

INTRUSION OF SUBSTITUENTS INTO THE CAVITY OF AROMATIC π -ELECTRON CLOUDS

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ABSTRACT

The bridged [14]annulenes are exceptional models for testing theories and providing quantitative data. Thus, the dihydropyrene system demonstrates that diatropic ring current effects on chemical shifts are of the same magnitude for carbon-13 as for hydrogen for the same position in space relative to the aromatic π -electron cloud. The continuing need for additional samples of bridged [14]annulenes has led to the development of new synthetic methods. These, in turn, have led to syntheses of bridged [18]annulenes, tetra-bridged cyclophanes, and substituted [2.2]metaparacyclophanes. The latter substances provide opportunity for quantitative measurement of the interaction of substituents with aromatic π -electron clouds.

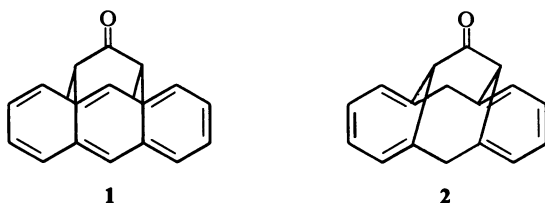
INTRODUCTION

An important aspect of recent studies of nonbenzenoid aromatic compounds has been the examination of annulenes containing larger Hückel systems than benzene¹. The study of the properties of such molecules is usually simplified when the aromatic perimeter is held rigid and more or less planar as in the appropriate bridged annulenes^{2,3}. Because of the suitability of bridged annulenes as models for testing theoretical concepts, there has been a continuing demand for samples of these molecules. This, in turn, has made necessary the development of better synthetic methods and these methods have provided access to still more molecules of theoretical interest. It is with these aspects that the following discussion is concerned.

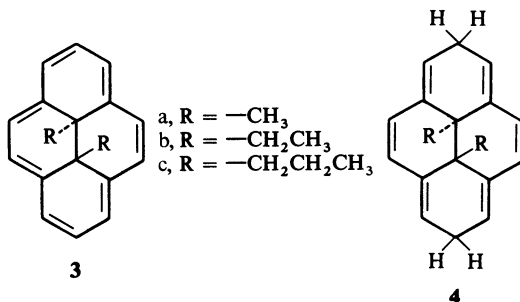
RING CURRENT CONTRIBUTIONS TO NMR CHEMICAL SHIFTS

As an example of the sort of testing of theoretical concepts for which bridged annulenes are especially well suited, can be cited some recent work on ring current contributions to n.m.r. chemical shifts⁴. In the case of protons, ring current effects are usually large compared to other factors affecting the value of the chemical shift, and this is dramatically evident for simple and bridged annulenes⁵⁻⁷. However, for heavier elements the ring current effect is less significant and is normally wholly overshadowed by other effects. Thus, past attempts to evaluate ring current effects have in large measure been frustrated by lack of suitable models in which these other

effects would be nullified or unimportant.^{8,9} Jones, Masamune and their colleagues⁹ suggested that the bridged annulenes would be most suitable for such a study, and Gunther, Vogel and their associates have measured the ¹³C-n.m.r. spectrum of the bridged [14]annulene **1**, comparing it to that of the dihydro derivative **2** as a non-aromatic model¹⁰.



Although the values found in this study are probably quite accurate, there is some change in geometry between **1** and **2**. In an attempt to examine a case where ring current effects would be maximized and suitable models would minimize other effects, we have measured the proton and carbon-13 n.m.r. spectra of the dihydropyrene derivatives **3** and **4**.



The data are summarized in *Figures 1* and *2*. Examination of molecular models suggests that for the atoms present in the internal R groups there is essentially no change in their position in space or in any of the other factors affecting chemical shift aside from ring current in comparing **3** and **4**.

In *Figure 3* the ring current effects on ¹³C and ¹H chemical shifts are plotted according to the position of these atoms in space relative to a theoretical plot derived from the Johnson and Bovey calculations for ring current effects¹¹. From these data one can conclude that the magnitude of the ring current effect on chemical shifts is essentially the same for carbon-13 as for protons when the atoms are located in the same position in space relative to the mean plane of delocalization of the aromatic π -electron cloud.

SYNTHETIC METHODS

Synthetic routes to the dihydropyrene derivatives have involved [2.2]-metacyclophanes and [2.2]metacyclophane-1,9-dienes³. From the time of Pellegrin¹² until recent years, the only generally useful synthesis of [2.2]-metacyclophanes was the Wurtz reaction. Even with improved methods the

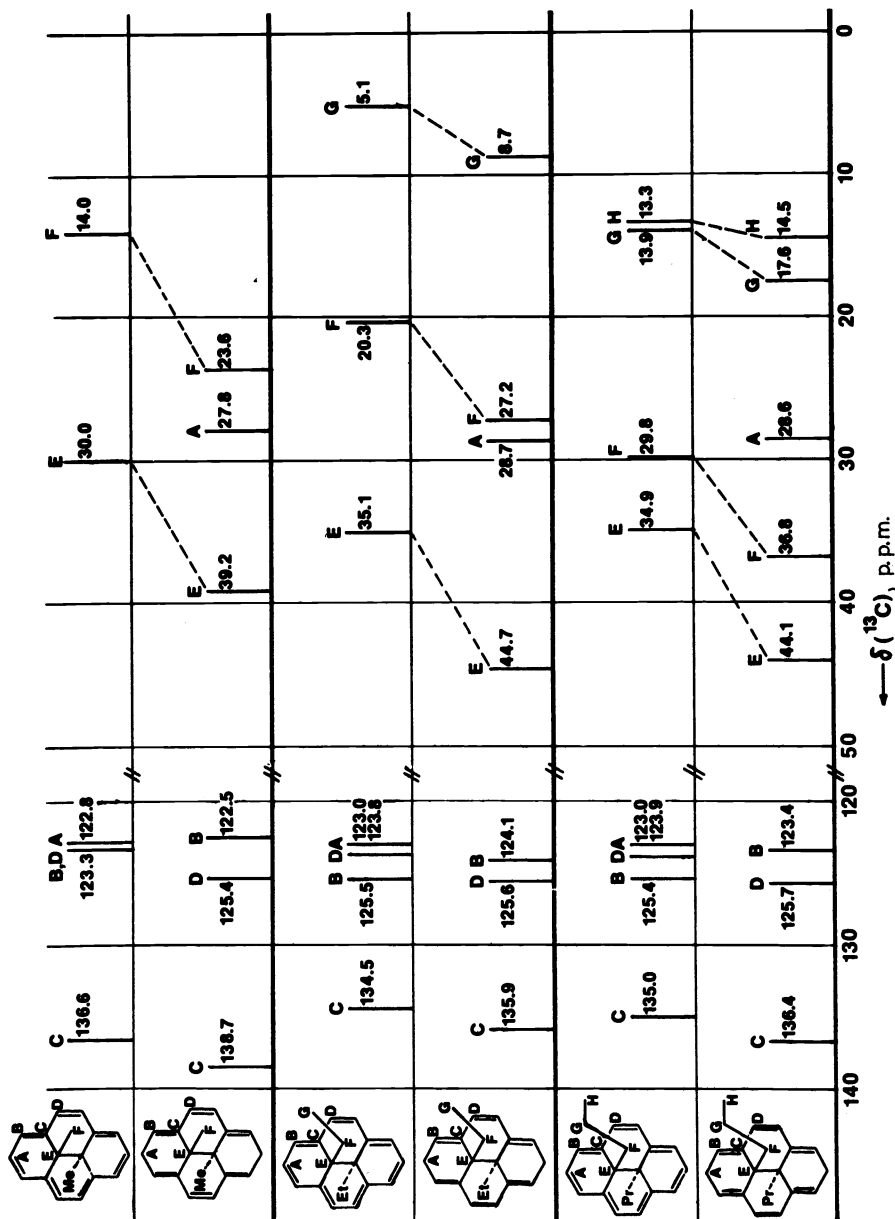


Figure 2. Schematic representation of the ^{13}C n.m.r. spectra of compounds 3a-c and 4a-c.

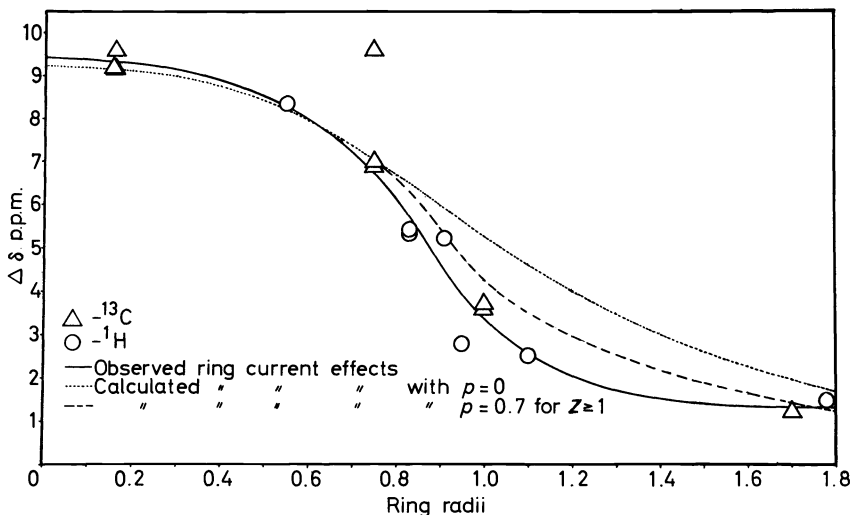


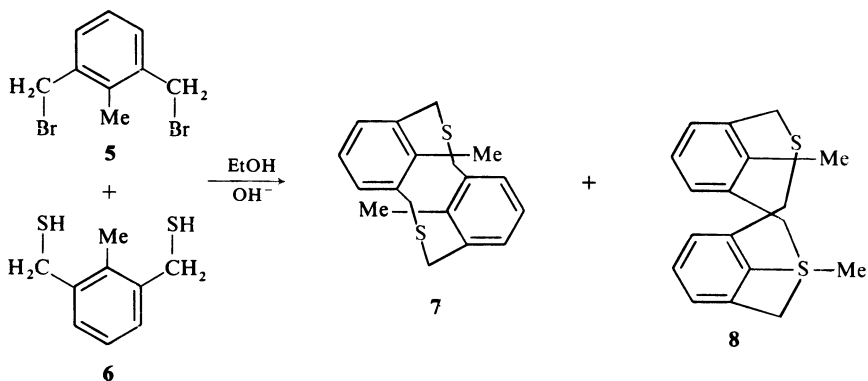
Figure 3. Correlation of ^1H and ^{13}C ring current effects for compounds 3a-c and 4a-c in comparison with theoretical predictions.

dimerization of *m*-xylylene dibromides via the Wurtz reaction proceeds in yields of only 20 to 30 per cent and no useful methods are available for converting the resulting [2.2]metacyclophanes to the corresponding [2.2]metacyclophane-1,9-dienes. Other methods that have been successfully employed for preparing larger cyclic dienes include the Wittig, Perkin, and Ramberg-Bäcklund reaction. However, in our hands all of these methods have failed in attempts to utilize them for the preparation of [2.2]metacyclophane-1,9-dienes.

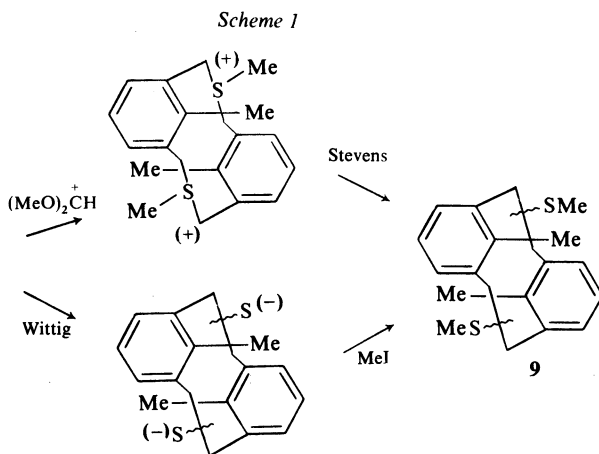
In 1970 we reported on a method for converting 2,11-dithia[3.3]metacyclophanes to [2.2]metacyclophane-1,9-dienes via extrusion of sulphur¹³. Concurrently with our own work studies had been initiated in a number of other laboratories on the preparation and synthetic applications of dithiacyclophanes¹⁴⁻¹⁶. In view of this broad range of interest some discussion of experimental procedures used seems warranted. In our experience, the formation of 2,11-dithia[3.3]metacyclophanes is best carried out by a coupling of a *m*-xylylene dihalide with a *m*-xylylene dimercaptan. To avoid the formation of trimers, tetramers and other polymers of higher molecular weight the experimental conditions for the coupling should provide high dilution. This is readily accomplished by adding a dilute mixture of the dihalide and dimercaptan in ethanol dropwise to a dilute ethanolic solution of base. Under these conditions formation of the 2,11-dithia[3.3]metacyclophane generally occurs in yields of 75 to 80 per cent, and thus makes dithiacyclophanes readily available as precursors for a variety of synthetic objectives.

For example, the coupling of 2,6-bis(bromethyl)toluene (5) with 2,6-bis(mercaptomethyl)toluene (6) provides the corresponding 9,18-dimethyl-2,11-dithia[3.3]metacyclophanes in an overall yield of 78 per cent (67 per cent of the *anti* isomer 7 and 11 per cent of the *syn* isomer 8). In contrast to the Wurtz reaction, which only gives [2.2]metacyclophanes of the *anti* configura-

tion, the coupling reaction to form dithia[3.3]cyclophanes normally gives both the *syn* and *anti* isomers, the relative amounts of which depend upon the nature of the substituents. However, the fact that *syn* isomers are formed provides access to otherwise inaccessible *syn*[2.2]cyclophanes.

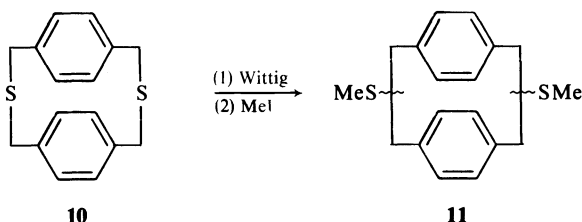


The extrusion of sulphur with concomitant formation of carbon-carbon double bonds was first accomplished in this series by effecting a Stevens rearrangement followed by a Hofmann elimination of dimethyl sulphide, as summarized in *Scheme 1*. This procedure has been generally useful for preparing [2.2]metacyclophane-1,9-dienes. In some instances, it is desirable to avoid strong methylating agents. A method recently developed, which has been quite successful now in a number of examples, is to carry out a Wittig rearrangement instead of a Stevens rearrangement¹⁷. The Wittig rearrangement, using either *n*-butyllithium or lithium diisopropylamide, occurs rapidly and usually in very high yield. It has been shown that both the Stevens and Wittig rearrangements exhibit chemically induced, dynamic nuclear polarization and presumably the two rearrangements follow very similar mechanistic pathways¹⁸. Thus, the mixture of isomers 9 formed via the Stevens

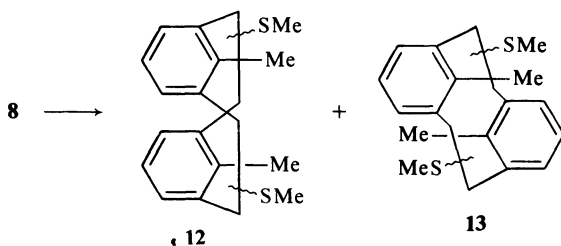


route is essentially identical to the mixture of isomers formed via the Wittig route.

In some instances, though, the Stevens and Wittig routes show striking differences. Thus, in the case of 2,11-dithia[3.3]paracyclophane (**10**), where 1,6 elimination provides an alternative pathway, the Stevens rearrangement fails completely, whereas the Wittig rearrangement followed by methylation gives the desired product **11** in 25 per cent yield¹⁷.



In another example, the Stevens rearrangement of **8** leads to a 1:3 mixture of *syn* to *anti* isomers (**12** and **13**). However, in the Wittig rearrangement the product is almost entirely **13** with only traces (1–2 per cent) of **12**.

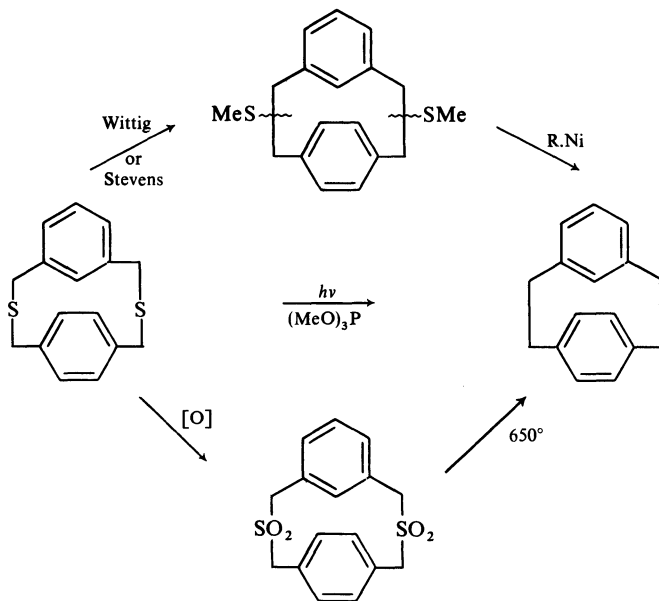


The extrusion of sulphur from dithia[3.3]cyclophanes to form [2.2]-cyclophanes as shown in *Scheme 2* can be accomplished by three general methods: (1) Stevens or Wittig rearrangement followed by desulphurization using Raney nickel¹⁶; (2) irradiation in the presence of trivalent phosphorus compounds^{19, 20}; and (3) oxidation to the corresponding bisulphone followed by pyrolysis^{21, 22}. Although the latter two methods generally proceed in high yield and can be very useful, the first method is best suited for larger scale operations.

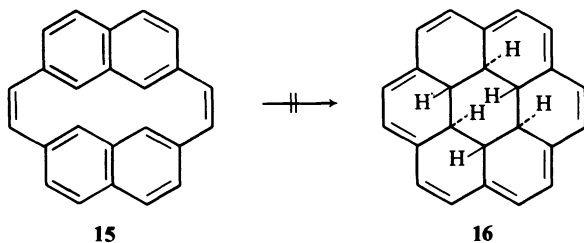
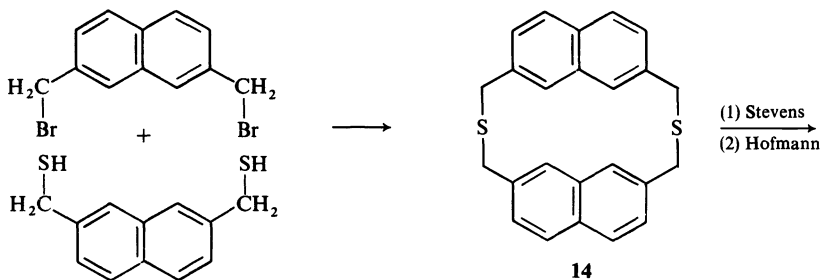
BRIDGED [18]ANNULENES

A molecule of obvious interest among the bridged [18]annulenes is hexahydrocoronene (**16**), in which the six internal SP^3 carbons are arranged in a chair conformation. We have explored its possible synthesis starting from 2,7-dimethylnaphthalene and utilizing the synthetic methods discussed above. Although the coupling reaction to give **14** proceeded well and the Stevens and Hofmann reactions were accomplished to provide **15**, it was not possible to effect either reductive or photochemical cyclization to hexahydrocoronene. In an analogous study, Davy and Reiss have also reported the synthesis of **15**.

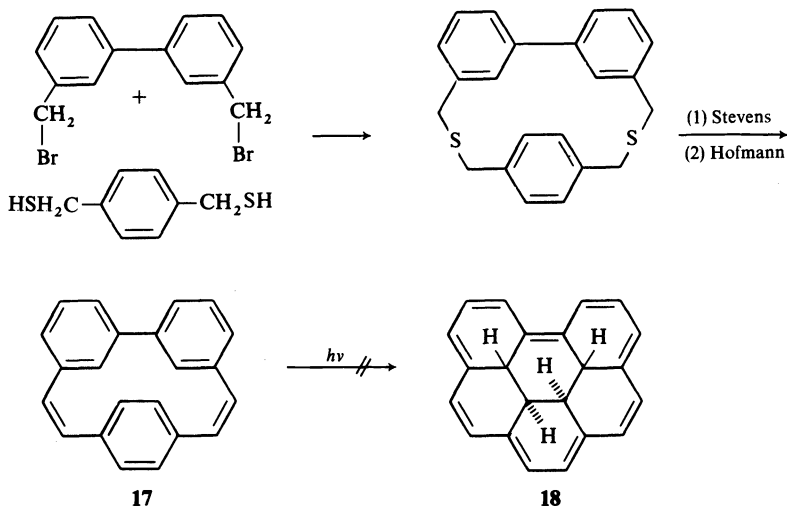
Scheme 2



Previously, it had been shown that irradiation of *anti*[2.2]metacyclophane-1,9-diene effects cyclization to *trans*-15,16-dihydropyrene²⁴. A possible extension of this type of photochemical approach to the synthesis of bridged [18]annulenes is the synthesis and irradiation of a biphenyl derivative such as 17. The synthesis of 17 has been accomplished in a straightforward



Scheme 3



manner as shown in *Scheme 3*. However, irradiation of **17** did not give the desired bridged annulene **18**, but rather led to recovery of starting material.

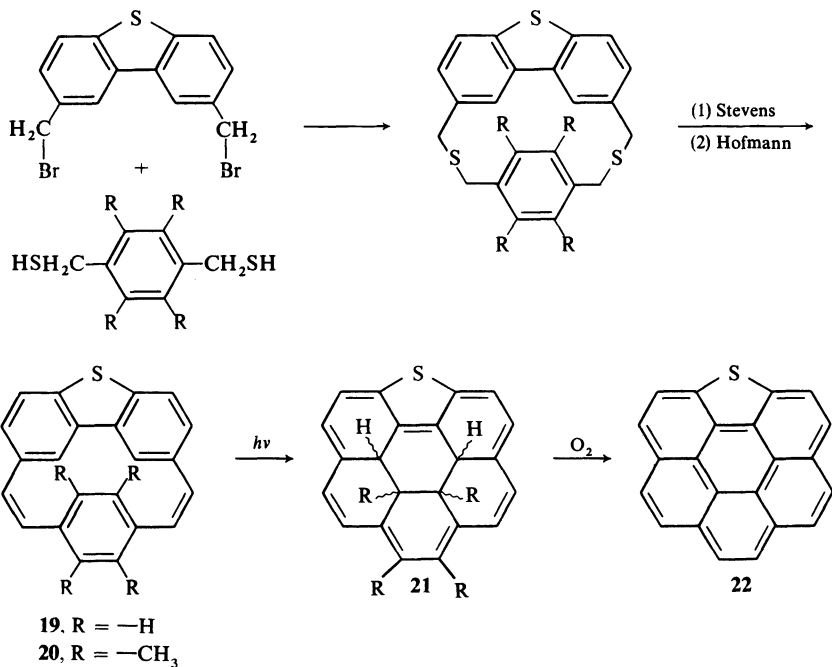
Examination of molecular models of **17**, as well as spectral evidence, indicated that the most stable conformation for the molecule is one in which the planes of the benzene rings of the biphenyl moiety are twisted almost to right angles. The possibility that such a conformation would be adverse to the desired photochemical cyclization led to an examination of other series in which the benzene rings of the biphenyl moiety would be held coplanar by a bridging atom or atoms. As summarized in *Scheme 4*, the first such example to be synthesized and irradiated was the dibenzothiophene derivative **19**. A solution of **19**, on irradiation, became a deep orange and the presence of the desired, bridged [18]annulene (**21**) was evident by n.m.r. analysis. The internal four protons of **21** appear as a multiplet in the region of τ 15.0–16.0²⁵. When air was admitted to the system during irradiation of **19**, the internal hydrogens were lost and thiacorone (**22**) was formed.

In an attempt to provide a bridged [18]annulene derivative with internal methyl substituents, the durene derivative **20** was prepared in an analogous way. Similarly, irradiation of **20** provided a photoproduct analogous to **21** with the expected chemical shifts for the internal hydrogens (τ 14.96) and the internal methyls (τ 13.74).

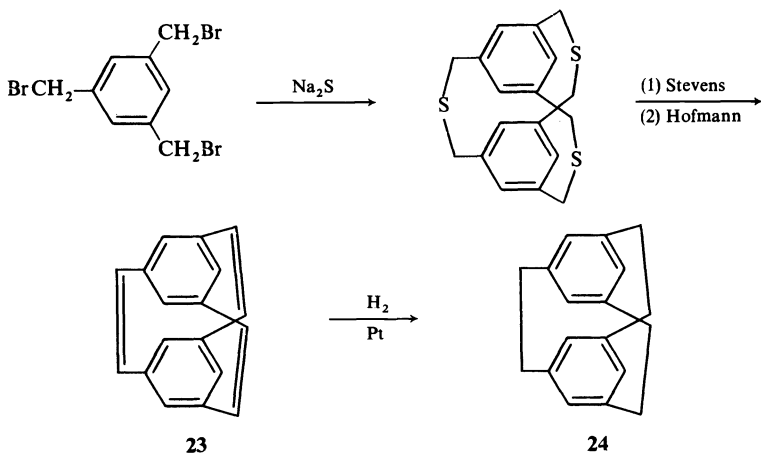
POLY-BRIDGED CYCLOPHANES

One opportunity provided by the synthetic methods discussed earlier was that it enabled the preparation of molecules in which the properties and behaviour of aromatic π -electron clouds could be examined under

Scheme 4



unusual circumstances. For example, the easy conformational flipping of 2,11-dithia[3.3]metacyclophanes made possible the synthesis of tris-bridged cyclophanes²⁷.



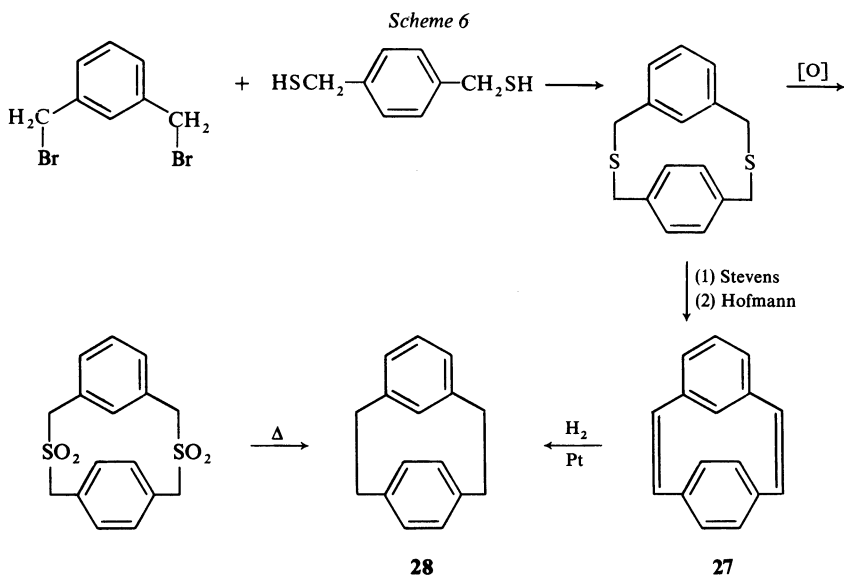
The extreme face to face crowding of the two aromatic π -electron clouds in **23** and **24** is clearly documented by the x-ray crystallographic analysis of **23** and the chemical and spectral behaviour of both **23** and **24**^{27, 28}.

For various reasons there is interest in obtaining similar molecules in which the number of bridges is four or more. Outlined in *Scheme 5* is a

synthesis of [2.2.2.2](1,2,4,5)-cyclophane (**26**)²⁹. The overall route is straightforward, probably the most noteworthy aspect being the pseudo-gem effect of the carbomethoxy groups in controlling the position of substitution during chloromethylation of **25**^{30, 31}.

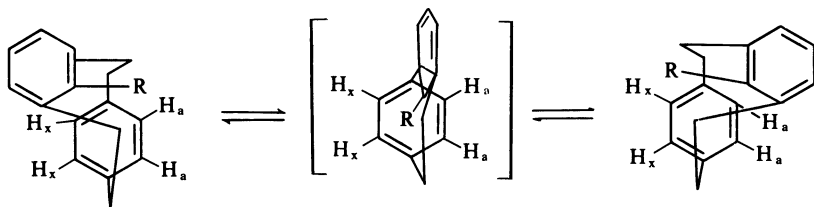
CONFORMATIONAL FLIPPING OF [2.2]METAPARACYCLOPHANES

A second type of molecule made readily available by these synthetic methods was [2.2]metaparacyclophane and its derivatives. Thus, as shown in *Scheme 6*, derivatives of either [2.2]metaparacyclophane-1,9-diene (**27**) or [2.2]metaparacyclophane (**28**) itself are readily formed and in good yield^{21, 32}.



A property of [2.2]metaparacyclophanes of particular interest is that of conformational flipping. As shown below, the transition state for conformational flipping must approach a perpendicular arrangement of the two aromatic rings with the internal substituent R of the meta-bridged ring intruding deeply into the cavity of the π -electron cloud of the para-bridged ring. Since the conformational flipping effects an exchange of the two types of aromatic protons of the para-bridged ring, the kinetic parameters for the process can readily be determined by n.m.r. techniques. The use of coalescence temperatures is not satisfactory for providing quantitative information. However, the continuous wave, double-irradiation procedure of Forsen and Hoffman³³ can be adapted quite satisfactorily for this purpose²¹. More recently, a selective pulse, Fourier transform method has been developed that is even more convenient and precise³⁴.

The study of conformational flipping rates, then, provides a good insight into the interaction of the internal substituent R with the aromatic π -electron

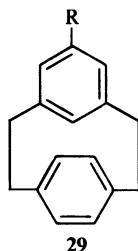


cloud of the para-bridged ring. Furthermore, the barrier to conformational flipping is highly sensitive to small changes. For example, the coalescence temperature for **27** is -96° , whereas that of **28** is 157° at 100 MHz. Quite evidently, the larger bond angles of the ethylene bridge in **27** are more important in relieving strain in the transition state than is the longer carbon-carbon bond length of the ethano bridge. The advantage of a more convenient temperature range has focused our attention on derivatives of **28**.

With internal substituents larger than hydrogen no conformational flipping of 8-substituted [2.2]metaparacyclophanes is observed within the normal experimental temperature range ($<200^\circ$). For **28** itself, the kinetic parameters for conformational flipping are $\Delta H^\ddagger = 17.0 \pm 0.5$ kcal/mole and $\Delta S^\ddagger = -8.8 \pm 2.4$ e.u. When deuterium is substituted for hydrogen at the 8-position, the rate of conformational flipping is 20 per cent faster.

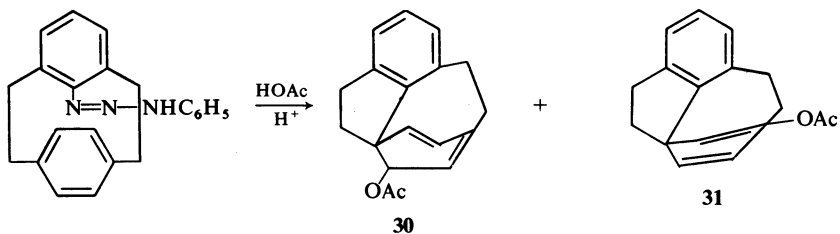
The most obvious interpretation of these data is that the critical factor affecting the rate of conformational flipping is the repulsive interaction in the transition state of the σ -electrons of the C—H bond with the π -electrons of the para-bridged aromatic π -electron cloud. On this basis it would be expected that remote substituents at the 5-position, as in **29**, would markedly affect the rate of conformational flipping. This is found to be the case. The conformational flip rate of 5-amino[2.2]metaparacyclophane (**29**, R = $-\text{NH}_2$) is only 19 per cent as fast as for **28**. In fact, electron-donating substituents ($-\text{NH}_2$, $-\text{OCH}_3$, and $-\text{H}$) can be nicely correlated by a Hammett plot²¹ with a $\rho = 1.05 \pm 0.09$. With strong electron-withdrawing

substituents ($-\text{NO}_2$, $-\text{C}(=\text{O})\text{CH}_3$, and $-\text{Br}$), a second effect occurs, probably involving stabilization of the ground state by an attractive interaction of the two aromatic rings, presumably of a charge transfer type.



Attempts to generate a carbonium ion at the 8-position of [2.2]metaparacyclophane have led to the rearranged products **30** and **31**.

The corresponding pyridine analogues **32** and **33** provide evidence that a nitrogen atom with its lone pair is better accommodated than a C—H bond



during conformational flipping. Thus, the coalescence temperature for conformational flipping of **33** is -55° at 100 MHz, and the stable conformation of **32** in the crystalline state is that in which the two aromatic rings are perpendicular to each other^{35, 36}.



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