# A Study of Steric Effects in [2.2]Metaparacyclophanes. A Steric Isotope Effect, Remote Substituent Effects on a Steric Barrier, and Other Steric Phenomena[1,2]

**S. A. Sherrod, R. L. da Costa, R. A. Barnes, and V. Boekelheide***

*Contribution from the Department of Chemistry, University of Oregon, Eugene, Oregon 97403.* *Received July 10, 1973*

**Abstract:** The conformational flipping of [2.2]metaparacyclophanes requires intrusion by the substituent at the 8 position into the $\pi$-electron cloud of the para-bridged ring. It is shown that the kinetics of this process can readily be followed by a double irradiation nmr technique. The Arrhenius factors observed for the conformational flipping of [2.2]metaparacyclophane itself are $\Delta H^{\pm} = 17.0 \pm 0.5$ kcal/mol and $\Delta S^{\pm} = -8.8 \pm 2.4$ eu. Substitution of deuterium for hydrogen at the 8 position showed a $k_D/k_H$ ratio of $1.20 \pm 0.04$, the largest steric isotope effect thus far observed. Similarly, substituents (F, Br, $NO_2$, $OCH_3$, $COCH_3$, and $NH_2$) placed at the 5 position have a marked effect on the rate of conformational flipping of [2.2]metaparacyclophane. The rate dependence on remote substituents has been interpreted in terms of two effects: a sterically induced polarity of the transition state resulting in a Hammett $\rho$ value of $+1.05 \pm 0.09$, and a ground-state attractive interaction of the two aromatic rings (with electron-withdrawing substituents) associated with a Hammett $\rho$ value of $-1.36 \pm 0.14$. Both Hückel and CNDO calculations support the picture of a polar transition state for conformational flipping of [2.2]metaparacyclophane. A possible anomalous steric interaction between fluorine and a benzene $\pi$-electron cloud, suggested by earlier work, has been investigated through a study of conformational preference in [2.2]-metaparacyclophanes with substituents on the para-bridged ring. However, the steric ordering deduced $H < F < CH_3 < Br$ is that generally accepted. [2.2](9,10)Anthracenometacyclophane (**41**) has been synthesized and its rate of conformational flipping has been shown to be 45 times as fast as that of [2.2]metaparacyclophane (**1**-*H*).

The previous paper in this series[3a] points out that in order for [2.2]metaparacyclophanes to undergo conformational ring flipping (only the meta-bridged ring can flip[4a]), a substituent at the 8 position must impinge on the $\pi$ cloud of the para-bridged ring. Molecular models suggest that even when the substituent is as small as hydrogen, the interaction will be a severe and presumably nonbonding one, and this prediction is substantiated by observation that in the parent compound (**1**-*H*) there is a sizable barrier ($\approx$20 kcal/mol) to ring flipping.[4] Ascribing a considerable portion of this barrier to repulsion involving the 8-H is consistent with the observation of much more facile ring flipping in 2,6-pyridino[2.2]paracyclophane,[3b] wherein the 8 carbon and hydrogen of **1**-*H* have formally been replaced by the smaller group, nitrogen and its lone pair of electrons.[4d] Severe crowding of the 8 hydrogen in the transition state for ring flipping should result in marked changes in the vibrational frequencies of the 8 C–H bond and be detectable in an isotope effect, appropriately termed a steric isotope effect in view of the source of the vibrational changes.[5]

Indeed, such conformational kinetic isotope effects, of which there are relatively few documented cases,[6] provide perhaps the clearest examples of steric isotope effects.[7] We undertook to measure a deuterium isotope effect on the ring flipping rate in **1**, firstly because we anticipated that the effect might be unusually large in this system, and secondly, because such an effect would serve as proof of a strong interaction between the 8-H and the para-bridged ring.

The possibility for carrying out such a steric isotope study had been made feasible by recent synthetic discoveries. First of all, Cram and his colleagues had shown that the acid-catalyzed rearrangement of [2.2]-paracyclophane readily gives [2.2]metaparacyclophane.[4a] Although this is a superior method for preparing [2.2]-metaparacyclophane itself, it is not very useful for derivatives with specific substitution. However, procedures utilizing 2,11-dithia[3.3]metaparacyclophanes as starting materials, as shown in our previous publications, do permit ready synthetic access to either [2.2]metaparacyclophane or [2.2]metaparacyclophane-1,9-diene derivatives with specific substitution patterns.[3] Thus, good synthetic routes were available to us to prepare derivatives of either **1** or **2**. Also, both **1** and **2** exhibit conformational flipping involving intrusion of the 8

(1) We thank the National Institutes of Health and the National Science Foundation for their support of this investigation.

(2) Preliminary accounts of portions of this work have appeared as communications: (a) S. A. Sherrod and V. Boekelheide, *J. Amer. Chem. Soc.*, 94, 5513 (1972); (b) S. A. Sherrod and R. L. da Costa, *Tetrahedron Lett.*, 2083 (1973).

(3) (a) V. Boekelheide, P. H. Anderson, and T. A. Hylton, *J. Amer. Chem. Soc.*, 96, 1558 (1974); (b) V. Boekelheide, K. Galuszko, and K. S. Szeto, *ibid.*, 96, 1578 (1974).

(4) (a) D. T. Hefelfinger and D. J. Cram, *J. Amer. Chem. Soc.*, 92, 1073 (1970); 93, 4767 (1971); D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *ibid.*, 88, 1324 (1966). (b) F. Vögtle, *Chem. Ber.*, 102, 3077 (1969). (c) S. Akabori, S. Hayashi, M. Nawa, and K. Shiomi, *Tetrahedron Lett.*, 3727 (1969). (d) One should recognize that although most of the barrier to flipping may have as its origin the nonbonding interaction between the 8-H and the para-bridged ring, much of the strain energy of the transition state will be distributed over various deformations, primarily angle bending. For example, see, F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 549.

(5) (a) L. S. Bartell, *Tetrahedron Lett.*, 13 (1960); (b) *J. Amer. Chem. Soc.*, 83, 3567 (1961); (c) *Iowa State J. Sci.*, 36, 137 (1961).

(6) (a) K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., *J. Amer. Chem. Soc.*, 85, 1199 (1963); 86, 1733 (1964); (b) L. Melander and R. E. Carter, *Acta Chem. Scand.*, 18, 1138 (1964); (c) C. Heitner and K. T. Leffek, *Can. J. Chem.*, 44, 2567 (1966); (d) R. E. Carter and L. Dahlgren, *Acta Chem. Scand.*, 23, 504 (1969); 24, 633 (1970).

(7) For other examples of steric isotope effects, see (a) H. C. Brown and G. J. McDonald, *J. Amer. Chem. Soc.*, 88, 2514 (1966); (b) H. C. Brown, E. Azzaro, J. G. Koelling, and G. J. McDonald, *ibid.*, 88, 2520 (1966); (c) G. H. Cooper and J. McKenna, *Chem. Commun.*, 734 (1966); (d) M. M. Green, M. Axelrod, and K. Mislow, *J. Amer. Chem. Soc.*, 88, 861 (1966); (d) J. Almy and D. J. Cram, *ibid.*, 91, 4459 (1969); (e) G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Scheppele, and R. L. Shone, *ibid.*, 89, 463 (1967); (f) D. N. Jones, R. Grayshan, and K. J. Wise, *J. Chem. Soc. C*, 2027 (1970).

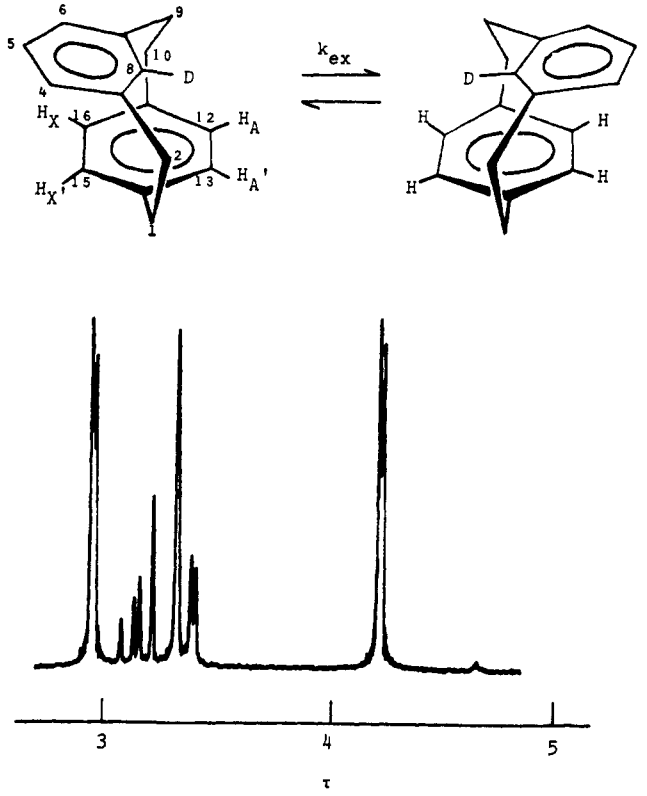
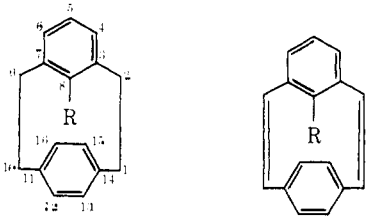



Figure 1. Aromatic portion of nmr spectrum (100 MHz) of 8-deuterio[2.2]metaparacyclophane (**1-*D***).

substituent into the π-electron cloud of the para-bridged ring. However, an important consideration was our desire to use nmr as a method of kinetic analysis, and the coalescence temperature at 100 MHz for conformational flipping of **1** is 157°, whereas that for **2** is −96°. Thus, we elected to study derivatives of **1** rather than **2**, because the kinetic analyses would be in a more convenient temperature range, and because the higher energy barrier to flipping in **1** implies a more severe steric crowding and therefore promised a larger isotope effect.

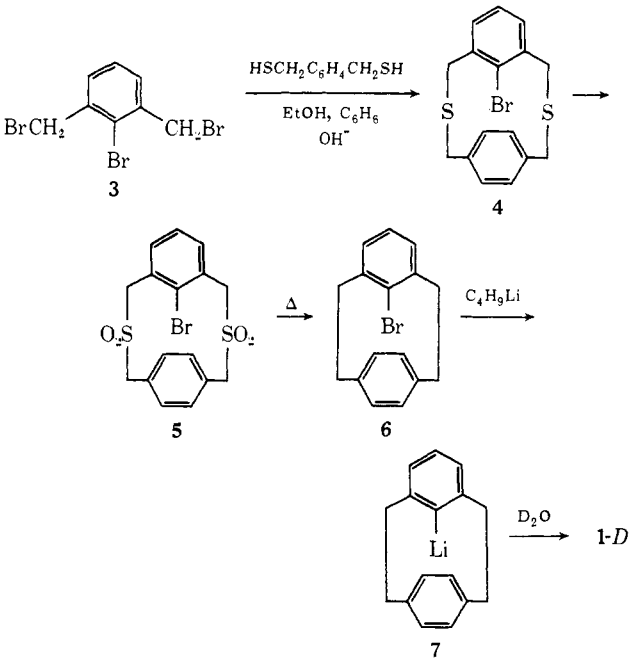



1-*H*, R = H
1-*D*, R = D

2

Two routes were available from 2,11-dithia[3.3]-metaparacyclophanes to derivatives of **1**. The first of these involved a Stevens rearrangement followed by a Hoffmann elimination to give derivatives of **2**. These, on catalytic hydrogenation, would then be converted to the desired derivatives of **1**. A second route involved oxidation of the 2,11-dithia[3.3]metaparacyclophanes to the corresponding bissulfones which, on pyrolysis, would extrude sulfur dioxide to give the desired derivatives of **1** directly. The latter route was selected as being shorter and, in our experience, was found to give better overall yields. Thus, oxidation of 9-bromo-2,11-dithia[3.3]metaparacyclophane (**4**),[8] prepared by the condensation of 2,6-bis(bromomethyl)-benzene (**3**) with 1,4-bis(mercaptomethyl)benzene, with *m*-chloroperbenzoic acid readily gave the bissulfone **5** in nearly quantitative yield (Scheme I). Pyrolysis of **5** at

**Scheme I**




500° under reduced pressure in a nitrogen flow system[9] then led to 8-bromo[2.2]metaparacyclophane (**6**) in 63% yield. Treatment of **6** with *n*-butyllithium in ether gave the lithium derivative **7**, which could be quenched with water to obtain the parent compound **1-*H***, or with deuterium oxide to obtain **1-*D***. Mass spectral analysis of a sample of **1-*D*** obtained in this way showed 95.7 ± 0.6% incorporation of deuterium with an nmr analysis indicating 94.9% deuterium at the 8 position.

As illustrated in Figure 1, the protons of the para-bridged ring in [2.2]metaparacyclophane appear as two narrow multiplets separated by over 1 ppm. Coalescence of ths AA′XX′ pattern in **1-*D*** appeared to occur at a temperature 2–5° lower than that required for **1-*H***,[10] but the distinction was subtle and drove us to a more precise method. For this purpose we chose the double-irradiation technique of Forsén and Hoffman.[11]

Upon sudden saturation of site X, the z-magnetization at site A, $M_z^A$, decreases due to conformational exchange according to eq 1, where $M_0^A$ is the initial magnetization, $T_1^A$ the longitudinal relaxation time of site A, and $k_{ex}$ the rate constant for conformational exchange; in the limit of infinite time $M_z^A$ is given by

$$dM_z^A/dt = M_0^A/T_1^A - M_z^A(k_{ex} + 1/T_1^A) \quad (1)$$

$M_0^A/(T_1^A k_{ex} + 1)$.[11] Rather than extract both $T_1^A$ and $k_{ex}$ from the decay curve, we found it convenient to measure $T_1^A$ and $M_0^A/M_{z\infty}^A$ independently, $k_{ex}$ being given by eq 2.

(8) F. Vögtle, *Tetrahedron Lett.*, 3193 (1969).

(9) M. Haenel and H. A. Staab, *Tetrahedron Lett.*, 3585 (1970).

(10) For **1-*H*** in perchlorobutadiene we observed $T_c$ 157°, $\Delta\nu$ = 131 Hz (100-MHz instrument). Our value appears inconsistent with that of Akabori, *et al.*[4c] ($T_c$ 187, $\Delta\nu$ = 184 Hz), but taken together with our Arrhenius data (*vide infra*) is consistent with that reported by Cram and Hefelfinger[4a] ($T_c$ 146, $\Delta\nu$ = 75 Hz, 60-MHz instrument). All temperatures in our work have been calibrated with either methanol or ethylene glycol, according to the equations of A. L. Van Geet, *Anal. Chem.*, **40**, 2227 (1968).

(11) S. Forsén and R. A. Hoffman, *Acta Chem. Scand.*, **17**, 1787 (1963); *J. Chem. Phys.*, **39**, 2892 (1963); 40, 1189 (1964).

**Table I.** Longitudinal Relaxation Times and Ring-Flipping Rates[a]

| Compd | Temp, °C | $(1/T_1^X) \times 10^2$,[b] $sec^{-1}$ | $(1/T_1^A) \times 10^2$,[b] $sec^{-1}$ | $M_0^A/M_{z\infty}^A$ | $k_{ex} \times 10^2$,[f] $sec^{-1}$ |
|---|---|---|---|---|---|
| [2.2]Metapara-cyclophane (**1-*H***) | 19.9 ± 0.3 | 7.61 ± 0.21 | 8.22 ± 0.26 | 1.172 ± 0.005[d] | 1.41 ± 0.06 |
| | 35.3 ± 0.3 | 7.06 ± 0.11 | 7.16 ± 0.14 | 1.949 ± 0.031[c] | 6.79 ± 0.16 |
| | 47.9 ± 0.3 | 6.01 ± 0.26 | 6.19 ± 0.23 | 3.31 ± 0.07[d] | 20.49 ± 0.88 |
| 8-Deuterio[2.2]-metaparacyclo-phane (**1-*D***) | 35.3 ± 0.3 | 6.71 ± 0.14 | 7.01 ± 0.13 | 2.163 ± 0.023[c,e] | 8.15 ± 0.17[e] |

[a] For degassed 10% solutions (by wt) in $CDCl_3$. [b] Error given is standard deviation of the slope based on ten or more points. [c] Standard deviation of the average of seven determinations acquired over 4 different days. Each determination was based on averages of ten or more integrals of both $M_0^A$ and $M_{z\infty}^A$. [d] Standard deviation of the average of three determinations. [e] Corrected for isotopic purity. [f] Standard deviation calculated according to normal propagation of independent errors.

**Table II.** Longitudinal Relaxation Times and Ring-Flipping Rates in [2.2]Metaparacyclophanes Bearing a Substituent at the 5 Position[a]

| Substituent | $(1/T_1^X) \times 10^2$, $sec^{-1}$ [b] | $(1/T_1^A) \times 10^2$, $sec^{-1}$ [b] | $M_0^A/M_{z\infty}^A$ [c] | $k_{ex} \times 10^2$, $sec^{-1}$ | $k_{rel}$ |
|---|---|---|---|---|---|
| Br | 9.95 ± 0.34 | 10.55 ± 0.46 | 1.694 ± 0.038 | 7.33 ± 0.54 | 1.08 |
| F | 8.98 ± 0.13 | 8.75 ± 0.13 | 1.819 ± 0.047 | 7.18 ± 0.42 | 1.06 |
| H | 7.06 ± 0.11 | 7.16 ± 0.14 | 1.949 ± 0.031 | 6.79 ± 0.16 | 1.00 |
| $NO_2$ | 12.05 ± 0.49 | 11.90 ± 0.48 | 1.395 ± 0.012[d] | 4.78 ± 0.24 | 0.705 |
| $OCH_3$ | 13.09 ± 0.36 | 12.98 ± 0.35 | 1.310 ± 0.012 | 4.03 ± 0.19 | 0.595 |
| $COCH_3$ | 13.10 ± 0.72 | 13.34 ± 0.69 | 1.282 ± 0.011 | 3.77 ± 0.24 | 0.556 |
| $NH_2$ | 10.78 ± 0.13 | 11.14 ± 0.21 | 1.110 ± 0.007[d] | 1.29 ± 0.09 | 0.189 |

[a] For degassed solutions in $CDCl_3$ at 35.0 ± 0.3°. [b] Error given is standard deviation of the slope based on ten or more points. [c] Standard deviation of the average of four or more determinations, each based on averages of ten or more integrals of both $M_0$ and $M_{z\infty}$. [d] In these cases the upfield signal was saturated and the downfield signal was integrated.

$$k_{ex} = (1/T_1^A)(M_0^A/M_{z\infty}^A - 1) \quad (2)$$

For $T_1$ measurements we employed a program written for a Varian XL-100 nmr spectrometer with a Varian 620/I dedicated computer.[12,13] The technique involves application of a 180° pulse to invert the z-magnitization at all sites, followed after a varied interval by an analyzing 90° pulse. Fourier transformation of the free induction decay gives a spectrum which reflects the instantaneous values of $M_z$ at each site. In general, for a system such as ours which involves chemical or conformational exchange recovery from the inverted to the equilibrium value of the z-magnetization at a given site would not be expected to follow simple first-order kinetics. However, in all cases dealt with in this study, the close similarity of $T_1$'s of sites A and X (Tables I and II) made recovery at each site effectively independent of exchange, as evidenced by good first-order kinetic behavior over 2 half-lives.

The calculated conformational exchange rate constants for **1-*H*** and **1-*D*** are given in Table I. The observed isotope effect, $k_D/k_H = 1.20 \pm 0.04$ ($\Delta\Delta F$ = 112 cal/mol), is twice as large per deuterium as any other conformational kinetic isotope effect of which we are aware. It is also an inverse effect in keeping with its steric origin. From the exchange rate constants for **1-*H*** measured at three temperatures have been calculated $\Delta H = 17.0 \pm 0.5$ kcal/mol and $\Delta S = -8.8 \pm 2.4$ eu. The uncertainties[14] in these values make an effort to dissect the isotope effect into enthalpic and entropic components unjustified by our method. However, extrapolation of our Arrhenius data predicts the observed coalescence temperature within 4°.[10] Thus the coalescence data provide a valuable independent check of the validity of our technique.

Due emphasis has been given to the fact that essentially all isotope effects may be traced to differences in zero-point vibrational energies, regardless of the particular origin of the changes in vibrational frequencies.[2a,6d,15] Hence the Streitwieser approximation[16] may be used to calculate that the above effect demands a net increase of 300 $cm^{-1}$ in the vibrational frequencies of the isotopic bond on going to the structurally crowded transition state.

Using the method and potential function of Bartell[5] one can calculate that the 8 hydrogen would have to come within 2.7 Å of the carbons in the para-bridged ring to produce the observed isotope effect. However, Karabatsos, *et al.*,[7e] have found the potential function used by Bartell too "hard" and have recommended use of the "softer" functions of Scott and Scheraga[17] and of Hendrickson.[18] Using the latter function and the method of Bartell the distance between the 8 hydrogen and the carbons of the para-bridged ring in the transition state may be approximated as 2.45 Å,[19a] which is

(12) We wish to thank Dr. R. Freeman and Dr. H. W. D. Hill of Varian for a copy of their program.

(13) R. Freeman and H. W. D. Hill, *J. Chem. Phys.*, 51, 3140 (1969); 53, 4103 (1970).

(14) Calculated by the method of R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Amer. Chem. Soc.*, 83, 3819 (1961).

(15) E. R. Thornton, *Annu. Rev. Phys. Chem.*, 17, 349 (1966).

(16) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, 80, 2326 (1958).

(17) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 42, 2209 (1965).

(18) J. B. Hendrickson, *J. Amer. Chem. Soc.*, 83, 4537 (1961).

(19) (a) In each of these calculations the following values were assumed: $l_m$ = 0.09 Å, $l_t$ = 0.25 Å.[5] The transition state was presumed to occur with the aromatic rings perpendicular to one another, and as an approximation the 8-H was taken as equidistant from the para-bridged ring carbons at that point. We appreciate but consider unlikely the possibility that the perpendicular orientation of the aromatic rings corresponds to a small local minimum in the energy surface. Were this to be the case, then the transition state reflected by the measured isotope effect and the substituent effects to follow would involve a somewhat less symmetric interaction between the 8-H and the $\pi$ cloud of the para-bridged ring. (b) A. W. Hanson, *Acta Crystallogr., Sect. B*, 27, 197 (1971).

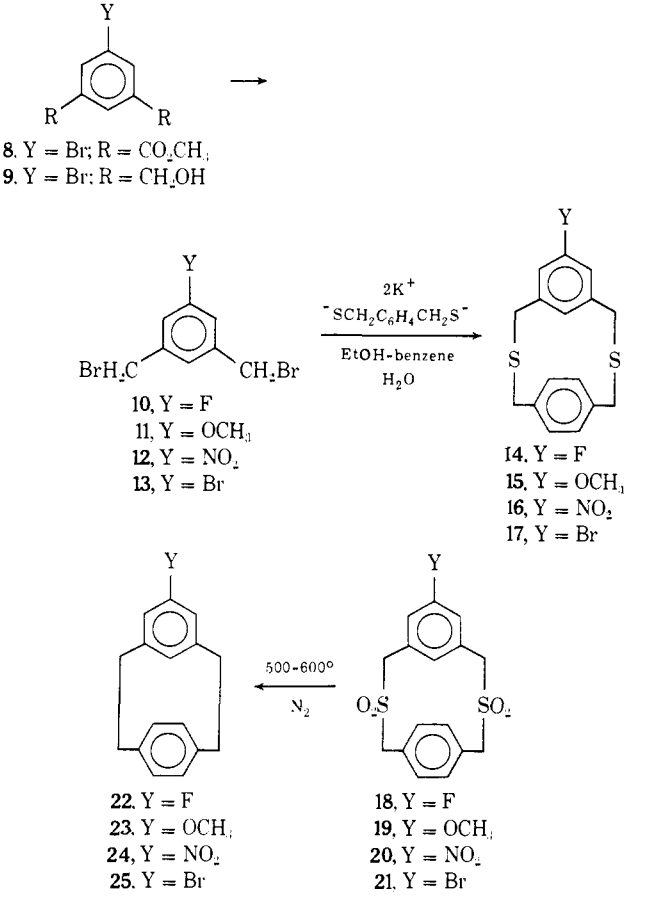
very reasonable in view of the estimated[2] value of 2.1 Å based on data from the X-ray crystallographic analysis of the related diene (**2**)[19b] and the assumption of a perpendicular transition state without any other distortions.

The observed isotope effect provides evidence of a significant interaction between the 8 hydrogen and the para-bridged ring in the transition state for conformational flipping. This suggested that remote substituents on the meta-bridged ring might also affect the rate of conformational flipping. The literature contains accounts of remote substituent effects on sterically hindered conformational changes in two classes of compounds. In one class, 4-substituted aniline derivatives[20] and 4-substituted 1-naphthylamine derivatives,[21] the observed effects on rates of nitrogen inversion correlate well with expectations based on resonance in the transition state. In the second class, substituted biphenyls and the related 1,1′-binaphthyls, the effect of remote substituents on hindered rotation about the interannular bond has been the object of several studies.[22] In this class a number of subtle influences may be operative, and the data have led to no unifying interpretation.[22f,23] In particular it should be noted that in neither of these classes of compounds is it at all obvious that the substituent effects reflect the nature of the steric interaction itself. In contrast, we believed that the unusual nature of the steric interaction in the barrier to ring flipping in [2.2]metaparacyclophanes, that is the interaction of a $\sigma$ bond with the $\pi$ cloud of a benzene ring, might respond directly in substituent effects.

The general route of coupling a dithiolate with a dibromide, oxidizing the resulting dithiacyclophane to a bissulfone, and pyrolyzing the latter to extrude sulfur dioxide was used to obtain [2.2]metaparacyclophanes substituted in the 5 position with fluoro, bromo, methoxy, and nitro groups. In all cases the required starting materials were synthesized by conventional routes, and the overall yields were gratifying.

A brief investigation of the influence of temperature on the products of bissulfone pyrolyses proved interesting. Pyrolysis of the methoxybissulfone **19** at 600° gave the desired 5-methoxy[2.2]metaparacyclophane (**23**) in 93% yield (Scheme II). However, pyrolysis at 500° gave a mixture which could be resolved by differential sublimation and was found to consist primarily of recovered bissulfone **19** and methoxycyclophane **23**. In addition there was obtained a trace amount of 6-methoxy-2-thia-2,2-dioxo[3.2]metaparacyclophane (**26**), the result of extrusion of only one sulfur dioxide moiety from the bissulfone. The relative amounts of these products demand that loss of $SO_2$ from monosulfone **26** to give **23** is faster than its loss from bissulfone **19** to give **26**. This may be the result of strain energy in **26** relative to **19**.

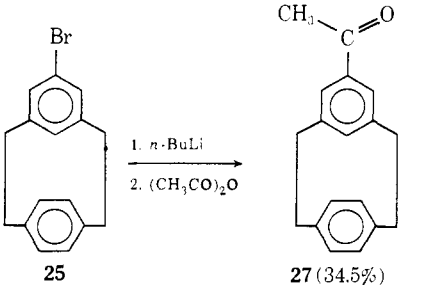
**Scheme II**




Alternatively, if loss of the first $SO_2$ from bissulfone **19** gives a diradical,[24] its very exothermic closure should give monosulfone **26** initially in a highly excited vibrational state, which might lose $SO_2$ competitively with collisional deactivation at the pressure employed (1.5 mm). Presumably the products of pyrolysis of the other bissulfones in the series would show a similar temperature dependence, but this point was not investigated.

Two of the substituted [2.2]metaparacyclophanes prepared by the above route were converted to others of interest. The bromo derivative **25** was treated with *n*-butyllithium and then with acetic anhydride to obtain the acetyl derivative **27** in 34.5% yield (Scheme III).

**Scheme III**




Hydrogenation of the nitro derivative **24** over platinum in ethyl acetate gave the amino compound **28** in the surprisingly low yield of 31.5%. Reduction of the highly strained para-bridged ring occurs under these con-

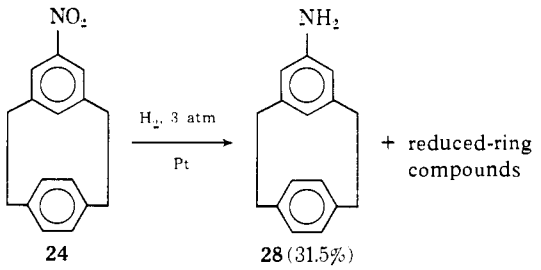
(20) (a) R. Adams and J. R. Gordon, *J. Amer. Chem. Soc.*, 72, 2454, 2458 (1950); (b) C. Buchanan and S. H. Graham, *J. Chem. Soc.*, 500 (1950).

(21) R. Adams and K. V. Y. Sundstrom, *J. Amer. Chem. Soc.*, 76, 5474 (1954).

(22) (a) R. Kuhn and O. Albrecht, *Justus Liebigs Ann. Chem.*, 458, 221 (1927); (b) W. E. Hanford and R. Adams, *J. Amer. Chem. Soc.*, 57, 1592 (1935); (c) M. Calvin, *J. Org. Chem.*, 4, 256 (1939); (d) J. W. Brooks, M. M. Harris, and K. E. Howlett, *J. Chem. Soc.*, 1934 (1957); (e) C. C. K. Ling and M. M. Harris, *ibid.*, 1825 (1964); (f) R. E. Carter and P. Berntsson, *Acta Chem. Scand.*, 23, 499 (1969).

(23) R. L. Shiner, R. Adams, and C. S. Marvel in "Organic Chemistry, An Advanced Treatise," 2nd ed, H. Gilman, Ed., Wiley, New York, N. Y., 1943, p 367.

(24) J. L. Kice in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, New York, N. Y., 1966, p 116.




ditions at a rate competitive with that of the nitro group.

The nmr procedure utilized in measuring the isotope effect was directly applicable to these substituted [2.2]-metaparacyclophanes. We were fortunate in having the narrow multiplets due to the AA'XX' para-bridged ring protons clearly separate from all other aromatic proton absorptions, which facilitated the $T_1$ measurements. The rate constants determined for the six derivatives are presented together with those of the parent in Table II.

The data clearly show that remote substituents do influence the rate of ring flipping in [2.2]metaparacyclophane, the most marked effect being a fivefold retardation due to the amino group. How then do substituents influence the rate? Since the motion is vibrational, the mass of a substituent will affect the vibrational energies. However, a simple calculation based on estimates of the ground-state vibrational frequency in the parent molecule and the change in the moment of inertia on substitution shows that the mass effect in this series can be no more than a few per cent.[25] In fact the mass effect is small compared to other factors; for example, bromine, which is the heaviest substitutent, has the fastest rate.

Although the substituents have been introduced at the most remote position in our system, one must consider the possibility that their presence may result in dimensional changes that facilitiate or inhibit the ring-flipping process. If, for example, the length of the carbon–hydrogen bond at the 8 position varied as a function of the substituent para to it, then a flipping rate dependence would result. Precise data on the length of aromatic carbon–hydrogen bonds as a function of substituents apparently are not available; but from a careful X-ray crystallographic study of benzene derivatives, Trotter found that the length of aromatic carbon–carbon bonds correlates nicely with the hybridization (bond angles) at the two carbon atoms involved.[26] That the length of aromatic carbon–hydrogen bonds should similarly correlate seems reasonable; if so, Trotter's X-ray data for nitrobenzene lead to the conclusion that the para C–H bond is about 0.01 Å longer than that in benzene. If an analogous difference in the 8 C–H bond length of **24** as compared to that in **1-*H*** exists in the transition state for ring flipping, at least a portion of the observed rate difference might be accounted for. One must note, however, that an increased C–C–C angle at C-8, which accompanies the increase in 8 C–H bond length, will serve to increase the separation between C-8 and the para-bridged ring in the transition state, *i.e.*, in terms of steric hindrance between the 8 hydrogen and the para-bridged ring, the dimensional changes induced by substituents are apt to be at least partially compensatory. Also, the nonbonding potential function[18] which gave a reasonable agreement with the observed steric isotope effect requires the relatively large range of about 0.12 Å in separation between the 8 hydrogen and the para-bridged ring, if the observed range in rates is to to be accounted for entirely by dimensional changes.[27] In view of these considerations we are inclined to believe that the small dimensional differences which 5-substituents must induce in the [2.2]metaparacyclophane systems are probably not large enough to account for a significant portion of the observed rate effects. An analogy is found in the work of Crawford and Ingle, who showed that the rate of rotation about the interannular bond in 4,4'-biquinolyl differed from that in the conjugate acid.[28] The authors attributed the difference to dimensional changes on protonation, but suggested that substituents not a part of the ring should have little or no effect.

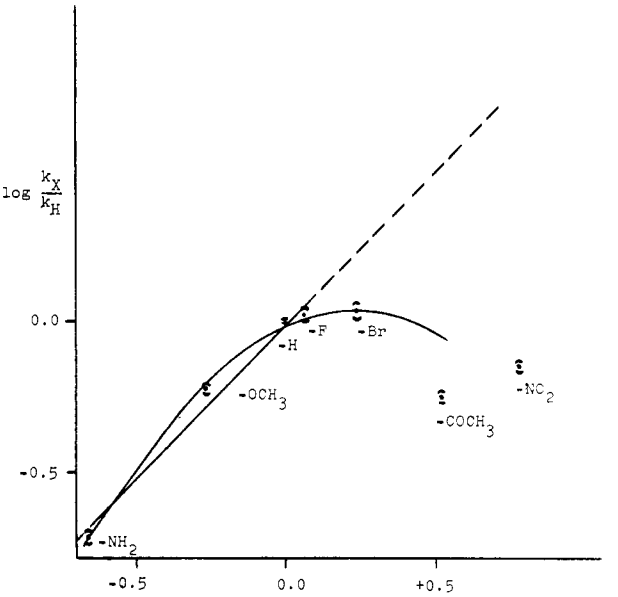



Figure 2. Hammett plot of rate data *vs.* $\sigma_p$.

Initially an effort to correlate the substituent effects with electronic factors seemed also futile, since both good donors, such as the amino group, and good acceptors, such as the nitro group, retard the flipping process. However, a Hammett plot[29] (Figure 2) of the data *vs.* $\sigma_p$ gives a relatively smooth curve, which suggests that there is some correlation with electronic factors, albeit not a simple linear one. Molecular orbital calculations at the level of simple Hückel theory[30] indicate that endwise interaction of a $\sigma$ bond with the $\pi$ system of a benzene ring, such as is envisioned for the transition state for ring flipping, should result in an increase in charge density on the remote end of the bond, due both

(25) Taking the ground-state vibrational frequency of the parent as 100 $cm^{-1}$, and allowing that a substituent doubles the moment of inertia, leads to a predicted mass effect (retardation of rate) of only 7%.

(26) J. Trotter, *Tetrahedron*, 8, 13 (1960).

(27) This estimate assumes, contrary to fact, that deformations[4d] in the transition state will not attenuate the energetic consequences of the hypothetical 0.12-Å increment in separation, and thus may be taken as a conservative lower limit.

(28) M. Crawford and R. B. Ingle, *J. Chem. Soc. B*, 1907 (1971).

(29) (a) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953). (b) By contrast, a Hammett plot *vs.* $\sigma_m$, which might have reflected the polar consequences of deforming the bonds to the methylene bridges, showed only very wild scatter.

(30) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961.

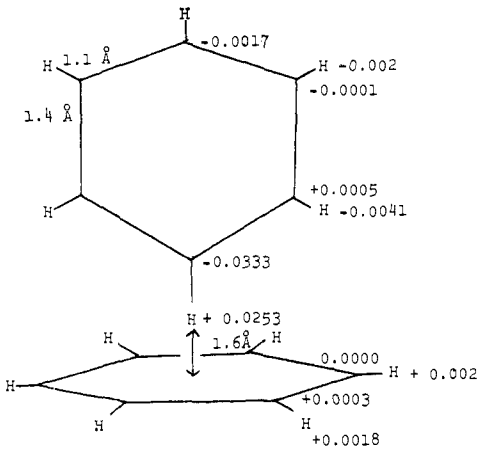



Figure 3. Charge distribution relative to that in benzene as given by the CNDO/2 method for two benzenes oriented as shown.

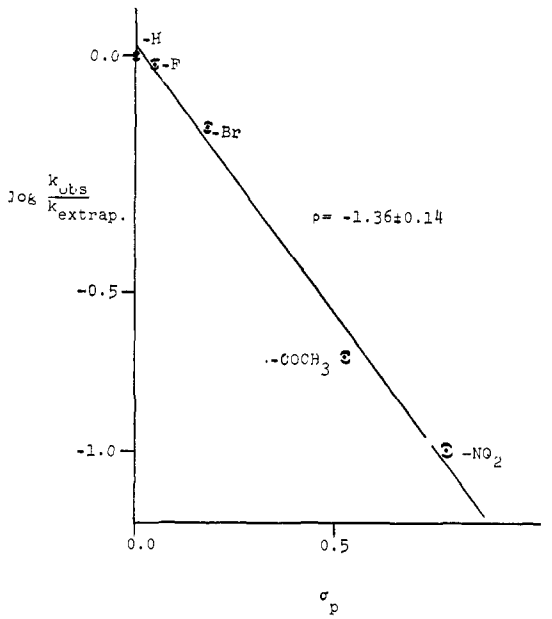



Figure 4. Hammett plot based on observed rates relative to those extrapolated from Figure 2.

to polarization of the bond, and to donation of charge density from the benzene ring. The symmetry allowed mixing of the unoccupied $\sigma^*$ level with the occupied lowest molecular orbital of the benzene $\pi$ system is an important component of the interaction with respect to changes in charge density. This prediction was corroborated at the much less approximate level of a CNDO/2 calculation.[31] As a model for the transition state, the calculation was carried out for two benzene rings oriented as shown in Figure 3, the separation chosen being that indicated for the midpoint in the flipping process in the absence of distortions, based on an X-ray crystallographic study of the analogous [2.2]metaparacyclophane-1,9-diene.[19b] Shown in Figure 3 are the changes in charge that occur when the benzene rings are brought from infinite separation to that illustrated; again one finds a polarization of the carbon–hydrogen bond directly over the $\pi$ cloud, with a net negative charge developing on its carbon atom.[32] Thus, molecular orbital theory predicts an increase in charge density at C-8 in the transition state for flipping, and this should result in a Hammett plot with a positive $\rho$. Figure 2 shows that points due to four substituents (amino, methoxy, hydrogen, and fluorine) comply with the prediction based on this transition-state effect by giving $\rho = 1.05 \pm 0.09$.[33] However, compounds containing substituents which are good electron acceptors show rates that are far slower than expected. Apparently, some opposing effect is dominant in the case of good acceptors and leads to a net retardation of rate. A measure of this effect may be had by constructing a Hammett plot based on the observed rates with electron accepting substituents as compared to the rates predicted by extrapolation of the linear correlation in Figure 2. Such a Hammett plot *vs.* $\sigma_p$ is given as Figure 4, and one sees that it successfully correlates the five points from hydrogen to nitro with an uncertainty in slope of 10% ($\rho = -1.36 \pm 0.14$). With this treatment the order of the rates associated with the acetyl and nitro derivatives is consistent with the trend, which suggests that their disturbing relationship in Figure 2 may be merely a consequence of their observed net effects being small differences between two relatively large opposing effects. We propose that the rate retardations observed for the electron acceptors may be a consequence of a ground-state effect. In the vibrational ground state of [2.2]-metaparacyclophanes the two aromatic rings are skewed to one another such that there is a considerable face to face interaction.[3a] That electron acceptors should stabilize such a ground state seems entirely reasonable by analogy to donor–acceptor complexes.[34]

Most examples of donor–acceptor complexes involve more highly substituted acceptors, such as the well-known 1,3,5-trinitrobenzene and picric acid derivatives, but some evidence for a stabilizing association between benzene and monosubstituted benzenes is available. Diehl found that the magnitude of the chemical shift induced by benzene as solvent in the nmr resonance frequency of meta protons in substituted benzenes correlates linearly with the dipole moment of the substituent: larger solvent effects were obtained with better electron acceptors.[35a] Although the geometry and even the molecularity of association remain in question here, the underlying principle may be common to all donor–acceptor complexation.[35b]

Direct evidence for donor–acceptor complexation in our substituted cyclophanes is unfortunately lacking. Interestingly, the uv spectrum of the nitro compound tails into the visible, but there is no prominant charge-transfer band; however, it is not obvious that one would be observed at the proposed level of donor–acceptor interaction.

(31) (a) J. A. Pople, *Accounts Chem. Res.*, 3, 217 (1970); (b) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970.

(32) Admittedly a flaw in the model is failure to distort one of the benzene rings as is the para-bridged ring in the cyclophanes. Allowing for such distortion at the simple Hückel level had little effect on the outcome. Including such distortion in the CNDO/2 calculation would have introduced severe nonbonding interactions between hydrogens on the two rings (which correspond to the methylene bridges in the cyclophane) with possibly irrelevant consequences. A CNDO/2 calculation on the total cyclophane was impractical due to the size of the matrices involved.

(33) Computer fitted according to the least-squares criterion.

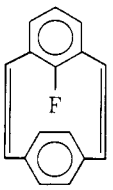
(34) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York, N. Y., 1969.

(35) (a) P. Diehl, *J. Chim. Phys. Physicochim. Biol.*, **61**, 13 (1964). (b) We are grateful to Professor W. Lwowski for calling this measure of complexation to our attention.

As seen above, the assumption that all substitutents induce a transition-state effect, whereas only electron acceptors induce a significant ground-state effect, allows a dissection of the two effects and a correlation of all of the data points in terms of one or the other of two Hammett functions, each having uncertainties in $\rho$ of less than 10%. We feel that the assumption that electron donors do not influence the stability of the cyclophane's conformational ground state is justified by the fact that donor–acceptor complexes between benzene and benzenes that are even multiply substituted with donors are apparently unknown.[34] This suggests that donor substituents on the cyclophanes should have at most a relatively small stabilizing influence on the conformational ground-state energy and may even be somewhat destabilizing. In this respect it is of interest that with aromatic compounds bearing good donors such as amino or methoxy, Diehl observed only relatively small (and of opposite sign from that with acceptors) chemical shifts induced by benzene as solvent.[35a]

The above work provides kinetic evidence that steric interaction between nonpolar moieties, by virtue of specific arrays of orbitals, may induce dipolar character.[36] The $\rho$ value alleged to result from this phenomenon is larger than that associated with the obviously polar process of ionizing benzoic acid. This phenomenon is probably very general, but it may play an important role only in special cases such as that studied here.

Presented in the previous paper was the remarkable observation that in spite of the presumably comparable sizes of hydrogen and fluorine, the diene **2** shows nmr coalescence of the sets of para-bridged ring protons at $-96°$ ($k = 203$ sec$^{-1}$), whereas the spectrum of the fluorodiene **29** remains unchanged even at 190° (estimated $k < 5$ sec$^{-1}$).[3a] If the entropy of activation required for ring flipping in these two compounds is estimated as about equal to that required in **1**-*H* (−8.8 eu), then the ring-flipping rate ratio, $k_2/k_{29}$, may be calculated to be greater than $10^{11}$ at 25°.

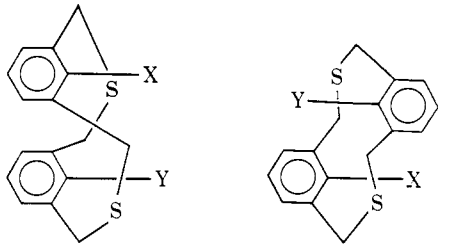



**29**

The difference in length between aromatic fluorine and aromatic hydrogen bonds is about 0.22 Å (1.30–1.08 Å)[37a] and the difference between the van der Waals radius of fluorine and that of hydrogen has been taken as 0.27 Å (1.47–1.20 Å);[37b] this gives a net steric difference of 0.49 Å in the two atoms as situated in dienes **2** and **29**. Quite possibly steric crowding in the transition states for ring flipping in the dienes is so severe that a difference of 0.5 Å intrudes upon a steep portion of the nonbonding potential function and accounts for the very large rate factor of $10^{11}$. That van der Waals potential curves for various pairs of weakly interacting, nonbonding atoms are similar in shape has been demonstrated.[38] However, this may not be true for strong interactions between specific arrays and orientations of atoms.

The possibility that the specific nature of the interaction between fluorine and a benzene $\pi$-electron cloud may be such that fluorine in such an environment is effectively larger than usual merits consideration. Some available evidence lends suggestive but not definitive support to this possibility. Sodium disulfide coupling of 1,6-bis(bromomethyl)toluene affords the dithiacyclophane **30** in a syn to anti ratio of 1:7,[39] whereas an analogous reaction affords difluorodithiacyclophane **31** as a single conformer,[40] which has been identified as syn by dipole moment measurements.[40b] Since the difluoro compound **31** has been shown to undergo ring flipping readily ($\Delta G_{157}° = 21.1$ kcal/mol),[40] the preponderance of syn conformer in this case must reflect the thermodynamic equilibrium. On the other hand, the syn and anti forms of **30** have been shown not to interconvert at reasonable temperatures,[39c] so the conformational ratio in this case must be kinetically determined. To the extent that this kinetic ratio is indicative of the relative thermodynamic stabilities, one can conclude that on going from the dimethyl derivative to the difluoro derivative there is a reversal in the conformational preference, which is in defiance of the fact that the carbon–fluorine dipoles seemingly should prefer a head-to-tail orientation.

Fluorine–fluorine attraction[41a] might be invoked, but this is contraindicated as a full explanation by the fact that in cyclophane **32** the thermodynamic ratio of conformers again favors syn (3:1[40b] or 2:1[39c]). A possible rationale would be that when sterically interacting with a benzene $\pi$-electron cloud fluorine is effectively larger than methyl.




**30**. X = Y = CH
**31**. X = Y = F
**32**. X = CH; Y = F

(36) The conclusion that the transition state for conformational flipping has polar character (the CNDO/2 calculation on the structure depicted in Figure 3 gives a net dipole moment of 0.327 debye) suggested that a dependence of the rate on solvent might be observable. Since the above measurements were carried out in the relatively nonpolar chloroform ($\mu = 1.02$ debye), for comparison the flipping rate of the parent compound **1**-*H* was determined in the much more polar acetonitrile ($\mu = 3.84$ debye, $d = 36.7$). The rate constant ratio, $K_{CD_3CN}/K_{CDCl_3}$, at 35.0 ± 0.3° was 0.96 ± 0.05; that is to say indistinguishable from unity by our technique. Since the alleged induced dipolar character of the transition state predominantly resides in the 8 carbon–hydrogen bond, where it is effectively shielded from interaction with solvent by the para-bridged ring, a less dramatic dependence of rate on solvent than on substituents is reasonable.

(37) (a) *Chem. Soc., Spec. Publ.*, **No. 11** (1958); (b) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

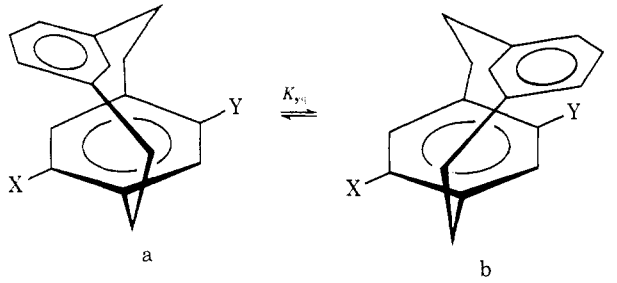
(38) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 529.

(39) (a) R. H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970); (b) R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, **96**, 1547 (1974); (c) F. Vögtle and P. Newman, *Tetrahedron*, **26**, 5299 (1970).

(40) (a) F. Vögtle and L. Schunder, *Chem. Ber.*, **102**, 2677 (1969); (b) P. H. Anderson and V. Boekelheide, *J. Org. Chem.*, **38**, 3928 (1973).

(41) (a) N. C. Craig and E. A. Entemann, *J. Amer. Chem. Soc.*, **83**, 3047 (1961); (b) N. D. Epiotis, *ibid.*, **95**, 3087 (1973).

Conformational flipping in [2.2]metaparacyclophanes seemed to offer an opportunity to probe this possibility. Asymmetric substitution of the para-bridged ring, as in **33**, **34**, and **35**, would render the two conformers nonequivalent and determination of the conformational equilibrium constants might provide a qualitative comparison of the substituents in terms of their steric interaction with the $\pi$-electron cloud of the meta-bridged ring. These compounds also would serve




**33**, X = F; Y = Br
**34**, X = F; Y = H
**35**, X = F; Y = $CH_3$

as relatively subtle probes for shielding of a fluorine nucleus by an aromatic ring current; one conformer of each compound would provide the potentially shielding orientation, while the fluorine chemical shift in the other conformer would seemingly provide an attractive standard, being measured for a species of identical primary structure.

Compounds **33**, **34**, and **35** were conveniently synthesized *via* the route shown in Scheme IV.

Proton nmr showed each of these compounds in solution to be a mixture of two conformers as expected, and the predominant conformer could be unambiguously assigned from the proton spectra by virtue of the well-documented influence of the meta-bridged ring's anisotropy on the chemical shifts of the para-bridged ring protons. Integration of the proton spectra provided a measure of the conformational equilibrium constant, but this measure was in some cases inherently of low precision due to the small numerical difference from which it was extracted. Where possible, a more precise measure was obtained by integrating the pair of singlets observed in proton-decoupled fluorine spectra. Fluorine chemical shifts could be assigned to specific conformers by reference to the proton spectra. The results are summarized in Table III.

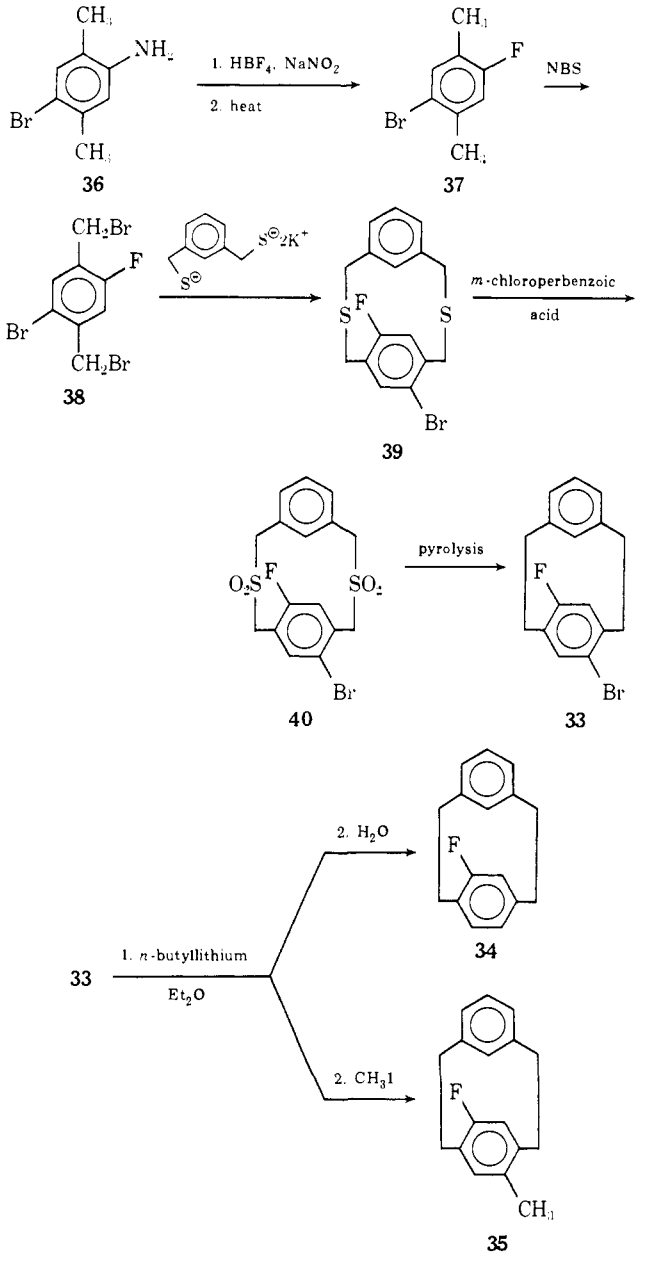
**Table III.** Conformational Equilibrium Constants and Fluorine Chemical Shifts

| Compd | Conformer a/conformer b By proton spectrum | Conformer a/conformer b By fluorine spectrum | Fluorine chemical shifts[b] Conformer a | Fluorine chemical shifts[b] Conformer b |
|---|---|---|---|---|
| **33** | 3.2 | 3.5 | +8.34 | +8.44 |
| **34** | 0.56 | 0.51 | +7.1 | +7.9 |
| **35** | 1.82 | *a* | +11.6 | +11.6 |

[a] Unresolved. [b] In ppm relative to fluorobenzene measured separately in the same solvent ($CDCl_3$) at the same concentration (0.5 *M*).

Admittedly, other factors could influence the conformational equilibria, but we feel that they are apt to be minor in comparison to steric interaction between

**Scheme IV**




the substituent and the meta-bridged ring. The data are qualitatively consistent with this viewpoint in terms of the relative steric bulk usually ascribed to the substituents. Thus, by this measure fluorine is larger than hydrogen but definitely smaller than methyl or bromine, and by inference methyl is smaller than bromine. These are the generally accepted steric relationships.[42]

The present experiment does not support the contention that fluorine, when strongly interacting with a benzene $\pi$-electron cloud, may be effectively larger than usual; however, the separation and orientation of fluorine and the $\pi$-electron cloud in compounds **33a**, **34a**, and **35a** differ from that in the anti forms of **31** and **32** and differ markedly from that in the transition

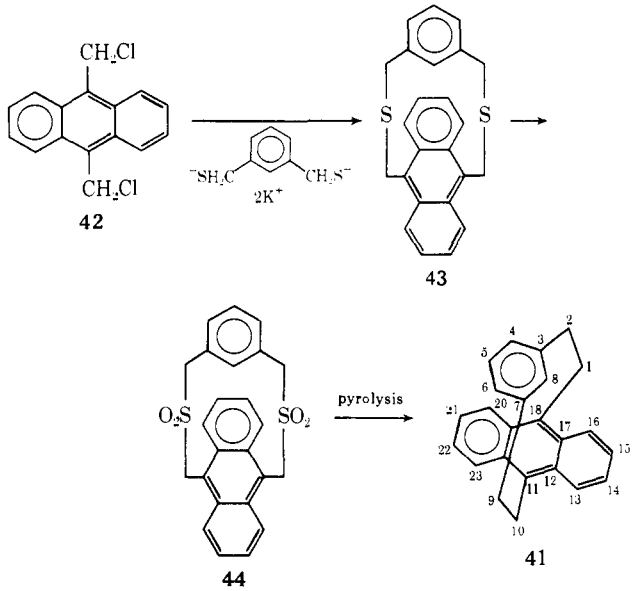
(42) (a) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Interscience, New York, N. Y., 1966, p 115. (b) The above gives 2.0 Å as the van der Waals radius of methyl. A value of 1.79 Å has also been used: J. F. Biellman, R. Hanna, G. Ourisson, C. Sandris, and B. Waegell, *Bull. Soc. Chim. Fr.*, 1429 (1960). (c) For other thermodynamic evidence that fluorine is larger than hydrogen, see H. C. Brown, D. Gintis, and L. Domash, *J. Amer. Chem. Soc.*, 78, 5387 (1956).

state for ring flipping in **29**. If a strong mixing of the filled fluorine orbitals and the $\pi$ system were required for an unusual effect, these differences may be important. On the other hand, the conformational preferences in **30**, **31**, and **32** may find a unifying rationale on other grounds. A very recent paper presented theoretical arguments for attractive interaction between pairs of formally nonbonding halogens and even between halogen and methyl where the symmetry and energy of unfilled levels in the moiety to which they are attached is appropriate.[41b] This may be true in the cyclophanes discussed above.

Finally one notes that in the two cases where a distinction is possible (**33** and **34**) the fluorines which are shielded by the meta-bridged ring appear *downfield* in the nmr from those which are not thus shielded. As in the previous paper[3a] shielding of fluorine by an aromatic ring current has proven to be an elusive, if existent, phenomenon. Even provision for model compounds which differ only in conformation from the test cases has shown other factors[43] to dominate the anticipated effect of a diamagnetic ring current.

As an outgrowth of our interest in the barrier to conformational flipping in [2.2]metaparacyclophanes, synthesis of the anthracene analog **41** and assessment of its conformational behavior were undertaken for comparative purposes. The synthesis was accomplished *via* the usual route, starting with 9,10-bis(chloromethyl)anthracene (**42**), but the end product, **41**, proved to be a relatively unstable compound (Scheme V).

**Scheme V**




Sublimation of **41** at 140° at 1 $\mu$ gave reasonably pure material, but attempts at further purification by column chromatography resulted in decomposition. It was possible to record an nmr spectrum, but a solution of the compound at room temperature began depositing a yellow precipitate, apparently of polymer, almost immediately. A nearly identical spectrum was observed with perchlorobutadiene as solvent, but raising the temperature of this solution in an effort to observe coalescence caused rapid loss of the product. Use of a small amount of hydroquinone in carbon tetrachloride as solvent was found to suppress polymerization for hours (implicating a radical chain process, presumably due to the strained central ring of the anthracene moiety) and allowed study of its nmr temperature dependence. At room temperature the anthracene protons give rise to a pair of AA'BB' patterns, which appear as four well-separated multiplets of moderate width. These could be assigned by comparison with the spectra of other anthracene derivatives, allowance for the shielding influence of the meta-bridged ring, and through decoupling experiments. At about 82° the multiplet due to protons at positions 20 and 23 coalesced with that due to protons at 13 and 16 ($\Delta\nu$ = 60 Hz). Coalescence was also noted for the terminal pairs of anthracene protons and for the methylene region. In that the multiplets are relatively narrow in comparison to their separation, $k_c = \pi\Delta\nu/2$ may be used as an approximation to the conformational flipping rate at coalescence.[44] This gives $k_{82}° = 133$ sec$^{-1}$ and $\Delta G^{\ddagger} = 17.5$ kcal/mol. Extrapolation of the Arrhenius data determined for **1-*H*** to 82° gives $(k_{41}/K_{1-H})_{82°} = 45$, $\Delta\Delta G^{\ddagger}_{82°} = 2.6$ kcal/mol. Two factors which are probably responsible for the more facile ring flipping process in **41** are apparent. Most obvious is the likelihood that the face of the meta-bridged ring experiences nonbonding repulsions involving the opposing terminal ring of the anthracene moiety. This would facilitate ring flipping by destabilizing the conformational ground state relative to that in **1-*H***. In addition, there is reason to believe that the transition state for flipping in **41** should be of lower energy than that involving **1-*H***. In each case a significant element of strain energy in the transition state must arise from out-of-plane distortion of the para-bridged ring. In the extreme this distortion tends to take the $\pi$ orbitals at the termini of the methylene bridges out of conjugation with the rest of the $\pi$ system. In **1-*H*** the effect is in the direction of reducing the resonance energy of a benzene ring to that of two ethylene units (cost in $E_{res} = 4\beta$), whereas in **41** the resonance energy of anthracene is reduced to that of two benzene rings (cost in $E_{res} = 3.314\beta$).[45] Of course the para-bridged rings in each case are already distorted in the ground state and the transition-state distortion may not approach the extreme referred to above; nevertheless, the above reasoning suggests that deformation of the para-bridged ring, and hence conformational ring flipping, will be less costly in terms of resonance energy in **41** than in **1-*H***.

## Experimental Section[46]

**9-Bromo-2,11-dithia[3.3]metaparacyclophane (4).** A solution of 1,4-bis(mercaptomethyl)benzene (3.2 g, 18.6 mmol, 1.1 equiv) and

(43) For a discussion of factors involved in fluorine chemical shifts, see V. W. Emsley and L. Phillips, *Progr. Nucl. Magn. Resonance Spectrosc.*, 7, 1 (1971).

(44) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

(45) "Supplemental Tables of Molecular Orbital Calculations," A. Streitwieser, Jr., and J. I. Brauman, with a "Dictionary of $\pi$-Electron Calculations," C. A. Coulson and A. Streitwieser, Jr., Vol. II, Pergamon Press, New York, N. Y., 1965.

(46) Elemental and mass spectral analyses were determined by Dr. S. Rottschaefer, University of Oregon Microanalytical Laboratories. Melting points are uncorrected and were taken with a Mel-Temp apparatus (for sealed-tube samples) or a Reichert hot-stage microscope. Infrared spectra were measured with Beckman IR-7 or IR-10 spectrophotometers. Nmr spectra were measured using a Varian XL-100 spectrometer; proton chemical shifts are reported in $\tau$ with tetramethyl-

sodium hydroxide (1.52 g, 38.1 mmol, 1.12 equiv) in 200 ml of nitrogen-saturated 60% aqueous ethanol and a solution of 2,6-bis(bromomethyl)bromobenzene (**3**)[47] (5.8 g, 17 mmol) in 200 ml of benzene were added separately, but simultaneously, from two Herschberg funnels over a period of 5 hr to a rapidly stirred solution of 200 ml of benzene and 400 ml of 95% ethanol in a 3-l. Morton flask. The reaction mixture was concentrated under reduced pressure. The resulting solid was taken up in dichloromethane and washed successively with 2 *M* sodium hydroxide, 2 *M* hydrochloric acid, and water, followed by drying over sodium sulfate. Concentration of the solution under reduced pressure gave 6.8 g of a waxy solid. Sublimation of this at 165° at 20 $\mu$ gave 2.9 g (48.7%) of a white solid. An analytical sample, recrystallized from carbon tetrachloride, melted at 247–248.5° (lit.[9] mp 225–226°). Since its melting point differed so widely from that reported, and since full characterization of the compound was not available in the literature, the following spectral data for **4** are provided: nmr ($CDCl_3$) narrow multiplet at 2.87 superimposed on an $A_2B$ from 2.70–3.03 (total 5 H, unshielded para-bridged ring protons and meta-bridged ring protons), narrow multiplet at 3.60 (2 H, shielded para-bridged ring protons), two superimposed AB quartets (total 8 H, methylene protons) at 6.22 ($J$ = 13.5 Hz, $\Delta\nu$ = 16 Hz) and 6.28 ($J$ = 16 Hz, $\Delta\nu$ = 25 Hz); mass spectrum *m/e* (rel intensity) 352 (70), 350 (68), 271 (15), 167 (47), 135 (60.5), 105 (100), 104 (37), 103 (28), 91 (70), 77 (28), 51 (17), 45 (28).

**9-Bromo-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (5).** To a solution of 2.90 g (8.3 mmol) of **4** in 150 ml of chloroform, cooled in an ice bath and stirred magnetically, was added 8.4 g of 85% pure *m*-chloroperbenzoic acid (41.5 mmol, 1.25 equiv). The flask was allowed to warm to room temperature over a period of several hours, and stirring was continued for 2 days. The precipitate was isolated by filtration and washed with several portions of chloroform. This gave 3.38 g (98.6%) of a white solid: mp >300°; nmr ($CF_3COOH$) 2.10–2.21 (2 H, A part of $A_2B$), narrow multiplet at 2.41 (2 H, unshielded para-bridged ring protons), 2.50–2.70 (1 H, B part of $A_2B$), narrow multiplet at 3.10 (2 H, shielded para-bridged ring protons), AB quartet centered at 5.23 (4 H, methylene, $J$ = 15.5 Hz, $\Delta\nu$ = 78 Hz), AB quartet centered at 5.21 (4 H, methylene, $J$ = 14 Hz, $\Delta\nu$ = 16 Hz); mass spectrum *m/e* (rel intensity) 416 (1.2), 414 (1.3), 288 (16), 286 (16), 207 (100), 184 (42), 182 (46), 104 (68), 103 (95), 77 (53).

**8-Bromo[2.2]metaparacyclophane (6).** Pyrolysis of bissulfones to give the corresponding ring-contracted cyclophanes was carried out in an apparatus consisting of a horizontal tube (18 mm in diameter) passing through two adjacent tube furnaces, each of which was 15 cm long. The first furnace provided a temperature that would induce sublimation of the bissulfone; the second was used at a higher temperature that would assure pyrolysis. A loose Pyrex wool plug separated the zones. A vacuum pump was connected at the exit from the second furnace, and a capillary nitrogen bleed was provided at the entrance to the first furnace. The bore of the capillary was chosen to provide, in conjunction with the vacuum pump, the desired pressure. The product was condensed on a water-cooled cold finger that was inserted into the tube at the exit from the second furnace. The portion of the tube passing through the hotter furnance was made of quartz, the junctions employing graded seals.

In two portions, 0.58 g (1.4 mmol) of bissulfone **5** was pyrolyzed in the above apparatus as follows. The sample of bissulfone was placed in the first furnace on an aluminum foil boat. While the system was being purged with nitrogen at a pressure of 1.2 mm, the second furnace was heated to 500° and then the first furnace was heated to 350°. After 12 hr the product was removed from the cold finger by dissolution in chloroform. The crude product was preadsorbed on silica gel and placed at the head of a 10 × 1.5 cm silica gel column packed in petroleum ether (30–60°). Elution with this solvent provided 253 mg (63%) of white crystalline product. An analytical sample was purified by preparative gas chromatography at 250° to give white crystals: mp 240–241° (sealed tube); nmr ($CDCl_3$) narrow multiplet at 2.75 (2 H, unshielded protons of para-bridged ring), $A_2B$ pattern at 2.8–3.4 (3 H, meta-bridged ring protons), narrow multiplet at 4.16 (2 H, shielded protons of para-bridged ring), a complex multiplet (ABCD) at 6.50–7.90 (8 H, methylene protons); mass spectrum *m/e* (rel intensity) 288 (37), 286 (38), 207 (100), 184 (29), 182 (33), 103 (56).

**[2.2]Metaparacyclophane (1-*H*).** A 15-ml two-necked flask was flame-dried under nitrogen purge. Then, 72.4 mg (0.25 mmol) of bromide **6** and 5 ml of dry ether (distilled from lithium aluminum hydride) were added. The solution was cooled in an ice bath and stirred magnetically while 0.54 ml of 1.4 *M* *n*-butyllithium (3 equiv) in hexane was added. The ice bath was replaced with a water bath at room temperature for 5 min; then the reaction mixture was again cooled in an ice bath and 1 ml of water was added. Additional ether was added, and the ether layer was separated, washed with brine, and dried over magnesium sulfate. Removal of solvent on a rotary evaporator gave 51.6 mg of white solid, which was chromatographed on an 8 × 1.5 cm silica gel column to obtain 47.6 mg (90%) of pure cyclophane **1-*H***, spectroscopically identical with previously reported samples.[3a,4a]

**8-Deuterio[2.2]metaparacyclophane (1-*D*).** Preparation of the deuterated compound was accomplished as described for **1-*H*** with the exception that the organolithium intermediate was quenched with deuterium oxide. The melting point and general physical properties of the product were in agreement with those of **1-*H***. By nmr, the 8-H of the sample integrated as only 0.051 H, indicating 94.9% deuteration of this position. As a result the meta and para coupling in the meta-bridged ring as seen in **1-*H*** was eliminated and the deuterio compound showed a clean $AB_2$ pattern for the meta-bridged ring protons. Comparison of the mass spectra of **1-*H*** and **1-*D*** indicated 95.7 ± 0.6% deuteration.

**6-Fluoro-2,11-dithia[3.3]metaparacyclophane (14).** The coupling of 3,5-bis(bromomethyl)fluorobenzene[48] (**10**, 5.64 g, 20 mmol) and 1,4-bis(mercaptomethyl)benzene (3.40 g, 20 mmol) was carried out in the same manner described previously for the preparation of **4**. Sublimation of the crude product gave 3.14 g (54%) of white crystals: mp 154–156°; nmr ($CDCl_3$) singlet at 3.1 (4 H, para-bridged ring protons), doublet at 3.31 (2 H, $J_{HF}$ = 10 Hz, outer meta-bridged ring protons), a broad singlet at 4.59 (1 H, internal proton of meta-bridged ring), a singlet at 6.16 (4 H, methylene protons), a singlet at 6.59 (4 H, methylene protons); mass spectrum *m/e* (rel intensity) 290 (100), 167 (19), 153 (25), 123 (38), 105 (53), 91 (41).

**6-Fluoro-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (18).** Dithiacyclophane **14** (0.87 g, 3 mmol) was oxidized with *m*-chloroperbenzoic acid (2.59 g, 15 mmol, 1.25 equiv) as described for the preparation of **5**. The product, a white solid, was separated by filtration, washed with saturated sodium bicarbonate and 10% hydrochloric acid, and dried to give 1.12 g (100%) of product. Sublimation of this at 340° and 0.2 mm gave white crystals: mp >300°; nmr ($CF_3CO_2H$) singlet at 2.61 (4 H, para-bridged ring protons), doublet at 2.80 (2 H, $J_{HF}$ = 8 Hz, outer meta-bridged ring protons), a broad singlet at 4.30 (1 H, internal meta-bridged ring proton), a singlet at 5.20 (4 H, methylene protons), a singlet at 5.60 (4 H, methylene protons); mass spectrum *m/e* (rel intensity) 354 (2.2), 226 (100), 211 (44), 198 (19), 122 (56), 104 (72).

**5-Fluoro[2.2]metaparacyclophane (22).** Bissulfone **18** (115 mg, 0.32 mmol) was pyrolyzed in the apparatus described for the preparation of **6**. The temperature of the first oven was 340°, that of the second, 600°, and the pressure was 2.1 mm. After 12 hr 66 mg of crude product was removed from the cold finger and was chromatographed on silica gel eluted with petroleum ether (30–60°) to obtain 55 mg (78.7%) of white crystals. An analytical sample, recrystallized from petroleum ether (30–60°), gave white crystals: mp 75–78°; nmr ($CDCl_3$) narrow multiplet at 2.82 (2 H, unshielded para-bridged ring protons), doublet at 3.54 (2 H, $J_{HF}$ = 9.6 Hz, outer meta-bridged ring protons), broad singlet at 4.81 (1 H, internal meta-bridged ring proton), multiplet at 6.67–7.02 (2 H, methylene protons), multiplet at 7.10–8.10 (6 H, methylene protons); mass spectrum *m/e* (rel intensity) 226 (15), 166 (50), 160 (100), 131 (100), 67 (94).

**6-Methoxy-2,11-dithia[3.3]metaparacyclophane (15).** The coupling of 3,5-bis(bromomethyl)anisole[48] (4.0 g, 13.6 mmol) and 1,4-bis(mercaptomethyl) benzene (2.13 g, 13.6 mmol) was carried out as described for the preparation of **4**. The isolated crude product (4.4 g) was sublimed at 10 $\mu$ to obtain 1.92 g (46.9%) of white

silane as an internal standard, and fluorine chemical shifts are in ppm relative to fluorobenzene as measured separately but in the same solvent at the same concentration. Mass spectra were measured at 70 eV with a Consolidated Model 21-110 spectrometer. Gas chromatography was carried out on a Varian 90-P3 instrument using a 6 ft × 0.25 in. aluminum column packed with 17% SE-30 on Chromosorb P. We thank the National Science Foundation for funds used toward the purchase of the Varian XL-100. All elemental analyses of new compounds gave experimental values within 0.3% of the calculated values, except 4 and **5**, which were within 0.5%, and **26** and **37**, which were within 0.6%.

(47) F. Vögtle, *Chem. Ber.*, 102, 1784 (1969).

(48) V. Boekelheide and R. W. Griffin, Jr., *J. Org. Chem.*, 34, 1960 (1969).

crystals: mp 157–158.5°; nmr ($CDCl_3$) singlet at 3.10 (4 H, para-bridged ring protons), singlet at 3.47 (2 H, outer meta-bridged ring protons), broad singlet at 4.77 (1 H, internal meta-bridged ring proton), singlet at 6.17 (4 H, methylene protons), singlet at 6.24 (3 H, methoxy protons), singlet at 6.59 (4 H, methylene protons); mass spectrum *m/e* (rel intensity) 302 (100), 135 (100), 121 (15), 105 (29), 104 (32), 91 (57).

**6-Methoxy-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (19).** Dithiacyclophane **15** (0.80 g, 2.64 mmol) was oxidized with *m*-chloroperbenzoic acid (2.27 g, 13.2 mmol, 1.25 equiv) as described for the preparation of bissulfone **5**. The crude product was washed with chloroform, dried, and weighed, 1.26 g (100%). Sublimation at 10 $\mu$ gave white crystals: mp >300°; nmr ($CF_3CO_2H$) singlet at 2.62 (4 H, para-bridged ring protons), singlet at 2.88 (2 H, outer meta-bridged ring protons), broad singlet at 4.42 (1 H, internal meta-bridged ring protons), singlet at 5.22 (4 H, methylene protons), singlet at 5.60 (4 H, methylene protons), a singlet at 6.04 (3 H, methoxy protons); mass spectrum *m/e* (rel intensity) 366 (15), 238 (53), 134 (100), 104 (33), 91 (37).

**5-Methoxy[2.2]metaparacyclophane (23).** Crude bissulfone **19** (202 mg, 0.55 mmol) was pyrolyzed in the apparatus described for the preparation of **6**. The temperature of the first oven was 370°, that of the second oven was 600°, and the pressure in the system was 1.5 mm. After 12 hr the crude product was removed from the cold finger with ether, and the ethereal solution was washed with saturated sodium bicarbonate solution and dried over sodium sulfate. Evaporation of the solvent left 72.6 mg of yellow oil, which was preadsorbed on silica gel and placed at the head of a silica gel column packed in petroleum ether. Elution with a 50% benzene–petroleum ether (30–60°) mixture gave 71.9 mg (93%) of colorless oil: nmr ($CDCl_3$) narrow multiplet at 2.84 (2 H, unshielded para-bridged ring protons), broad singlet at 3.69 (2 H, unshielded para-bridged ring protons), narrow multiplet at 4.05 (2 H, shielded para-bridged ring protons), broad singlet at 5.01 (1 H, internal meta-bridged ring protons), singlet at 6.26 (3 H, methoxy protons), multiplet at 6.70–6.97 (2 H, methylene protons), multiplet at 7.22–8.06 (6 H, methylene protons); mass spectrum *m/e* (rel intensity) 238 (100), 223 (20), 134 (70), 91 (30).

**6-Methoxy-2-thia-2,2-dioxo[3.2]metaparacyclophane (26).** Bissulfone **19** (66 mg) was pyrolyzed as above with the exception that the temperatures of the first and second ovens were 320 and 500°, respectively. The crude product (37.1 mg) was removed from the cold finger and placed in a 1 cm × 30 cm tube which had one end sealed and which was wrapped with a heating element in a way that would provide a decreasing temperature gradient from the sealed end to the open end. The open end was attached to a vacuum system to provide 10 $\mu$ pressure, and the sample was differentially sublimed. Analysis by nmr showed that the most volatile component was cyclophane **23** and that the least volatile component was bissulfone **19**. A small amount of white crystalline solid of intermediate volatility was obtained and is thought to be monosulfone **26**. An nmr spectrum of **26** in $CF_3CO_2D$ was obtained by the Fourier transform technique, and showed an AB pattern at 2.89 and 3.25 (4 H, $J_{AB}$ = 8 Hz, para-bridged ring protons), broad singlets at 3.15 and 3.25 (each 1 H, meta-bridged ring protons), a broad singlet at 4.73 (1 H, internal H of meta-bridged ring), singlets at 5.32 and 5.78 (each 2 H, methylene proton adjacent to sulfone), a singlet at 5.99 (3 H, methoxy protons), a multiplet at 6.96–7.21 (4 H, methylene protons). The mass spectrum of **26** showed signals at *m/e* (rel intensity) 302 (20), 238 (100), 223 (22), 134 (45).

**3,5-Bis(bromomethyl)nitrobenzene (12).** This was prepared by bromination of 5-nitro-*m*-xylene as reported[49] except *N*-bromosuccinimide in $CCl_4$ was used as the brominating agent. The product isolated by recrystallization was a light-yellow crystalline solid: mp 100–104° (lit.[49] mp 105–106.5°); nmr ($CDCl_3$) doublet at 1.79 (2 H, $J$ = 1.6 Hz), triplet at 2.24 (1 H, $J$ = 1.6 Hz), singlet at 5.37 (4 H, methylene protons).

**6-Nitro-2,11-dithia[3.3]metaparacyclophane (16).** Dibromide **12** (1.00 g, 3.25 mmol) and 1,4-bis(mercaptomethyl)benzene (0.61 g, 3.58 mmol, 1.1 equiv) were coupled by the method described for the preparation of **4**. The crude product was sublimed at 140° (15 $\mu$) to obtain 456 mg (44%) of yellow crystals: mp 173–175°; nmr ($CDCl_3$) poorly resolved doublet at 2.12 (2 H, $J_{meta}$ = 1.3 Hz, meta-bridged ring protons), singlet at 3.08 (4 H, para-bridged ring protons), broad singlet at 4.03 (1 H, internal meta-bridged ring proton), singlets at 6.14 and 6.49 (each 4 H, methylene protons); mass spectrum *m/e* (rel intensity) 317 (79), 105 (100), 90 (44).

**6-Nitro-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (20).** Dithiacyclophane **16** (424 mg, 1.35 mmol) was oxidized with *m*-chloroperbenzoic acid (6.7 mmol, 1.25 equiv) as described for the preparation of **5**. The product, after being thoroughly washed with chloroform, weighed 438 mg (86.3%) and was a light-yellow solid: mp >300°; nmr ($CF_3CO_2H$) broad singlet at 1.59 (2 H, meta-bridged ring protons), singlet at 2.59 (4 H, para-bridged ring protons), broad singlet at 3.35 (1 H, internal meta-bridged ring proton), singlets at 5.18 and 5.45 (each 4 H, methylene protons). An analytical sample was sublimed at 310° (5 $\mu$); mass spectrum *m/e* (rel intensity) 381 (0.2), 253 (100), 149 (30), 104 (98), 77 (59).

**5-Nitro[2.2]metaparacyclophane (24).** Bissulfone **20** (299 mg) was pyrolyzed in three portions in the apparatus described for the preparation of **6**. The temperature of the first oven was 400°, that of the second was 600°, the pressure was 1.5 mm, and the time allowed for each pyrolysis was 24 hr. The combined crude product was chromatographed on silica gel using a 30% benzene–petroleum ether (30–60°) mixture as eluent. This gave 182 mg (92%) of light-yellow crystals: mp 146–148°; ir 1530, 1350 $cm^{-1}$ ($NO_2$); nmr ($CDCl_3$) poorly resolved doublet at 2.31 (2 H, $J_{meta}$ = 1.4 Hz, meta-bridged ring protons), narrow multiplet at 2.74 (2 H, unshielded para-bridged ring protons), narrow multiplet at 4.05 (2 H, shielded para-bridged ring protons), broad singlet at 4.14 (1 H, internal meta-bridged ring proton), multiplets at 6.66–6.88 (2 H) and 6.96–7.88 (6 H) due to methylene protons; mass spectrum *m/e* (rel intensity) 253 (100), 104 (50), 103 (25), 91 (17), 77 (33); uv (cyclohexane) 273 nm ($\epsilon$ 8060, tails into the visible).

**5-Amino[2.2]metaparacyclophane (28).** Cyclophane **24** (120 mg), 20 mg of platinum oxide, and 10 ml of ethyl acetate were subjected to hydrogenation at room temperature and 3 atm pressure for 2 hr. Nmr analysis suggested that reduction was incomplete. New catalyst (10 mg) was added and hydrogenation was continued as above for 4 hr. Filtration to remove catalyst and evaporation of the solvent left a crude oil which was chromatographed on a silica gel plate (1 = 200 × 200 mm) with benzene as the eluent. Four mobile components with $R_f$'s 0.565, 0.265, 0.183, and 0.088 were isolated and respectively identified as: 11.5 mg of starting material (9.6% recovery), 4.8 and 40.5 mg of red oils which according to nmr apparently had undergone reduction of the para-bridged ring, and 33.3 mg of brownish crystals (31.5%) which gave an nmr appropriate for the desired product. This material was rechromatographed as above to obtain 28.9 mg of light tan crystals, mp 104–111°, and was then sublimed at 3 $\mu$ to obtain white crystals, mp 113–114°; nmr ($CDCl_3$) narrow multiplet at 2.85 (2 H, unshielded protons of para-bridged ring), doublet at 3.93 (2 H, $J_{meta}$ = 1.6 Hz, meta-bridged ring protons), narrow multiplet at 3.98 (2 H, shielded para-bridged ring protons), triplet at 5.21 ($J_{meta}$ = 1.6 Hz, 1 H, internal proton of meta-bridged ring), broad singlet at 6.67 (2 H, amine protons), multiplet at 6.70–7.00 (2 H, methylene protons), multiplet at 7.28–8.10 (6 H, methylene protons); ir 3470 and 3385 $cm^{-1}$ ($NH_2$); mass spectrum *m/e* (rel intensity) 223 (100), 208 (15), 119 (78), 91 (14).

*Anal.* Calcd for $C_{16}H_{17}N$: mol wt, 223.136. Found (high resolution mass spectrum): mol wt, 223.137.

**Dimethyl 5-Bromoisophthalate (8).** 5-Bromoisophthalic acid[50] (24.3 g) was dissolved in 250 ml of methanol contained in a 500-ml round-bottomed flask. A solution of 14 ml of sulfuric acid in 50 ml of methanol was added and the reaction mixture was boiled under reflux for 20 hr. When stored overnight at 0°, crystallization occurred. Filtration, washing with a few milliliters of cold methanol, and drying gave 22.5 g (82.5%) of white crystals: mp 88–89°; nmr ($CDCl_3$) triplet at 1.41 (1 H, $J_{meta}$ = 1.3 Hz), singlet at 6.04 (6 H, methyl protons); mass spectrum *m/e* (rel intensity) 274 (49), 272 (53), 243 (94), 241 (100), 215 (21), 213 (24), 75 (64), 74 (38), 28 (41).

**3,5-Bis(hydroxymethyl)bromobenzene (9).** Diester **8** (21.9 g) in 80 ml of dry tetrahydrofuran was added dropwise to a stirred suspension of 3.9 g of lithium aluminum hydride in 30 ml of tetrahydrofuran. After addition was complete, the mixture was boiled under reflux for 30 min and then the excess lithium aluminum hydride was decomposed by dropwise addition of a saturated aqueous sodium sulfate solution. The ether layer was removed and the precipitate was washed with additional ether. The combined ethereal solution was washed with saturated brine, dried over sodium sulfate and concentrated on a rotary evaporator to give 13.7 g

(49) W. S. Reich, G. G. Rose, and W. Wilson, *J. Chem. Soc.*, 1234 (1947).

(50) E. W. Crandall and L. Harris, *Org. Prep. Proced.*, **1**, 147 (1969).

of off-white crystals (79%). Recrystallization from benzene gave white crystals: mp 90–91°; nmr ($CDCl_3$) broad singlet at 2.55 (2 H), broad singlet at 2.71 (1 H), singlet at 5.32 (4 H, methylene protons), broad singlet at 8.16 (2 H, hydroxyl protons); mass spectrum *m/e* (rel intensity) 218 (57), 216 (60), 186 (21), 184 (22), 137 (40), 107 (27), 91 (100), 79 (65), 78 (45), 77 (93), 51 (39), 31 (46).

**3,5-Bis(bromomethyl)bromobenzene (13).** To diol **9** (13.0 g, 0.06 mol), dissolved in 400 ml of mechanically stirred, refluxing benzene, was added dropwise 17.3 g (0.064 mol, 1.6 equiv) of phosphorus tribromide. After addition, stirring and refluxing were continued 2 hr, the reaction mixture was cooled to room temperature, and water was added. The benzene layer was separated, washed with water and brine, and dried over magnesium sulfate. Removal of solvent on a rotary evaporator gave a crude product which was chromatographed on silica gel (eluted by a 50% mixture of benzene and petroleum ether (30–60°)) to obtain 13.8 g of a yellowish solid (67%). A sample prepared for analysis by sublimation gave white crystals: mp 95–98°; nmr ($CDCl_3$) doublet at 2.52 (2 H, $J_{meta}$ = 1.5 Hz), triplet at 2.67 (1 H, $J_{meta}$ = 1.5 Hz), singlet at 5.60 (4 H, methylene protons); mass spectrum *m/e* (rel intensity) 345 (13), 344 (28), 342 (27), 340 (11), 265 (54), 263 (100), 261 (62), 184 (42), 182 (35), 103 (38), 77 (42), 51 (66).

**6-Bromo-2,11-dithia[3.3]metaparacyclophane (17).** Tribromide **13** (5.1 g, 0.015 mol) and 1,4-bis(mercaptomethyl)benzene (2.83 g, 1.1 equiv) were coupled by the method described for the preparation of **4**. Sublimation of the crude product (160° (10 $\mu$)) afforded 3.09 g of white solid (58.7%). Recrystallization from methylene chloride gave white crystals: mp 184–185°; nmr ($CDCl_3$) doublet at 2.87 (2 H, $J_{meta}$ = 1.5 Hz, meta-bridged ring protons), singlet at 3.08 (4 H, para-bridged ring protons), triplet at 4.46 (1 H, $J_{meta}$ = 1.5 Hz, internal meta-bridged ring proton), singlets at 6.17 and 6.61 (4 H each, methylene protons); mass spectrum *m/e* (rel intensity) 352 (53), 350 (48), 186 (19), 184 (22), 167 (24), 105 (100), 104 (37), 91 (50).

**6-Bromo-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (21).** Dithiacyclophane **17** (2.39 g, 6.8 mmol) was oxidized with 6.9 g of 85% *m*-chloroperbenzoic acid (34 mmol, 1.25 equiv) as described for the preparation of **5**. The product was isolated as 2.52 g (89%) of white solid. Sublimation gave white crystals: mp >300°; nmr ($CF_3CO_2H$) broad singlet at 2.37 (2 H, meta-bridged ring protons), singlet at 2.59 (4 H, para-bridged ring protons), broad singlet at 4.17 (1 H, internal meta-bridged ring proton), singlet at 5.21 and broadened singlet at 5.61 (each 4 H, methylene protons); mass spectrum *m/e* (rel intensity) 416 (3.3), 414 (2.5), 288 (96), 286 (100), 207 (96), 184 (47), 182 (48), 104 (95), 103 (99), 77 (80).

**5-Bromo[2.2]metaparacyclophane (25).** Bissulfone **21** (950 mg) was pyrolyzed in five portions in the apparatus described for the preparation of **6**. The temperature of the first oven was 360°, that of the second was 610°, and the pressure was 2.4 mm. Five hours was allowed for each pyrolysis. The combined crude products were chromatographed on silica gel eluted with petroleum ether (30–60°) to obtain 0.568 g of white crystals: nmr ($CDCl_3$) narrow multiplet at 2.84 (2 H, unshielded protons of para-bridged ring), doublet at 3.09 (2 H, $J_{meta}$ = 1.5 Hz, meta-bridged ring protons), narrow multiplet at 4.02 (2 H, shielded protons of para-bridged ring), triplet at 4.65 (1 H, $J_{meta}$ = 1.5 Hz, internal meta-bridged ring proton), multiplet at 6.70–6.98 (2 H, methylene protons), multiplet at 7.18–8.10 (6 H, methylene protons). Recrystallization of a sample from hexane gave white crystals: mp 84.0–84.7°; mass spectrum *m/e* (rel intensity) 288 (52), 286 (53), 207 (100), 184 (31), 182 (35), 104 (47), 103 (72), 77 (45).

**5-Acetyl[2.2]metaparacyclophane (27).** Bromide **25** (65 mg, 0.23 mmol), a magnetic stirring bar, and 2 ml of dry ether were placed in a 15-ml septum-sealed flask purged with nitrogen. The solution was stirred in an ice bath and 0.25 ml of a 1.6 *M* solution of *n*-butyllithium in hexane (0.4 mmol, 1.75 equiv) was added *via* a syringe. The ice bath was removed and the mixture was stirred for 15 min. Then the mixture was again cooled in an ice bath and 50 mg of freshly distilled acetic anhydride (2.1 equiv) was added *via* a syringe. The ice bath was removed and stirring was continued for 1 hr. The sample was subjected to an ether–water work-up. Concentration of the ether layer gave 58.7 mg of crude product. This was placed on a 200 × 200 × 1 mm silica gel plate and eluted with benzene. The most mobile component (19.3 mg, $R_f$ 0.75) was isolated and identified as [2.2]metaparacyclophane. The second component (19.8 mg, $R_f$ 0.22) was isolated and shown to be the desired acetyl derivative (34.5%). The sample was further purified by recrystallization from hexane to give white crystals: mp 91–93°; nmr ($CDCl_3$) doublet at 2.63 (2 H, $J_{meta}$ = 1.6 Hz, meta-bridged ring protons), narrow multiplets at 2.81 and 4.17 (2 H each, para-bridged ring protons), triplet at 4.32 (1 H, $J_{meta}$ = 1.6 Hz, internal meta-bridged ring proton), multiplet at 6.73–7.00 (2 H, methylene protons), multiplet at 7.08–7.96 (6 H, methylene protons); uv (cyclohexane) $\lambda_{max}$ (log $\epsilon$) 253 nm (4.02), 292 (3.03), 303 sh (2.90), 330 sh (1.90); mass spectrum *m/e* (rel intensity) 250 (100), 208 (16), 207 (79), 146 (44), 145 (21), 131 (15), 104 (18), 103 (30), 77 (27), 43 (31).

*Anal.* Calcd for $C_8H_{18}O$: mol wt, 250.136. Found (high resolution mass spectrum): mol wt, 250.137.

**2-Bromo-5-fluoro-*p*-xylene (37).** Tetrafluoroboric acid (188 ml) and water (94 ml) were added to a solution of 34.5 g of 4-bromo-2,5-xylidine[51] (mp 94–95°; lit. 96°) in 94 ml of tetrahydrofuran. A white paste of the tetrafluoroborate salt formed. While the paste was stirred and cooled in an ice–salt bath, a saturated aqueous solution of sodium nitrite (19 g) was added dropwise. After the mixture had been stirred for 1 hr, the precipitate was collected by filtration, washed with 5% tetrafluoroboric acid and methanol, and was dried. The salt (33.3 g, 74%) was suspended in 150 ml of toluene and the mixture was boiled under reflux. After decomposition of the salt was complete, the solvent was removed by fractional distillation and the product was vacuum distilled (90° (18 mm)) to obtain 14.6 g (42%) of a colorless liquid which when cooled gave a white solid: mp 11–12°; nmr ($CDCl_3$) doublet at 2.69 (1 H, $J_{HF\ meta}$ = 7.5 Hz), doublet at 3.14 (1 H, $J_{HFortho}$ = 10 Hz), singlet at 7.69 (3 H, methyl protons), broadened singlet at 7.80 (3 H, methyl protons); mass spectrum *m/e* (rel intensity) 204 (54), 202 (56), 123 (100), 77 (14), 51 (16).

**5-Fluoro-2,4-bis(bromomethyl)bromobenzene (38).** A solution of **37** (14 g, 68 mmol), *N*-bromosuccinimide (26 g, 146 mmol, 1.04 equiv), and 0.2 mg of benzoyl peroxide in 400 ml of carbon tetrachloride was heated under reflux while being irradiated with a 200-W tungsten lamp. The reaction was complete in 30–40 min. After filtration the solvent was removed from the filtrate and the solid product was dissolved in a benzene–petroleum ether (30–60°) mixture and cooled to give crystals, mp 76–95°. Recrystallization from the same solvent mixture gave 4.6 g (19%) of yellowish crystals: mp 96–97°; nmr ($CDCl_3$) doublet at 2.38 (1 H, $J_{HFmeta}$ = 7 Hz), doublet at 2.78 (1 H, $J_{HFortho}$ = 10 Hz), singlet at 5.48 (2 H, methylene protons), broadened singlet at 5.57 (2 H, methylene protons adjacent to fluorine); mass spectrum *m/e* (rel intensity) 364 (4.8), 362 (15), 360 (15), 358 (5.5), 283 (48), 281 (100), 279 (52), 202 (67), 200 (67), 120 (20), 101 (34), 75 (24).

**14-Bromo-17-fluoro-2,11-dithia[3.3]metaparacyclophane (39).** Fluorotribromide **38** (2.7 g, 7.5 mmol) and 1,3-bis(mercaptomethyl)-benzene (1.42 g, 8.25 mmol, 1.1 equiv) were coupled by the method used to obtain **4**. The isolated crude product was sublimed over 36 hr (155° (2 $\mu$)) to obtain 1.30 g (47%) of white solid. Resublimation gave white crystals: mp 107.5–110°; nmr ($CDCl_3$) multiplet at 2.65–3.00 (4 H, due to external meta-bridged ring protons and the proton vicinal to bromine), doublet at 3.27 ($J$ = 10 Hz, 1 H, proton vicinal to fluorine), broad singlet at 4.08 (1 H, internal meta-bridged ring proton), doublet of doublets at 5.81 ($J_{gem}$ = 13 Hz, $J_{HF}$ = 1 Hz, 1 H, methylene proton $\gamma$-syn to fluorine), doublet at 5.93 (1 H, $J_{gem}$ = 13 Hz, methylene proton $\gamma$-syn to bromine), doublets at 6.30 and 6.46 (each 1 H, $J_{gem}$ = 13 Hz, methylene protons $\gamma$-anti to fluorine and bromine), singlet at 6.45 (4 H, methylene protons adjacent to the meta-bridged ring); mass spectrum *m/e* (rel intensity) 370 (87), 368 (83), 289 (48), 136 (64), 135 (76), 105 (100), 91 (62).

**14-Bromo-17-fluoro-2,11-dithia-2,2,11,11-tetraoxo[3.3]metaparacyclophane (40).** Dithiacyclophane **39** (1.19 g, 3.2 mmol) was oxidized with 3.25 g of 85% pure *m*-chloroperbenzoic acid (16 mmol, 1.25 equiv) by the procedure used to obtain **5**. This gave 1.31 g (94.5%) of product. Sublimation gave white crystals: mp >300°; nmr ($CF_3CO_2H$) doublet at 2.10 (1 H, $J_{HFmeta}$ = 6.5 Hz), multiplet at 2.16–2.75 (3 H, meta-bridged ring protons), doublet at 2.87 (1 H, $J_{HFortho}$ = 10 Hz), broad singlet at 3.78 (1 H, internal meta-bridged ring proton), doublets at 4.62 and 4.90 ($J$ = 14.3 Hz, each 1 H, protons $\gamma$-syn to Br or F), singlet at 5.46 (4 H, methylene protons), doublets at 5.31 and 5.37 ($J$ = 14.3 Hz, each 1 H, protons $\gamma$-anti to Br or F); mass spectrum *m/e* (rel intensity) 434 (0.5), 432 (0.5), 306 (10), 304 (10), 225 (52), 104 (100), 103 (20), 78 (18).

**12-Bromo-15-fluoro[2.2]metaparacyclophane (33).** Crude bissulfone **40** (518 mg) was pyrolyzed in three portions in the apparatus described for the preparation of **6**. The temperature of the first furnace was 340°, that of the second was 600°, and the pressure was 2.5 mm. The crude product was chromatographed over silica gel with petroleum ether (30–60°) to obtain 279 mg (77%) of prod-

(51) J. J. Blanksma, *Chem. Weekbl.*, 10, 136 (1913); *Chem. Abstr.*, 7, 1493 (1913).

uct. Sublimation gave white crystals: mp 92.5–94°; nmr ($CDCl_3$) showed a mixture of two conformers, complex pattern at 2.6–3.3 due to exo para-bridged ring protons (total 1 H) and external meta-bridged ring protons (3 H), a doublet at 3.89 ($J$ = 7 Hz, endo proton meta to fluorine), a doublet at 4.31 ($J$ = 11 Hz, endo proton ortho to fluorine), and a narrow multiplet at 4.31 due to the internal meta-bridged ring protons of each isomer (total integral of this region is 2 H), complex multiplet from 6.50 to 8.00 (8 H, methylene protons). The ratio of the two conformers was determined by comparing the integrals of the doublets at 3.89 and 4.31 (corrected for internal meta-bridged ring proton), and the assignment of conformers was based on consideration of chemical shifts together with H–F coupling constants. The $^{19}F$ spectrum consisted of an asymmetric multiplet from +8.18 to 8.55 ppm. Broad bandwidth proton decoupling reduced this to singlets at 8.34 and 8.44 ppm of relative integrals 0.777 and 0.223, respectively. Mass spectrum was $m/e$ (rel intensity) 306 (26), 304 (26), 225 (70), 224 (22), 104 (100), 78 (27).

**12-Fluoro[2.2]metaparacyclophane (34).** A 5-ml flask containing **33** (39.5 mg, 0.13 mmol) and a magnetic stirring bar was purged with nitrogen and sealed with a septum. Dry ether (5 ml) was introduced *via* a syringe and the resulting solution was cooled in an ice bath and stirred while 0.2 ml of a 1.6 $M$ solution of $n$-butyllithium in hexane (0.32 mmol, 2.5 equiv) was introduced. The ice bath was removed and, after 30 min at room temperature, 2 ml of water was added. The separated ether layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was chromatographed over silica gel and eluted with petroleum ether (30–60°). This gave 26.8 mg (91.5%) of a clear oil which was 98% pure by vpc analysis. Its nmr spectrum ($CDCl_3$) consisted of three complex multiplets: 2.80–3.38 (4.36 H, aromatic protons not shielded by ring current), 4.10–4.50 (2.64 H, shielded aromatic protons), and 6.38–8.00 (8 H, methylene protons). Three meta-bridged ring protons may be subtracted from the integral of the first multiplet and the internal meta-bridged ring proton subtracted from the integral of the second multiplet to obtain 1.36 H and 1.64 H as the integrals due to the unshielded and shielded para-bridged ring protons, respectively. Then algebraic manipulation gives the ratio of exo to endo isomers present in the solution as 1.78:1. The $^{19}F$ nmr spectrum consisted of a doublet of doublets at +7.9 ppm ($J_{ortho}$ = 11.5 Hz, $J_{meta}$ = 7.5 Hz, rel integral = 0.665) and a doublet of doublets at +7.1 ppm ($J_{ortho}$ = 11.5 Hz, $J_{meta}$ = 7.0 Hz, rel integral = 0.335), which gives the isomeric ratio as 1.99:1. Broad bandwidth proton decoupling reduced the spectrum to two singlets. The mass spectrum of **34** was as follows: $m/e$ (rel intensity) 226 (70), 211 (18), 104 (100), 78 (23).

*Anal.* Calcd for $C_{16}H_{15}F$: mol wt, 226.116. Found (high resolution mass spectrum): mol wt, 226.117.

**12-Fluoro-15-methyl[2.2]metaparacyclophane (35).** A mixture of 51.7 mg (0.17 mmol) of **33** and 0.25 ml of a 1.6 $M$ solution of $n$-butyllithium (0.4 mmol, 2.35 equiv) was prepared as described for the preparation of **34**. Then the solution was cooled in an ice bath and 113 mg (0.8 mmol, 4.7 equiv) of methyl iodide (distilled from molecular sieves) was introduced. The mixture was allowed to come to room temperature and was stirred 1 hr. The ethereal solution was washed with water and brine and was dried over magnesium sulfate. Removal of solvent gave the crude product which was chromatographed over silica gel by elution with petroleum ether (30–60°) to obtain 35.4 mg (83%) of clear oil that was 95% pure by vpc analysis (the impurity was fluorocyclophane **34**). The nmr spectrum of **35** ($CDCl_3$, the integrals are normalized to a total of 16.9 protons expected for the mixture) showed a multiplet from 2.84 to 3.34 (3.97 H, outer meta-bridged ring protons and exo para-bridged ring protons), multiplet from 4.17 to 4.50 (1.90 H, endo para-bridged ring protons, and internal meta-bridged ring protons), multiplet from 6.54 to 8.03 and singlet at 7.59 (total 10.0 H, methylene protons and exo methyl protons), singlet at 8.35 (1.01 H, endo methyl protons). Corrected for the impurity **34**, the endo methyl protons would integrate as 1.063 H. Since there are three methyl protons in **35**, the exo methyl protons must integrate as 1.937 H and the exo:endo ratio would be 1.82. The $^{19}F$ nmr spectrum consisted of a perturbed triplet at +11.6 ppm (as well as minor absorptions due to **34**). Proton decoupling reduced this to a broad singlet. The mass spectrum of **35** showed $m/e$ (rel intensity) 240 (63), 225 (29), 104 (100), 78 (32).

**2,11-Dithia(9,10)anthraceno[3.3]metacyclophane (43).** 9,10-Bis(chloromethyl)anthracene[52] (0.64 g, 2.34 mmol) was dissolved in 400 ml of hot toluene. The solution was cooled to room temperature and 1,3-bis(mercaptomethyl)benzene (0.5 g, 2.94 mmol, 1.25 equiv) was added. The resulting solution was added dropwise over a 2-hr period to a solution of potassium hydroxide (0.30 g, 5.34 mmol, 1.15 equiv) in 1 l. of 95% ethanol and 500 ml of benzene stirred vigorously in a 5-l. Morton flask. The mixture was allowed to stir overnight and the solvent was removed on a rotary evaporator. After the crude product was taken up in chloroform and water, the separated chloroform layer was washed with brine and dried over magnesium sulfate. Removal of solvent gave a yellow solid which was absorbed at the origin of a 4 × 8 cm silica gel column and eluted with 40% benzene–petroleum ether (30–60°) to obtain 0.53 g (61%) of yellow crystals: nmr ($CDCl_3$) multiplets at 1.56–1.80 and 2.40–2.66 (each 4 H, anthracene protons), multiplet at 3.36–3.74 (3 H, meta-bridged ring protons), singlet at 5.13 (4 H, methylene protons), broad singlet at 6.08 (1 H, internal meta-bridged ring proton), singlet at 6.76 (4 H, methylene protons). Recrystallization from methylene chloride gave yellow crystals, mp 262–267° dec. An attempt to further purify the compound by sublimation at 10 $\mu$ resulted in decomposition. The mass spectrum of the sample obtained from methylene chloride showed $m/e$ (rel intensity) 372 (100), 235 (81), 205 (84), 135 (29), 91 (21).

**2,11-Dithia-2,2,11,11-tetraoxo(9,10)anthraceno[3.3]metacyclophane (44).** Dithiacyclophane **43** (308 mg, 0.83 mmol) was oxidized with 0.75 g of 85% $m$-chloroperbenzoic acid (3.65 mmol, 1.1 equiv) by the procedure used to prepare **5**. The product was collected by filtration, washed with chloroform, dried, and found to weigh only 197 mg (55%). Therefore, the filtrate was extracted with saturated sodium carbonate solution, dried over magnesium sulfate, and concentrated to 5 ml. The yellow crystals which resulted were collected, washed with a small amount of carbon tetrachloride, dried, and found to weigh 194 mg (total yield of crude bissulfone = 108%). Sublimation gave yellow crystals: mp >300°; nmr ($CDCl_3$) multiplets at 1.50–1.70 and 2.20–2.36 (each 4 H, anthracene protons), multiplet at 2.82–3.50 (3 H, meta-bridged ring protons), singlets at 4.31 and 6.15 (each, 4 H, methylene protons), broad singlet at 6.23 (1 H, internal meta-bridged ring protons); mass spectrum $m/e$ (rel intensity) 436 (5), 308 (97), 204 (48), 202 (28), 104 (100), 64 (34), 44 (53).

**(9,10)Anthraceno[2.2]metacyclophane (41).** Bissulfone **44** (84.3 mg, 0.27 mmol) was pyrolyzed in the apparatus described for the preparation of **6**. The temperature of the first furnace was 400°, that of the second was 600°, and the pressure was 2 mm. After 90 min the crude product (37.6 mg) was removed from the cold finger and sublimed at 140° and 1 $\mu$ to obtain 30 mg (35%) of a yellow solid, mp 140–160° dec. Attempted purification by chromatography on silica gel resulted in decomposition, and polymerization in solution made recrystallization impractical. The nmr spectrum ($CDCl_3$) of the crude product (numbering follows scheme illustrated in text) showed: multiplet at 1.55–1.80 (2 H, protons at positions 13 and 16), multiplet at 2.10–2.35 (2 H, protons at positions 20 and 23), multiplet at 2.35–2.60 (2 H, protons at positions 14 and 15), multiplet at 2.80–3.05 (2 H, protons at positions 21 and 22), broad singlet at 3.72 (3 H, meta-bridged ring protons), multiplet at 5.6–6.5 (3 H, internal meta-bridged ring proton and methylene protons), multiplet at 6.70–8.00 (6 H, methylene protons). Saturation of the singlet at 3.72 caused marked sharpening of the broad singlet at 6.00 which indicates that the latter signal is due to the internal meta-bridged ring proton. Saturation of the multiplets at 1.55–1.80 or 2.80–3.05 collapsed the multiplets at 2.35–2.60 or 2.10–2.35, respectively, to singlets. When a solution of 3 mg of **41** and 0.2 mg of hydroquinone as a stabilizer in $CCl_4$ was heated to about 80°, the multiplets at 1.55–1.80 and 2.35–2.60 coalesced with, respectively, the multiplets at 2.10–2.35 and 2.80–3.05. The mass spectrum of **41** showed $m/e$ (rel intensity) 308 (100) and 104 (20).

*Anal.* Calcd for $C_{24}H_{20}$: mol wt, 308.156. Found (high resolution mass spectrum): mol wt, 308.157.

**Rates of Conformational Ring Flipping.** Plots of the integral of site A, corresponding to $M_{A\infty}$, as a function of the decoupling power situation at site X showed that more than enough power was available to effectively saturate the irradiated site. In all cases, the separation between sites A and X ($\Delta\nu$) was on the order of 1 ppm or more, and direct saturation of one of the sites resulting from situating the decoupling power $\Delta\nu$ away from that site was shown to be less than 2%. To compensate partially for any such direct saturation and for the reduction in instrumental sensitivity at high decoupling power, all measurements were made with the decoupling power on; $M_{A\infty}$ was measured with the decoupling power irradiating site X, and $M_{A0}$ was measured with the decoupling power $\Delta\nu$ to the opposite side of signal A from signal X.

(52) A. E. Kretov and V. V. Litvinov, *Zh. Prikl. Khim.* (*Leningrad*), **35**, 464 (1962); *Chem. Abstr.*, **56**, 15441c (1962).