. The hydrophobic nature of this interaction was verified by studying the effect of **1e** on the fluorescence intensity of 8-anilinonaphthalenesulfonate (ANS): a twofold enhance-

ment was observed for complexed vs. uncomplexed ANS. While it is tempting to ascribe these effects to formation of an inclusion complex as pictured in Figure 6B, we feel that the data are as well and probably better interpreted in terms of the interaction portrayed in Figure 6A, a more classical stacking complex involving the E–E conformation of **1e**.

It is known[44-46] that hydrophobic stacking interactions are quite sensitive to the surface area of the components. Simple stacking complexes of **1** involving its E–E conformation are thus expected to be more stable than those involving the F–F or F–E conformations.[56] If an inclusion complex à la Figure 6B were formed, one would expect to observe upfield shifts of protons H3, H4, and H6 in the complex that were comparable to one another. This is not observed. Although H3 and H4 experience substantial upfield shifts, proton H6 does not. This is consistent with the interaction portrayed in Figure 6A but not Figure 6B. The substantial upfield shifts of the aliphatic protons are also consistent with this picture. It is difficult to interpret the fluorescence enhancement values in terms of favoring one model over the other as one has no quantitative enhancement-hydrophobicity model to use.

Conclusions

The term "inclusion complex" has been used in the literature to refer to a variety of complexation phenomena. We feel that our work reported here suggests that one should be relatively discriminating in use of this term since it implies a geometry of the complex that does not necessarily follow from anomalously large stability constants. The complexities of issues surrounding the geometry of inclusion complexes is well documented from current work on this question in the context of cyclodextrins.[59] In addition we draw the following concrete conclusions.

(1) Cyclophanes such as **1** may be prepared in an efficient and high-yield manner. (2) The hexadiyne spacers of **1** keep the aromatic rings well separated. (3) The generous dimensions of **1** permit it a considerable degree of conformational mobility. (4) Stacking complexation of **1e** with aromatics in water is interpretable in terms of the pseudoclassical picture of Figure 6A.[60]

Experimental Section

Methodology. NMR spectra were determined at 100 or 270 MHz. Spectra were in general first order at the higher field. In those cases that were not, chemical shifts were assigned by simulation of the aromatic proton three-spin system (see Figure 3). Concentrations employed were 0.02 M expect for those spectra determined in water and Me₂SO. In these solvents chemical shifts were extrapolated to infinite dilution by varying sample concentration from ca. 0.15 to ca. 0.008 M. Fluorescence enhancement measurements were carried out in pH 7.54 buffer using an Aminco-Bowman spectrophotofluorometer. The fluorescer, 8-anilinonaphthalene-1-sulfonic acid (ANS), was 0.01 M. When made 0.011 M in **1e** a fluorescence enhancement of 1.5-fold was observed. Assuming a K_{assoc} of ca. 50 M^{-1} this corresponds to the ANS's being 70% complexed and a fluorescence enhancement of twofold. Emission at 5300 Å was observed. Elemental analyses were performed by Galbraith.

NMR Complexation Studies. All NMR spectra were obtained on a Bruker FT WH-270 instrument with a memory size of 16 K, using sodium 3-trimethylsilylpropionate-*2,2,3,3-d₄* (TSP) as internal or external reference under ambient conditions (26 °C).

The change in chemical shift of hexyltrimethylammonium bromide[47] (**8**) protons was measured as a function of the concentration of **4e** or **1**, which were weighed into the NMR tubes in increments.

Standard 25-mL stock solutions of **8** in pD 7.5 buffer were made.

The pD 7.5 buffer was prepared by dissolving potassium dihydrogen phosphate (340 mg, 2.5 mmol) and sodium hydroxide (83 mg, 2.05 mmol) in 1 mL of D₂O to exchange for deuterium. The mixture was dried in vacuo at room temperature for 2 days and then dissolved in 45.5 mL of D₂O. The resulting pD 7.53 (measured on a pH meter

standardized with a buffer in H₂O) buffer was stored in a desiccator.[58] The results were found not to change by substituting D₂O for the D₂O buffer, or by using potassium hydroxide in place of sodium hydroxide when preparing the buffer.

In the studies with triethyl(α-naphthylmethyl)ammonium chloride[54] (**9**), both host (**4e** or **1**) or guest (**9**) chemical shifts were measured as a function of the other component.

The component whose chemical shifts were observed was weighed in first, 1.0 mL of pD 7.5 buffer was pipetted into the NMR tube using micropipets (500 μL), and the volume was checked by weighing. The other component was weighed into the NMR tube in increments.

The data were treated by the method of Hanna and Ashbaugh[48] on a Harris computer using a program derived by us and previously used by Chen.[53]

Self-association constants were obtained for **4e** and **1** in the presence of hexyltrimethylammonium bromide salt (**8**) using published methods.[51,53]

Hexyl 2,5-Dihydroxybenzoate (2d). A mixture of 40 g (0.26 mol) of 2,5-dihydroxybenzoic acid, 160 mL of 1-hexanol, and 20 mg of *p*-TSA in 140 mL of toluene was refluxed for 9.5 h with azeotropic removal of water. Workup and distillation afforded 57.5 g (93% yield) of **2d**, bp 160–185° (1 mm), mp 30–35 °C. NMR: δ (CDCl₃, 100 MHz) 0.92 (3 H, t, *J* = 7 Hz), 1.40 (6 H, m), 1.76 (2 H, bt, *J* = 7 Hz), 4.34 (2 H, t, *J* = 7 Hz), 6.84 (1 H, d, *J* = 9 Hz), 7.01 (1 H, d of d, *J* = 2,9 Hz), 7.28 (1 H, d, *J* = 2 Hz), 7.2–7.8 (1 H, broad).

Anal. (C₁₃H₁₈O₄) C, H.

n-Hexyl 2-Hydroxy-5-propargyloxybenzoate (3d). A mixture of 118 g (0.5 mol) of **2d**, 82 mL of 80% propargyl bromide (Aldrich) (0.74 mol), and 75 g of anhydrous potassium carbonate in 1 L of acetone was refluxed with stirring for 7 h. Workup afforded 134 g of a crude oil, a benzene solution of which was percolated through a 6 × 80 cm column of silica gel to afford 79 g (58% yield) of **2d** as an oil, bp 170 °C (1 mm). NMR: δ (CDCl₃, 100 MHz) 0.91 (3 H, t, *J* = 7 Hz), 1.35 (6 H, m), 1.76 (2 H, broad t, *J* = 7 Hz), 2.52 (1 H, t, *J* = 2.5 Hz), 4.32 (2 H, t, *J* = 7 Hz), 4.62 (2 H, d, *J* = 2.5 Hz), 6.88 (1 H, d, *J* = 9 Hz), 7.12 (1 H, d of d. *J* = 2,9 Hz), 10.48 (1 H, s).

Anal. (C₁₆H₂₀O₄) C, H.

Copper Coupling of 3d. Diyne 5d. A mixture of 63 g (0.26 mol) of **3d** and 101 g (0.56 mol) of copper acetate in 1.3 L of dry pyridine was stirred at 40 °C (bath temperature) for 4 h. The reaction mixture was poured into 2.4 L of 4 M hydrochloric acid and worked up to afford 46.2 g of a crude oil which solidified after percolation (CHCl₃) through a short silica gel column. Recrystallization (EtOAc) afforded 27 g (43% yield) of **5d**, mp 101–103 °C. NMR: δ (CDCl₃, 100 MHz) 0.92 (6 H, t, *J* = 7 Hz), 1.38 (12 H, m), 1.80 (4 H, bt), 4.36 (4 H, t, *J* = 7 Hz), 4.74 (4 H, s), 6.94 (2 H, d, *J* = 9 Hz), 7.14 (2 H, d of d, *J* = 2,9 Hz), 7.42 (2 H, d, *J* = 2 Hz).

Anal. (C₃₂H₃₈O₈) C, H.

Alkylation of 5d. 6d. A mixture of 27.1 g (0.49 mol) of **5d**, 23.8 mL (0.214 mol) of 80% propargyl bromide, and 49 g of K₂CO₃ in 406 mL of acetone was refluxed with stirring for 74 h. The reaction mixture was evaporated under vacuum and the residue was partitioned between CHCl₃ and water. The organic layer afforded on evaporation and recrystallization (C₆H₆) 23 g (75% yield) of **6d**, mp 100–102 °C. NMR: δ (CDCl₃, 270 MHz) 0.90 (6 H, t, *J* = 7.0 Hz), 1.34 (8 H, m), 1.44 (4 H, m), 1.75 (4 H, pentet, *J* = 6.8 Hz), 2.51 (2 H, t, *J* = 2.4 Hz), 4.29 (4 H, t, *J* = 6.8 Hz), 4.73 (4 H, d, *J* = 2.6 Hz), 4.74 (4 H, s), 4.73 (4 H, d, *J* = 2.6 Hz), 7.06 (2 H, d of d, *J* = 9.2, 2.6 Hz), 7.10 (2 H, d of d, *J* = 9.2, 0.9 Hz), 7.39 (2 H, d of d, *J* = 2.6, 0.9 Hz).

Anal. (C₃₈H₄₂O₈) C, H.

Oxidative Cyclization of 6d. 1d. To a stirred solution of 15.5 g (0.86 mol) of anhydrous cupric acetate in 600 mL of dry pyridine at 44 °C was added over 3.5 h a solution of 21.2 g (0.034 mol) of **6d** in 500 mL of pyridine. After stirring at 44 °C for an additional 2.5 h the mixture was poured into 2.2 L of 6.5 M hydrochloric acid and extracted with CHCl₃. The CHCl₃ layer was washed with saturated brine, dried over anhydrous Na₂SO₄, and evaporated. The residue, 20 g, was recrystallized from benzene (150 mL) to afford 14.2 g (67% yield) of **1d** as needles, mp 154–155 °C.

Anal. Calcd for C₃₈H₄₀O₈: C, 73.06; H, 6.45; mol wt, 264. Found: C, 73.16; H, 6.51. Molecular weight (isopiestic method,[36] azobenzene standard): 587, 615.

Cyclomer **1d** is insufficiently volatile to obtain an electron impact mass spectrum. As shown below, however, the EI/MS of its hexadecahydro derivative can be obtained. Formation of **1d** is accompanied by some (but unknown amounts of) higher oligomers, as the EI/MS

of the product arising from hydrogenation of the mother liquors from the above recrystallization of **1d** showed peaks at approximately *m/e* 1284–1288 (calcd for cyclodimer, 1281). NMR: δ (CDCl₃, 270 MHz), 0.90 (6 H, t, *J* = 6.6 Hz), 1.33 (8 H, m), 1.44 (4 H, m), 1.72 (4 H, pentet), 4.27 (4 H, t, *J* = 6.6 Hz), 4.77 (4 H, s), 4.84 (4 H, s), 7.03 (2 H, d, *J* = 9.0 Hz), 7.10 (2 H, d of d, *J* = 2.9, 9.0 Hz), 7.39 (2 H, d, *J* = 3.1 Hz).

When the cyclooxidation was carried out as above, except that the cupric acetate was added to **6d** instead of vice versa, **1d** was isolated in 36% yield, mp 150–153 °C. Hydrogenation of **1d** afforded **7d** as an oil, $R_f^{CHCl_3}$ 0.18. NMR: δ (CDCl₃, 0.90 (6 H, t), 1.32–1.75 (32 H, m), 3.98 (4 H, t, *J* = 5.7 Hz), 4.27 (4 H, t, *J* = 6.8 Hz), 6.59 (2 H, d, *J* = 9.2 Hz), 6.66 (2 H, d, *J* = 2.9, 9.2 Hz), 7.17 (2 H, d, *J* = 2.9 Hz). MS: *m/e* 640.3965 (calcd for C₃₈H₅₆O₈, 640.3975).

Anal. (C₃₈H₅₆O₈) C, H.

Saponification of **7d** (KOH in methanol) afforded **7a**, mp 152–154 °C, in 66% yield, identified by comparison with a sample prepared from **7b** and by mixture melting point.

Saponification of 1d. 1a. A solution of 5.12 g (8.2 mmol) of **1d** in 250 mL of THF was added to a solution of 25 g (0.45 mol) of KOH in 250 mL of methanol (both solutions had been nitrogen purged). The mixture was stirred at room temperature for 30 min and was then evaporated in vacuo (water bath at 35 °C) over 30 min. Water was added and the mixture was extracted with ethyl acetate (this afforded 96 mg of "neutrals" that were discarded). The clear aqueous layer was acidified with hydrochloric acid and the resulting suspension was centrifuged. The precipitate was washed with water and dissolved with warming (63 °C) in a mixture of 30 mL of water and 16 mL of 2 M NaOH. Cooling afforded 1.62 g of a powder. Concentration of the filtrate afforded an additional 1.46 g (total yield 3.08 g, 77% yield) of the sodium salt. This could be recrystallized from water but the crystalline material could not be obtained in a completely anhydrous form. NMR: δ (D₂O, TSP reference) 4.89 (8, 4 H, s), 7.04 (2 H, m, H-4, H-6), 7.09 (2 H, m, H-3).

Anal. Calcd for C₂₆H₁₄O₈Na₂: C, 62.41; H, 2.82; Na, 9.19. Found: C, 59.81; H, 3.29; Na. 7.66.

The potassium salt **1e** was prepared similary. NMR: see Figure 3.

Anal. Calcd for C₂₆H₁₄O₈K₂: C, 58.63; H, 2.65; K, 14.68. Found: C, 53.61; H, 3.20; K, 12.80.

The potassium salt was acidified to give the diacid. NMR: δ (Me₂SO-*d₆*) 5.01 (4 H, s), 5.05 (4 H, s), 7.11–7.21 (5.9 H, m).

Anal. Calcd for C₂₆H₁₆O₈: C, 68.41; H, 3.53. Found: C, 66.67; H, 3.94.

Methyl 2-Hydroxy-5-propargyloxybenzoate (3b). A mixture of 17.3 g (0.1 mol) of **2b**, 10.9 mL (17.2 g, 0.14 mol) of propargyl bromide, and 58 g of K₂CO₃ in 250 mL of acetone was stirred under reflux for 5 h. The reaction mixture was evaporated and the residue was partitioned between water and ether. The ether layer was extracted with 1 M NaOH, and the alkaline layer was acidified. Filtration of the resulting precipitate afforded after recrystallization (3:1 MeOH–H₂O) 11 g (52% yield) of **3b**, mp 70.5–71.5 °C. NMR: δ (CDCl₃) 2.50 (1 H, t, *J* = 2 Hz), 3.94 (3 H, s), 4.66 (2 H, d, *J* = 2 Hz), 6.93 (1 H, d, *J* = 10 Hz), 7.18 (1 H, d of d, *J* = 3, 10 Hz), 7.43 (1 H, d, *J* = 3 Hz).

Anal. (C₁₁H₁₀O₄) C, H.

Methyl 2-Hydroxy-5-propargyloxybenzoate Dimer (5b). A solution of 11 g (53 mmol) of **3b** and 26 g (130 mmol) of cupric acetate monohydrate in 350 mL of pyridine was stirred at 44 °C for 2.5 h. The bulk of the pyridine was removed in vacuo and the reaction mixture was worked up to afford 9.5 g (86% yield) of **5b** as an off-white solid, mp 158–164 °C, mp 164–169 °C after recrystallization from EtOAc-C₆H₆. NMR: δ (CDCl₃) 3.94 (6 H, s), 4.70 (4 H, s), 6.87 (2 H, d, *J* = 10 Hz), 7.13 (2 H, d of d, *J* = 3, 10 Hz), 7.33 (2 H, d, *J* = 3 Hz), 10.40 (2 H, s).

Anal. (C₂₂H₁₈O₈) C, H. Calcd mol wt: *m/e* 410.100 16. Found: 410.100 04.

Bis(propargyloxy)-5b. 6b. A mixture of 10 g (24 mmol) of **5b**, 5.5 mL (8.68 g, 73 mmol) of propargyl bromide, and 24 g of K₂CO₃ in 200 mL of acetone was stirred under reflux for 24 h. Workup afforded 10 g (83% yield) of **6b**, mp 148 °C (C₆H₆). NMR: δ (CDCl₃) 2.52 (2 H, t, *J* = 2.4 Hz), 3.90 (6 H, s), 4.74 (4 H, d, *J* = 2.4 Hz), 4.74 (4 H, s), 7.07 (2 H, d of d, *J* = 2.6, 9.1 Hz), 7.12 (2 H, d of d, *J* = 0.9, 9.1 Hz), 7.40 (2 H, d of d, *J* = 0.9, 2.6 Hz).

Anal. (C₂₈H₂₂O₈) C, H.

Cyclization of 6b. 1b. To a stirred solution of 4.5 g (22 mmol) of

cupric acetate monohydrate in 400 mL of pyridine maintained at 44 °C was added over 2 h a solution of 4.5 g (9.2 mmol) of **6b** in 400 mL of pyridine contained in a dropping funnel. After stirring for an additional 1 h the pyridine was removed in vacuo, the residue was taken up in CHCl₃, and the CHCl₃ layer was washed with 1 M hydrochloric acid and with water and evaporated. The solid residue (4 g) was taken up in CHCl₃ and percolated through a short column of silica gel. Evaporation of the eluate afforded 3 g of **1b** as an off-white solid, mp 270 °C (C₆H₆). NMR: δ (CDCl₃, 270 MHz) 3.87 (6 H, s), 4.76 (4 H, s), 4.85 (4 H, s), 7.04 (2 H, d, *J* = 8.9 Hz), 7.11 (2 H, d of d, *J* = 3.0, 8.9 Hz), 7.41 (2 H, d, *J* = 3.0 Hz).

Anal. (C₂₈H₂₀O₈) C, H. Calcd mol wt: *m/e* 484.1158. Found: 484.117 34.

Hydrogenation of 1b. 7b. Hydrogenation of **1b** (10% Pd/C, C₆H₆, atmospheric pressure) afforded after 4 h **7b**, mp 87–89 °C (hexane). NMR: δ (CDCl₃, 270 MHz) 1.57–1.76 (16 H, m), 3.86 (6 H, s), 3.91 (4 H, t, *J* = 5.6 Hz), 3.99 (4 H, t, *J* = 5.6 Hz), 6.60 (2 H, d, *J* = 9.2 Hz), 6.69 (2 H, d, *J* = 3.1 Hz), 7.15 (2 H, d, *J* = 2.9 Hz).

Anal. (C₂₈H₃₆O₈) C, H. *m/e* 500.

Saponification of **7b** afforded the acid **7a**, mp 150–155 °C. NMR: δ (CDCl₃, 270 MHz) 1.56–1.88 (16 H, m), 3.93 (4 H, t, *J* = 5.7 Hz), 4.18 (4 H, t, *J* = 5.5 Hz), 6.73 (2 H, d, *J* = 9.0 Hz), 6.89 (2 H, d of d, *J* = 3.3, 9.0 Hz), 7.41 (2 H, d, *J* = 3.1 Hz).

Anal. (C₂₆H₃₂O₈) C, H. Calcd mol wt: *m/e* 472.209 71. Found: 472.2090.

The following compounds were prepared for reference purposes (all were obtained in analytically pure form): methyl 2,5-dipropargyloxybenzoate (**4b**), mp 60–63 °C; 2,5-dipropargyloxybenzoic acid (**4a**), mp 139 °C; methyl 2,5-dipropyloxybenzoate, an oil; 2,5-dipropyloxybenzoic acid, an oil.

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Orbital Interactions. 6. The Birch Reduction as a Tool for Exploring Orbital Interactions through Bonds. Through-Three-Bond Interactions[1]

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Abstract: Product and relative rate data have been obtained for the Birch reduction (Li/liquid NH_3/*tert*-butyl alcohol) of a number of 1,4-methanobiphenylenes. The rates of reduction of the double bond in *exo*- and *endo*-1,4,4a,8b-tetrahydro-1,4-methanobiphenylene (*exo*- and *endo*-**16**) are respectively 141 and 78 times greater than the rate of reduction of norbornene. However, the reduction of the aromatic rings in *exo*- and *endo*-**16** showed little enhancement compared with the rates of reduction of *exo*- and *endo*-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylenes (*exo*- and *endo*-**19**), respectively. The double bonds of *exo*- and *endo*-1,4,4a,5,8,8b-hexahydro-1,4-methanobiphenylenes (*exo*- and *endo*-**18**) are little affected compared with norbornene. Interactions between the vacant MOs in these and other molecules were explored with the aid of extended Hückel calculations. The results of these calculations demonstrated the presence of sizable through-bond interactions in *exo*-**16**. However, net through-space interactions in the vacant MO manifold are predicted to prevail in *endo*-**16**. A causal connection between the presence of orbital interactions and the rates of Birch reduction of exo and endo compounds **16**, **18**, and **19** was established within the framework of the mechanism of the reaction. A linear relationship between ln (rate of reduction) of a substrate and its LUMO energy was observed.

Introduction

Hoffmann and his co-workers have delineated two distinct mechanisms which give rise to long-range interactions between remote orbitals: orbital interactions through space (OITS) and orbital interactions through bonds (OITB).[2-4] The more familiar OITS result from the direct spatial overlap of the interacting orbitals.[3] Consequently the magnitude of this type of interaction is strongly attenuated with distance, being negligible for interorbital separations >2.7 Å.[2a] However, OITB are a longer range phenomenon since they are relayed by the connecting σ framework with which the interacting orbitals overlap.[3,4] For example, extended Hückel (EH) calculations on some model dehydropolyenyl systems, C_nH_n, such as **1** ($n = 4$), show a regular exponential diminution of the
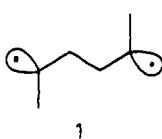
coupling of the radical lobes with distance. Nevertheless a

sizable interaction of 0.2 eV was calculated for a through-seven-bond interaction in C_8H_8 in which the interorbital separation is about 8.7 Å.

OITS and OITB may lead to different level orderings of the resulting MOs. Thus through-space interactions between two orbitals generally lead to the level ordering "S" below "A".[3,5] The resulting level ordering from OITB often (but not always) depends on the parity of the number m of the intervening σ bonds, generally being "S" below "A" for even values of m and "A" below "S" for odd values of m.[2a] Therefore, for even m, OITS and OITB reinforce one another to give a sizable net interaction. For odd m, however, the two modes of interaction oppose each other, the net outcome depending on the molecular geometry.[6]

Physical consequences of OITB have been extensively studied using spectroscopic techniques.[8-10] For instance, ESR studies indicate the presence of two[11] through-two-bond and one through-three-bond interactions between the radical lobe and β hydrogen in **2**,[12] and triple through-three-bond interactions in **3**.[13] Photoelectron spectroscopy (PES) has revealed through-three-bond interactions between the π orbitals in the dienes **4a**[14] and **5**,[15] although the net result in the latter com-