# [2n]Cyclophanes: Paracyclophane to Superphane

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The cyclophane era is generally regarded as having begun with the description of di-*p*-xylylene by Brown and Farthing in 1949.[1] Their interest arose out of the experiments of Szwarc,[2] who showed that pyrolysis of *p*-xylene gave a linear polymer, and extraction of such polymers led to their first isolation of di-*p*-xylylene.

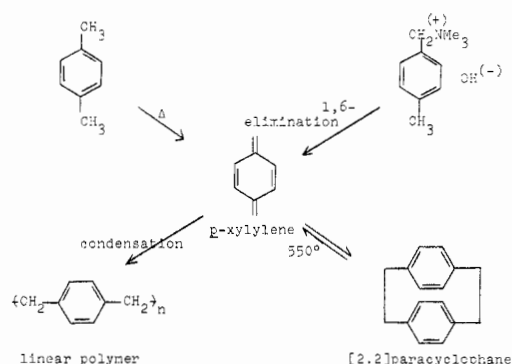[2.2]Paracyclophane

(formerly, di-*p*-xylylene)
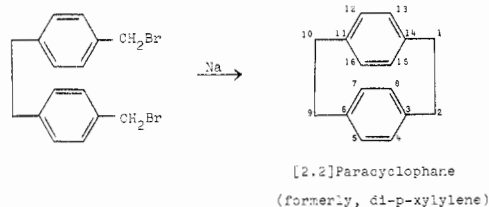
Simultaneously and independently, Cram and Steinberg[3] had become interested in rigid molecules of known geometry for testing questions of bonding, strain energies, and interactions of π-electron systems, and they prepared di-*p*-xylylene by design, via the intramolecular Wurtz coupling of 1,2-bis(4'-bromomethylphenyl)-ethane.

Cram and Steinberg also introduced the cyclophane nomenclature, now commonly used for these compounds.[4] By this nomenclature, cyclophane designates a molecule having a bridged aromatic ring. Each bridge is indicated by a number, corresponding to the number of bridge members, placed in a bracket before the name. The position of the bridges can be designated by the usual names of ortho, meta, and para or by numbers in parentheses following the brackets to indicate the positions of attachment on the aromatic ring. Thus, the name [2.2]paracyclophane for the molecule shown above could equally well be called [2.2](1,4)cyclophane. For multibridged cyclophanes, where all of the bridges are the same, the numbering can be simplified by simply using a subscript number to indicate the number of bridges.[4] For indicating positions of substituents in cyclophanes, the numbering of the molecule begins at the first bridge member of the longest bridge and then continues around as illustrated for [2.2]paracyclophane.

Although cyclophane chemistry as an area of research became recognized through the pioneering efforts of

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Scheme I

Cram, it should be noted for historical accuracy that the first synthesis of a cyclophane was that of Pellegrin,[5] who prepared di-*m*-xylylene ([2.2]metacyclophane) by the Wurtz coupling of *m*-xylylene dibromide in 1899; the second was that of Baker, Banks, Lyons, and Mann,[6] who prepared di-*o*-xylylene ([2.2]ortho-cyclophane) in 1945, again by a Wurtz coupling reaction.

In the years following Cram's initial study, a large number of [2.2]cyclophanes were prepared and their properties examined, both through the efforts of Cram and his research group as well as those of many others who entered the field.[7] The discussion of this earlier work will be brief, though, because of the abundance of good recent reviews[7] and because this report is primarily concerned with multibridged [2n]cyclophanes and the newly developed synthetic methods that have made possible the preparation of previously inaccessible members of the series.

(1) (a) C. J. Brown and A. C. Farthing, *Nature (London)*, **164**, 915 (1949); (b) A. C. Farthing, *J. Chem. Soc.*, 3621 (1953); (c) C. J. Brown, *ibid.*, 3265 (1953).

(2) M. Szwarc, *J. Chem. Phys.*, **16**, 128 (1948).

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

(4) F. Vögtle and P. Neumann, *Tetrahedron*, **26**, 5847 (1970). These authors suggested the use of [mn] for designating multibridged cyclophanes when all of the bridges are the same.

(5) M. Pellegrin, *Recl. Trav. Chim. Pays-Bas*, **18**, 458 (1899).

(6) W. Baker, R. Banks, D. R. Lyon, and F. G. Mann, *J. Chem. Soc.*, 27 (1945).

(7) For reviews, see (a) B. H. Smith, "Bridged Aromatic Compounds", Academic Press, New York, 1964; (b) D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, **4**, 204 (1971); (c) S. Misumi and T. Otsubo, *ibid.*, **11**, 251 (1978); (d) F. Vögtle and G. Hohner, *Top. Curr. Chem.*, **74**, 1 (1978).

Synthetic Methods

As shown below, vapor-phase pyrolysis of *p*-xylene leads to *p*-xylylene which, on condensation, may lead to [2.2]paracyclophane or other low molecular weight products as well as to a high molecular weight polymer. Industrially, it is apparently preferable to convert *p*-xylene to [2.2]paracyclophane by pyrolysis in steam at 900 °C,[8a] and then vapor-phase pyrolysis of [2.2]para-cyclophane at 550 °C and 0.5-mm pressure deposits the polymer of *p*-xylylene as a uniform film.[8b] *p*-Xylylene can also be produced by the thermal decomposition of 4-methylbenzyltrimethylammonium hydroxide,[9] and this is still the preferred laboratory procedure for preparing [2.2]paracyclophane (Scheme I).

The preparation of *anti*-[2.2]metacyclophane and [2.2]orthocyclophane, as well as variously substituted derivatives, can often be done conveniently by the Wurtz coupling reaction, although the yields are only in the range of 20–30%.[10]

anti-[2.2]Metacyclophane

[2.2]Orthocyclophane
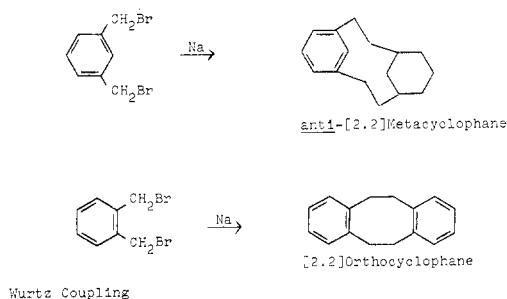
Wurtz Coupling

In the period between 1950 and 1970, the 1,6-elimination procedure and the Wurtz coupling reaction were the general procedures for making cyclophanes. In 1969, Vögtle introduced the concept of preparing dithiacyclophanes followed by oxidation and extrusion of sulfur dioxide as a method of preparing *anti*-[2.2]-metacyclophanes.[11] Independently, we had subjected dithiacyclophanes to the Stevens rearrangement followed by a Hofmann elimination as a method of preparing *anti*-[2.2]metacyclophane-1,9-dienes, which spontaneously valence-tautomerize to *trans*-15,16-dihydropyrenes.[12] Subsequently, the method of ring contraction of dithiacyclophanes has been extended to include the Wittig rearrangement[13] and the benzyne–Stevens rearrangement;[14] the elimination step has been extended to include sulfoxide pyrolyses[14] and the base-catalyzed elimination of sulfinate;[15] and the extrusion of sulfur has been extended to include both

Scheme II
Dithiacyclophane–Sulfur Extrusion Scheme
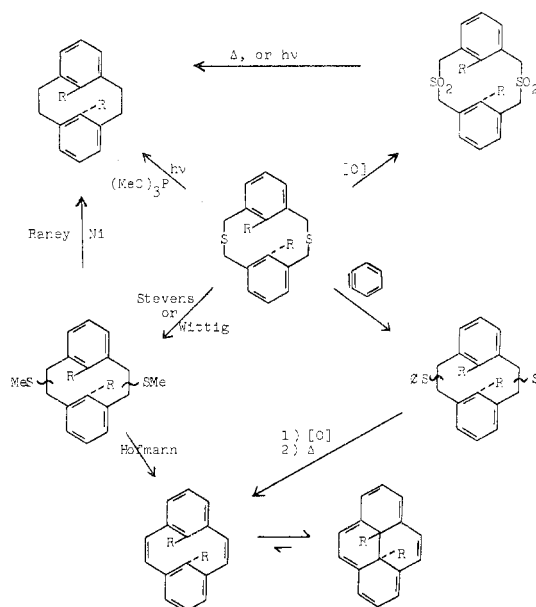
Chart I
Possible Symmetrical [2$_n$]Cyclophanes
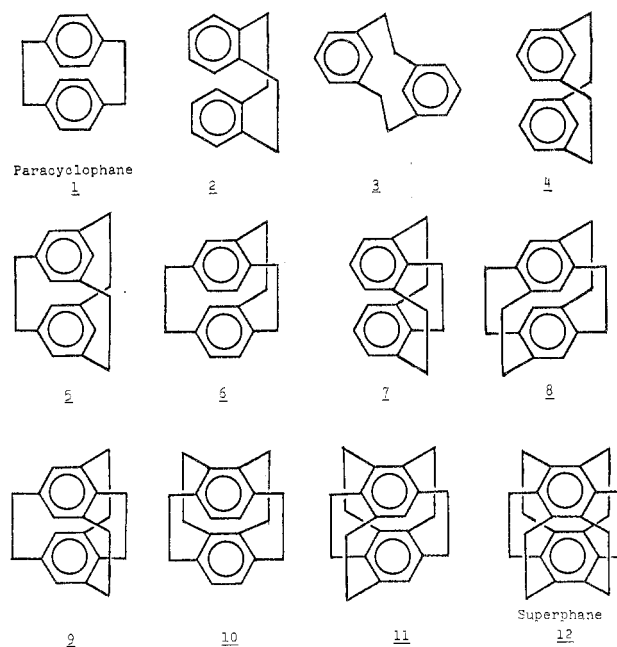
pyrolyses[11,16,17] and photolyses of sulfones[18–20] as well as photolyses of sulfides.[21,22] The high yields encountered in the syntheses of dithiacyclophanes coupled with the versatility and power of the methods for extruding sulfur have made this overall route the method of choice for synthesizing cyclophanes since 1970 and has led to the synthesis of some remarkable compounds, including multilayered cyclophanes,[7c,23,24] stepped cy-

(8) (a) W. F. Gorham, German Patent 1 085 763, July 21, 1960; *Chem. Abstr.*, **55**, 22920h (1961); (b) W. F. Gorham, *J. Polym. Sci., Part A-1*, **4**, 3027 (1966).

(9) (a) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, **82**, 1428 (1960); (b) H. E. Winberg and F. S. Fawcett, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, 1973, p 883.

(10) W. L. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 943 (1961).

(11) (a) F. Vögtle, *Angew. Chem.*, **80**, 258 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 274 (1969); (b) F. Vögtle, *Chem. Ber.*, **102**, 3077 (1969).

(12) (a) R. H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, **92**, 3510 (1970); (b) R. H. Mitchell and V. Boekelheide, *J. Chem. Soc., Chem. Commun.*, 1555 (1970); (c) R. H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970); (d) R. H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, **96**, 1547 (1974).

(13) R. H. Mitchell, T. Otsubo, and V. Boekelheide, *Tetrahedron Lett.*, 219 (1975).

(14) (a) T. Otsubo and V. Boekelheide, *Tetrahedron Lett.*, 3881 (1975); (b) T. Otsubo and V. Boekelheide, *J. Org. Chem.*, **42**, 1085 (1977).

(15) J. S. H. Yan, M.Sc. Thesis, University of Victoria, 1978.

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

(17) S. A. Sherrod, R. L. da Costa, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **96**, 1565 (1974).

(18) W. Rebafka and H. A. Staab, *Angew. Chem.*, **85**, 831 (1973).

(19) R. Gray, L. G. Harruff, J. Krymowski, J. Peterson, and V. Boekelheide, *J. Am. Chem. Soc.*, **100**, 2892 (1978).
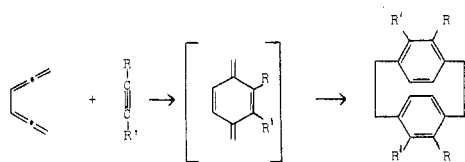
(20) R. S. Givens and P. L. Wylie, *Tetrahedron Lett.*, 865 (1978).

(21) V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, 405 (1973).

(22) J. Bruhin and W. Jenny, *Tetrahedron Lett.*, 1215 (1973).

(23) T. Otsubo, T. Kohda, and S. Misumi, *Tetrahedron Lett.*, 2507 (1978).

Scheme III

clophanes,[7c,25] annulenophanes,[26] [2.2](3,7)-tropolonoparacyclophane,[27] dibenzo-*trans*-15,16-dimethyldihydropyrenes,[28] and kekulene.[29] The procedures available for the dithiacyclophane–sulfur extrusion method are summarized in Scheme II using [2.2]metacyclophane as an example.

All of the possible symmetrical [2$_n$]cyclophanes are listed in Chart I. As discussed earlier, compounds 1, 2, and 3 were first made by either the dimerization of *p*-xylylene or the Wurtz reaction. The dithiacyclophane–sulfur extrusion procedure now made the syntheses of all three of these compounds much more convenient and provided examples of the previously unknown *syn*-[2.2]metacyclophane (4) as well.[30] Also, the dithiacyclophane–sulfur extrusion procedure provided a remarkably facile synthesis of the first multibridged [2$_n$]cyclophane, [2$_3$](1,3,5)cyclophane (5).[31] Alternatively, elaboration of existing [2.2]cyclophanes could be done to provide multibridged cyclophanes. This was first accomplished by Truesdale and Cram, who converted [2.2]paracyclophane to [2$_3$](1,2,4)-cyclophane (6), at the same time demonstrating some very interesting transannular chemistry peculiar to cyclophanes.[32] A combination of the dithiacyclophane–sulfur extrusion procedure and the further elaboration of bridges then permitted the first synthesis of a tetrabridged cyclophane, [2$_4$](1,2,4,5)cyclophane (8).[33]

At about this time, Hopf introduced a new method for preparing *p*-xylylenes that made substituted [2.2]-paracyclophanes readily available (see Scheme III).[34] Having suitably substituted [2.2]paracyclophanes thus available, Hopf was able to use these substituents as anchor points for creating additional bridges and shortly thereafter reported a second synthesis of [2$_3$](1,2,4)-cyclophane (6),[35] as well as the synthesis of [2$_4$]-(1,2,3,5)cyclophane (9).[36]

A consideration of the remaining unknown [2$_n$]-cyclophanes, compounds 7, 10, 11, and 12, suggested

that their syntheses by the known methods, adding one bridge at a time, would be slow and extremely tedious. We turned to the exploration of new approaches for the syntheses of these most highly bridged, and highly strained, cyclophanes. It had been shown by Cava that pyrolysis of 1,3-dihydroisothianaphthalene 2,2-dioxide in solution at 300 °C gave [2.2]orthocyclophane (2) in good yield.[37] Similarly, Jensen had found that boiling benzocyclobutene under reflux yielded [2.2]orthocyclophane in addition to polymer.[38] However, Errede found that pyrolysis of (2-methylbenzyl)trimethylammonium hydroxide (15) followed by condensation of the volatile products at −78 °C gave mainly the spirotriene 17, with only a modest quantity of 2 being formed.[39] This raised the question of whether *o*-xylylene (16), the presumed intermediate in each of these reactions, was converted directly to 2 or whether the normal Diels–Alder product 17 was being formed first in each case and then undergoing thermal rearrangement to 2. If the former were the case, a synthetic scheme could be imagined in which the generation of *o*-xylylene units appropriately placed in each deck of a cyclophane would result in the generation of two new bridges. If the spirotriene 17 were a necessary intermediate in the process, then such an attempted synthesis would be expected to fail, since the geometry of the cyclophane intermediate would probably not allow the formation of such a spirotriene.

Although the concerted dimerization of 16 to give 2
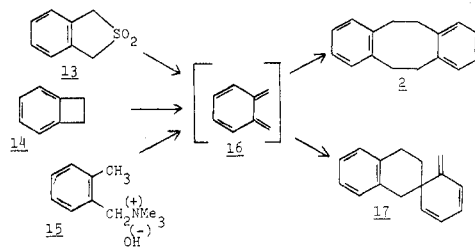
directly is forbidden by the rules for conservation of orbital symmetry, it seemed likely that *o*-xylylene would behave analogously to *p*-xylylene and so undergo stepwise radical dimerization to 2 without the intervention of 17. Benzocyclobutenes appeared to be the most suitable precursors for generating *o*-xylylene moieties to test this idea.

Furthermore, Hart had observed that trichloromethylpentamethylbenzene (18) lost hydrogen chloride
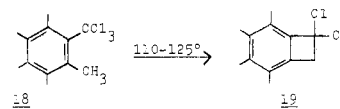
on melting at 110–125 °C to give the benzocyclobutene derivative 19.[40] To test whether the thermal loss of hydrogen chloride from *o*-chloromethyltoluenes was a general reaction, we pyrolyzed α,α′-dichlorodurene (20a) at 700 °C and found benzo[1,2:4,5]dicyclobutene (21a) in fair yield.[19] Although the desired dimerization of 21, via the appropriate *o*-xylylene intermediates, to give

(24) T. Otsubo, H. Horita, and S. Misumi, *Synth. Commun.*, 6, 591 (1976).

(25) T. Umemoto, T. Otsubo, and S. Misumi, *Tetrahedron Lett.*, 1573 (1974).

(26) M. Matsumoto, T. Otsubo, Y. Sakata, and S. Misumi, *Tetrahedron Lett.*, 4425 (1977).

(27) N. Kato, Y. Fukazawa, and S. Ito, *Tetrahedron Lett.*, 1113 (1979).

(28) R. H. Mitchell, R. J. Carruthers, and L. Mazuch, *J. Am. Chem. Soc.*, 100, 1007 (1978).

(29) F. Diederich and H. A. Staab, *Angew. Chem.*, 90, 383 (1978); *Angew. Chem., Int. Ed. Engl.*, 17, 372 (1978).

(30) D. Kamp and V. Boekelheide, *J. Org. Chem.*, 43, 3470 (1978).

(31) V. Boekelheide and R. A. Hollins, *J. Am. Chem. Soc.*, 95, 3201 (1973).

(32) E. A. Truesdale and D. J. Cram, *J. Am. Chem. Soc.*, 95, 5825 (1973).

(33) (a) R. Gray and V. Boekelheide, *Angew. Chem.*, 87, 138 (1975); *Angew. Chem., Int. Ed. Engl.*, 14, 107 (1975); (b) R. Gray and V. Boekelheide, *J. Am. Chem. Soc.*, 101, 2128 (1979).

(34) (a) H. Hopf, *Angew. Chem.*, 84, 471 (1972); *Angew. Chem., Int. Ed. Engl.*, 11, 419 (1972); (b) H. Hopf and F. Th. Lenich, *Chem. Ber.*, 107, 1891 (1974); (c) I. Böhm, H. Herrmann, K. Menke, and H. Hopf, *ibid.*, 111, 523 (1978).

(35) S. Trampe, K. Menke, and H. Hopf, *Chem. Ber.*, 110, 371 (1977).

(36) W. Gilb, K. Menke, and H. Hopf, *Angew. Chem.*, 89, 177 (1977); *Angew. Chem., Int. Ed. Engl.*, 16, 191 (1977).

(37) M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, 81, 4266 (1959).

(38) F. R. Jensen, W. E. Coleman, and A. J. Berlin, *Tetrahedron Lett.*, 15 (1962).

(39) L. A. Errede, *J. Am. Chem. Soc.*, 83, 949 (1961).

(40) (a) H. Hart and R. W. Fish, *J. Am. Chem. Soc.*, 82, 749 (1960); (b) H. Hart, J. A. Hartlage, R. W. Fish, and R. R. Rafos, *J. Org. Chem.*, 31, 2244 (1966).

Scheme IV

Scheme V

Scheme VI

Scheme VII
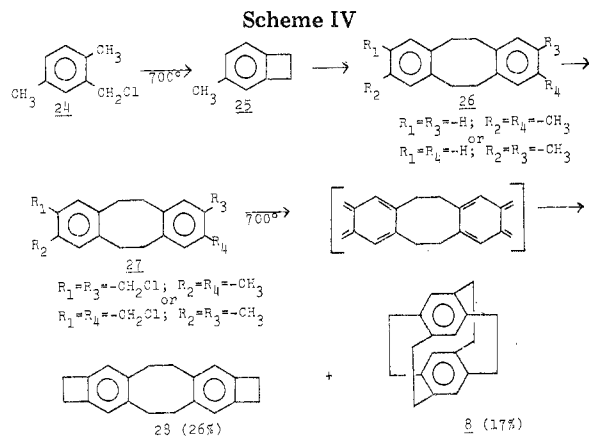
[2₄](1,2,4,5)cyclophane (8) did not occur as had been hoped, the generality of the pyrolytic method for converting α-chloromethyltoluenes to benzocyclobutenes was established. Independently and simultaneously with our work, Schiess also discovered this method of preparing benzocyclobutenes.[41] The pyrolysis of *o*-chloromethyltoluenes is a remarkably clean, convenient, and, generally, highly efficient process for preparing benzocyclobutenes.

When the pyrolysis was repeated with **20b**, the corresponding dimethyl derivative **21b** was formed, and this was converted via the dithiacyclophane–sulfur extrusion procedure to the paracyclophane **22**. It was
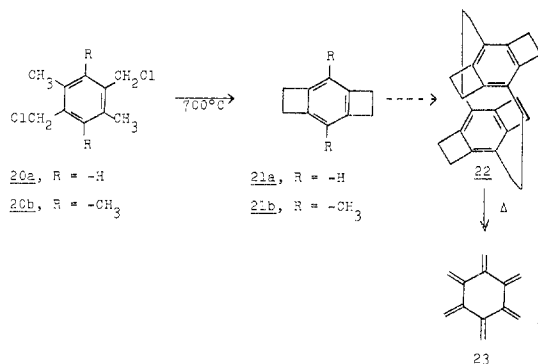
hoped that pyrolysis of **22** would result in a double *o*-xylylene dimerization to give [2₆](1,2,3,4,5,6)-cyclophane (**12**). Instead, the product was hexaradialene (**23**).[42]
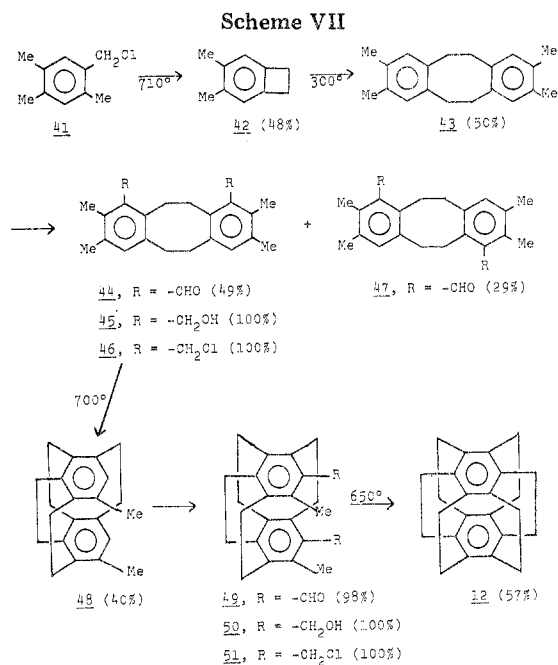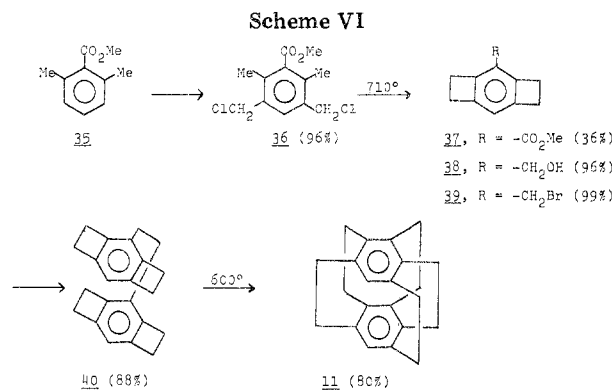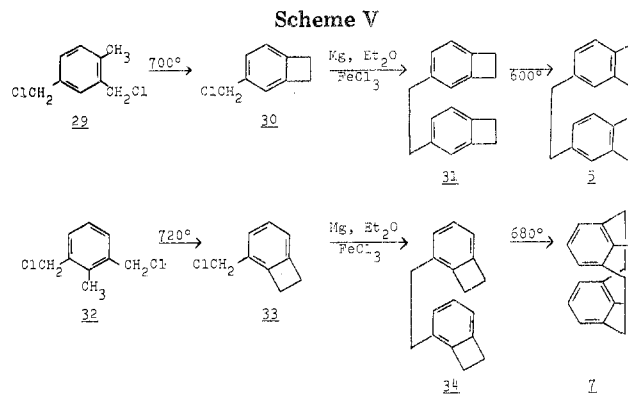
Since the failure of **22** to undergo thermal isomerization to **12** was probably the result of a more ready cleavage to a *p*-xylylene than to an *o*-xylylene, other cyclophane molecules were examined in an attempt to observe *o*-xylylene dimerization. As outlined in Scheme IV, 2,5-dimethylbenzyl chloride (**24**) is readily converted in good yield to **27** in three steps. Pyrolysis of **27** at 700 °C then gave a mixture of **28** and [2₄](1,2,4,5)cyclophane (**8**). Since recycling of **28** through the pyrolysis step converts it also to **8**, the overall yield of [2₄](1,2,4,5)-cyclophane is reasonably satisfactory.[43]

The generality of the benzocyclobutene-dimerization method for preparing multibridged cyclophanes was

then quickly established by syntheses of [2₃](1,2,4)-cyclophane (**5**)[44] and [2₃](1,2,3)cyclophane (**7**),[45] as outlined in Scheme V.

Extension of these general methods to the synthesis of [2₅](1,2,3,4,5)cyclophane (**11**) then followed[46] (see Scheme VI). This rather simple reaction scheme in-

(41) (a) P. Schiess and M. Heitzmann, *Helv. Chim. Acta*, 61, 844 (1978); (b) P. Schiess, M. Heitzmann, S. Rutschmann, and R. Stäheli, *Tetrahedron Lett.*, 4569 (1978).

(42) L. G. Harruff, M. Brown, and V. Boekelheide, *J. Am. Chem. Soc.*, 100, 2893 (1978). For other syntheses of hexaradialene, see ref 41a and A. J. Barkovich, E. S. Strauss, and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 99, 8321 (1977).

(43) V. Boekelheide and G. Ewing, *Tetrahedron Lett.*, 4245 (1978).

(44) (a) G. D. Ewing and V. Boekelheide, *J. Chem. Soc., Chem. Commun.*, 207 (1979); see also W. G. L. Aalbersberg and K. P. C. Vollhardt, *Tetrahedron Lett.*, 1939 (1979).

(45) (a) B. Neuschwander and V. Boekelheide, *Israel J. Chem.*, 20, in press. (b) See H. Hopf, J. Kleinschroth, and A. E. E. Murad, *ibid.*, 20, in press, for a synthesis of the dimethyl derivative of 7 as well as the acid-catalyzed rearrangement of [2₃](1,2,4)cyclophane.

(46) P. F. T. Schirch and V. Boekelheide, *J. Am. Chem. Soc.*, 101, 3125 (1979).

Scheme VIII
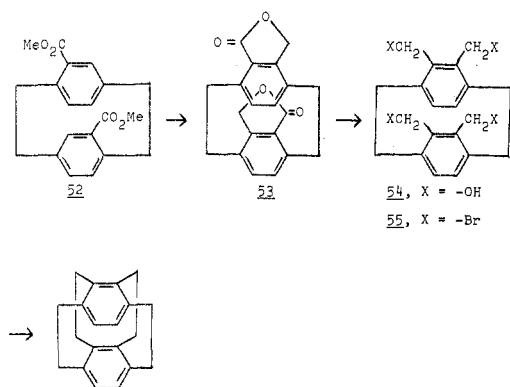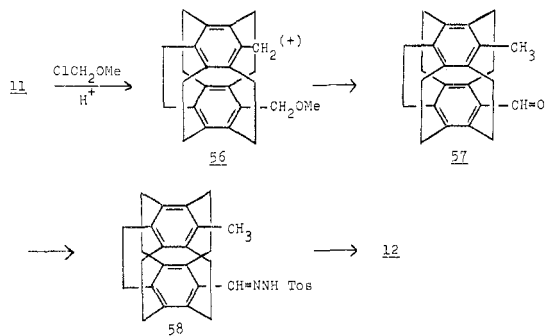

volves six steps for the conversion of **35** to **11** and proceeds with an overall yield of 23%, so that there is no difficulty in preparing gram quantities of **11**. The final pyrolysis in which four bridges are formed in one step in a yield of 80% is quite remarkable.

Finally, these methods were extended to the ultimate example, $[2_6](1,2,3,4,5,6)$cyclophane (**12**), for which the trivial name superphane has been proposed[47] (Scheme VII).

At the time, the synthesis of intermediate **48** provided the first example of a $[2_4](1,2,3,4)$cyclophane. However, simultaneously with our studies Kleinschroth and Hopf prepared the parent molecule, **10**, as shown in Scheme VIII.[48]

Unexpectedly, but understandably, chloromethylation of $[2_5](1,2,3,4,5)$cyclophane (**11**) gives the aldehyde **57**, presumably via transannular hydride ab-

straction of the intermediate carbonium ion **56**.[49] Treatment of **57** with tosylhydrazide, followed by a transannular carbene insertion reaction,[32] provides an alternate, and quite probably more convenient, synthesis of superphane.[49]

One of the more interesting questions regarding the multibridged $[2_n]$cyclophanes is the change in distance between decks as additional bridges are added. In [2.2]paracyclophane this distance is 3.093 Å[50] whereas for $[2_3](1,3,5)$cyclophane-1,9,17-triene it is 2.80 Å,[51a] for $[2_4](1,2,4,5)$cyclophane (**8**) 2.688 Å,[51b] for $[2_5]$-$(1,2,3,4,5)$cyclophane (**11**) 2.65 Å,[52] and for $[2_6]$-

(1,2,3,4,5,6)cyclophane (**12**) 2.628 Å.[52] In superphane (**12**) the molecule is symmetrical, with each benzene ring being perfectly planar. Comparative studies of the physical and chemical properties of the multibridged $[2_n]$cyclophanes should provide further insight into questions of bonding and strain in these caged molecules.

Although this Account has been concerned with symmetrical $[2_n]$cyclophanes, three unsymmetrical $[2_n]$cyclophanes are known and quite possibly others are capable of being synthesized. The known unsymmetrical $[2_n]$cyclophanes are [2.2]metaparacyclophane (**59**),
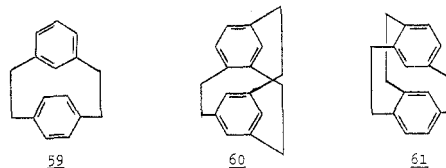
$[2_3](1,2,4)(1,3,5)$cyclophane (**60**), and $[2_3](1,2,4)(1,2,5)$-cyclophane (**61**), and all three have been synthesized by the dithiacyclophane–sulfur extrusion route.[17,53] However, the first synthesis of [2.2]metaparacyclophane (**59**) was accomplished by an acid-catalyzed rearrangement of [2.2]paracyclophane,[54] and recently Hopf, Kleinschroth, and Murad have shown that the aluminum chloride catalyzed rearrangement of $[2_3](1,2,4)$-cyclophane is a superior method for preparing **61**.[45b]

The combination of the thermal elimination of hydrogen chloride from o-chloromethyltoluenes to give aromatic cyclobutenes together with the pyrolytic dimerization of appropriate derivatives of such aromatic cyclobutenes appears to be an overall synthetic method of general utility. Certainly, it is a convenient, efficient method for preparing multibridged cyclophanes. Often syntheses of novel molecules, even when successful, do not provide a sufficient sample for further studies. In contrast, the overall pyrolytic methods described here have permitted the syntheses of $[2_5](1,2,3,4,5)$-cyclophane and of superphane in gram quantities, allowing adequate studies of their physical and chemical properties to be made.

One of the obvious possible extensions of the present work is the synthesis of other multibridged cyclophanes having various aromatic moieties, such as naphthalene or anthracene, or heteroaromatic moieties, such as pyridine or thiophene, as the decks in the cyclophane molecule.

Another possible extension, of perhaps even broader application, would be to employ hetero analogues of benzocyclobutene. In a preliminary study directed toward this end, we have found that gas-phase pyrolysis of o-hydroxymethylthiophenol (**62**) at 750 °C and
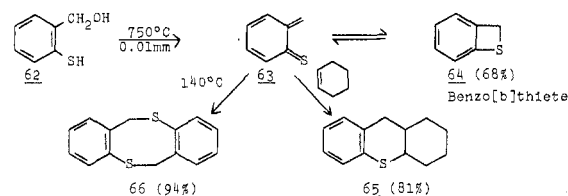
0.01-mm pressure readily gives benzo[b]thiete (**64**) in good yield.[55,56] Presumably, loss of water first occurs

(47) Y. Sekine, M. Brown, and V. Boekelheide, *J. Am. Chem. Soc.*, **101**, 3126 (1979).

(48) J. Kleinschroth and H. Hopf, *Angew. Chem.*, **91**, 336 (1979); *Angew. Chem., Int. Ed. Engl.*, **18**, 329 (1979). By a variation of this procedure Kleinschroth and Hopf have also prepared [2₄](1,2,4,5)cyclophane (Professor Hopf, private communication).

(49) P. F. T. Schirch and V. Boekelheide, unpublished work.

(50) K. Lonsdale, H. J. Milledge, and K. V. K. Rao, *Proc. R. Soc. London, Ser. A*, **555**, 82 (1960).

(51) (a) A. W. Hanson, *Acta Crystallogr., Sect. B*, **28**, 2287 (1972); (b) A. W. Hanson, *ibid.*, **33**, 2003 (1977).

(52) A. W. Hanson, private communication.

(53) M. Nakazaki, Y. Yamamoto, and Y. Miura, *J. Org. Chem.*, **43**, 1041 (1978).

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

to give *o*-thioquinonemethide (**63**) which, by valence tautomerization, gives benzo[*b*]thiete (**64**). That valence tautomerization occurs much more readily with the sulfur analogue **64** than in the parent benzocyclobutene case is shown by the easy reaction of benzo-[*b*]thiete (**64**) with boiling cyclohexene, presumably via **63**, to give the Diels–Alder adduct **65**. Heating **64** in the absence of a dienophile results in dimerization to **66**, in close analogy to the behavior of benzocyclobutene.[38]

When a similar gas-phase pyrolysis of *N*-phenyl-*o*-(hydroxymethyl)aniline (**67**) was carried out, the product was not the expected *N*-phenylbenzo[*b*]azetine (**69**)[57] but was, instead, acridine (**71**).[55] Apparently, the
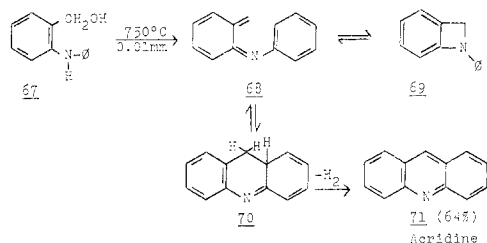
intermediate *o*-quinonemethide imine (**68**) undergoes

(55) Y.-L. Mao, Doctoral Dissertation, University of Oregon, 1979.

(56) W. J. M. van Tilborg and R. Plomp (*Recl. J. R. Netherlands Chem. Soc.*, **96**, 282 (1977)) have described the preparation of benzo[*b*]thiete in 45% yield by the gas-phase pyrolysis of thianaphthene 1,1-dioxide at 1000 °C.

(57) E. M. Burgess and L. McCullagh, *J. Am. Chem. Soc.*, **88**, 1580 (1966).

triene cyclization to **70**, followed by an irreversible thermal dehydrogenation to acridine.

Although the yield of acridine in this pyrolytic, one-step synthesis is good, it seemed that in terms of the proposed mechanism it would be improved if the starting material were at the right oxidation level to avoid the thermal dehydrogenation. This proved to be true. When *N*-phenylanthranilic acid (**72**) was pyrolyzed at 750 °C, acridone (**74**) was isolated in 87% yield.
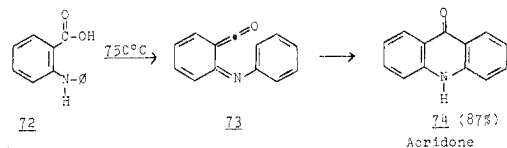
Presumably, in this case loss of water gives the ketene imine **73** which, by triene cyclization followed by tautomerization, gives acridone (**74**) directly.

The results of these preliminary studies suggest that the pyrolytic formation of hetero analogues of *o*-xylylenes and their use in synthesis has considerable potential. However, the more important conclusion is that gas-phase pyrolysis is a synthetic method of general utility. It is usually clean, convenient, and efficient, and frequently has advantages over other synthetic methods for accomplishing the same goals.

Benzocyclobutene and Related Compounds

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Benzocyclobutene and related compounds represent a unique compromise between the thermodynamic stability associated with a benzenoid aromatic system and the kinetic reactivity of a strained cyclobutene. In the next lower homologue, benzocyclopropene, reactivity is the dominant feature while the next higher homologue, indan, is too unreactive toward ring opening to be of much interest.

Physical and chemical studies have been directed primarily at determining how the fused benzene and cyclobutene rings interact with one another. Early efforts in this area were comprehensively reviewed by Klundt.[1] For synthetic as well as mechanistic reasons, there has recently been a new surge of interest in benzocyclobutene chemistry. This Account chronicles some of the more salient features of this resurgence.

Randolph P. Thummel was born in 1945 and raised in Upper Montclair, N.J. He received a B.S. degree from Brown University in 1967 followed by a Ph.D. degree from the University of California at Santa Barbara where he worked with Bruce Rickborn. After a 2-year postdoctoral stay with Paul Gassman at The Ohio State University, he joined the faculty of the University of Houston where he is currently an Associate Professor.

Synthesis

The first synthesis of a benzocyclobutene derivative was reported by Finkelstein in 1910,[2] but it was not until 1956 that Cava and Napier succeeded in preparing the parent compound.[3] Since that time this once thought to be elusive molecule has been prepared by a variety of approaches. We will look at three recently developed methods which complement each other in their design. The pyrolytic approach starts with the aromatic ring intact and closes one or more fused rings. The Diels–Alder approach starts with the small ring intact and builds up the aromatic nucleus. Finally, the cooligimerization route creates both rings simultaneously.

Very early in the history of benzocyclobutene, it was discovered that pyrolytic methods could be employed for straightforward access to this compound from easily available starting materials. Cava and Deana showed

(1) I. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(2) H. Finkelstein, *Chem. Ber.*, **43**, 1528 (1910).

(3) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **78**, 500 (1956).