

Cyclophane Chemistry: Bent and Battered Benzene Rings

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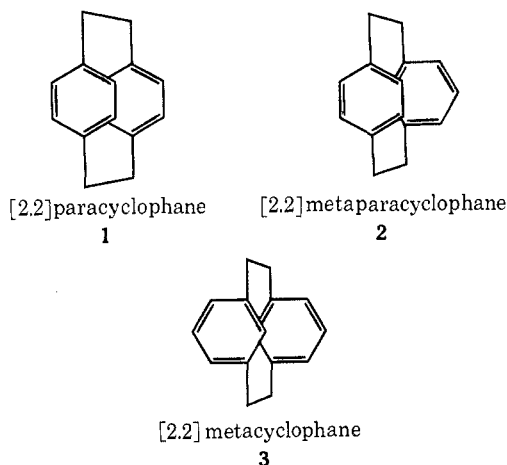
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As the structural theory of organic chemistry has reached maturity, more investigations have been directed toward defining its boundaries. Experimentalists have synthesized internally tortured molecules with inherent suicidal tendencies that skirt a fine line between isolability and self-destruction. Theorists have progressed from rationalizing what is observed to predicting what extremes of deformity (even degeneracy) might be incorporated into organic structures before molecular collapse or fragmentation occurs.

Cyclophanes, in which more than two atoms of an aromatic ring are incorporated into a larger ring system, provide a fine vehicle for the study of molecular strain.¹ The question "how bent can a benzene be?" represents a challenge in molecular design and synthesis. The question "how will benzene rings behave when compressed face-to-face?" provides a basis for correlation between physical properties and reactivity on the one hand and deviations from normal molecular structure on the other.

Examples of the extremes in molecular deformation that yielded to organic synthesis are found in compounds **1-3**. The history¹ of the most strained of



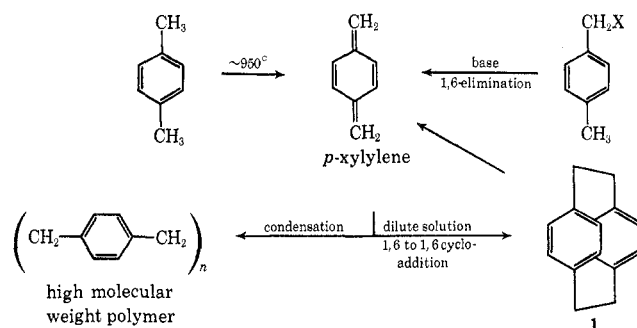
these (**1**) is as unlikely as its structure. Pyrolysis of *p*-xylylene produces poly-*p*-xylylene, the polymer formed from the intermediate tetraene, *p*-xylylene. Extraction^{2a,b} of polymer gave trace amounts of [2.2]-paracyclophane (**1**) much as natural product chemists traditionally extracted natural polymers to obtain smaller molecules for structure elucidation. The melting point and crystal structure of **1** were an-

(1) (a) D. J. Cram, *Rec. Chem. Progr.*, **20**, 71 (1959); (b) R. W. Griffin, Jr., *Chem. Rev.*, **63**, 45 (1963); (c) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964.

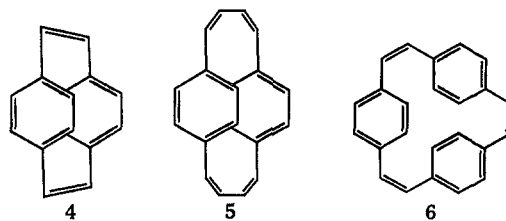
(2) (a) C. J. Brown and A. C. Farthing, *Nature (London)*, **164**, 915 (1949); (b) A. C. Farthing, *J. Chem. Soc.*, 3261 (1953); (c) C. J. Brown, *ibid.*, 3265 (1953).

nounced^{2a} simultaneously, with no other structural information. At the time (1949), molecular structure determination by chemical degradation or designed synthesis usually preceded X-ray crystal structure determination.

A designed synthesis of **1** was reported in 1951 along with that of higher homologs of the [*m.n*]paracyclophanes.³ The substance is now a commercial monomer⁴ prepared by the pyrolysis of *p*-xylylene.^{4c} The best laboratory synthesis of **1**⁵ involves a 1,6 elimination followed by a 1,6 to 1,6 cycloaddition reaction to give **1**. The pyrolysis of *p*-xylylene, the vapor-plating polymerization of **1**, and this synthesis⁵ of **1** all involve *p*-xylylene⁶ as a highly unstable intermediate, detectable in dilute solution at low temperatures.



Other highly distorted cyclophanes with beautiful symmetry properties have yielded to designed syntheses. Classically conjugated but orbitally unconjugated compounds **4**, **5**, and **6** were prepared.⁷ Benzene rings



have been stacked like club sandwiches in substances **7**⁸ and **8**.⁹ Benzene rings resisting deformation past a

(3) D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **73**, 5691 (1951).

(4) (a) W. F. Gorham, *J. Polym. Sci., Part A-1*, **4**, 3027 (1966); (b) *Chem. Eng. News*, **43**, 35 (Feb 22, 1965); (c) *Chem. Eng. News*, **43**, 41 (Mar 1, 1965).

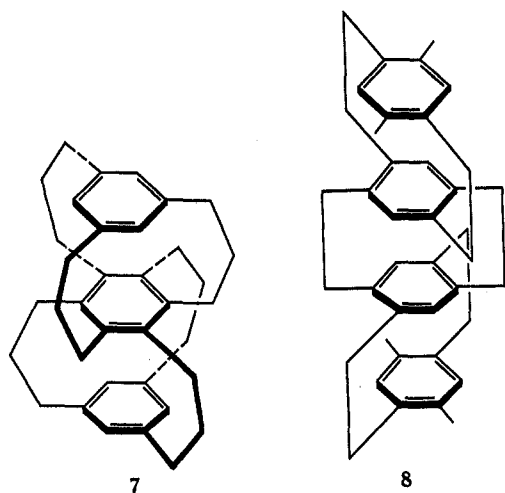
(5) H. E. Winberg and F. S. Fawcett, *Org. Syn.*, **42**, 83 (1963).

(6) L. A. Errede and M. Szwarc, *Quart. Rev., Chem. Soc.*, **12**, 301 (1958).

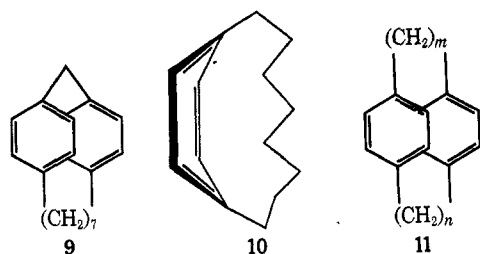
(7) (a) K. C. Dewhirst and D. J. Cram, *J. Amer. Chem. Soc.*, **80**, 3115 (1958); (b) D. J. Cram and K. C. Dewhirst, *ibid.*, **81**, 5963 (1959).

(8) A. J. Hubert, *J. Chem. Soc. C*, 13 (1967).

(9) D. T. Longone and H. S. Chow, *J. Amer. Chem. Soc.*, **92**, 994 (1970).



certain point have thus far defied synthesis of homologs smaller than [7.1]paracyclophane (**9**)¹⁰ and [8]paracyclophane (**10**).¹¹



The physical and chemical properties of homologous aliphatic hydrocarbons form a continuous progression. Because of bond-angle deformation and nonbonded interactions, cyclic homologous hydrocarbons exhibit properties that are discontinuous. The properties of cyclopropane or cyclodecane could hardly be predicted from those of cyclopentane, cyclohexane, and cycloheptane. Similarly, the properties of the $[m.n]$ paracyclophanes (**11**) with $m = (n \pm 1) < 4$ are astonishingly different from those with m and n equal to or greater than 4.¹² A visual demonstration involves the color of the 1:1 π complexes of the $[m.n]$ paracyclophanes with tetracyanoethylene.^{12b} With $m = n = 4$, a yellow complex is formed similar to that of *p*-xylene. With $m = 3$, $n = 4$, the complex is purple; with $m = n = 3$, deep blue; with $m = 3$, $n = 2$, orange; with $m = n = 2$, red.

The conformational simplicity enforced by the ring system of the $[m.n]$ cyclophanes coupled with the unique geometry of the cycles provide a means of investigating transannular steric and electronic effects in systems relatively free of structural ambiguities. Possible charge delocalization from one benzene ring into the second makes the study of substituent effects in aromatic substitution interesting. Questions of prohibited, restricted, and free rotation of the benzene rings with respect to one another as a function of bridge

length and point of attachment provide interesting problems. The effect of compression on the thermal and photolytic behavior of the cyclophanes with low values of m and n invites investigation. Finally, these molecules and their derivatives possess intriguing symmetry properties, worthy of study in their own right, and useful in the investigation of reaction mechanisms.

This paper reviews some of the recent studies of the chemistry of the $[m.n]$ cyclophanes where m and n are 3 or less. Unlike their higher homologs these compounds depart in their properties and behavior from their open-chain models. Since detailed molecular structure and strain energies are necessary to understanding of physical and chemical properties, these topics occupy the first section. The subject of barriers to ring rotation naturally follows, and the unusual reactions that reflect the strain of the [2.2]cyclophanes are discussed in the third section. Finally, transannular effects in the aromatic ring reactions of the cyclophanes are reviewed.

Structure and Strain

The early X-ray structure of [2.2]paracyclophane (**1**)^{2c} indicated a rigid, face-to-face molecule with three mirror planes and bent benzene rings. A recent and highly refined structure^{13a} reveals that, even at 93°K, the substance equilibrates between two structures in which the methylene bridges are slightly de eclipsed.^{13b} In this molecular motion the benzene rings rotate about an axis perpendicular to and passing through the center of each face. The angle swept by this rotation is about 6°. A cross section and face view of the molecule are found in Chart I. Noteworthy structural features include the stretched σ benzyl-benzyl bond, the bent benzene rings, the abnormal bond angles, and particularly the distances between the two benzene rings. The normal intermolecular distance between stacked aromatic nuclei in crystals is 3.40 Å,¹⁴ whereas 2.78 Å is the shortest distance observed in **1**. These structural abnormalities correlate with the unusual physical and chemical properties discussed in future sections.

The highly refined crystal structure of tetrahydro-[2.2]paracyclophane (**4**) does exhibit the expected rigid, centered, face-to-face geometry,¹⁵ a side profile of which is found in Chart II. An interesting feature of this structure is the location of the aromatic hydrogens. These lie significantly out of the plane of the 3, 4, 5, and 6 carbons of one benzene ring, *bent toward the other benzene ring*. This structural feature probably reflects the strong π - π repulsions between the two benzene rings which result in an increased π -electron den-

(10) D. J. Cram and M. F. Antar, *J. Amer. Chem. Soc.*, **80**, 3103 (1958).

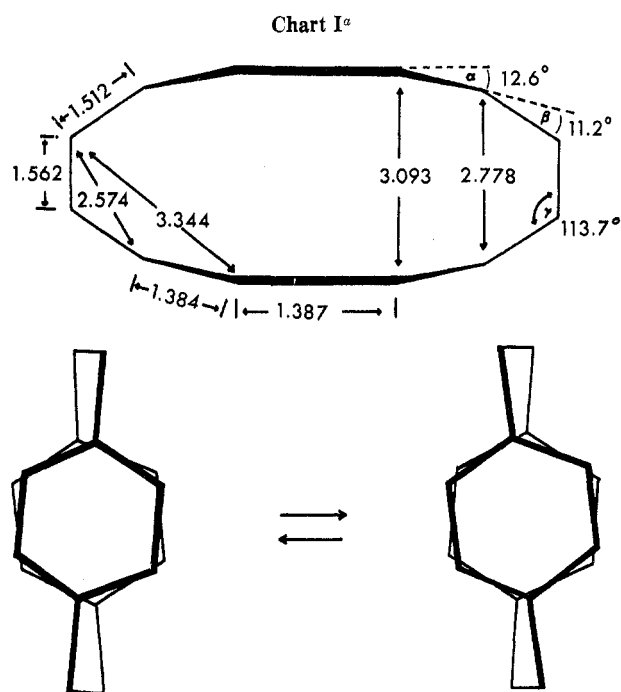
(11) D. J. Cram, C. S. Montgomery, and G. R. Knox, *ibid.*, **88**, 515 (1966).

(12) (a) D. J. Cram, N. L. Allinger, and H. Steinberg, *ibid.*, **76**, 6132 (1954); (b) D. J. Cram and R. H. Bauer, *ibid.*, **81**, 5971 (1959).

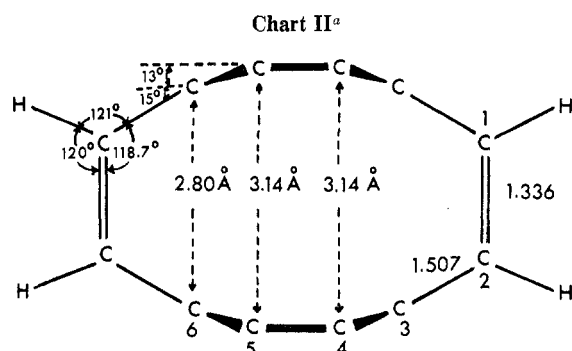
(13) (a) K. N. Trueblood, J. Bernstein, and H. Hope, private communication. We warmly thank these authors for this information in advance of publication; (b) K. Lonsdale, H. J. Milledge, and K. V. K. Rao, *Proc. Roy. Soc., Ser. A*, **555**, 82 (1960).

(14) J. M. Robertson, "Organic Crystals and Molecules," Cornell University Press, Ithaca, N. Y., 1953, p 213.

(15) C. L. Coulter and K. N. Trueblood, *Acta Crystallogr.*, **16**, 667 (1963).



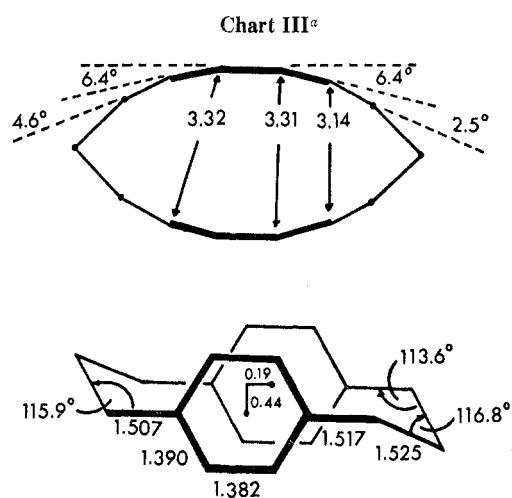
^a Crystal structure of [2.2]paracyclophane.



^a Side profile of tetradehydro[2.2]paracyclophane (4).

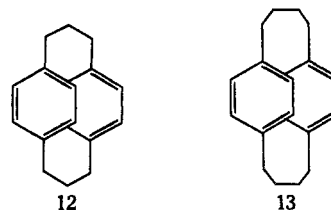
sity on the outside faces of the benzene rings. The molecule adjusts somewhat by a rehybridization of the aromatic carbons to increase the p character of their σ bonds. A consequence is that the following four atoms do not lie in the same plane: C-3, C-4, C-5, and the hydrogen attached to C-4 (see Chart II for numbering). In a normal benzene ring these atoms would occupy one plane. This structural feature undoubtedly is also present in [2.2]paracyclophane itself, although the hydrogens were not located because of the molecular movement in the crystal.

The π - π repulsions are also evident in the crystal structure of [3.3]paracyclophane (**12**)^{16a} whose benzene rings are less bent from planar structures. The benzene rings are decentered, and the bridges are chair- rather than boatlike,^{16a} as can be seen in Chart III. Again the aromatic hydrogens of each benzene ring are bent toward the hydrogens of the opposite benzene ring. Although molecular models of **12**

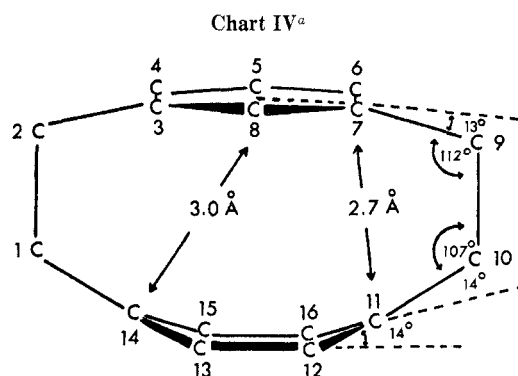


^a Different views of the crystal structure of [3.3]paracyclophane (**12**).

suggest a highly symmetrical geometry, the crystal structure shows that, to decrease π - π repulsions between the rings, the molecule has maximized its dissymmetry. In solution at room temperature the nmr spectrum^{16b} indicates a boat:chair conformation ratio of 2:1 with a free-energy barrier for the boat-chair conversion of about 11.7 kcal/mole.



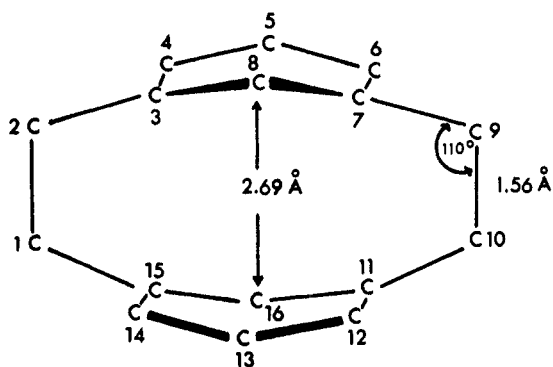
Only a preliminary crystal structure is available for [2.2]metaparacyclophane (**2**).¹⁷ A profile of the molecule (side view) is found in Chart IV. The para ring is more badly bent from its normal planar configuration than in [2.2]paracyclophane. The meta ring is also bent into a slight chair, with C-8 above the plane of C-3, C-4, C-6, and C-7, and C-5 below. The substance contains the smallest number of atoms (seven) in a known molecule that forms a chain connecting the



^a Side view of crystal structure of [2.2]metaparacyclophane (**2**).

(16) (a) P. K. Gantzel and K. N. Trueblood, *Acta Crystallogr.*, **18**, 958 (1965); (b) F. A. L. Anet and M. A. Brown, *J. Amer. Chem. Soc.*, **91**, 2389 (1969).

(17) K. N. Trueblood and M. J. Crisp, private communication. We warmly thank the authors for this information given in advance of publication.

Chart V^a

^a Side view of crystal structure of [2.2]metacyclophane (**3**).

para ends of a benzene ring. As in **1**, the two aromatic rings of **2** violate each others' normal van der Waals radius.

The crystal structure of [2.2]metacyclophane (**3**) shows equally interesting deformations.¹⁸ Of the syn and anti forms, only the anti (step form) is known. As indicated in Chart V, the benzene rings are again bent from planarity into shallow boats. Thus, C-8 is out of the plane of C-3, C-4, C-6, and C-7 away from the transannular ring by 0.143 Å, and C-5 is bent in the same direction by 0.042 Å. The closest approach of the two benzene rings to one another is 2.69 Å, and involves C-8 of one ring and C-16 of the other. This distance is smaller than that found in any of the other cyclophanes and results in bond formation between these atoms upon electrophilic substitution and in other reactions.¹⁹

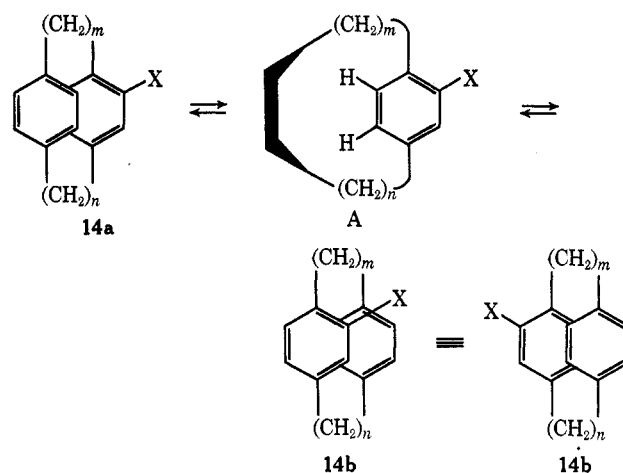
These crystal structures demonstrate the presence of considerable strain and compression energy in the smaller cyclophanes. Their strain energies have been determined:²⁰ [2.2]paracyclophane (**1**), 31 kcal/mole; [3.3]paracyclophane (**12**), 12 kcal/mole; [6.6]paracyclophane, 2 kcal/mole; [2.2]metaparacyclophane (**2**), 23 kcal/mole; [2.2]metacyclophane (**3**), 13 kcal/mole. Thus the resulting values correlate nicely with both those based on crystal structures and those predicted by application of theory to molecular models.^{13, 15, 16, 20} Clearly, [2.2]paracyclophane has the highest strain energy, and [6.6]paracyclophane is like an open-chain compound. This progression of strain energies in the homologous [*m.n*]paracyclophanes correlates beautifully with the progression of chemical and spectral properties of the same compounds.^{12, 21}

Steric Inhibition of Ring Rotation

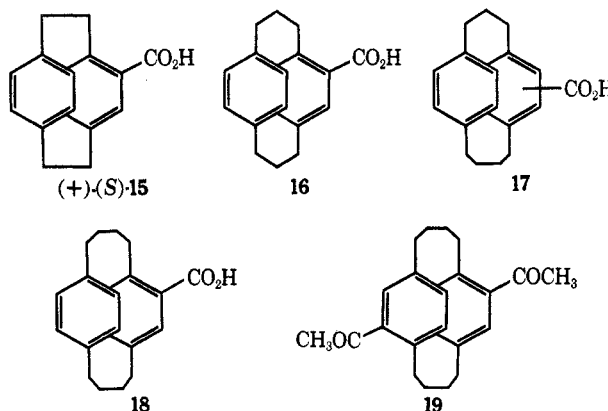
An engaging aspect of cyclophane chemistry is the symmetry properties of the parent hydrocarbons and their derivatives. The smaller cycles are distributed more equally in the three dimensions than most other

molecules. Most ball-like molecules are rigid by virtue of their *bonding interactions*. The smaller cyclophanes are rigid because of their *nonbonding interactions*. The rigidity and small nonbonded atomic distances in these cyclophanes lead to the possibility of stable conformational isomers, and the energy barriers to ring rotation of both benzene nuclei and carbon bridges have been studied.

Structures **14a** and **14b** are enantiomeric and possibly interconvertible through transition state A. Carboxylic acids **15**,^{22a,d} **16**,^{22b} and **17**^{22c} were resolved;



18 was not resolvable,^{22c} indicating facile benzene ring rotation at room temperature. When heated to 160°, **17** racemized slowly with an estimated activation energy²³ of 33 kcal/mole, but acid **16** failed to racemize at temperatures up to 240°.^{22b} The methyl ester of **15** did racemize at 200°, but only by a methylene-bridge-cleaving mechanism (see later section).²³ From the temperature-dependent nmr spectrum of diacetyl[4.4]-paracyclophane **19**,²³ the barrier to ring rotation was estimated²³ as ~15 kcal/mole at 15°. Rotation of the benzene ring about the aryl-alkyl bond (structure A), detectable by racemization in the paracyclophane sys-



(18) C. J. Brown, *J. Chem. Soc.*, 3278 (1953).

(19) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1974 (1961).

(20) (a) R. H. Boyd, *Tetrahedron*, **22**, 119 (1966); (b) C. Shieh, D. C. McNally, and R. H. Boyd, *ibid.*, **25**, 3653 (1969).

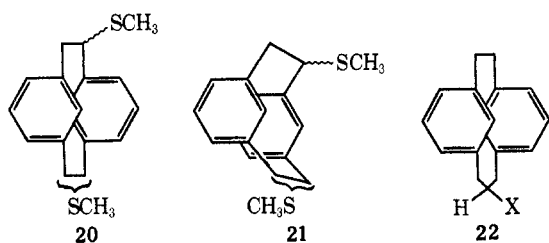
(21) M. Sheehan and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 3553 (1969).

(22) (a) D. J. Cram and N. L. Allinger, *ibid.*, **77**, 6289 (1955); (b) M. Sheehan, Ph.D. Dissertation, University of California, Los Angeles, Calif., 1969; (c) D. J. Cram, W. J. Wechter, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **80**, 3126 (1958); (d) the absolute configuration of 4-carboxy[2.2]paracyclophane (**15**) has been determined [V. H. Falk and K. Schlögl, *Angew. Chem.*, **80**, 405 (1968)].

(23) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 3517 (1969).

tems, requires the two hydrogens to pass the other aromatic ring, and, in the case of bent benzene rings, conversion from one boat form to the other. This interconversion occurs easily in the unstrained [4.4]-paracyclophane with 16 atoms in the large ring and does not occur at reasonable temperatures in [3.3]-paracyclophane with 14 atoms in the large ring. Stuart-Briegleb molecular models of compounds **15**–**18** uniquely allow both the assembly and the correct prediction of room temperature behavior with respect to ring rotation.

Bridge-substituted derivatives **20** and **21** of *anti*- and *syn*-[2.2]metacyclophane have been prepared and did not interconvert detectably under conditions of their manipulation.²⁴ Indeed, [2.2]metacyclophane (**3**) was found by nmr techniques not to undergo ring inversion at temperatures up to 180°. ²⁵ An activation energy of >27 kcal/mole was estimated for such a process.²⁵ However, 2-substituted [3.2]metacyclophanes (**22**) were found to ring-invert at 60–120° with activation energies of 15.8–19.1 kcal/mole.²⁶



Ring rotation in [2.2]metaparacyclophane (**2**) is complicated by the possibility of rotation of each of *two different rings* with respect to one another. These processes are identified by formulas B and C for the transition states. Differentiation between possibilities of para ring, meta ring, or both ring rotations was made through a combination of optical and nmr techniques.^{27a} That some ring rotation occurred with an activation energy of 21 kcal/mole was demonstrated^{27a,b} by nmr techniques, focusing on the aldehydic hydrogen of compound **23** where X = CHO. That rotation of both rings did not occur up to temperatures of 200° was shown by the complete absence of racemization when optically active ester **23** was heated to 200°. ^{27a} Nmr analysis of methylene proton change indicated that the meta ring did rotate; thus, the para ring did not. Ester **23** and other derivatives of **2** with substituents in the same position crystallized only in form **23**, with the substituent and meta ring anti to one another (Chart VI). As a result, rates of **23** → **24** and equilibrium constants for **23** ⇌ **24** were determined. Isomer **23** was favored by factors that varied between 1 and 7, depending mainly on the bulk of the substituent.^{27a}

The activation energies for meta ring rotation in

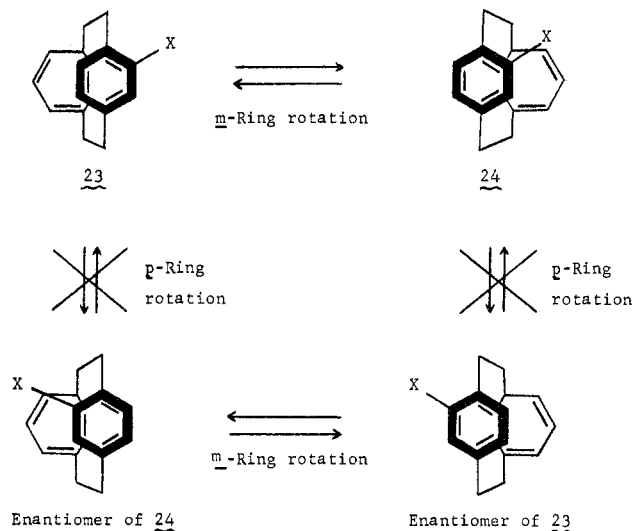
(24) R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3510 (1970).

(25) F. Vögtle, *Tetrahedron Lett.*, 3623 (1968).

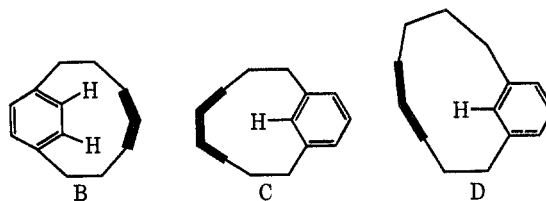
(26) R. W. Griffin, Jr., and R. A. Coburn, *J. Amer. Chem. Soc.*, **89**, 4638 (1967).

(27) (a) D. T. Hefelfinger and D. J. Cram, *ibid.*, **92**, 1073 (1970); (b) F. Vögtle, *Chem. Ber.*, **102**, 3077 (1969).

Chart VI



[2.2]metaparacyclophane (20.6 kcal/mole)^{27a} and in derivatives of [3.2]metacyclophane (16–19 kcal/mole)²⁶ are very close. In each case an aromatic hydrogen passes through the center of an 11-membered ring, a portion of which is part of the second aromatic nucleus. Formulas C and D, in which one benzene ring is roughly

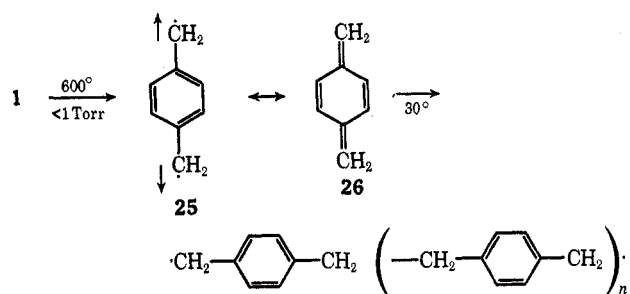


perpendicular to the other, illustrate how well molecular models correlate and can be used to predict what is observed. Thus, C and D illustrate a rotation that occurs rapidly at room temperature, and B illustrates a rotation not available at even high temperatures.

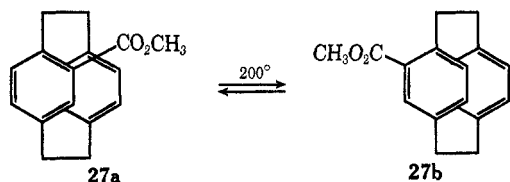
Reactions That Reflect the Strain in the [2.2]Cyclophanes

The 31-kcal strain energy²⁰ of [2.2]paracyclophane (**1**), coupled with its almost rigid structure,¹³ give rise to reactions of the bridge carbons that exhibit features peculiar to the system. Ring cleavage by a thermal process can relieve the strain in the molecule. The nature of the cleavage and fates of the intermediates have been investigated. Pyrolysis at 600° of [2.2]-paracyclophane (**1**) and some of its derivatives produces two fragments^{4a} which are sufficiently stable under low pressure (<1 Torr) that recombination is delayed until the vapor comes in contact with a surface at 30° where it forms a polymer. Whether the intermediates are diradical **25** or tetraene **26**, they combine in quantitative yield to form a "living polymer" which retains a concentration of free radicals of 5–10 × 10⁻⁴ mole/mole of tetraene.

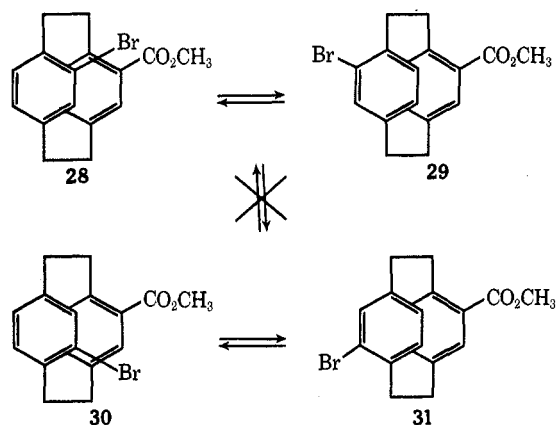
Another example is the racemization without decomposition of optically active ester **27** when heated to 200°. ²³ An examination of molecular models of **27**



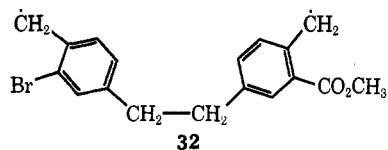
provides the convincing conclusion that ring rotation cannot occur in this system without ring rupture.



The data²³ show that cleavage of only one benzyl-benzyl bond occurred at this temperature, followed by aryl rotation and benzyl-benzyl bond formation. Isomers **28** and **29** equilibrated at 200°, as did isomers **30** and **31**, but no leakage occurred between the two equilibrating mixtures. Clearly, each isomer would have produced the other three if *p*-xylylene intermediates intervened. The equilibrium **28** \rightleftharpoons **29** had $K = 9$, and **30** \rightleftharpoons **31**, $K = 1.1$ at 200°. Molecular models indicate that the bromine and ester groups in **28** are highly compressed. That the intermediates are di-



radical **32** was demonstrated by capture of the diradical formed from the parent hydrocarbon **1**. When heated

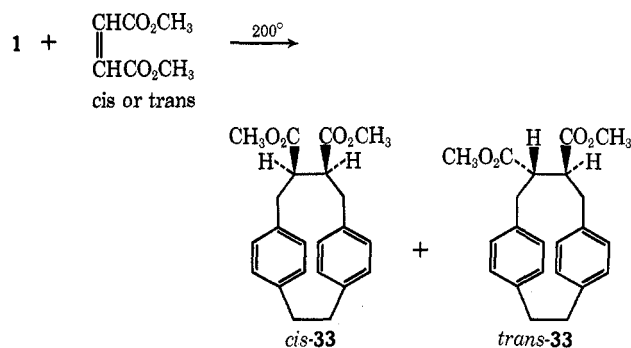


at 250° in 1,4-diisopropylbenzene (a good H· source), **1** gave *p,p'*-dimethylbibenzyl²³ in 21% yield.

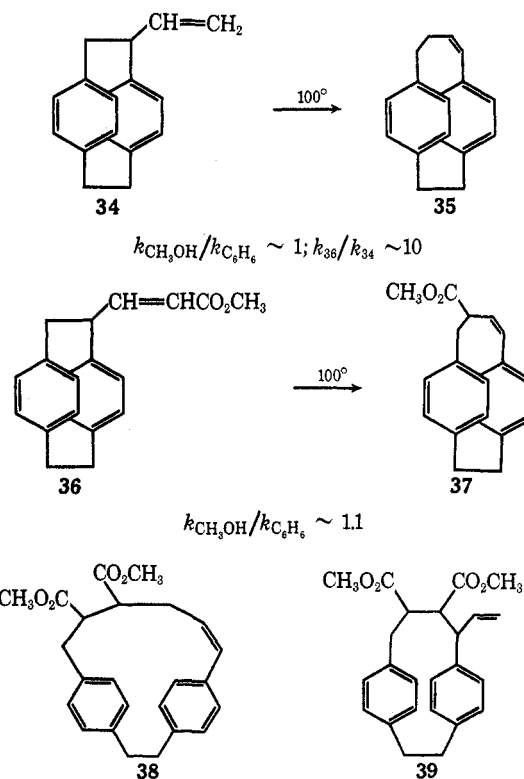
Formulas **28**–**31** represent only one enantiomer in each case, and the reactions are formulated as if *only the bromine-carrying benzene ring* underwent rotation. The actual experiments involved racemates. To determine if only one (which one?) or both rings rotated with respect to one another, optically pure **28** was

partially converted to **29**. Recovered **28** was partially racemized and **29** was completely racemic.²⁸ Clearly, both benzene rings of **28** rotated with respect to one another during the isomerization to **29**, but by an unequal number of 180° turns. Otherwise, optically active **28** would give racemic **28**, as was indeed observed as a competing reaction.

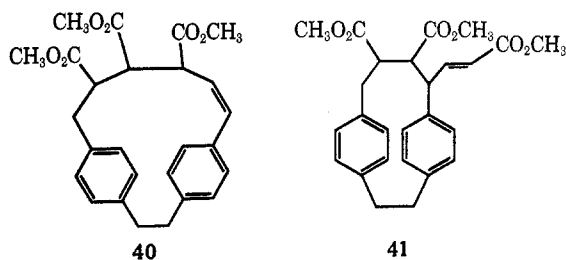
Dimethyl maleate or fumarate copolymerizes with styrene by a radical path to give ABAB polymers. This fact, coupled with the intervention of diradicals in the above reactions, suggested that either ester might react with [2.2]paracyclophane (**1**) in a 1,2- to 1,12-cycloaddition reaction. Accordingly, when heated at 200° in either ester, **1** gave *cis* and *trans* esters (**33**) in about equal amounts to give a combined yield of 60%.²³



Further application of the thermal cleavage of the benzyl-benzyl bond was observed in the ring expansion at 160° of 1-vinyl[2.2]paracyclophane (**34**) to give *cis*-1,2-dehydro[4.2]paracyclophane (**35**) in 90% yield.²⁹

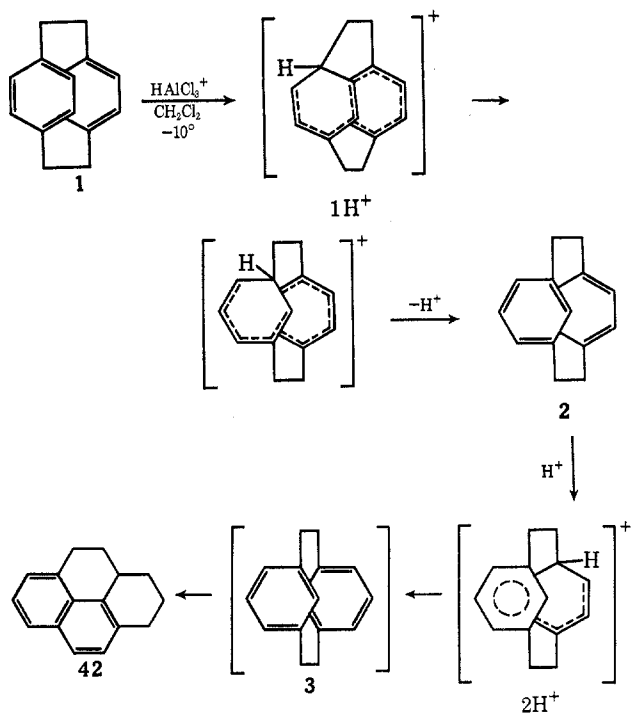


(28) E. A. Truesdale and D. J. Cram, unpublished results.
(29) M. E. Delton and D. J. Cram, unpublished results.



Rate comparisons for this reaction, for **36** \rightarrow **37**, for **34** in dimethyl fumarate or maleate to give **35**, **38**, and **39**, and for **36** in dimethyl fumarate or maleate to give **37**, **40**, and **41** support the diradical mechanism.

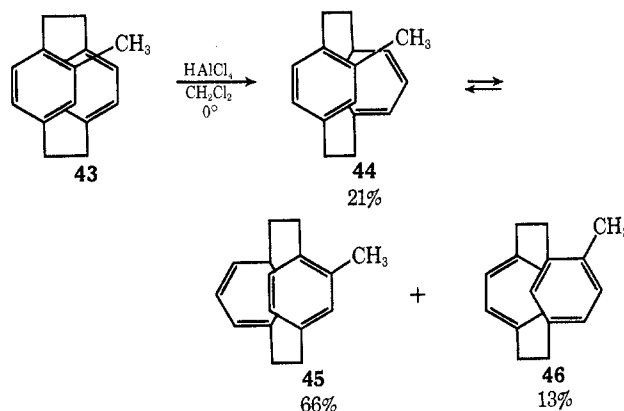
The conversion of [2.2]paracyclophane (**1**) to [2.2]-metaparacyclophane³⁰ (**2**) by treatment with strong acid occurs in 44% yield, with pyrene derivative **42** (10%) as a by-product. A 25% decrease in strain energy is realized in **1** \rightarrow **2**, and a further decrease of 44% would accompany [2.2]metaparacyclophane (**2**) \rightarrow [2.2]metacyclophane (**3**). That the latter reaction probably occurs is indicated by the production of the pyrene compound **42**. Pyrene derivatives are also formed in electrophilic substitution¹⁹ of **3** by bond formation between C-8 and C-16 (Chart V), which in **3** are only 2.7 Å distant.



The nmr spectrum of the deep red protonated [2.2]-paracyclophane (**1-H⁺**) was readily observed³¹ in $\text{SO}_2\text{ClF}-\text{HSbF}_6$ solutions at -78° , and this conjugate acid was stable to about -10° . The structure of **1** (Chart I) suggests that much strain should be relieved by protonation of the bridgehead position, rehybridizing that carbon to sp^3 . Similarly, protonation of **2** on the

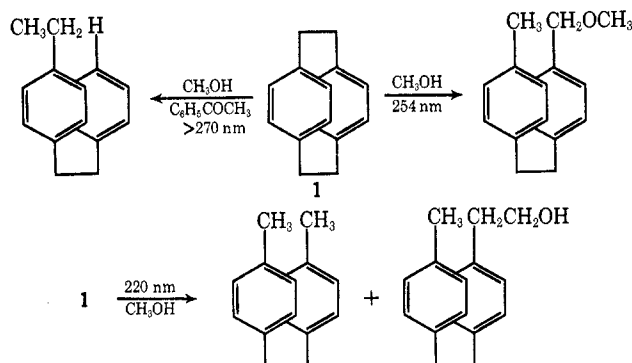
para ring bridgehead, **2-H⁺**, would relieve strain further. In fact, the stability of **2-H⁺** could provide both the driving force for the first rearrangement, **1** to **2-H⁺**, and greatly reduce the tendency for **2-H⁺** \rightarrow **3** to occur.

Acid treatment of 4-methyl[2.2]paracyclophane (**43**)³¹ produced a mixture (70%) of **44**, **45**, and **46**, mainly products of bridge migration in the nonmethylated ring. Optically pure **43** produced the equilibrating mixture of optically pure **44** \rightleftharpoons **45**, which crystallized solely as **45**.³² Clearly, the rearrangement occurs by a reaction path free of open-chain or symmetrical intermediates.



Photolysis of [2.2]metaparacyclophane (**2**) gave [2.2]metacyclophane (**3**) in 43% yield.³² The course of this reaction is not clear, but benzvalene- or prismane-type intermediates may be implicated. The conversions of **1** to **2** and **2** to **3** coupled with the already extensive range of derivatives of **1**³³ and **2**³¹ available should provide a rich source of derivatives of **3**, which have been relatively scarce and difficult to prepare.

Photolysis of [2.2]paracyclophane (**1**) in methanol gave different products depending on the wavelength of light used and the presence or absence of a photosensitizer.³⁴ Use of optically active compounds **47-50**



demonstrated that racemization occurred much faster and in far better yields than the reactions leading to the open-chain materials.³⁵ In methanol with 254-nm light racemization of optically pure **47**, **48**, and **49**

(32) M. E. Delton, R. E. Gilman, and D. J. Cram, unpublished results.

(33) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 3534 (1969).

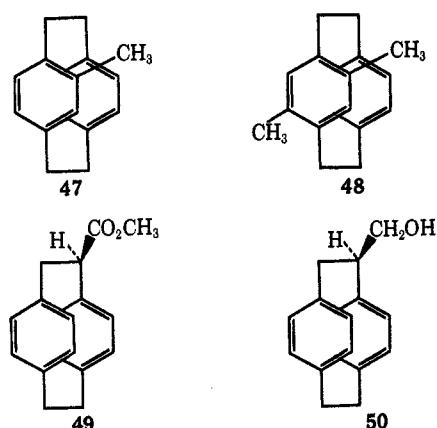
(34) R. C. Helgeson and D. J. Cram, *ibid.*, **88**, 509 (1966).

(35) M. H. Delton and D. J. Cram, *ibid.*, **92**, 7623 (1970).

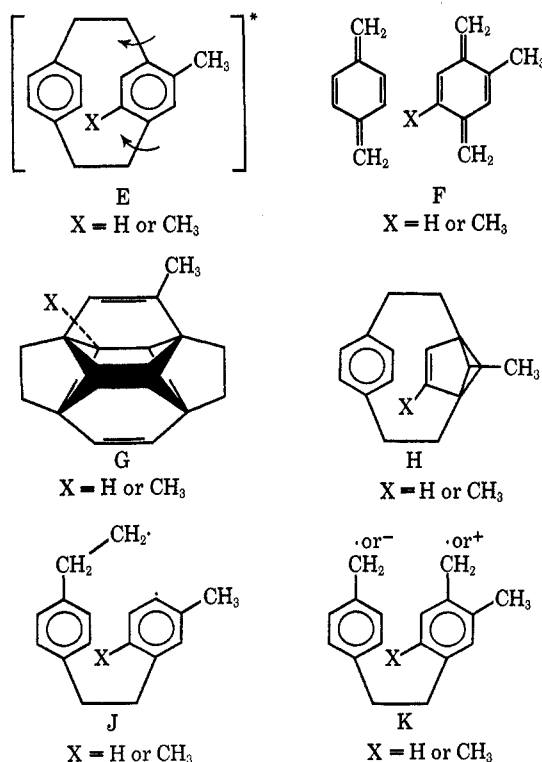
(30) D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *J. Amer. Chem. Soc.*, **88**, 1324 (1966).

(31) D. T. Hefelfinger and D. J. Cram, *ibid.*, in press.

gave 68–97% of starting material of <1% optical purity. In acetone with >270-nm light, **47** and **50**

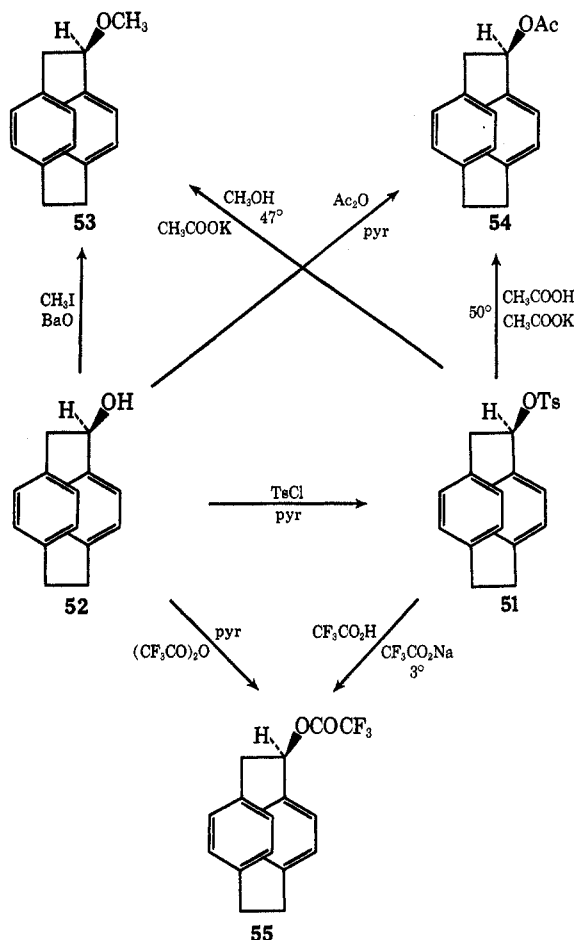


also racemized by photosensitized processes.³⁵ Intermediate states E, F, G, H, J, and K can all be envisioned as offering possible explanations for racemization of **47**. Formally, **48** might also racemize *via* E, F, J, or K, but its racemization is incompatible with G or H as intermediates (equilibration of several H-like intermediates might explain racemization of **48**). Racemizations of **49** and **50** cannot proceed through E-, G-, or H-like stages, which leaves F-, J-, and K-like species as possible reaction intermediates. Of these, F provides the most attractive explanation for the sensitized process, and K, for the nonsensitized process.



The strain energy of 31 kcal/mole for [2.2]paracyclophane²⁰ (**1**) is reflected in the above cleavage reactions of the system. The peculiar geometry, as well as the strain energy, made the nucleophilic substitution, addition, and elimination reactions in the side chain of the

Chart VII



system worthy of examination.³⁶ The stereochemistry of solvolytic substitution of optically active 1-tosyloxy-[2.2]paracyclophane (**51**) was examined in the three trigostatic stereochemical reaction cycles³⁷ formulated in Chart VII. Conversions **52** → **51**, **52** → **53**, **52** → **54**, **52** → **55** all went with retention of configuration since the carbon–oxygen bond at the chiral center was undisturbed. The methanolysis, acetolysis, and trifluoroacetolysis reactions of tosylate **51** (prepared from alcohol **52**) were all carried out and gave methyl ether **53**, acetate **54**, and trifluoroacetate **55** of the same *optical purity and configuration* as that obtained directly from alcohol **52**. Thus, only three chiromers were involved in these three, three-reaction stereochemical cycles,³⁷ and the solvolysis reactions occurred with *complete retention of configuration*.³⁶ The acetolysis reaction rates of tosylate **51**³⁶ were comparable to that of α -phenylneopentyl tosylate³⁸ and $\sim 10^3$ faster than that of 2-butyl tosylate. Acetolysis of α -phenylneopentyl tosylate proceeded with little stereospecificity.³⁸

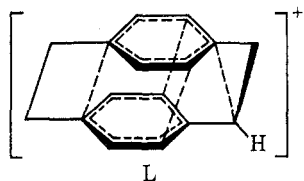
The high stereospecificity in the solvolyses of tosylate **51**,³⁶ coupled with the unexpectedly high rate of reaction, suggests participation of the β -phenyl in the

(36) (a) R. E. Singler, R. C. Helgeson, and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 7625 (1970); (b) R. E. Singler and D. J. Cram, *ibid.*, in press.

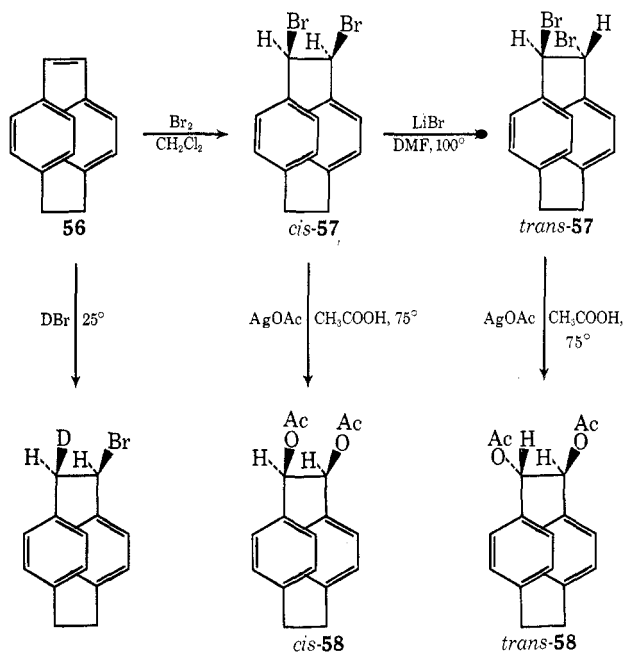
(37) D. J. Cram and D. C. Garwood, *ibid.*, **92**, 4575 (1970).

(38) S. Winstein and B. K. Morse, *ibid.*, **74**, 1133 (1952).

ionization to form the highly strained, bridged carbonium ion L, which is opened in a second stage to give product. Both formation of L and its decomposition must go with complete inversion of configuration, which provides complete overall retention for the solvolyses. Ion L carries a positive charge distributed in both rings, and its formation reflects exchange of bond angle strain in the side chain for release of π - π repulsion strain between the neutral benzene rings of the starting material. The skewing of the system to form L correlates with the already slightly skewed crystal structure of [2.2]paracyclophane itself.¹³



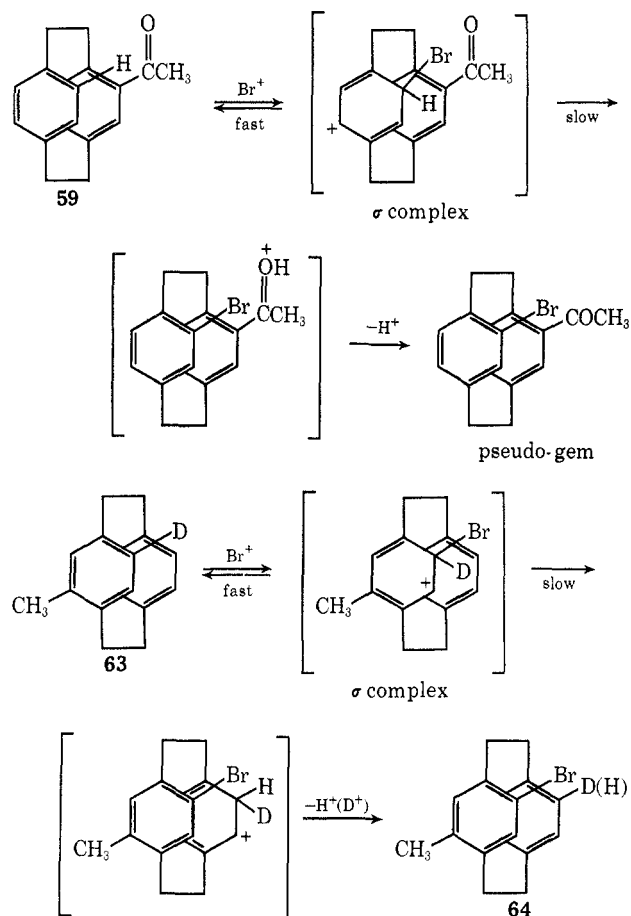
The stereochemical course of several polar addition and substitution reactions in the bridge of the [2.2]-paracyclophane system are best explained on the basis of L-like intermediates.^{36a} Thus, deuterium bromide and bromine add entirely *cis* to 1,2-dehydro[2.2]paracyclophane (**56**), and acetylation of the adducts provides acetates that are the products of substitution with retention of configuration. Treatment of *cis*-1,2-dibromo[2.2]paracyclophane (*cis*-**57**) with lithium bromide in dimethylformamide gave entirely *trans*-**57**, acetylation of which gave only *trans* diacetate (*trans*-**58**).



Transannular Effects in the Reactions of the Benzene Rings of [2.2]Paracyclophanes

Crystal structures, combustion strain energies, and activation energies for ring rotations in the smaller [m.n]cyclophanes reflect the consequences of the proximity of the benzene rings to one another. The substitution, addition, and complexation reactions of the

Chart VIII



aromatic rings of these substances are equally unusual, the [m.n]paracyclophanes being the most studied. The early work^{1a} established that acylation, nitration, and halogenation reactions were the only practical ways of substituting the hydrocarbons, and the closer the benzene rings were held together the faster substitution occurred.^{22c} An electron-withdrawing substituent in one ring deactivated both rings toward further electrophilic attack when m and $n < 4$.^{22c,39} The lower homologs were found to be the better π bases,^{12b} and it was only when $m = n > 4$ that both rings could act independently in complexing tricarbonylchromium.⁴⁰

The recent work has centered on transannular directive influences of substituents in one ring of [2.2]-paracyclophane (**1**) on the position of electrophilic substitution in the second ring. A related theme has involved the transannular substituent effects on π basicity of **1**.

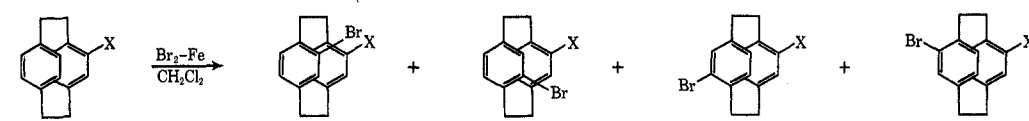
The directive effects of a substituent in one ring on the position of electrophilic substitution in the other ring are both obvious and unusual in bromination reactions.⁴¹ The results with 4-acetyl- (**59**), 4-nitro-

(39) (a) D. J. Cram and R. W. Kierstead, *J. Amer. Chem. Soc.*, **77**, 1186 (1955); (b) D. J. Cram and H. P. Fischer, *J. Org. Chem.*, **30**, 1815 (1965); (c) D. J. Cram and A. C. Day, *ibid.*, **31**, 1227 (1966).

(40) D. J. Cram and D. I. Wilkinson, *J. Amer. Chem. Soc.*, **82**, 5721 (1960).

(41) H. J. Reich and D. J. Cram, *ibid.*, **91**, 3505 (1969).

Table I
Products of Bromination of Monosubstituted [2.2]Paracyclophanes



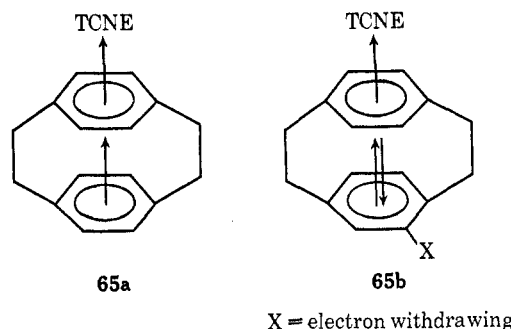
X	pseudo-gem, %	pseudo-ortho, %	pseudo-para, %	pseudo-meta, %
COCH ₃ (59)	59		6	8
NO ₂ (60)	70	3	6	8
CN (61)		16	28	26
Br (62)		16	26	6

(**60**), 4-cyano- (**61**), and 4-bromo[2.2]paracyclophane (**62**) as substrates are given in Table I. These results are not consistent with the product pattern predicted by a ground-state electrostatic model based on transannular resonance interactions. The correlation that emerges is that *predominant substitution occurs pseudo-gem to the most basic positions or substituents in the already substituted ring.*

The mechanism indicated in Chart VIII for operation of transannular influences involves rapid and reversible formation of σ complexes followed by rate-determining proton transfers to acceptor sites on the originally substituted ring. The geometry of **1** is suited for such proton transfer, because the proximity of the rings hinders normal approach of the usual external bases. Thus, electrophiles enter and depart from the faces of the system by the least hindered paths. The most striking example of transannular directive influences is found in the exclusive or predominant pseudo-gem-directing effects of the basic-oxygen-containing functional groups, **59** and **60**. The cyano group does not have the proper geometry to accept the proton, and no pseudo-gem product is formed from **61**.

The mechanism also accounts for the transfer of deuterium in the bromination of **63**, as illustrated in Chart VIII, from the position para to the methyl group to the pseudo-para position in **64**.⁴¹ Product **64** was found to contain 0.45 atom of deuterium in the unsubstituted ring, while the accompanying *o*-bromo product had 0.83 atom of deuterium in the substituted ring. Additionally, an isotope effect was found for reaction at the para position of **63** with $k_H/k_D = 3.7$.

Transannular influences are also apparent in the π - π salt formation of paracyclophanes and tetracyanoethylene. The π -base strengths as measured by equilibrium constants (K) are in the order²¹ [3.3] > [4.3] > [2.2] > [4.4] > [6.6] \sim open-chain model. With the exception of [2.2]paracyclophane, the order correlates with the distance of the two benzene rings from one another: the closer the two rings, the greater the



π -base strength, the nonbound benzene ring releasing electrons to the bound ring, **65a**. For 4-substituted [2.2]- and 5-substituted [3.3]-paracyclophanes with electron-withdrawing groups, a correlation²¹ was found for σ_m and ΔE , the difference in transition energies between substituted and unsubstituted salts. In this series the complexation (**65b**) is presumed to occur with the nonsubstituted ring affected by transannular influences.

The near rigidity and conformational homogeneity of the smaller cyclophanes originate both from their polycyclic structures and their powerful nonbonded interactions. The synthesis of the most compressed substance, [2.2]paracyclophane, depends on aromatization of the near-aromatic tetraene, *p*-xylylene. The bulk of the reactions of the smaller cyclophanes are channeled toward release of compression energies in their rate-determining transition states. In one reaction or another of [2.2]paracyclophane itself, every bond of the molecule has been broken except the σ framework of the benzene rings. The wealth of wondrous chemistry of this beautifully symmetrical compound perhaps is rivaled only by that of cyclopropane, which possesses about the same strain energy. The chemistry of these two substances will be completed only when chemists tire of tinkering with them.

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