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PHYSICAL, CHEMICAL, AND SOME BIOLOGICAL PROPERTIES OF STRAINED RING HYDROCARBONS

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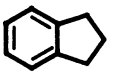
Abstract - Several strained ring and electronically activated hydrocarbons have been synthesized via cobalt and thermally mediated methodology. These include cyclobuta[1,2-d] and [1,2-c] benzyne, 2,3:6,7-dicyclobutabiphenylene, cyclobuta-[b]triphenylene, tricyclobuta[b,h,n]triphenylene, dicyclobuta-[b,g] and [b,h]phenanthrene, 1,2-cyclopropa-4,5-cyclobutabenzene, 2,3:5,6-dicyclobutapyridine, [2.2.2](1,2,4)cyclophane and cyclophene, and 1,2-bis(trimethylsilyl)benzocyclobutadiene. In addition to the mapping of their strain related and electronically dictated physical and chemical properties, the potential mutagenic behavior of these compounds has been determined in the Salmonella typhimurium test (Ames test).

INTRODUCTION

In 1930 Mills and Nixon proposed (1) that differences in reactivity between indan and tetralin could be rationalized in terms of strain-induced bond fixation: 1 is favored over 2.



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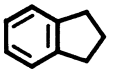

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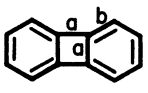
A later theoretical study showed the opposite Kekulé structure to be favored (2); finally, the experimental data were shown (3) to be ambiguous.

In 1965 and 1968 two papers (4,5) appeared dealing with the relation between strain and carbon acidity in benzocyclobutene and biphenylene 3. In these it was postulated that angle strain in the four-ring results in rehybridization of the ring-juncture carbons, placing more p-character in the constrained cyclobutene bonds a and,in consequence, excess s-character in bond b. This change is reflected as an increase in the electronegativity of the strained ring carbons, hence there is increased acidity at the α-carbons and decreased reactivity toward electrophilic substitution.



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Although a dibrominated benzocyclobutene had been known since 1909 (6), the search for related systems was not begun until 1956 (7). Since that time, several synthetic approaches have been developed. Especially noteworthy are (23): polar eliminations proceeding through o-quinodimethane intermediates (7,8,9), pyrolytic extrusion of CO_2 (10), N_2 (11), SO_2 (12), HX (13), and Te (14), Diels-Alder cycloaddition (15), additions to benzyne (16-19), cobalt-catalyzed acetylene oligomerization (20), catalytic dehydrogenation (21), and electrocyclic ring closure (22) of cycloctatetraene derivatives.

The isolation of benzocyclobutene and the demonstration of benzyne as an intermediate (24) led to the proposal in 1963 that benzocyclopropene "should at least be capable of transient existence and quite probably could exist as a stable entity" (25). The first benzocyclopropene was isolated in 1964 (26a) and the parent system was prepared shortly thereafter (26b). Again a variety of preparative methods exist; prominent among them are: photolysis of 3H-indazoles (26a,27), Alder-Rickert cleavage of 1,6-methano[10] annulene cycloadducts (26b,28), base-mediated dehydrohalogenation of related alicyclic systems (29-35), and 1,2-eliminations from o-lithio benzyl ethers and esters (36,37). These methods furnish, in addition to the parent compound, a variety of even more highly strained cyclopropaarenes (38).

Although a thermodynamic study of benzocyclobutene (39) shows little loss of aromatic character (ΔH_{H_2} for benzocyclobutene only 3.0 kcal mole^{-1} more negative than for o-xylene), the unusual geometric constraints of these systems lead to some interesting chemistry. Thus, it has been noted (40,41) that fusion of a four-ring to a pyridine or quinoline nucleus profoundly affects basicity in a manner consistent with the Streitwieser/Finnegan model. Nuclear metalation, as above, is directed α to the strained ring of benzocyclobutene (4,5,18,42); the same reaction on benzocyclopropene fails due to ring opening (43). Electrophilic substitution of benzocyclobutenes is clearly directed β to the 4-ring (5,44-47), but is complicated by ring opening, an unusual protodealkylation. When warmed, benzocyclobutenes open to o-xylylene intermediates, which are excellent enophiles in the Diels-Alder reaction (20,23). Ease of opening the 4-ring is dramatically affected by substituents, and may be correlated with ^{13}C chemical shifts of the aliphatic carbons (48).

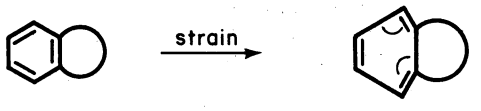
Not surprisingly, ring opening of the benzocyclopropenes is still more facile. Thus, benzocyclopropene itself dimerizes at 80° to give 9,10-dihydrophenanthrene (49), and Birch reduction gives only ring-opened products (36). Halogenolysis of the 3-ring is a characteristic reaction (26b,34,49), although I_2 has been found to add directly across the strained benzene bond as well (26b). The enhanced reactivity of this bond also permits its participation in cycloaddition reactions (49) with a number of dienes. Ag^I-catalyzed ring opening provides a wide variety of products (32,50), in addition to affording (51) a convenient thermometric approach to ring strain.

The structures of these molecules have been analyzed in various ways. X-ray diffraction results (15e,51-57) do not lend themselves to ready generalization, especially in their ambiguity on the issue of molecular planarity. Interestingly, neither dicyclopentenobenzocyclobutene (58a) nor dodecafluorotricyclobutabenzene (58b) exhibit bond-fixation, the benzene ring preferring a perfectly hexagonal carbon arrangement. Attempts to obtain structural information by NMR have also been reported (59).

Information about electronic configurations derives primarily from spectroscopic data. UV (7,12,15,31,32,34,35,60,61) and IR (31) spectra are instructive, the former exhibiting small shifts in λ_{max} and large increases in ε, and the latter showing enhanced double-bond character in the benzene nucleus. Photoelectron spectra (60) and ionization potentials (61) are strongly dependent on the hyper-conjugative capability of the substituents on the benzene ring (including the strained ring itself). ESR has been observed in the radical anions of benzocyclobutene and various naphthocycloalkenes (62), and offers supporting evidence for the postulated hybridization changes.

Some of the most useful evidence, however, comes from ^1H- and ^{13}C-NMR. Although proton shifts of nearly all new systems have been reported (8,15, 31,32,34,35,63), it is the interpretation of splitting (59,64,65,66) that provides some of the most consistent information about partial bond fixation and loss of aromatic character. The case is much the same for ^{13}C spectra, where, in addition to the usual reports of shifts (15,20,32,34) several articles offering interpretation of both chemical shifts and splitting (^{13}C-^{13}C, ^{13}C-^{19}F, and ^{13}C-^1H) have appeared (67,68).

The data appear to support a certain amount of bond-fixation and distortion in singly annulated benzenes, as suggested by structure 4. This is indicated



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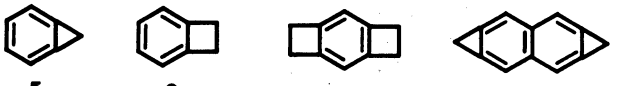
by H-H and ^{13}C-H couplings, and the increasingly high field shifted absorption of the carbon atoms α to the strained ring. Proton chemical shifts are ambiguous due to counteracting effects of ring current, rehybridization, and substituents.

At the outset of our work only few strained ring activated benzenes had been prepared: 3 (69), and 5-8 (26b,7,12b,32). It was of interest to determine what degree of benzene ring deformation could be achieved when the latter is



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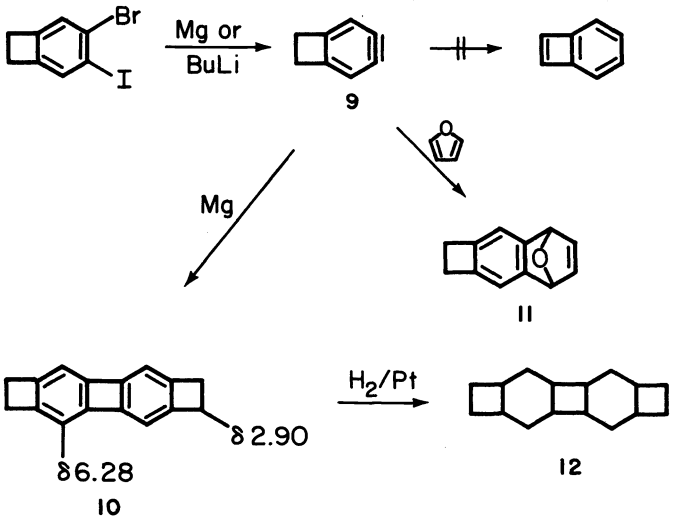
exposed to several small strain and electronically activating annulated rings. It was hoped that bond-fixation might manifest itself in the proton and carbon NMR-spectra, the electronic absorptions, and the chemical reactivity with respect to hydrogenation, oxidation, and cycloaddition reactions. Moreover, the synthesis of novel multiply activated polycyclic hydrocarbons was envisaged, the potential mutagenic acitivity of which appeared to present a valuable property to be determined in an effort to understand mechanisms of mutagenesis and carcinogenesis by aromatic compounds (70). The postulated requirements for carcinogenic potential are: planarity, olefinic character of certain bonds, extensive delocalization, ability to intercalate, and more than one reactive site. The synthesis of new electronically and strain-activated hydrocarbons and the measurement of their mutagenic potential should indicate whether these postulated criteria are correct and what their relative merit may be.

CYCLOBUTA[1,2-d]- AND [1,2-c]-BENZYNE AS PRECURSORS TO ACTIVATED HYDROCARBONS

o-Benzyne has been the subject of numerous theoretical investigations (71) pointing to considerable molecular distortion of its structure. Thus, the formal triple bond is short, and the bond-angles reflect its desire to be linear as in a typical alkyne. It seems reasonable to assume that a chemical modification of the o-benzyne nucleus which leads to augmentation of this structural distortion will result in increased stability of the strained triple bond (72). One such modification could be fusion to strained rings, for instance as in benzocyclobutenes, in which the fused ring leads to changes in the benzene nucleus described by structure 4. Therefore, stabilization of the benzyne ring might be achieved by fusion to a four-membered ring at the 4,5-positions represented by cyclobuta[1,2-d]benzyne 9. Although this species is still expected to be reactive, its added stability might manifest itself in its relatively greater ease of formation from an appropriate precursor when compared with model compounds in which the fused ring is less strained (and hence less stabilizing). This in turn might allow a larger concentration of the benzyne to be built up in solution leading to increased rates of dimerization to the corresponding interesting biphenylene 10 (72,73). The latter constitutes a potentially activated hydrocarbon in which three four-rings are linearly and alternatingly fused to two benzene rings.

When 4,5-bromoiodobenzocyclobutene (74) was treated with either n-butyllithium or magnesium the reactive benzyne 9 was generated and trapped with furan to give 11 in 70% yield (75). In the absence of trapping agent, however, dimer 10 was obtained (12-15%) in addition to a complicated mixture of substituted



biphenylderivatives. Although 9 could in principle isomerize to benzocyclobutadiene via two 1,5-hydrogen shifts this pathway does not seem to be operating, since products due to benzocyclobutadiene (73) could not be detected.

The most striking feature in the physical properties of 10 is the relatively high field proton chemical shifts of the aromatic protons ($CDCl_3$), indicating a potentially strain related decrease of diatropism (76). However, comparison with the less strained model compounds 13 and 14 derived from the corresponding bromoiodoindan and tetralin (77) shows similarly high field shifted absorptions (δ6.50,6.33), whereas durene resonates at lower field (δ6.81). It appears that these unusual chemical shifts are induced at least in part by the increased paratropism imparted by the cyclobutadienoid (78) central four-ring in the biphenylenes 10, 13, and 14, but other effects (vide supra) must also be contributors. The ^{13}C-NMR chemical shift (from TMS) of the aromatic carbons α to a strained ring decreases with increasing molecular distortion (66,68). For example, the absorption for this carbon moves from δ122.1 in benzocyclobutene 6, to δ114.7 in benzocyclopropene 5, and δ117.3 in 1,2:4,5-dicyclobutabenzene 7. A ^{13}C-NMR spectrum of 10 reveals a corresponding aromatic peak at δ113.0 suggesting that it might experience strain to an even greater degree than these models, as would be expected on simple inspection. Thus, 7 gains relief from strain by stretching the saturated four-ring bond to 1.56A° (54a). Fusion of a benzene ring (as in 10) should compress this value to approximately the distance found in biphenylene itself: 1.426A° (52), a significant distortion.

A readily interpretable trend is detected in the electronic spectra, where incremental bathochromic shifts of 5-6nm are observed for the high wavelength bands (Figure 1) as the strain of the annulated ring increases. The spectrum of 10 shows tailing into the visible region giving the compound its yellow color.

Chemical tests indicate that biphenylene 10 is an unusually reactive hydrocarbon. When exposed to H_2/PtO_2 rapid uptake of six molar equivalents of hydrogen with concomitant decolorization signals the formation of the completely saturated 12. Under the same conditions 4,5-diphenylbenzocyclobutene was recovered unchanged from the hydrogenation mixture containing 12. Similar hydrogenation of 10 with Raney nickel resulted in hydrogenation and hydrogenolysis of the central four-ring. Oxidation of 10 proceeded slowly in air and rapidly on treatment with one equivalent of meta-chloroperbenzoic acid to give unidentified products. On the other hand models 13 and 14 proved to be quite air stable. When 10 was heated with dimethyl maleate in a sealed tube the yellow bis-adduct 15 (R=CO_2CH_3) was obtained as a mixture of isomers, possibly through the intermediacy of the bis-o-xylylene derived from 10.

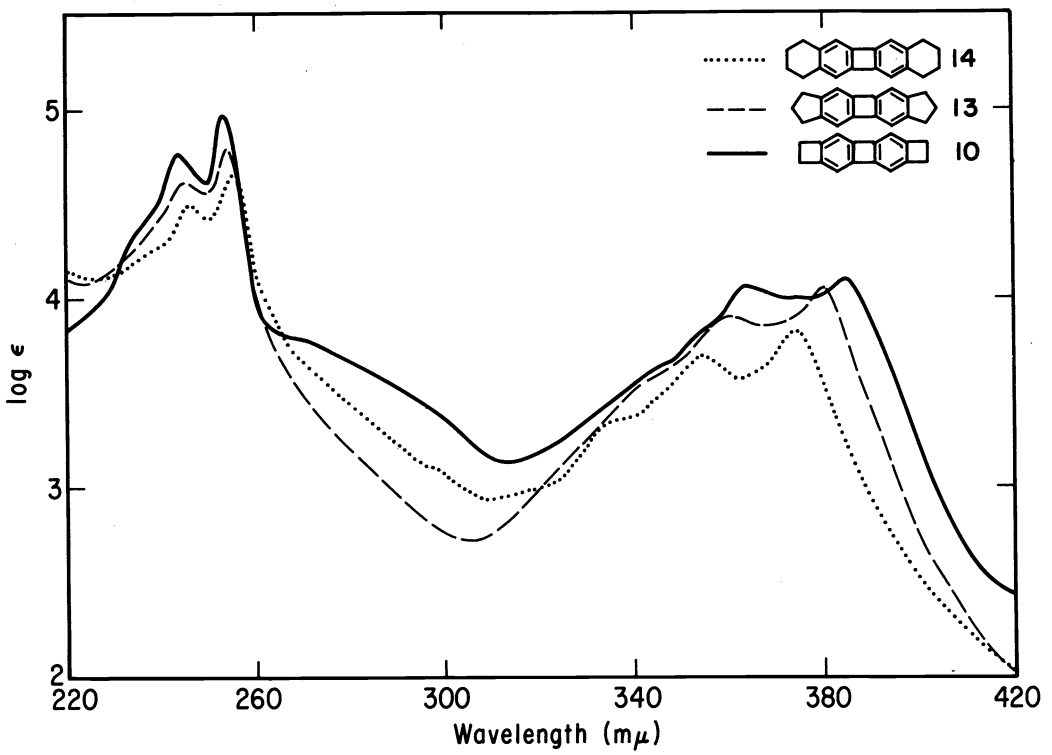
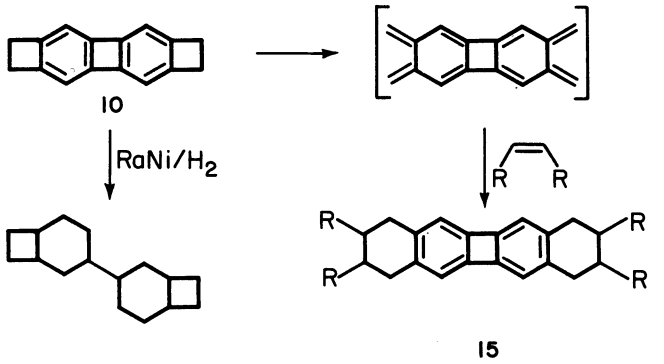


Fig. 1. Electronic spectra of biphenylenes 10, 13, and 14 (95% ethanol).



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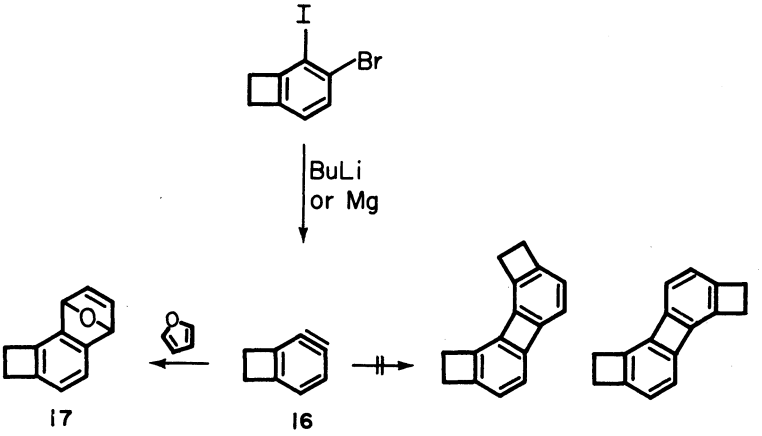
In summary, the dimer 10 of cyclobuta[1,2-d]benzyne 9. is a highly activated polycyclic hydrocarbon the physical and chemical properties of which appear to indicate considerably reduced aromatic character.

With regards to the anticipated reactivity of 9 it is interesting to compare the respective yields of dimer formation (under identical conditions) in the reactions leading to 10 (15%), 13 (4%) and 14 (2.5%). It seems that as the ring fused to the benzyne becomes more strained, dimerization becomes more efficient, the greatest change occurring when going from 13 to 10. It is quite logical that good yields of biphenylene can only be obtained when the stationary concentration of dehydrobenzene is high, while at the same time that of the dehydrobenzene precursor or of any other species which might interact with the dehydrobenzene is low (72). The obtained results indicate that the triple bond in 9 is formed more readily than that of its higher homologs allowing higher concentrations of benzyne to be built-up either freely in solution or near the metal surface in the case of magnesium. More efficient dimerization is the result. Hence, 9 appears to be a benzyne

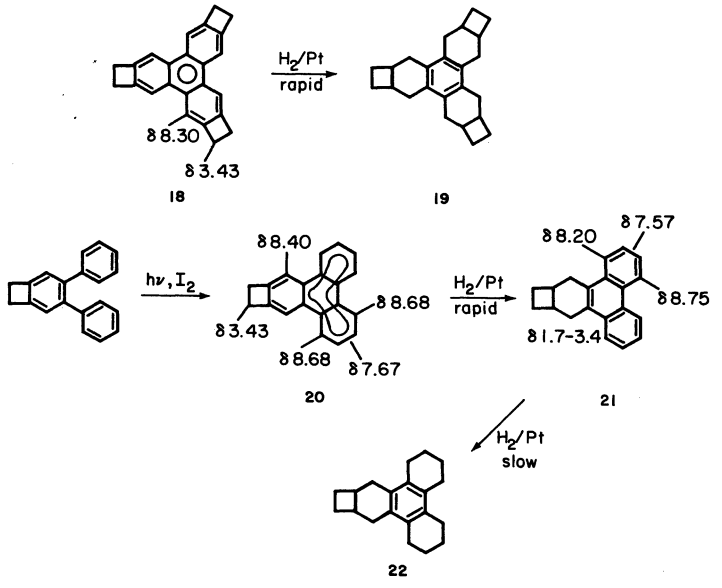
kinetically stabilized by strained ring fusion.

If indeed 9 experiences a stabilizing distortion of its "acetylenic" bond due to the linearly annulated four-ring, then a completely analogous argument would predict destabilization of the benzyne moiety by angular fusion as in the other isomer of 9, cyclobuta[1,2-c]benzyne 16. This species may be



generated (79) in furan solvent from 3,4-iodobromobenzocyclobutene to be trapped as 17 in 59% yield. However, when generated in ether or THF only biphenylderivatives were formed and no dimers. This suggests that 16 is generated only slowly and rapidly reacts with its organometallic precursor to furnish the observed product mixtures. Obviously, a more quantitative measure of the relative reactivity of 9 and 16 would be desirable (24,72), but these preliminary findings seem to corroborate the expectation that 16 is a more reactive benzyne than 9.

When concentrated solutions of 4,5-bromoiodobenzocyclobutene (74) are reacted with magnesium a formal trimer of 9 is obtained in low yield (80), the tricyclobutatriphenylene 18, a unique polycyclic hydrocarbon activated by three annulated four-rings. Its isolation poses an interesting question: will the three strained rings act cumulatively in their effect on the π-(and σ-) framework or will the consequences of strain remain localized? Inspection of the proton NMR spectra does not allow a clear cut answer. Thus, 18 exhibits a sharp singlet in the aromatic region at higher field (δ8.30) than the analogous proton in triphenylene itself (δ8.56). Comparison with the singly activated model 20, prepared by the iodine catalyzed photooxygenation of 4,5-diphenylbenzocyclobutene, reveals a chemical shift inbetween (δ8.40) those of 18 and triphenylene for the same position (measured under identical



conditions of concentration, solvent, and temperature). However, the effects are not dramatic, possibly as a result of the counterbalancing phenomena of bond fixation (which should lead to decreased diatropism), and rehybridization (4,5) (which should cause deshielding of the hydrogens α to the strained ring). The changes (or lack thereof) occurring in going from 20 to 21 also prove instructive. Here the "bay region" protons ($H_{7,8}$) located away from the activated ring appear to be affected very little by the presence (or absence) of the strained benzocyclobutene moiety (δ8.68→δ8.75), and similar behavior is exihibited by the non-bay region protons. In fact, it appears as if 20 is composed of an intact phenanthrene unit fused to an activated benzene ring.

Again, the electronic spectra are more readily understood within the framework of bond fixation. Along the series bathochromic shifts of all major peaks are observed (Figure 2), a possible manifestation of decreased HOMO-LUMO gaps and/or ground state structures increasingly resembling their excited state counterparts.

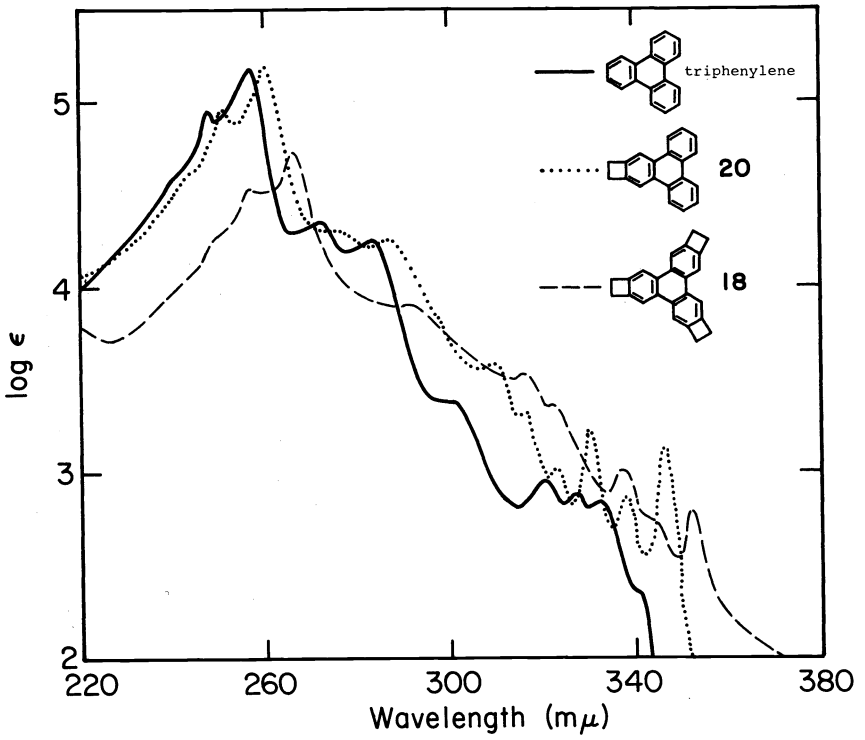


Fig. 2. Electronic spectra of triphenylene, 18, and 20, (95% ethanol).

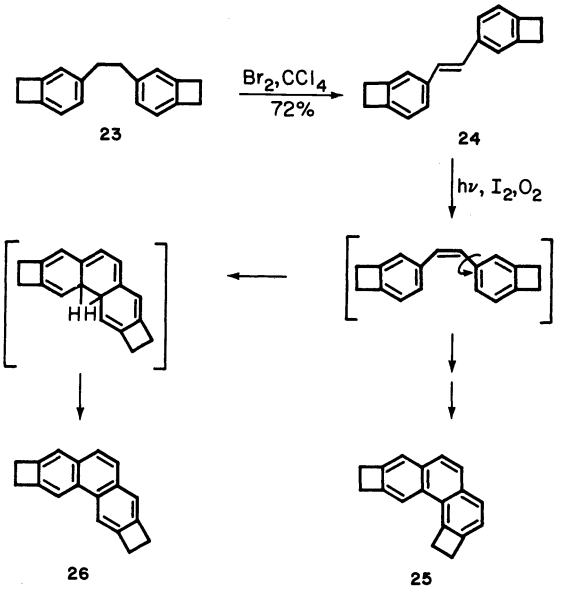
However, most illuminating are the chemical reactivity data in hydrogenations. Whereas the parent triphenylene is exceedingly difficult to reduce with hydrogen (81) both 18 and 20 are hydrogenated at ambient temperatures and pressures using platinum catalyst. In competition experiments 18 proves to be more reactive by an order of magnitude, ultimately providing the dodecahydro-derivative 19 in which all activated rings are saturated. Compound 20 initially rapidly reduces the strained benzene ring to 21 and then slowly absorbs more hydrogen to furnish 22. 4,5-Diphenylbenzocyclobutene proved inert to these reaction conditions. The above findings demonstrate that it is possible to activate a normally rather inert aromatic polycyclic hydrocarbon to exhibit a certain degree "olefinic" behavior by simple fusion to strained rings.

TWO ISOMERIC ACTIVATED BENZENOIDS: DICYCLOBUTA[b,g] AND [b,h] PHENANTHRENE

The studies on the above series of triphenylenes suggested that it might be of interest to compare isomeric activated polycyclic benzenoids in their physical and chemical behavior since differences based on the number of substituent

effects would presumably be negligible. Moreover, it was felt that choosing a hydrocarbon with demonstrated olefinic reactivity in a certain region of its topology might allow a further fine tuning of the effects of strain by small ring fusion. The phenanthrene nucleus with its $C_{9,10}$-"olefinic" K-region (82) was selected as a suitable target system.

The hydrocarbon 23 is readily available (55%) by the cotrimerization of three moles of 1,5-hexadiyne catalyzed by $CpCo(CO)_2$ (20). When treated with bromine the trans-stilbene derivative 24 is formed which may be readily oxidatively photocyclized (83) to the two isomeric activated phenanthrenes 25 and



26 in the (statistical) ratio of 2:1 as colorless crystalline materials (84). Interestingly, none of the third possible isomer, dicyclobuta[c,g]phenanthrene, containing two bay region four-rings, was formed, possibly for steric reasons. The proton NMR-chemical shifts for the two compounds 25 and 26 may be compared (Table 1) to each other and the calculated values (85) for the hypothetical models 2,3,5,6- and 2,3,6,7-tetramethylphenanthrene (calculated by assuming additive effects of progressive methyl substitution on the phenanthrene nucleus). Although it appears that the protons α to the strained rings in

TABLE 1. ^{1}H-NMR shifts (δ) of phenanthrenes
(the numbering follows that of the parent system)

	$H_{1,8}$	$H_{2,7}$	$H_{3,6}$	$H_{4,5}$	$H_{9,10}$
phenanthrene	7.81	7.48	7.55	8.62	7.64
25	7.32,7.55	7.08	—	7.88	7.45
2,3,5,6-tetramethyl-phenanthrene	7.48,7.51	7.18	—	8.47	7.47
26	7.35	—	—	8.17	7.48
2,3,6,7-tetramethyl-phenanthrene	7.43	—	—	8.17	7.43

25 and 26 resonate at slightly higher field, other absorptions, particularly those of the 9,10-hydrogens, occur at almost identical positions when compared to the (presumably) largely strain free models. Apparently, again the strain effects remain basically localized in the neighborhood of the straining ring, and their reflection in the proton NMR-spectrum is attenuated by counterbalancing forces. One rather striking deviation from this similarity of chemical shifts in the series is the unusally high field shifted absorption for the bay region protons $H_{4,5}$ in 25 (δ7.88) in comparison with the corresponding resonance in phenanthrene (δ8.62) or that calculated for the tetramethylated model (δ8.47). This is most likely a manifestation of changes in the steric effect on chemical shifts in the bay region. Thus, in 25 one of the sterically deshielding protons of phenanthrene has been replaced by a "tied back" four-ring methylene group, hence the remaining bay region proton is relatively uncrowded and resonates at a position more in line with the rest of the absorptions. The difference between the calculated and the observed value (Δδ=0.59ppm) could be a measure of the much disputed true bay region steric effect in phenanthrene and its derivatives (86).

Compared with the parent phenanthrene both 25 and 26 show a similar incremental shift to higher wavelength of the low energy bands in the electronic spectrum (Figure 3) although the remainder of the spectrum is more bathochromically shifted for the "bay region isomer" 25. A more striking difference

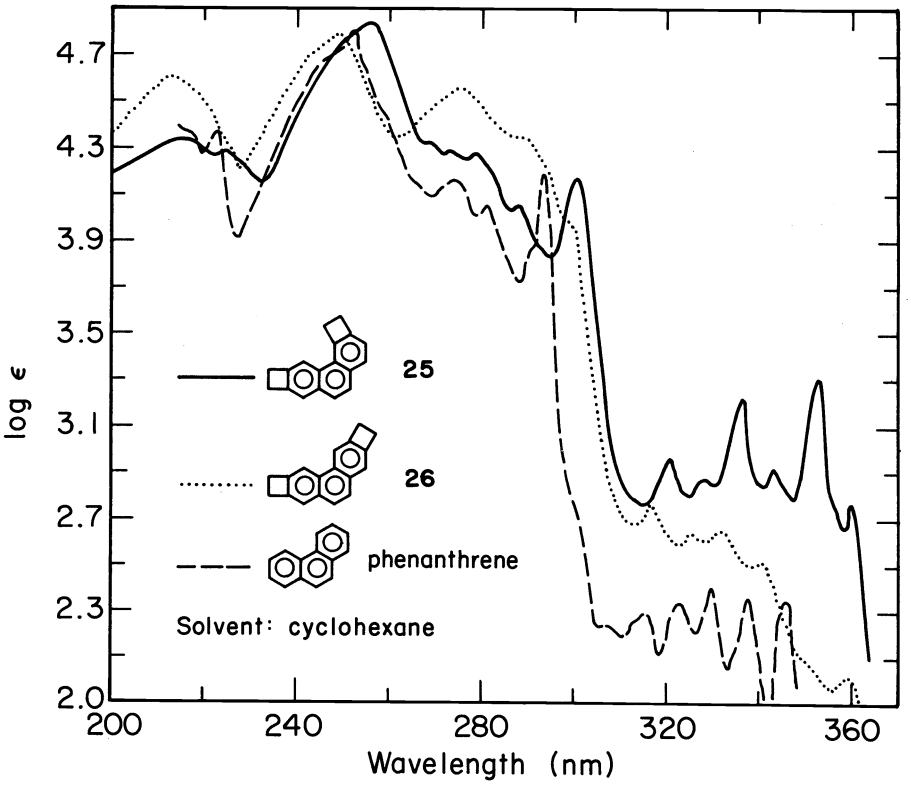
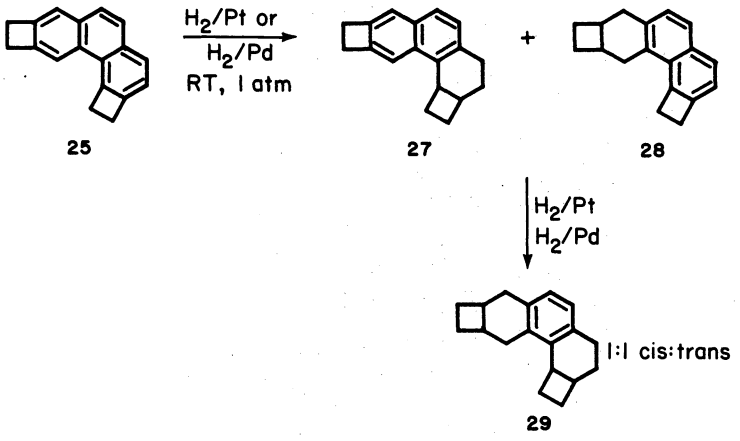


Fig. 3. Electronic spectra of 25, 26, and phenanthrene (cyclohexane).

is seen in the extinction coefficients where 25 shows much more pronounced absorption maxima above 300nm.

The consequences of strained ring activation are reflected in the chemical behavior of 25 and 26. For example, rapid hydrogenation of 25 occurs under mild conditions exclusively at the outside rings and in a stepwise manner via the tetrahydroderivatives 27 and 28 to eventually give 29 as a close to equal mixture of isomers. This contrasts drastically with the behavior of phenanthrene itself which hydrogenates under pressure and only at the K-region (87). Interestingly, in competitive hydrogenations, 25 is found to be more reactive than 26 by a factor of 2, as might be expected on the basis of bond-fixation

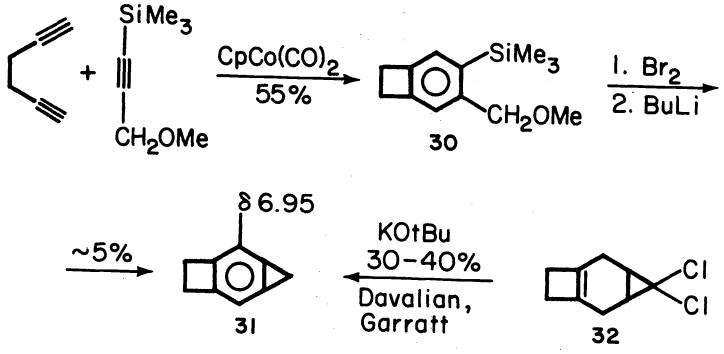


arguments. On the other hand, the simple benzocyclobutene derivative 23 reacts only very slowly under the above conditions.

Compounds 25 and 26 thus emerge as activated benzenoids with unusual physical and chemical properties, the bay region isomer 25 being on the whole more affected by the strained ring fusion.

1,2-CYCLOPROPA-4,5-CYCLOBUTABENZENE

The successful synthesis of the highly strained biphenylene 10 indicated that the limits of stability of strained benzenes might be pushed further. Moreover, since 10 exhibited interesting chemical behavior, part of which could be attributed to bond fixation effects, the question was raised whether it might be possible to synthesize the lower homolog of 1,2:4,5-dicyclobutabenzene 7, the four-ring annulated benzocyclopropene 31, and whether this compound would adopt a cyclohexatrienic electronic configuration. Indeed, a rapid synthesis of 31 was found by combining cobalt mediated methodology (20) with Radlick's approach to benzocyclopropenes (36). The requisite precursor 30 was obtained by cocyclization of 1,5-hexadiyne with trimethylsilylpropargylmethylether. Bromodesilylation furnished 4-bromo-5-methoxymethylbenzocyclobutene which was lithiated with n-butyllithium at -70°C and then briefly heated to yield (88) the desired hydrocarbon 31, a colorless unstable oil of pungent odor. This compound is also available (34) from 1,2,3,6-tetrahydrophthalic ester in six



steps (ca. 6% overall yield) the last step utilizing the Billups procedure (30,31) for the synthesis of benzocyclopropenes on 32.

Although easily polymerizable and generally reactive via transformations proceeding through opening of the three-membered ring the proton NMR spectrum of 31 shows a rather "normal" aromatic absorption further corroborating the suspicion that it is the potentially paratropic cyclobutadienoid central four-ring that is responsible for most of the upfield shift of the aromatic hydrogens in 10. On the other hand the ^{13}C-NMR signal of the sp^2-carbons α to the two strained rings appears at even higher field (δ110.0) than the corresponding

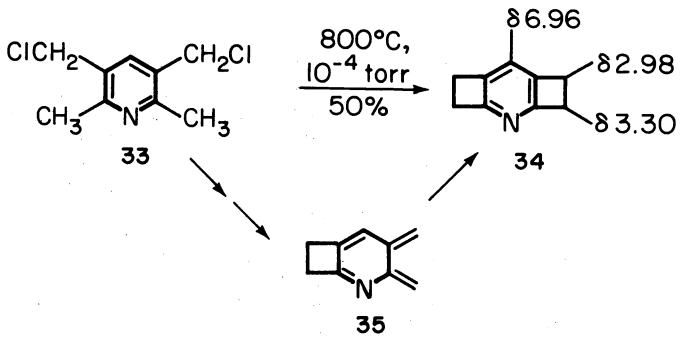
carbon in 10, a strong indication of the increased strain in the system. Moreover, the electronic spectrum has bands (λmax 285,288,295nm) at higher wavelengths than that of 7 (12b) (λmax 276,280,286 nm). These spectral data and the preliminary chemistry of 31 classify this compound as the currently most strained simply annulated benzene ring. Nevertheless, 31 retains appreciable aromaticity and its isolation suggests that approaches to lower homologs might be fruitful.

2,3:5,6-DICYCLOBUTAPYRIDINE

The aromaticity of pyridine is estimated (89) to be less than that of benzene (ca. 21 kcal/mol). Thus, it might be more readily susceptible to bondfixation and some indication along these lines has been noted in the literature (40,41) dealing with monocyclobutapyridines. The question remains then whether multiple strained ring fusion would lead to a drastic reduction of diatropism and increased bond localization in the system.

When the dichloride 33 was exposed to flash vacuum pyrolysis conditions double HCl elimination occurred (13) to give (41e,90) on basic work-up the most highly strained pyridine currently known, 2,3:5,6-dicyclobutapyridine 34.

Compared with the pyridinic proton (δ7.10) in 2,3,5,6-tetramethylpyridine the corresponding absorption for 34 is shifted to higher field, albeit again only



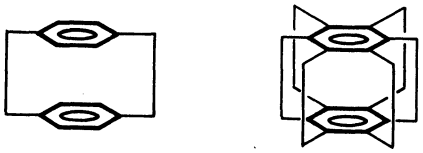
by a small amount. On the other hand, the effect of ring fusion on the aromatic carbon atom α to both rings is clearly evident in the ^{13}C-NMR spectrum where a doublet is observed at δ124.4 (J=163.5 Hz). The position of this peak is at considerably higher field than the absorptions for similar carbon atoms in various cycloalkenopyridines (41e), and the relatively large coupling constant is a strong indication of considerable rehybridization at this position (c.f. $J_{^{13}C-H}$ for 2,3,5,6-tetramethylpyridine: 152.6 Hz). This rehybridization effect may also be detected in a measurement of the decreased basicity of the system (41e). Whereas 1,2,3,4,5,6,7,8-octahydroacridine ("2,3:5,6-dicyclohexapyridine") has a higher pK_a (8.09) than pyridine (5.30) due to the substituent effect of the alkyl groups, 34 is less basic (4.40) reflecting the electron withdrawing power of the strained ring.

Bathochromic shifts are again observed in the electronic spectrum of 34 when compared with appropriate model compounds, the incremental amounts being comparable to those observed in the hydrocarbon series.

The fact that 34 maintains a considerable amount of residual aromatic character is indicated by its spectral characteristics, its isolation under conditions conducive to equilibration with the o-quinodimethane (o-lutidylene) 35, and an activation barrier to ring opening comparable to that in benzocyclobutene. When heated to 200°C in bis(trimethylsilyl)acetylene a bisadduct is obtained, which on oxidation and desilylation furnishes acridine. Thus, again it appears that simple aromatic systems are capable of maintaining extensive delocalization despite the considerable molecular distortion to which they are exposed when fused to several small rings (91). In the pyridine series this suggests that cyclopropapyridines might be stable enough to be isolated, and doubly annulated systems might reveal the so far elusive property of clear bondfixation in an aromatic molecule.

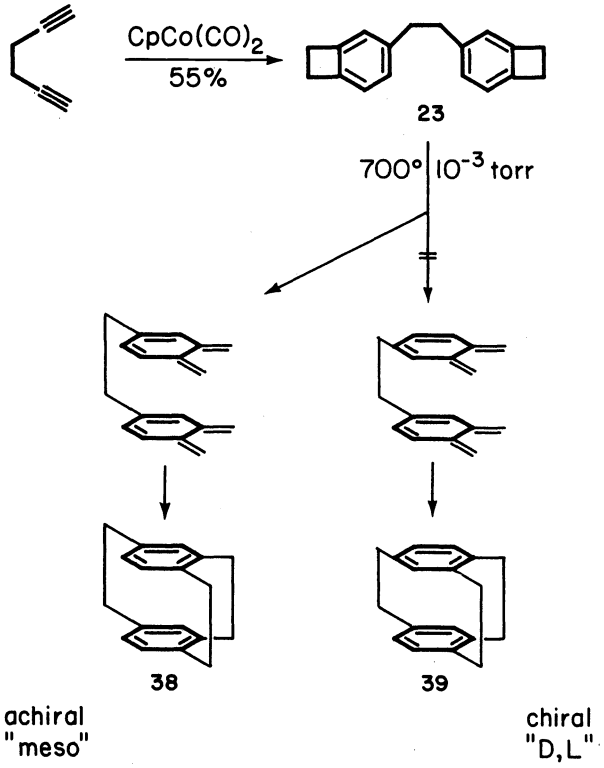
LAYERED ACTIVATED BENZENES: [2.2.2](1,2,4)CYCLOPHANES

Bridging a benzene ring at the para-positions by relatively short carbon chains induces strain and significant distortions from planarity (91,92). [2.2]Paracyclophane 36, for example, in which two benzene rings are forced into close proximity by two ethylene bridges has a strain energy of 31-33 kcal mole^{-1} and boat like benzene rings with deviations from coplanarity of 12°-13°. It is not surprising that the intriguing properties of this molecule have induced chemists to explore the synthesis of more highly strained analogs containing additional saturated or unsaturated bridges, culminating in the recent synthesis of superphane 37 (13). We have developed a rapid synthetic entry into the series which combines transition metal catalyzed methodology en route



36 37

to benzocyclobutenes (20) with intramolecular cycloadditions of bis-o-xylylenes. The latter approach was discovered independently by Boekelheide and coworkers and successfully applied in combination with pyrolytic HX-eliminations to the synthesis of various cyclophanes (13,93).

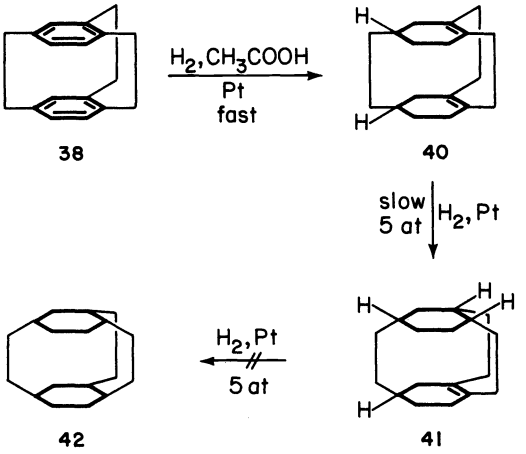


We had observed earlier that the bisbenzocyclobutene 23 turns into a colorless brittle polymer when heated to 200°C in benzene (sealed tube). Since it was suspected that in the solution phase sequential opening of the four-rings led to intermolecular cycloadditions, the pyrolysis of 23 was repeated in the gas phase under flash-vacuum conditions to ensure intramolecular reaction pathways. Indeed, under these conditions excellent conversions to the cyclophane 38 were observed (94) furnishing this compound in two simple steps from commercially available material, a synthetic route that compares favorably with other syntheses (93b,95). Interestingly, none of the chiral isomer 39 (95c) was detected, possibly due to a relatively high kinetic barrier leading to this compound, or, more likely, due to the (presumed) higher

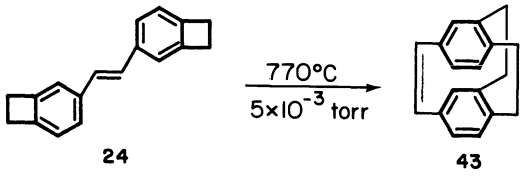
thermodynamic stability of the (according to models) less distorted 38 formed under equilibrating conditions.

The physical properties of 38 (95a), particularly the NMR and electronic spectra, appear to reflect the (presumed) nonplanarity of the aromatic nuclei, the face to face crowding of the two π-clouds, and the eclipsing of the bridging methylene groups. To what extent bond fixation in the benzene rings is a contributor to the observed high-field shifts of the aromatic protons (δ6.05,6.17, and 6.37) in the NMR spectrum, and the bathochromic shifts in the ultraviolet spectrum (λmax 223, 291, 305sh nm)compared to [2.2]paracyclophane is difficult to ascertain, and might be more easily estimated by a study of the chemical behavior of 38.

Indeed, some preliminary chemistry of 38 had been reported (95a), in particular an unusual [4+2]cycloaddition to one of the benzene rings with dimethyl acetylene dicarboxylate, pointing to cyclohexatrienic reactivity. Further evidence along these lines could be obtained more recently (94) in hydrogenation experiments. For example, facile uptake of four mole H_2 occurs under mild conditions (PtO_2, CH_3COOH, 22°C) to give 40 and small amounts of 41. At higher hydrogen pressure increasing amounts of 41 are generated at the expense of 40 (5 atm H_2, 5 days, 40:41 = 1:1), but complete hydrogenation to 42 has not been possible. Treatment with m-chloroperbenzoic acid provided a mixture of oxidized compounds.



The ready availability of stilbene 24 from previous work suggested the intriguing possibility of generating a dehydrocyclophane ("cyclophene") analog to 38 by the described pyrolytic approach. Sublimation of 24 through a hot quartz tube enabled cis-trans-isomerization around the olefinc bond followed by intramolecular closure to yield the desired hydrocarbon 43 (94). Disappointingly,

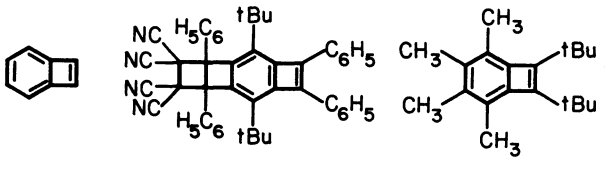


introduction of the additional unsaturation does not dramatically alter the physical characteristics typical of 38. In particular, the ^1H- and ^{13}C- NMR spectra are unexceptional, although the electronic spectrum tails to fairly high wavelengths (350nm). It remains to be seen whether bond fixation is inducible via molecular distortions due to short bridges. The chemical methodology detailed above should prove valuable in synthetic routes to lower homologs of $[2]^n$ cyclophanes.

1,2-BIS(TRIMETHYLSILYL)BENZOCYCLOBUTADIENE, AN ANTIAROMATIC LIGAND

All of the compounds discussed to this point derived their activation from fusion to strained rings or bridges. An additional mode of activation may be

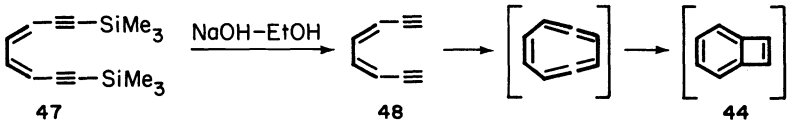
found in destabilizing electronic arrangements leading to unfavorable π-topologies: the antiaromatic 4n-π periphery (76,78). In this respect benzocyclobutadiene 44 as a planar 8π-system should be the prototype of the class of electronically activated benzenes and a great deal of work has been devoted



44 45 46

to its isolation (73). Due to its extreme reactivity in dimerizations and oxidations 44 has only been directly observable under matrix isolation conditions (96). Although several substituted derivatives are known (e.g. 45,46) (97,98) which derive their relative stability from the steric blocking effect of two substituents at the 1,2-positions, none of them contain protons directly bound to the π-pheriphery. Hence proton magnetic resonance data have not been useful in determining the nature of induced ring current effects and the possible (anti) aromatic character of 44. On the other hand X-ray crystallographic investigations on 45 and 46 indicate strong alternation of single and double bonds along the π-cycle (97,98b).

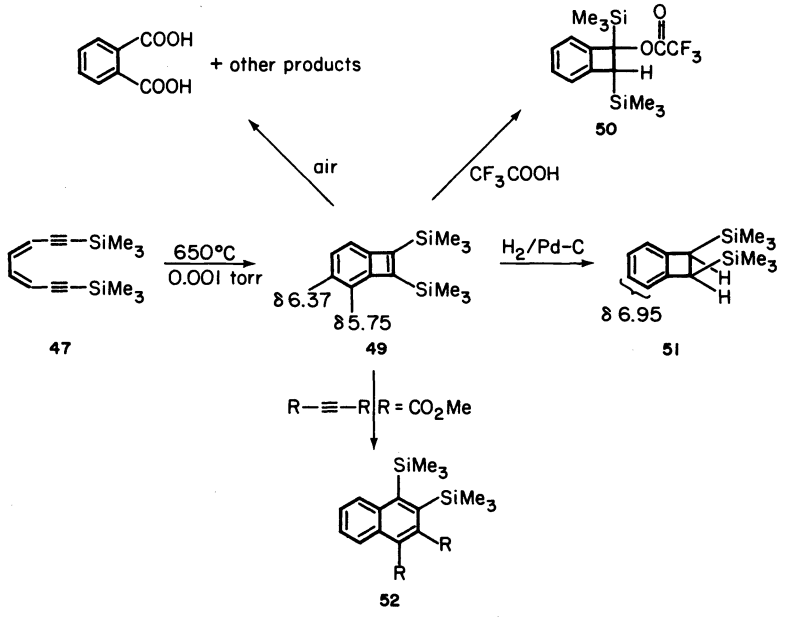
In order to gain access to a minimally substituted benzocyclobutadiene derivative we turned our attention to the dienediyne 47. This compound had been reported to furnish 44 as a reactive intermediate on desilylation, indicating that the unsubstituted system 48 was capable of a remarkably facile electrocyclic ringclosure sequence (99). Could 47 constitute an appropriate starting



47 48 44

material for a kinetically substituted benzocyclobutadiene?

When 47 was flash pyrolyzed at 650°C a new air-sensitive orange-red oil was formed (100) exhibiting physical and chemical characteristics commensurate only with structure 49, the least substituted benzocyclobutadiene known and the first to allow the determination of ring current effects in the system. The most striking features in the physical properties of 49 are to be found

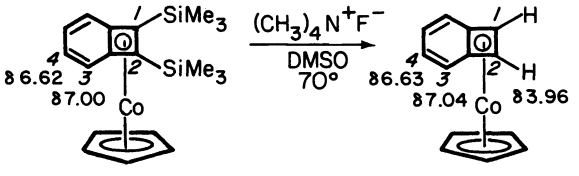


in the proton NMR and the electronic spectrum. The former shows unusually high field absorptions indicating the presence of strong paramagnetic ring-current contributions to the induced ring current and presumably bond fixation. Notably, the absorptions of the protons α to the activating ring are assigned to be at higher field (δ5.75) in analogy to similar assignments made in other cyclobutadienoids (78). The electronic spectrum showed peaks extending into the visible (λmax 472) with considerable fine structure.

On hydrogenation a colorless 6Π-electronic derivative 51 was generated which serves as an ideal reference to 49. This compound has normal aromatic NMR peaks and an unexceptional benzenic UV-spectrum. Thus, the effect of symmetrically mixing-in a double bond with the benzene Π-framework is dramatic: 49 is an air sensitive, reactive compound with spectral properties consistent with the presence of high lying HOMOs and low lying LUMOs in accord with the theoretical predictions for a planar 4-n Π-system (73,78), 51 behaves as a normal benzocyclobutene. Nevertheless, the isolation and characterization of 49 proves that the benzocyclobutadiene nucleus may be extensively kinetically stabilized. In fact, the neat compound may be recovered unchanged after several hours at 150°C, polymerization setting in at higher temperatures. On the other hand, sterically unencumbered reagents succeed in converting 49 to other derivatives: air leads to oxidation to phthalic acid and other compounds, CF_3COOH adds to the cyclobutene bond to furnish an isomeric mixture of 50, and angular[4+2]cycloaddition occurs with dimethyl acetylene dicarboxylate to ultimately give the naphthalene 52. This chemical behavior clearly characterizes the molecule as a truly electronically activated Π-system.

According to the Dewar-Chatt-Duncanson model (101) interaction of 49 with a suitable metal should lead to an increased HOMO-LUMO gap and thus to increased stability and a decreased paramagnetic contribution to the ring current in the antiaromatic ligand (102). Moreover, not only should the latter become more diatropic on complexation but the relative ordering of the chemical shifts of the benzenic protons might reverse since the system should now show naphthalenoid magnetic behavior with relatively low field α-protons, rather than cyclobutadienoid character (78). Whereas the effect of stabilization of antiaromatic systems on transition metal complexation is well documented (73,78, 103), corresponding ring current changes have not been measured due to the absence of suitable test compounds.

When dienediyne 47 was exposed to $CpCo(CO)_2$ in refluxing n-octane the sandwich complex 53 was obtained (104) as brown-red crystals. In this compound the "aromatic" proton signals have moved to substantially lower field when compared with the corresponding signals in 49. Moreover, the atoms α- to the complexed four-ring experience the strongest deshielding. The relative assignment of this signal was made possible via the conversion of 53 to 54 by fluorodesilylation, and the observation of the coupling of $H_{3,6}$ to $H_{1,2}$. Since an inspection of the NMR-spectra of model compounds (105) reveals that the anisotropy of the mononuclear coordinatively saturated CpCo-unit is shielding, the observed shifts are most readily explained by assuming that complexation to cobalt converts the antiaromatic 49 into an aromatic ligand. The originally paratropic cyclobutadienoid ring becomes diatropic most strongly deshielding protons closest to it. This effect is analogous to that observed in the NMR spectra of polycyclic benzenoid hydrocarbons (e.g. naphthalene) where atoms in the vicinity of other benzene rings experience increased deshielding. The recently reported geometrical changes occurring when the fully substituted benzocyclobutadiene 46 is complexed to the $Fe(CO)_3$ moiety (98b) are also interpretable in this manner.



53 54

MUTAGENESIS STUDIES

Polycyclic benzenoid aromatic hydrocarbons are known to intercalate into DNA (106), they and their metabolic epoxides are active as frame shift mutagens (107), and they may be activated by mammalian liver extracts to similar activity (108). Abundant evidence demonstrates their capability to covalently bind to DNA and DNA-models (109). Mutagens appear to be carcinogens and vice versa (107,110), although there have been caveats regarding the indiscriminate use of the Salmonella typhimurium test (111). There have been only few studies on the mutagenic (and carcinogenic) potential of nonbenzenoid polycyclic hydrocarbons and systems of unusual topology (112).

Several of the activated aromatic systems reported in this paper were subjected to the Ames test in DMSO solvent with and without metabolic activation (S9 rat liver microsomal fraction) on strains TA 1538, TA 1537, TA98, and TA100. The cyclopropacyclobutabenzene 31 and the benzocyclobutadiene 49 were found too unstable to be tested. The following six compounds were not mutagenic with the above strains (no enhancement of reversions over spontaneous): the activated triphenylenes 18, 20, the bisbenzocyclobutene 23 and its pyrolysis product, the cyclophane 38, the dicyclobutapyridine 34, and the symmetrical dicyclobutaphenanthrene 26. Dose related increases in the number of revertants several fold over spontaneous were observed for four compounds: the stilbene 24 (TA 1537 with activation), the cyclophene 43 derived from it (TA 1537 with activation), the chloromethyl pyridine 33 (TA 100 with and without activation, toxic to bacteria at 5000µg/plate), and the bay region activated dicyclobutaphenanthrene 25 (TA 100, threefold enhancement over spontaneous at 5µg/plate, with activation). Parallel runs reconfirmed the inactivity of phenanthrene, and the strong activity of benz[a]pyrene.

Stilbene oxide and stilbene itself (on activation) may induce mutations in Salmonella typhimurium (113), hence the activity of 24 is not surprising, although the as yet unknown relative mutagenic potency would be of interest. Cyclophene 43 might be regarded as an activated stilbene, and the occurrence of mutagenicity in this compound (but not the dihydroderivative 38) suggests that metabolic activation of the bridging double bond could be responsible for this activity. As might be expected the potential alkylating agent 33 shows activity, but the activated pyridine 34 derived thereof does not. This could be a consequence of "incorrect" topology (e.g. for intercalation), alternatively 34 might be metabolized via nonmutagenic pathways. Finally, the activity of the bay region cyclobutaphenanthrene 25 as opposed to its isomer 26 is highly interesting. Compound 25 is the first polycyclic benzenoid hydrocarbon activated to mutagenic potency by fusion to strained rings. This finding suggests that caution should be exercised in any synthetic procedures aimed at the isolation of new derivatives of this type. The origin of this activity might be the electronic and steric distortion induced by the bay region four-ring. Substitutions in the bay region of polycyclic aromatic hydrocarbons may inhibit (114) or cause (117) carcinogenic activity, methyl substitution may change the metabolic pathways to involve benzylic alkylating agents (115), and detoxification mechanisms may be blocked by this type of molecular alteration (115,116). To what extent the substitution pattern in 25 and 26 plays a role in their physiological activity is not clear. The corresponding tetramethylderivatives which would constitute attractive standards are unknown. The finding that 1,2,3,4-tetramethylphenanthrene is a weak carcinogen (118) might be significant in this connection. These investigations are only in their infancy and need to be pursued vigorously.

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