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Supplementary Material Available: Tables of final fractional atomic coordinates, thermal parameters for all three structural analyses, and structure factor amplitudes are available for the structure of Va (19 pages). Ordering information is given on any current masthead page.

An Experimental Measure of Cavity Size in Macrocyclic Cyclophane-Based Host Molecules

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Abstract: The synthesis of rigid (**3a–f**) and flexible (**4a–f**) cyclophanes is described. They exhibit DNMR effects in their proton NMR spectra associated with conformational changes as in eq 1. The rates of these processes were studied as a function of the size of the alkyl group that rotates through the cyclophane's cavity. Isobutyl ester **3e** appears to be at the transition between small and large (as defined by this experimental probe) groups. The cavity of **3** closely approximates the size of an isobutyloxycarbonyl group.

There is considerable current interest in molecules possessing cavities sufficiently large to accommodate guests. Historically preeminent are the cyclodextrins.[1] Catalytic activity arising from substrate molecules' insertion into the cavity and interaction with the peripheral hydroxyl groups of the cyclodextrin has been a fruitful if simple model of enzyme catalysis.[2-4] Enlargement of the cyclodextrin cavity by attachment of simple hydrophobic residues[5] and cavity-spanning bridges[6,7] leads to substantially enhanced hydrophobic binding of guests.

Several toroidal molecules possessing faces of aromatic rings have been prepared as synthetic analogues of cyclodextrins.[8-10] While admitting to considerable structural diversity, these cyclodextrin analogues all possess hydrocarbon-like ("hydrophobic") cavities, are water soluble, and exhibit binding of aromatic substrates with varying degrees of selectivity. Construction of macrocyclic molecules whose cavities are lined with particular functional groups has been pursued by Cram[11] and Lehn.[12]

We have synthesized and examined for hydrophobic binding ability a series of [8.8]arenophanes.[13a-d] This work has raised in our minds certain questions dealing with the concept of cavity size in macrocyclic molecules, especially with regard to the possibility of constructing artificial enzymes wherein substrate binding and selectivity is determined by this structural feature. With hydrophobic complexation as a probe we have found two structural features to be of importance in defining cavity size. A rigid spacer group is required, e.g., **3a** as opposed to **4a**.[13b,c] In the absence of this rigidity the cyclophane exists in a collapsed conformation and complexation is not observed. The lateral dimensions of the cavity are important. While [8.8](1,4)benzenophanes (e.g., **3**) cannot accommodate aromatic guests within their cavity,[13a] the analogous [8.8](2,6)naphthalenophanes can.[13d]

We report here the synthesis and conformational study of several [8.8](1,4)benzenophanes possessing rigid (**3a–g**) and flexible (**4a–g**) bridges (see Scheme I). These molecules were chosen for three reasons: they represent a synthetically accessible series of substituents of smoothly increasing size; the conformational process involving rotation of the alkoxycarbonyl group through the cavity (or more properly the dependence of this on group size) is a measure of cavity size; comparison of the rigid (**3**) with flexible (**4**) series gives a measure of the dependence of cavity size on bridge type. This latter possibility was especially interesting, as a related study of (1,4)naphthalenophanes (e.g., **6**) suggested that those cyclophanes having flexible bridges have a *larger* cavity than those with rigid bridges.[13c]

Results

The conformational model employed is summarized in eq 1. Cyclophanes of the type **3** or **4** exist in two limiting diastereomeric forms, achiral syn and chiral anti. Rotation about either phenyl's 1,4-axis interconverts the syn and anti. Two consecutive rotations of opposite rings interconverts *R* and *S anti* and is an identity operation on the syn isomer. This process also interconverts the diastereotopic protons of the ether bridges' methylene groups, H_A and H_B or $H_{A'}$ and $H_{B'}$ respectively. By virtue of the substitution pattern of **3** and **4** these rotations require passage of one alkoxycarbonyl group ("e" in eq 1) through the cavity.

Depending on the barriers involved, one may study these rotations by either classical methods for interconverting diastereomers or by dynamic NMR (DNMR[14]).

(1) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer-Verlag: New York, 1977.
(2) Heinrich, N.; Cramer, F. *J. Am. Chem. Soc.* **1967**, *87*, 1121.
(3) Van Etten, R. L.; Sebastian, J. F.; Groves, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(4) Breslow, R.; Campbell, P. *Biorg. Chem.* **1971**, *1*, 140.
(5) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.
(6) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 711.
(7) Breslow, R.; Doherty, J. B.; Guillot, G.; Hersh, C. L. *J. Am. Chem. Soc.* **1978**, *100*, 3227.
(8) Tabushi, I.; Kimura, Y.; Yamamura, K. *J. Am. Chem. Soc.* **1981**, *103*, 6486.
(9) (a) Odashima, K.; Soga, T.; Koga, K. *Tetrahedron Lett.* **1981**, *22*, 5311. (b) Soga, T.; Odashima, K.; Koga, K. *Ibid.* **1980**, *21*, 4351. (c) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *Ibid.* **1980**, *21*, 4347. (d) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504.
(10) Vogtle, F.; Muller, W. M. *Angew. Chem.* **1982**, *94*, 138.
(11) Lein, G. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 301.
(12) Behr, J. P.; Lehn, J. M.; Moras, D.; Thierry, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 701.
(13) (a) Jarvi, E. T.; Whitlock, H. W. *J. Am. Chem. Soc.* **1980**, *102*, 657. (b) Whitlock, B. J.; Jarvi, E. T.; Whitlock, H. W. *J. Org. Chem.* **1981**, *46*, 1832. (c) Adams, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 1602. (d) Jarvi, E. T.; Whitlock, H. W. *Ibid.* **1982**, *104*, 7196.

(14) Abbreviations used here: NMR, proton NMR; DNMR, proton dynamic NMR; T_c, coalescence temperature for DNMR interconversion of two spins; $\Delta\nu$, inherent chemical shift difference (in Hz) of two nuclei in a ^1H NMR spectrum.

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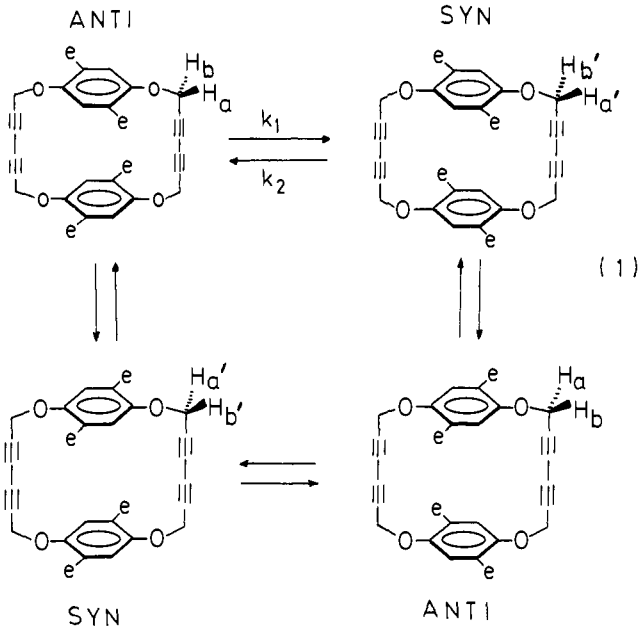
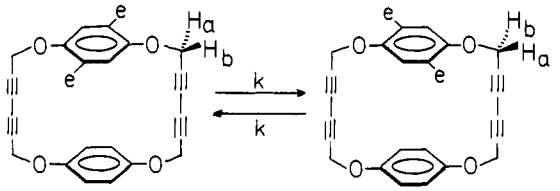


(1)

Conformational independence of the two rings requires that passage of a group through the cavity be governed by the group's size and not by the size of substituents on the distal ring. Unsymmetrical cyclophane **5c** was synthesized to check this assumption. The conformational situation here (eq 2) is similar to



(2)

the above except that here there is only one chiral isomer. Rotation about the substituted ring's axis effects interconversion of all H_A–H_B pairs whereas rotation about the bottom ring's axis results only in interconversion of its four protons. We have shown[13a,c,15] that cyclophanes of this type present a negligible barrier to passage of an unsubstituted benzene face through the cavity. Thus only rotation of the top ring should be measurable.

Synthesis. Reaction of di-propargyl ethers of dialkyl 2,5-dihydroxyterephthalates **1a–f** (ca. 0.05 M) with cupric acetate in pyridine at 40–45 °C reproducibly affords 10–30% yields of the corresponding dimer cyclophanes **3a–f**. These will be referred to as "rigid". Free acid **3a** was prepared by saponification (lithium hydroxide[16]) of propyl ester **3c**. Mass spectrometry confirmed the proposed dimeric structures. Proton NMR spectra of **3a–f** (see below) were all quite similar and consistent with the structures shown. Hydrogenation of the rigid cyclophanes afforded **4a–f**. These will be referred to as "flexible". In several cases appreciable yields (10–20%) of cyclotrimers, e.g., **7c**, could be isolated from the cyclization reaction. These were characterized by mass spectrometry and NMR spectroscopy. Unsymmetrical isomer **5c** was prepared from a 10:1 mixture of **1i** and **1c**.

Static Conformation. Rigid cyclophanes **3a–g** exhibit closely similar proton NMR spectra, the only important differences being those associated with the alkyl ester part of the spectra. Those with the smaller substituents showed appreciable broadening (or coalescence) of multiplets arising from DNMR effects at room temperature but in the low temperature limit reverted to the system norm. The bridge methylene groups of **3a–g** appear as two overlapping AB quartets (see Figure 1). The ratio 1.5:1 of the high- and low-field components and chemical shift differences within the quartets were remarkably constant over the series (Table I). While assignment as to which is syn and which is anti could not be made,[17] the similarity of the spectra is consistent with closely related conformations for **3a–g**. Cyclization shifts (Table II), a measure of the inter-ring interaction, are all quite small.[13a–d] One may safely conclude that the rings are mutually parallel and well separated.[15]

Table I. Chemical Shift Differences and Geminal Coupling Constants of Bridge Methylene Groups and Equilibrium Ratios of Anti and Syn Isomers of Rigid Cyclophanes[a]

compd	ester	$\Delta\nu$, Hz	J_{AB}	anti:syn ratio
3b	ethyl	51.7	16.9	1.70
		62.8	16.6	
3c	propyl	54.8	16.9	1.67
		63	16.9	
5c	propyl	57	17.6	
3d	decyl	44.7	16.9	1.55
		60.2	16.9	
3e-A	isobutyl	67.3	17.2	1.69
3e-B		64.5	16.9	
3f-A	neopentyl	66.6	16.6	1.6[b]
3f-B		57.2	17.1	

[a] Data are at 270 MHz ($CDCl_3$). That isomer with the smaller $\Delta\nu$ is arbitrarily assigned as anti. [b] Estimated from crude reaction mixture:isomers do not interconvert.

Table II. Cyclization Shifts of Aromatic Protons of Cyclophanes 3, 4, and 5c[a]

compd	ester	spacer	Δ_{cyc} in $CDCl_3$ (py-d_5)
3a	methyl	rigid	−0.085 (−0.044)
4a	methyl	flexible	−0.357 (−0.286)
3b	ethyl	rigid	−0.092 (−0.035)
4b	ethyl	flexible	−0.357
3c	*n*-propyl	rigid	−0.087 (−0.038)[b]
4c	*n*-propyl	flexible	−0.339 (−0.259)
4c	*n*-propyl	flexible	−0.339 (−0.259)
3d	*n*-decyl	rigid	−0.081[b] (+0.009,[b,c] −0.013[d])
4d	*n*-decyl	flexible	−0.354
3e	isobutyl[e]	rigid	−0.095,[c] −0.084[d]
4e-A	isobutyl	flexible	−0.087[d]
3f	neopentyl[e]	rigid	−0.10,[c] −0.117[d]
4f-A	neopentyl	flexible	−0.074[c]
5c	*n*-propyl	rigid	−0.087, −0.036[f]

[a] Negative Δ_{cyc} corresponds to an upfield shift on cyclization; see ref 13a. [b] Both isomers present. [c] Δ_{cyc} of major isomer. [d] Of minor isomer. [e] Of separate isomers. [f] Of unsubstituted ring.

As evidenced by their proton NMR spectra the flexible series of cyclophanes, **4a–g** differ markedly in conformation from their rigid counterparts. Typical of the spectra of the flexible series is that of ethyl ester **4b** shown in Figure 2. Large cyclization shifts of the aromatic protons are seen (Table II), indicating a collapsed conformation,[13,15] although the isobutyl (**4e**) and neopentyl (**4f**) esters are abnormal in this respect. Whereas the rigid cyclophanes exist as an equilibrium mixture of syn and anti isomers with $K_{eq} \sim 1.7$, spectra of the flexible cyclophanes always showed but one AB quartet for the ether methylene groups. Considering the large chemical shifts involved, this strongly suggests that only one (presumably anti) isomer is present in the flexible cyclophanes. Marked anisochronicity within all three bridge methylene pairs[18] was observed, as were large variations in three-bond coupling constants of these protons (see Figure 2). From these observations and the similarity of the spectra within the flexible series, one may reasonably conclude that **4a–g** share a common collapsed conformation characterized by considerable cross-ring interaction of

(15) Adams, S. P.; Whitlock, H. W. *J. Org. Chem.* **1981**, *46*, 3474.
(16) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.
(17) Application of chiral shift reagents to aid in this assignment was unsuccessful.
(18) A single-crystal X-ray structure of a closely related tricyclic cyclophane shows the four atom fragment Ar-O-CH_2-CH_2 to be coplanar with a consequently well-defined endo–exo sense. Brown, A.; Whitlock, H. W. *Tetrahedron Lett.*, in press.

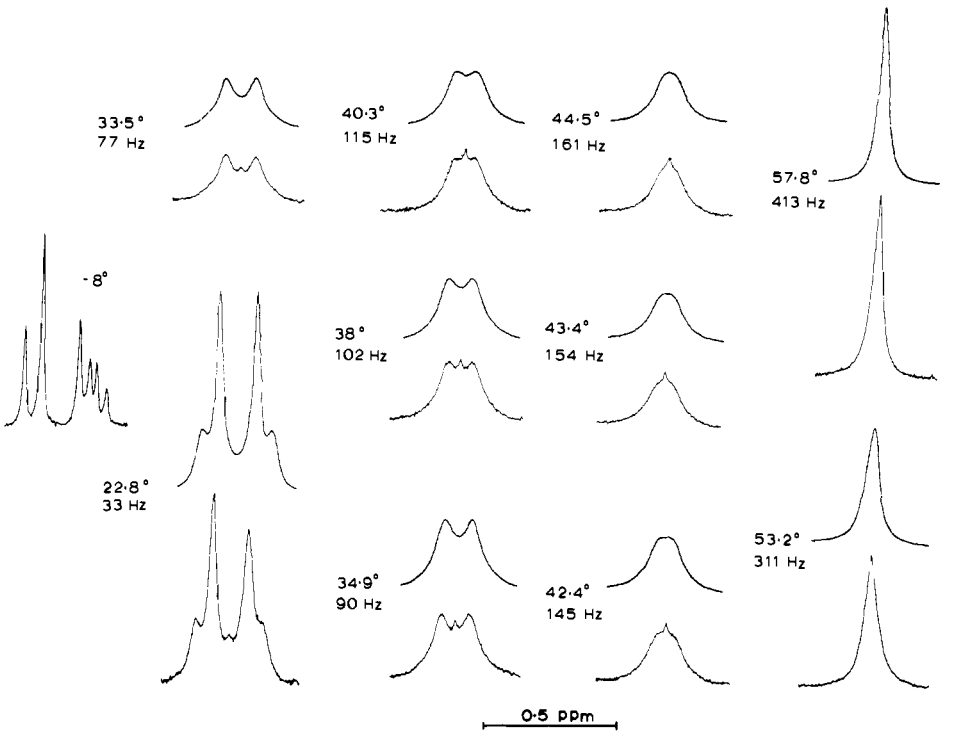


Figure 1. Proton NMR spectra, experimental and simulated pairs, of the bridge methylene AB quartet (centered at δ 5.44) of **3b** at different temperatures (270 MHz, in C_6D_5Br). Number captions are °C and exchange frequency (k_{exch}^{-1}) at that temperature. The low-temperature limiting spectrum is labeled −8 °C. The top spectrum of each pair is that calculated for the indicated k_{exch}, using the resting parameters J_{AB} = 16.9 Hz and $\Delta\nu_{AB}$ = 52 Hz. A linear regression gives ln ($k_{exch}K^{-1}$) = 20.23 − 6632 K^{-1}, r = −0.9978 (see Table III).

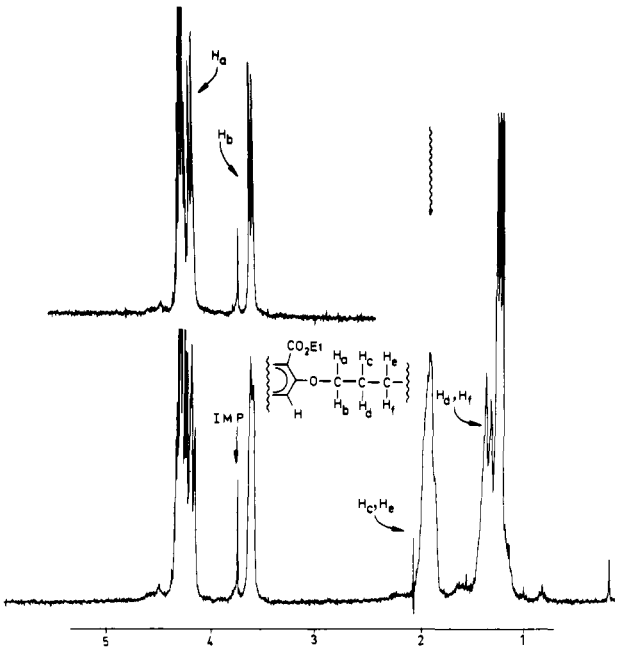


Figure 2. Proton NMR spectrum of **4b** in C_6D_5Br (270 MHz). The top spectrum shows the AB quartet for H_a and H_b, resulting from irradiation of the H_c–H_e multiplet at δ 2.0. Irradiation at the H_d–H_f multiplet (δ 1.5) affords the following couplings for the H_A–H_B pairs: J_{AB} = 9 Hz, J_{AC} = 12.5 Hz, J_{BC} = 3.7 Hz, $J_{AD} - J_{BD}$ = 0 Hz; all values ±0.3 Hz. The bottom (undecoupled) spectrum shows the ABX_3 ethoxy group pattern. Heating leads to reversible coalescence of H_a and H_b and of the H_c–H_e and H_d–H_f multiplets (see Discussion).

the phenyl's alkoxycarbonyl appendages. It is noteworthy, considering molecular models and the dynamic effects discussed below, that the flexible cyclophanes clearly do *not* exist in an "open" conformation wherein the bridges approximate all-anti hexane backbones.

Dynamic Conformational Effects. In summary, rigid cyclophanes bearing the smaller ester alkyl groups exhibit dynamic effects of their NMR spectra as expected by eq 1. As the alkyl group gets larger, the DNMR behavior disappears but the cyclophanes can then be separated into syn and anti isomers whose interconversion was studied by classical kinetic techniques. We discuss the ethyl esters in detail.

The ^1H NMR spectrum of rigid ethyl ester **3b** is temperature sensitive in a manner that is typical of this series of cyclophanes. Its behavior is summarized in Figure 1. Under ambient conditions (probe temperature ~22 °C), one observes the expected sharp ethyl ester pattern and a single aromatic CH peak. The bridge CH_2 protons appear as a broadened AB pattern (Figure 1, 22.8 °C). Cooling the sample results in the expected sharpening process until the low-temperature limiting spectrum is reached at ca. −6 °C. This shows two isomers to be present in the ratio of 60:40. Raising the sample temperature above ambient results in progressive broadening until coalescence occurs at 42 °C. Above this temperature the now singlet undergoes the expected sharpening process.

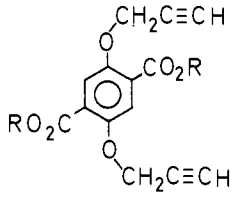
The experimental spectra were simulated via the closed form expression first derived by Heidberg et al.[19] which affords the intensity of an AB quartet (absorption mode) as a function of observe frequency, coupling constant J_{AB}, chemical shift difference $\Delta\nu_{AB}$, and line width in absence of exchange, and rate constant k_{exch} for interconversion of the A and B spins.[20] Simulation of the spectra in Figure 1 in this manner, treating them as a single AB pair rather than the more complicated interconverting AB (anti) and A′B′ (syn) mixture as in eq 1, assumes superposition of the two AB quartets involved. In this case one merely recasts the kinetic interpretation of k_{exch}.[20,21a,22b] The temperature de-

(19) Heidberg, J.; Weil, J. A.; Janusonis, G. A.; Anderson, J. K. *J. Chem. Phys.* **1964**, *41*, 1033.

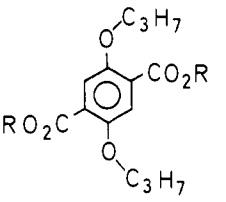
(20) Rotation about the distal ring's axis effects syn:anti conversion but not interconversion of the spins of the proximal CH_2 group. This k_{exch} as measured by the DNMR method[21,22] equals $4k_1k_2(k_1 + k_2)^{-1}$ where k_1 and k_2 are first-order rate constants defined as in eq 1. Measured by direct syn:anti interconversion (e.g., **3e**), however, $k'_{exch} = 2(k_1 + k_2)$. By symmetry this analysis is independent of a particular proton assignment.

(21) (a) Gutowski, H. S.; Saika, A. *J. Chem. Phys.* **1953**, *21*, 1688. (b) Gutowski, H. S.; Holm, C. H. *Ibid.* **1956**, *25*, 1228. (c) Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 3185.

Scheme I



1



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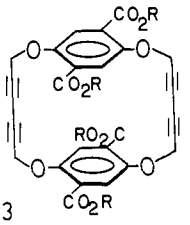
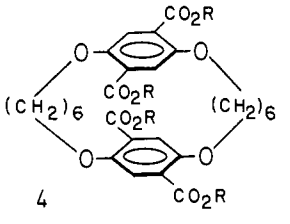
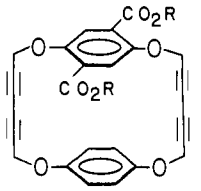


3



4

1-5 a: R=CH_3
b: R=C_2H_5
c: R=n-C_3H_7
d: R=n-$C_{10}H_{21}$
e: R=iso-butyl
f: R=neo-pentyl
g: R=H
h: acid chloride
i: CO_2R=H



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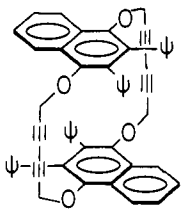
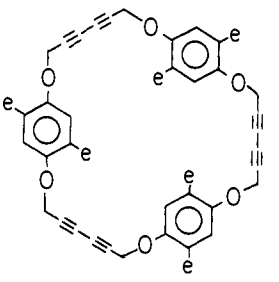
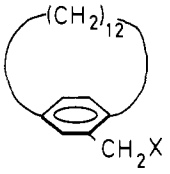


6 Ψ = CH_2O_2CR



7 e = CO_2R



8 X = OH, Br, CO_2Et

pendence and the spectrum in Figure 1 are typical of the rigid cyclophane series. In all cases except **3a** and **3g**, low-temperature limit spectra of the rigid series shows the bridging methylene groups as two overlapping AB quartets in the ratio of ca. 60:40, the low-field doublets being directly superimposed and the high-field doublets being separated by 5–10 Hz (Table I). Rapid reduction on warming to a single AB system (Figure 1) thus occurs well below the coalescence temperature T_c.[14] The simulation parameters used for **3b**, J_{AB} = 16.9 Hz and $\Delta\nu_{AB}$ = 52 Hz, were those associated with the major component at low temperature.

An interesting characteristic of these cyclophanes is the frequently observed marked temperature dependence of chemical shift differences of diastereotopic methylene protons. This is particularly pronounced in the flexible series **4** (see below) and can cause problems in simulations since (a) being unable to freeze out the equilibrium involved,[23] one cannot compute the weighted average of $\Delta\nu_{AB}$ at a given temperature, (b) one thus cannot, in general, separate DNMR effects on observed peak separations from the changing inherent $\Delta\nu_{AB}$, and (c) $\Delta\nu_{AB}$ generally decreases with temperature and occasionally approaches zero at what should be T_c. These difficulties can be surmounted in many cases. In the rigid ethyl case (**3b**) the temperature dependence of $\Delta\nu_{AB}$ is small enough over the temperature range employed to be ignored. An approximately linear dependence of $\Delta\nu_{AB}$ on temperature permits an empirical correction in many cases. Most importantly however, the calculated shape of a coalescing AB quartet is remarkably sensitive to $\Delta\nu_{AB}$ and J_{AB} used. This has been cleverly exploited to determine both $\Delta\nu_{AB}$ and AB interconversion rates from peak width at T_c and J_{AB}. From our perspective, this sensitivity affords a most effective check on the parameters used. Incorrect choices for $\Delta\nu_{AB}$, and to a lesser extent line width, will not permit simulation of a spectrum for any k_{exch}. Each calculated peak of Figure 1 was thus iterated to best fit[25] on $\Delta\nu_{AB}$. The value of $\Delta\nu_{AB}$ = 52 ± 2 Hz obtained by simulation from 23 to 58 °C is in good agreement with that calculated from line width at T_c[24] and that of the major component at −8 °C. An Arrhenius plot of the data for **3b** over the temperature range 22.8–57.8 °C afforded activation parameters: $\Delta H^{\ddagger}$ = 13.2 kcal and $\Delta S^{\ddagger}$ = −7 eu with r = 0.998 (see Table III). Noting the usual caveats pertaining to DNMR-derived activation parameters, we point out the small absolute value of activation of entropy of **3b**.

Variable-temperature spectra of methyl ester **3a** (over the temperature range −6–51 °C, T_c = 3°), propyl ester **3c** (over the range of 24–86 °C, T_c = 86 °C), and acid **3g** (in pyridine-d_5 over the range −49.5 to ambient, T_c = −30 °C) were analyzed similarly to those of **3b**. The results are presented in Table III.

Isobutyl ester **3e**, while initially isolated as the usual mixture of conformers, showed no DNMR effects in the accessible temperature range. Fractional recrystallization of this material however permitted isolation of the two isomers substantially free of one another. The separate isomers **3e–A** (the less stable and less soluble) and **3e–B** are conformationally unstable, reverting to a common equilibrium mixture (63:37) with a half-life of approximately 5 h at room temperature. Kinetics of their interconversion was followed by classical NMR techniques, integrating the overlapping but not superimposed high-field components of the AB quartets assigned to the bridge methylene groups.[26] Activation parameters for k_{exch}[20] derived from equilibration at 24, 51, and 71 °C, and starting from both isomers, are in Table III.

Neopentyl ester **3f** could likewise be separated into two isomeric forms. Mass spectrometry and proton NMR spectroscopy showed them to be the expected pair of conformational isomers. Heating the pure isomers for 30 h at 150 °C in bromobenzene-d_5 led to no interconversion. One may thus calculate a lower limit for the barrier to their interconversion of 35 kcal mol^{-1} at 150 °C.

Decyl ester **3d** exhibited DNMR effects but reliable values for k_{exch} could not be obtained. Comparison of its spectra with those of propyl ester **3c** at similar temperatures showed clearly that its interconversion processes were substantially slower than those of the propyl ester. The unsymmetrical dipropyl ester **5c** was examined in the standard manner. It closely resembled tetrapropyl ester **3c** with the following qualifications. Only one isomer was present, as required by its substitution pattern. The four protons of the unsubstituted phenyl were equivalent down to 10 °C. This phenyl enjoys unrestricted rotation. As suggested by the similarity of the spectra of the tetraester syn and anti isomers, there was only a small chemical shift difference ($\Delta\nu \sim$ 4Hz) of the protons of the methylene bridge distal to the substituted ring. The methylene groups proximal to the substituted ring showed the

(22) (a) Martin, M. L.; Martin, G. J.; Delpuech, J.-J. "Practical NMR Spectroscopy"; Heyden: 1980; Chapter 8. The expression for a ± on p 310 is quoted incorrectly from ref 19. (b) *Ibid.*; Chapter 8, section 1.3.0.

(23) A conformational process approximating a chair-chair flip is the most likely cause of this temperature dependence.[18] In related [8.8](1,4)-naphthalenophanes we have observed the DNMR aspects of this[13c] but only at quite low temperatures (ca. −90 °C).

(24) Kost, D.; Zeichner, A. *Tetrahedron Lett.* **1974**, 4533.

(25) Criteria for best fit used were peak separation, line width, maximum:minimum ratio, and visual comparison. Above T_c only line width can be used.

(26) An iterative overlapping Lorentzian deconvolution program was used for accurate area measurements of mixtures of 3e-A and 3e-B.

Table III. Coalescence Temperatures and Activation Parameters for Conformational Rotations as per Eq 1[a]

compd	ester	T_c, °C	$\Delta G^{\ddagger}_{Tc}$, kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	notes
			Rigid Series				
3g	(acid)	−30	11.8				*b, d*
3a	methyl	3	13.4	13.4	12.1	−4.3	*b, e*
3b	ethyl	42.4	15.3	15.3	13.2	−7	*b, e*
3c	*n*-propyl	85.9	17.4	17.2	15.4	−6	*b, e*
5c	*n*-propyl	79.6	17.1	16.8	15.8	−3.4	*b, e*
3d	*n*-decyl	>100	>18				*b, e*
3e	isobutyl			23.3	14.2	−30.4	*f*
3f	neopentyl			>35			*f*
			Flexible Series				
4g	(acid)	8.2	13				*b, d*
4a	methyl	86	17.2				*b, f*
4b	ethyl	152	19.7				*c, f*
4c	propyl	>169	23.1				*c, d, g*

[a] T_c refers to the coalescence temperature for interconversion of the diastereotopic OCH_2 proton pair. Values not listed were not available in a reliable form. Activation parameters are for the kinetic scheme of eq 1 (see ref 20). [b] 270 MHz. [c] 200 MHz with decoupling from vicinal protons. [d] In pyridine-d_5. [e] In $CHCl_3$-d. [f] In bromobenzene-d_5. [g] The value listed under $\Delta G^{\ddagger}_{Tc}$ is for 169 °C. T_c is appreciably higher than this.

expected marked nonequivalence (Table I) and DNMR behavior. Activation parameters derived from the usual DNMR analysis are in Table III. The similarity in behavior of **3c** and **5c** is marked.

Flexible cyclophanes **4a–g**, prepared by hydrogenation of their acetylenic congeners, showed related DNMR behavior. The complexity of their NMR spectra, correctly viewed as an interconverting six-spin system, imposed considerable uncertainty on determination of activation parameters of their conformational interconversions. For comparison purposes we discuss ethyl ester **4b** in detail.

In the NMR of **4b**, the ethereal CH_2 group (H_A and H_B) (see Figure 2), appears as two multiplets at δ 4.14 and 3.88 ($CDCl_3$). Irradiation of the H_C–H_E multiplet at δ 2.02 reduces H_A and H_B to an AB quartet centered at δ 4.01, J_{AB} = 8.8 Hz,[27] $\Delta\nu_{AB}$ = 71.6 Hz. The H_A–H_B chemical shift difference is markedly temperature dependent. Over the temperature range 23–131 °C, it obeys the linear relation (200 MHz, C_6D_5Br) $\Delta\nu_{AB}$ (Hz) = 172 − 0.48T (T = °C) with r = −0.998. Above 131 °C a strong negative deviation associated with DNMR effects is observed. Coalescence is observed at 152 °C (C_6D_5Br, 200 MHz, decoupling from vicinal protons). From the extrapolated chemical shift differences at this temperature one may calculate $\Delta G^{\ddagger}$ = 20 kcal at 152 °C. Instrumental limitations prevented reliable estimation of enthalpy and entropy of activation. Similar behavior was observed for the methylene group of the ethyl ester part structure. At 23 °C it appeared as the AB part of an ABX_3 system, $\Delta\nu_{AB}$ = 6.9 ± 0.1 Hz, J_{AB} = 11.1 ± 0.2 Hz centered at δ 4.05 (C_6D_6Br, 270 MHz). Coalescence to an A_2X_3 pattern occurred at approximately 114 °C.

Methyl ester **4a** and propyl ester **4c** behaved in a similar manner, the former affording $\Delta G^{\ddagger}$ = 17.2 kcal at 86 °C (T_c). With decoupling line-shape analysis of propyl ester **4c** indicates $\Delta G^{\ddagger}$ = 23 kcal mol^{-1} at 169 °C although the coalescence temperature was somewhat above this and beyond the instrument's temperature range. Attempted application of the saturation transfer technique of Forsen and Hoffman[28] to these somewhat refractory cases were promising but gave no acceptable lifetimes. Neither isobutyl (**4e**) nor neopentyl (**4f**) esters gave any indication of syn–anti interconversion on prolonged heating. Minimum barriers of 29 kcal mol^{-1} (for **4e**, no (~5%) isomerization after 19 h at 64 °C) and 34 kcal mol^{-1} (for **4f**, no isomerization after 75 min at 151 °C) may be calculated.

Discussion

It is generally recognized[21c,22] that accurate determination of activation parameters via DNMR techniques is fraught with uncertainty, principally due to difficulties associated with accurate temperature measurement. We view the results reported in Table III to be accurate if summarized in the following manner: (1) In the rigid series the barrier to rotation of a group through the cavity increases smoothly with size of the group in the order COO^- < COOMe < COOEt < COOPr < COOdecyl < COOisobutyl < COOneopentyl. This is seen in $\Delta G^{\ddagger}$ values at coalescence and at 25 °C, coalescence temperature, and enthalpies of activation where available. (2) A similar monotonic increase in barrier with size of the ester alkyl group holds in the flexible series. (3) In the rigid series entropies of activation are all small and negative with one striking exception. Isobutyl ester **3e** is qualitatively much more stable toward syn–anti conversion than its smaller congeners. This is due primarily to its large negative entropy of activation, ca., −30 eu.

There is little data in the literature that can be compared with our results. Conformational flips of [2.2]- and [3.3]cyclophanes have elicited some interest[29] but these are quite congested systems. A sharp increase in the rotational barrier of methoxy vs. methyl in a [16]paracyclophane has been reported by Oki.[30] Paracyclophanes with smaller bridges, [10] to [12], exhibit restricted rotation of an unsubstituted benzene face. Second-order substituent effects on this have been studied in **8**.[31] Resolution of a disubstituted [12]paracyclophane was reported some years ago by Lüttringhaus.[32] Extensive work probing the cavity size of cyclodextrins by varying the size of the binding substrate has been carried out.[1-5] The systems here are somewhat more abstract however since we are measuring "simple" repulsive steric forces uninfluenced by, for example, hydrophobic complexation effects. That in fact was the purpose of this work. We interpret our data in the following manner:

(1) The simplest view of molecules such as **3** is as a molecular box, a box being able to accommodate all comers equally up to a given size, at which point they are sharply excluded. This simplistic model is inadequate. There is a constant barrier increment of about 2 kcal mol^{-1} as we go from acid to methyl to ethyl to propyl ester. This is primarily an enthalpic effect. Similar results in a more restricted series based on **6** were noted by us previously.[13c] In the absence of force field calculations, the origin of this effect remains obscure, but there are several aspects that are empirically quite fascinating. The hole in **3** is really quite substantial, and yet it can discriminate quite nicely between a series of small groups. Cyclophanes such as **3** were designed with rigidity of the bridges in mind. And yet our results imply a rather soft

(27) Bothner-By, A. K. *Adv. Magn. Reson.* **1965**, *1*, 195–316.
(28) (a) Forsen, S.; Hoffman, R. A. *J. Chem. Phys.* **1963**, *39*, 2892. (b) Forsen, S.; Hoffman, R. A. *Ibid.* **1964**, *40*, 1189. (c) Hoffman, R. A.; Forsen, S. *Ibid.* **1966**, *45*, 2049.
(29) Review: Forster, H.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429.
(30) Sakamoto, K.; Oki, M. *Tetrahedron Lett.* **1973**, *3989*.
(31) Nakazaki, M.; Yamamoto, K.; Okamoto, S. *Tetrahedron Lett.* **1969**, 4597.
(32) Luttringhaus, A.; Gralheer, H. *Liebigs Ann. Chem.* **1940**, *550*, 67.

deformable interior of the molecules.

It is clear that alkyl group size, as measured by our experimental probe, does not parallel *A* values.[33] One does not expect this to be the case, as engulfment of an alkyl group in the transition state for rotation (eq 1) is a quite different (and more sensitive) measure of size than 1,3 interactions in a substituted cyclohexane.[33b] One could use the $\Delta G^{\ddagger}$ values of Table III to define a new alkyl size parameter. The result would be of somewhat limited use however as it would be quite sensitive to the nature of the cyclophane involved. Nevertheless, it is gratifying that there is agreement between one's intuitive concept of size (i.e., volume) of alkyl groups and the ordering in Table III. It is unfortunate that the data on decyl ester **3d** were too imprecise to permit numerical comparison of it with propyl ester **3c**, as its rotational barrier is appreciably higher than that of **3c**. This might be due to a kite-tail effect of the long decyl chain: simple rotation of the aromatic ring leaves the decyl tail lagging behind in the hole. On the other hand it could arise from the more mundane situation wherein decyl is at the size plateau common to all *n*-alkyl groups over a certain length.

(2) The **3**-cavity is smaller than a neopentyl group. Separate esters **3f-A** and **3f-B** are stable toward interconversion for some time at 130 °C and for approximately 1 year at room temperature. At least 20 kcal mol^{-1} separates the rotational barriers of the *n*-alkyl esters from those of the neopentyl esters.

(3) The behavior of isobutyl ester **3e** serves as an enlightening bridge between these two barrier extremes. On a free energy basis it suffers an appreciably higher barrier to rotation (6–7 kcal mol^{-1}) than the *n*-alkyl esters. Comparison of activation parameters (Table III) shows that this is primarily an entropic effect, the enthalpic barrier being comparable to those of the *n*-alkyl esters. This latter is consistent with our view that transannular interactions are not the governing factor here. While there is considerable uncertainty associated with the $\Delta S^{\ddagger}$ for **3d** (−30.4 eu), it is certainly large and negative relative to those of the *n*-alkyl esters. This large negative jump in $\Delta S^{\ddagger}$ is expected if the **3** cavity can just accommodate the isobutyl ester in a relatively unstrained but highly organized transition state. A decrease of 4–5 eu per hindered internal rotor lost has been used to estimate changes in standard entropy on going from alkane to cycloalkane.[34,35] A freezing in the transition state of the six single bonds of the isobutyl ester group is consistent with the $\Delta S^{\ddagger}$ value found for **3d**, although the close numerical agreement is certainly fortuitous. We thus see that **3d** is on the entropic edge of death: addition of one further methyl group to produce a neopentyl ester results in a qualitative change in rotational behavior.

(4) Flexible cyclophanes **4a–f** exist statically in a collapsed and compact conformation (see above). Although the values are not very accurate, one sees from Table III that rotational barriers of the flexible cyclophanes are uniformly 3–4 kcal mol^{-1} higher than those of their rigid counterparts. The collapsed conformation and increased barrier go hand in hand is intuitively gratifying. It is, however, in contrast with our earlier results on **6** and related [8.8](1,4)naphthalenophanes,[13c] wherein sample cooling did not lead to DNMR broadening of potentially diastereotopic methylene proton pairs. Since there is otherwise a modicum of consistency between rotational barriers found in the isosteric acyloxymethyl (**6**-rigid) and alkoxycarbonyl (**3a–d**) series, it would now appear that in the former work DNMR effects were absent (**6**-flexible) because of accidental isochronicity.

(5) Acids **3g** and **4g** have to date been examined only in a single solvent (pyridine-d_5) wherein they exist presumably as salts. It follows from Table III that the carboxylate group is smaller than methyl ester. In this solvent then, there is no special barrier associated with movement of a carboxylate anion from external solvent into the less polar cavity interior.[36]

Experimental Section[37]

Preparation of Acetylenic Ethers 1. Diethyl 2,5-bis(propargyloxy)-terephthalate (**1b**), mp 142–144 °C (EtOH), was prepared in 88% yield by treatment of diethyl 2,5-dihydroxyterephthalate[38] with excess propargyl bromide and potassium carbonate in refluxing acetone for 19 h. Anal. ($C_{18}H_{18}O_6$) C, H.

Dimethyl ester 1a, mp 132.5–133.5 °C (EtAc–hexane), was prepared in 39% yield from **1b** (refluxing methanol containing potassium carbonate). Anal. ($C_{17}H_{14}O_6$) C, H.

Acid 1g (anal. ($C_{14}H_{10}O_6$) C,H) isolated in 36% yield, was esterified (1% sulfuric acid in methanol) to **1a**.

Dipropyl ester 1c, mp 128.5–129.5 (EtAc), was prepared in 55% yield by reaction at 25 °C of **1b** with 1-propanol containing sodium methoxide. Additional diester was obtained by esterification of recovered acid **1g**.

Didecyl ester 1d, mp 80–81 °C (hexane) was prepared in 50% yield from acid **1g** (DMF, excess *n*-decyl bromide, potassium carbonate, 70 °C, 12 h).[39]

Isobutyl and neopentyl esters 1e and **1f** were prepared in 70–80% yield by refluxing the acid chloride **1h** (from acid **1g** and oxalyl chloride) overnight with an excess of the corresponding alcohol in benzene. Isobutyl ester **1e**, mp 87–88 °C (hexane). Anal. ($C_{22}H_{26}O_6$) C, H. Neopentyl ester **1f**, mp 103–104.5 °C (hexane). Anal. ($C_{24}H_{30}O_6$) C, H.

Bis(propargyloxy)benzene (1i), mp 49.5–50.5 °C (95% EtOH) was prepared in 74% yield from hydroquinone.

Octahydro derivatives of 1a–f (2a–f) were prepared by catalytic hydrogenation (10% Pd/C in EtAc): **2a** (R = Me), mp 78–80 °C (hexane); **2b** (R = Et), 29.5–31 °C (hexane); **2c** (R = Pr), mp 37–39.5 °C (hexane); **2d** (R = decyl), mp 35–38 °C (hexane); **2e** (R = *i*-Bu), 47–49 °C (hexane); **2f** (R = neopentyl), mp 88–90 °C (hexane).

Preparation of Cyclic Dimers (3a–f). A typical procedure, preparation of **3c**, is given. A solution of 1.5 g (4.2 mM) of dipropyl ester **1c** in 100 mL of pyridine was added dropwise over a 2-h period to 5.5 g (27.5 mM) of cupric acetate dihydrate in 150 mL of pyridine at 45 °C. The residue remaining after distillation of the pyridine at reduced pressure was slurried with cold 10% hydrochloric acid. Extraction with chloroform gave a dark residue which after purification by chromatography (silica gel, $CHCl_3$) was crystallized to give **3c** (10% yield), mp 190–192 °C dec (EtAc–hexane), as a mixture of syn and anti isomers: ^{1}H NMR δ ($CDCl_3$): 7.498 (1 H, s, Ar *H*), 4.971 (1 H, *J* = 17 Hz, $OCH_AC{\equiv}C$), 4.768 (0.6 H) and 4.737 (0.4 H) (d, *J* = 17 Hz, $OCH_BC{\equiv}C$), 4.242 (2 H, t, *J* = 7 Hz, $COOCH_2$), 1.713 (2 H, sextet, *J* = 7 Hz, CH_2) 0.982 (3 H, t, *J* = 7 Hz, CH_3). Anal. ($C_{40}H_{40}O_{12}$, *m/e* 712.2517) C, H; *m/e* 712.2517.

Similarly prepared in 10% yield from **1d** was decyl ester **3d**, mp 122–124 °C (EtAc) observed as a mixture of two isomers: δ ($CDCl_3$) 7.493 (1 H, s, Ar H), 4.961 (0.4 H) and 4.949 (0.6 H) (d, *J* = 17 Hz, $CH_AC{\equiv}C$), 4.783 (0.6 H) and 4.739 (0.4 H) (d, *J* = 17 Hz, $CH_BC{\equiv}C$), 4.3 (2 H, m, $COOCH_2$), 1.2–1.7 (16 H, m, CH_2), 0.89 (3 H, tr, CH_3). Anal. ($C_{68}H_{96}O_{12}$), C, H.

Coupling of diisobutyl ester **1e** afforded two isomeric dimers of **3e**. Crystallization from benzene gave the less soluble isomer **3e-A**, mp 201–204 °C, the minor component, in 10% yield: ^{1}H NMR δ ($CDCl_3$) 7.520 (1 H, s, Ar H), 4.978 (1 H, d, *J* = 17 Hz, $CH_AC{\equiv}C$), 4.728 (1 H, d, *J* = 17 Hz, $CH_BC{\equiv}C$), 4.080 (1 H, dd, *J* = 7, 11 Hz, $COOCH_A$), 4.057 (1 H, dd, *J* = 6.4, 11 Hz, $COOCH_B$), 1.998 (1 H, nonet, *J* = 7 Hz, $CH_2CH(CH_3)_2$), 0.957 (3 H, d, *J* = 7 Hz, CH_3), and 0.947 (3 H, d, *J* = 7 Hz, CH_3); mass spectrum, *m/e* 768.3149 (calcd for $C_{44}H_{48}O_{12}$, 768.3143). From the mother liquor, the more soluble isomer **3e-B** contaminated by ca. 15% **3e-A** was obtained: ^{1}H NMR δ ($CDCl_3$) 7.509 (1 H, s, Ar H), 4.980 (1 H, d, *J* = 17 Hz, $ArOCH_A$), 4.740 (1 H, d, *J* = 17 Hz, $ArOCH_B$), 4.053 (2 H, d, *J* = 7 Hz, $COOCH_2CH$), 1.954 (1 H, nonet, *J* = 7 Hz, $-CH_2CHMe_2$), 0.953 (6 H, d, *J* = 7 Hz, $-CH_3$).

Coupling of neopentyl ester **1f** afforded upon crystallization of the crude product two isomeric dimers of **3f**: **3f-A** (the less soluble isomer), mp >250 °C dec from 230 °C ($CHCl_3$–hexane) in 8.5% yield; ^{1}H NMR δ ($CDCl_3$) 7.551 (1 H, s, ArH), 4.982 (1 H, d, *J* = 17 Hz, $OCH_AC{\equiv}C$), 4.735 (1 H, d, *J* = 17 Hz, $OCH_BC{\equiv}C$), 3.985 (1 H, d, *J* = 11 Hz, $OCH_A{}^tBu$), 3.967 (1 H, d, *J* = 11 Hz, $OCH_B{}^tBu$), 0.959 (9 H, s, $(CH_3)_3C$); mass spectrum, *m/e* 824.3768 (calcd for $C_{48}H_{56}O_{12}$, 824.377). **3f-B** (mp 197–201 °C dec ($CHCl_3$–hexane) in 5% yield; ^{1}H NMR δ ($CDCl_3$) 7.534 (1 H, s, ArH), 4.977 (1 H, d, *J* = 17.3 Hz, $OCH_AC{\equiv}C$),

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(36) This work was supported by the National Science Foundation.

(37) Proton nuclear magnetic resonance spectra were determined on a Bruker WH-270 (270 MHz) or a JEOL FX-200 at 200 MHz. Upper temperature limits on the two machines are 150 and 200 °C, respectively. The effect of solvent on DNMR effects (chloroform-*d*, toluene-d_8, pyridine-d_5) was examined for the case of **3b**. After correction for chemical shift differences, no effects were found.

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(39) Jarvi, E. T. Ph.D. Thesis, University of Wisconsin–Madison, 1981.

4.766 (1 H, d, J = 17.3 Hz, $OCH_BC{\equiv}C$), 3.967 (2 H, s, CH_2), 0.963 (9 H, s, $(CH_3)_3C$); mass spectrum, m/e 824.3773 (calcd for $C_{48}H_{56}O_{12}$, 824.3770).

Due to the decreased solubilities of **3a** and **3b**, the crude product was isolated after acidification by filtration (a dark brown solid). Extraction of this solid with hot acetone afforded a light colored solid which could be purified by trituration and crystallization. Thus obtained in 14% yield was **3a**: mp >250 °C (CH_2Cl_2); ^1H NMR δ ($CDCl_3$) 7.49 (1 H, s, ArH), 4.88 (2 H, br s, $OCH_2C{\equiv}C$), 3.901 (3 H, s, OCH_3). Anal. ($C_{32}H_{24}O_{12}$, m/e 600.1266) C, H; m/e 600.1268.

From **1b**, dimer **3b** was obtained in 15% yield, mp >250 °C dec from 230 °C; ^1H NMR δ ($CDCl_3$) 7.490 (1 H, s, ArH), 4.89 (2 H, unresolved AB q, $OCH_2C{\equiv}C$), 4.348 (2 H, q, J = 7 Hz, OCH_2CH_3), 1.339 (3 H, tr, J = 7 Hz, CH_3); ^1H NMR δ ($CDCl_3$, -7 °C) 5.005 (1 H, d, J = 17 Hz, $OCH_AC{\equiv}C$), 4.813 (0.6 H) and 4.773 (0.4 H) (d, J = 17 Hz, $OCH_BC{\equiv}C$); mass spectrum, m/e 656.1891 (calcd for $C_{36}H_{22}O_{12}$, 656.1892).

Preparation of Mixed Dimer 5c. Slow addition of a solution containing 0.725 g (2 mM) of propyl ester **1c** and 1.87 g (10 mM) of bis(propargyloxy)benzene (**1i**) in 150 mL pyridine to a solution of 25 g (125 mM) of copper acetate in 440 mL of pyridine at 45 °C gave after workup a dark brown solid. Extraction with acetone afforded 2.6 g of acetone-soluble material. Chromatography of this crude product afforded 0.26 g of a light brown oil from which could be isolated by crystallization 55 mg (10% yield) of **5c** as colorless needles: mp 218 °C dec; ^1H NMR δ 7.498 (1 H, s, Ar'H), 6.896 (2 H, s, ArH), 4.978 (1 H, d, J = 17.6 Hz, $Ar'OCH_A$), 4.767 (1 H, d, J = 17.6 Hz, $Zr'OCH_B$), 4.729 (2 H, s, $ArOCH_2$), 4.267 (1 H, d of t, J = 11, 7 Hz, $COOCH_A$), 4.217 (1 H, d of t, J = 11, 7 Hz, $COOCH_B$), 1.7 (2 H, sextet, J = 7 Hz, $CH_2CH_2CH_3$), 0.977 (3 H, t, J = 7 Hz, CH_3); mass spectrum, m/e 540.1786 (calcd for $C_{32}H_{28}O_8$, 540.1782).

Hexadecahydro Derivatives (4a-f). Each dimer (**3** series) was catalytically hydrogenated (10% Pd/C, EtAc) to the corresponding hexadecahydro derivative (**4** series).

4a: mp 170.5-171.5 °C (EtAc-hexane); ^1H NMR δ ($CDCl_3$) 7.005 (1 H, s, ArH), 4.116 (1 H, dd, J = 7.4, 9.2 Hz, $ArOCH_A$), 3.880 (1 H, dd, J = 7.4, 4.4 Hz, $ArOCH_B$), 3.888 (3 H, s, CH_3), 1.5-2.0 (4 H, m, CH_2). Anal. ($C_{32}H_{42}O_{12}$, m/e 616.2517) C, H; m/e 616.2519.

4b: mp 140-142 °C (EtAc-hexane); ^1H NMR δ ($CDCl_3$) 7.000 (1 H, s, ArH), 4.380 and 4.333 (2 H, q of q, J = 11.1, 7.4 Hz, $COOCH_{A,B}CH_3$),[40] 4.146 (1 H, dd, J = 12.5, 8.8 Hz, $ArOCH_A$), 3.881 (1 H, dd, J = 8.8, 3.7 Hz, $ArOCH_B$), 1.5-2.0 (4 H, m, CH_2), 1.404 (3 H, t, J = 7 Hz, CH_3); mass spectrum, m/e 672.3143 (calcd for $C_{36}H_{48}O_{12}$, 672.3145).

4c: mp 102.5-104 °C (hexane); ^1H NMR δ ($CDCl_3$) 7.018 (1 H, s, ArH), 4.261 and 4.226 (2 H, q of t, J = 10.7, 7 Hz, $COOCH_{A,B}$), 4.129 (1 H, dd, J = 8, 9 Hz, $ArOCH_A$), 3.876 (1 H, m, $ArOCH_B$), 1.78 (2 H, hex, J = 7 Hz, $CH_2CH_2CH_3$), 1.5-2.0 (4 H, m, CH_2), 1.022 (3 H, t, J = 7 Hz, CH_3). Anal. ($C_{40}H_{56}O_{12}$, m/e 728.3768) C, H; m/e 728.3769.

4d, a wax: ^1H NMR δ ($CDCl_3$) 7.005 (1 H, s, ArH), 4.26 (2 H, m, $COOCH_2$), 3.87 and 4.11 (2 H, m, $ArOCH_2$), 1.3-2.0 (20 H, m, CH_2), 0.882 (3 H, t, CH_3).

4e (isomer **4e-A**): mp 83.5-84.5 °C (hexane); ^1H NMR δ ($CDCl_3$) 7.280 (1 H, s, ArH), 3.9-4.1 (4 H, m, $ArOCH_2$ and $COOCH_2$), 2.031 (1 H, nonet, J = 6.6 Hz, CH_2CHMe_2), 1.4-1.8 (4 H, m, CH_2), 0.995 (6 H, d, J = 6.6 Hz, CH_3); mass spectrum, m/e 784.4395 (calcd for $C_{44}H_{64}O_{12}$, 784.4394).

4f (from isomer **3f-A**): mp 163.5-165.5 °C (hexane); ^1H NMR δ ($CDCl_3$) 7.319 (1 H, s, ArH), 4.059 (2 H, t, J = 5.6 Hz, $ArOCH_2$), 3.990 (1 H, d, J = 11 Hz, $COOCH_A$), 3.917 (1 H, d, J = 11 Hz, $COOCH_B$), 1.75-1.2 (4 H, m, CH_2), 0.999 (9 H, s, $(CH_3)_3C$); mass spectrum, m/e 840.5021 (calcd for $C_{48}H_{72}O_{12}$, 840.5020).

Registry No. 1a, 84119-03-9; **1b**, 84119-02-8; **1c**, 84119-05-1; **1d**, 84119-06-2; **1e**, 84119-07-3; **1f**, 84119-08-4; **1g**, 84119-04-0; **1h**, 84119-09-5; **1i**, 34596-36-6; **2a**, 84119-15-3; **2b**, 84119-10-8; **2c**, 84119-11-9; **2d**, 84119-12-0; **2e**, 84119-13-1; **2f**, 84119-14-2; **3a**, 84130-28-9; *syn*-**3b**, 84118-93-4; *anti*-**3b**, 84171-55-1; *syn*-**3c**, 84172-82-7; *anti*-**3c**, 84119-16-4; *syn*-**3d**, 84118-95-6; *anti*-**3d**, 84171-56-2; *syn*-**3e**, 84118-96-7; *anti*-**3e**, 84171-53-9; *syn*-**3f**, 84118-97-8; *anti*-**3f**, 84171-54-0; **3g**, 84119-00-6; **4a**, 84118-92-3; **4b**, 84130-29-0; **4c**, 84118-94-5; **4d**, 84130-30-3; **4e**, 84130-31-4; **4f**, 84118-98-9; **4g**, 84119-01-7; **5c**, 84118-99-0; diethyl 2,5-dihydroxyterephthalate, 5870-38-2; propargyl bromide, 106-96-7; hydroquinone, 123-31-9.

(40) $\Delta\nu_{AB}$ = 6.9 ± 0.4 Hz; A:B inner:outer intensity ratio = 12 ± 0.7.

Reactivity of Coordinated Disulfides. 1. Nucleophilic Cleavage of the Sulfur-Sulfur Bond

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Abstract: The rates of nucleophilic cleavage of the activated sulfur-sulfur bond in $[(en)_2Co(S(SR)CH_2CH_2NH_2)]^{3+}$ complexes have been measured in $(H/Li)ClO_4$ aqueous media (μ = 1.00 M) as a function of $[H^+]$, temperature, attacking nucleophile (OH^- and thiols), and R group (R = methyl, ethyl, isopropyl, *tert*-butyl, and valinyl). For all reactions, except base hydrolysis of the *tert*-butyl complex, heterolytic sulfur-sulfur bond cleavage leads to the thiolato complex $[(en)_2Co(SCH_2CH_2NH_2)]^{2+}$ and organic products derived from the pendant RS^+ moiety. The *tert*-butyl complex decomposes primarily by S_N1cB cobalt-sulfur bond fission. For all reactions, except the base hydrolysis of the valinyl complex, the observed rate law is rate = k_2[disulfide][nucleophile], consistent with a simple S_N2 mechanism. Decomposition of the valinyl complex is apparently complicated by the presence of diastereoisomers that react at different specific rates. In the thiol reactions, $k_2 = a + b/(H^+)$, indicating that both free thiol (RSH) and dissociated thiolate anion (RS^-) attack the coordinated disulfide linkage. For the reaction of 2-mercaptoethanol with the complex having R = methyl at 25 °C, a = 1.22 ± 0.05 M^{-1} s^{-1} (ΔH_a^* = 13.4 ± 0.1 kcal/mol, ΔS_a^* = -13.2 ± 0.4 eu) and b = 0.32 ± 0.02 s^{-1} (ΔH_b^* = 6.4 ± 0.1 kcal/mol, ΔS_b^* = -39.3 ± 0.4 eu), and for the reaction of OH^- with this complex k_2 = (1.70 ± 0.04) × 10^6 M^{-1} s^{-1} (ΔH^* = 19.0 ± 0.4 kcal/mol, ΔS^* = 37 ± 1 eu). In accordance with the S_N2 mechanism, the observed reaction rates for those complexes with simple alkyl R groups depend mainly on the steric bulk of the R group (k_2 decreasing by ca. 10^5 on going from R = CH_3 to $C(CH_3)_3$) and the nucleophilicity of the attacking moiety ($RS^- > OH^- > RSH$). Comparisons with literature data show that the specific rates of sulfur-sulfur bond cleavage in disulfides activated by coordination to cobalt(III) are 10^{10}-10^{11} times greater than those of comparable noncoordinated disulfides.

Cleavage of the sulfur-sulfur bond in disulfides by nucleophiles has been postulated to occur by a variety of mechanisms, the most important of which are as follows: (1) direct S_N2 attack on the sulfur-sulfur bond (eq 1),[2]

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