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Review Commentary

Unusual reactivity of highly strained cyclophanes†

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ABSTRACT: An essential feature of the concept of aromaticity has been the stability and lack of reactivity of aromatics relative to that of other unsaturated compounds. Contrary to this general experience, high and unusual reactivity is encountered when simple, monocyclic benzene rings are bent by short bridges into a boat-shaped conformation, as is the case in small [*n*] paracyclophanes ($n \leq 8$) and [*n*]metacyclophanes ($n \leq 7$). This is illustrated, mostly with examples taken from the authors' own work, for thermal and photochemical behavior and reactions with electrophiles, nucleophiles and dienophiles. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: highly strained cyclophanes; reactivity

INTRODUCTION

Towards the middle of the 19th century, chemists started to realize that a certain class of unsaturated organic compounds, often isolated from fragrances and therefore called 'aromatic,' had the common property of being unusually unreactive in comparison with 'normal' unsaturated compounds such as olefins. Thus, aromatics in general, and benzene in particular, are surprisingly resistant towards addition reactions such as hydrogenation or halogenation and, if reactions do occur, they proceed predominantly by substitution rather than by addition, signaling a high tendency of the unsaturated aromatic nucleus to regain its original 'aromatic' state.

Even after Kekulé had proposed his famous oscillating cyclohexatriene structure for benzene,[1] it was this unreactivity of benzene which for a long time caused considerable problems and even retarded the general acceptance of Kekulé's formula; in fact, it took nearly 100 years of search and struggle to understand fully the special aromatic properties of benzene on the basis of quantum theory.[2]

Against this background, it appears understandable that after the discovery of high and unusual reactivity in small and strained cyclophanes, it was originally (but erroneously) believed that their aromaticity was reduced in favor of a cyclohexatriene-like structure.[3] This review is intended to illustrate, mostly on the basis of work from our own group, the exceptional reactivity of the bent benzene rings of these cyclophanes and to discuss the factors which cause this enhanced reactivity.

The definition of 'small' for cyclophanes is somewhat arbitrary and depends on the category: for [*n*]metacyclophanes (**1**), significant bending of the benzene ring and concomitant strain are usually encountered when the bridge contains seven or fewer links ($n \leq 7$), whereas for [*n*]paracyclophanes (**2**), where the bridgeheads are further apart, this occurs for $n \leq 8$.

SYNTHESES AND STRUCTURES

Although this review is primarily concerned with the reactions of small cyclophanes, a brief survey of their syntheses and structures seems appropriate. As has been discussed elsewhere in more detail,[4] the usual strategy for the synthesis of cyclophanes, *i.e.* the closure of a bridge across the *meta*- or *para*-positions of the benzene ring, is not applicable to small representatives because the 'ends will not meet;' the result is polymerization rather than ring closure. Therefore, one has to construct a precursor that already contains the bridge, together with an entity having an energy content high enough to allow subsequently conversion into a (bent and strained) benzene ring. Different groups have developed different strategies to meet these goals;[5] in our approach,[4] often a 1,2-bismethylene substituted cyclic compound such as **3** (or an acyclic equivalent to be cyclized at an intermediate stage) is the starting point to prepare either the propellane **4** for the synthesis of **1**, or the Dewar benzene **5**, which can be converted into **2** by heating or by irradiation (Scheme 1).

From x-ray crystal structure determinations[4c] of

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Dedicated to Prof. Dr Maitland Jones, Jr, on the occasion of his 60th birthday.

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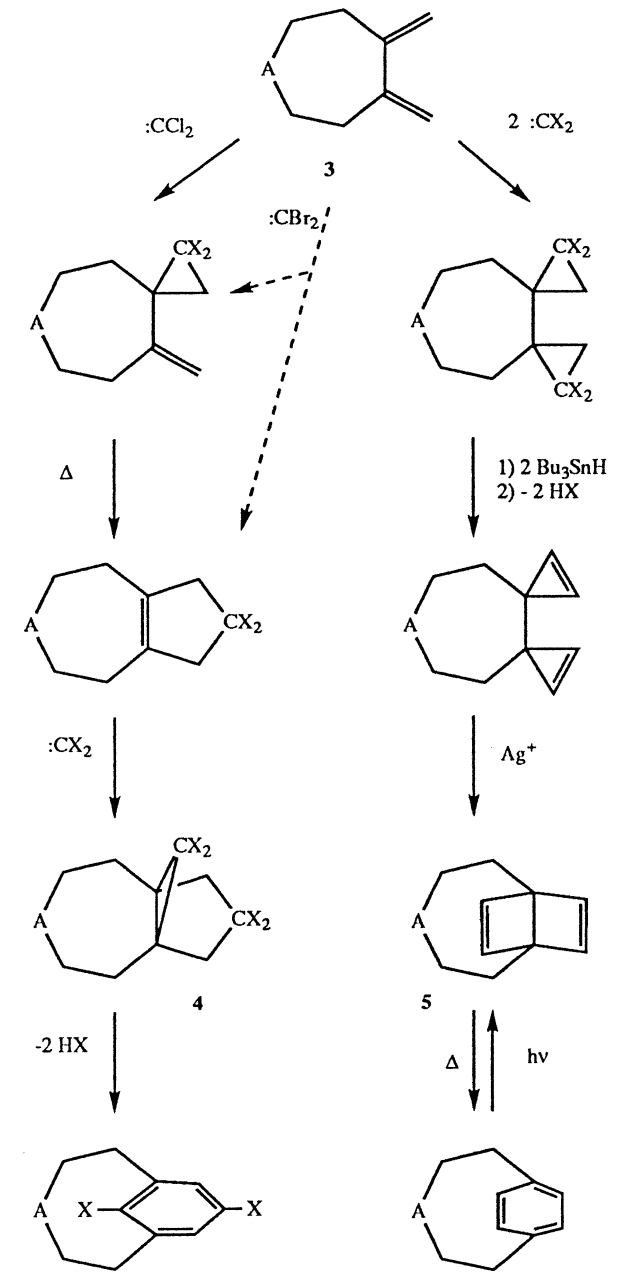
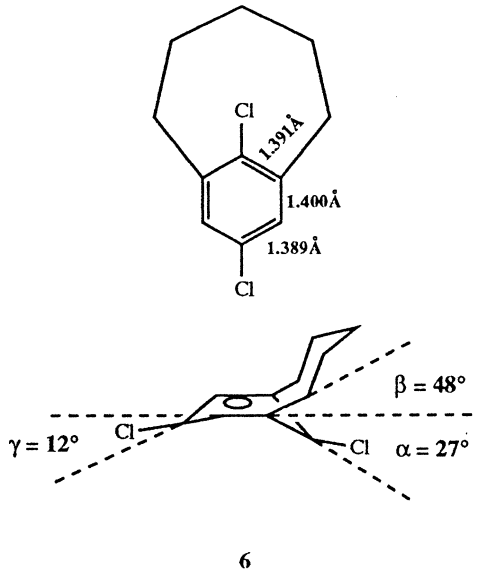


Scheme 1



6

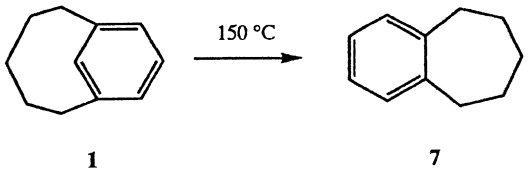
Scheme 2

several derivatives of **1** and **2** {see in particular Scheme 2 for data on 8,11-dichloro[5]metacyclophane (**6**: **1**, $A = CH_2$; $X = Cl$)[6], and also from theoretical calculations,[4c] it appeared to our initial surprise that in spite of substantial boat-shaped distortion, the bond lengths in the benzene rings of such small cyclophanes are fully delocalized and thus 'aromatic' according to this criterion. This seemed to be in contradiction to their high reactivity and 'cyclohexatriene-like' behavior to be described below. Equally compelling, the second important criterion for aromaticity was also fulfilled: NMR spectroscopic investigations proved the presence of a ring current which was (at least) equal to that of analogous planar benzene derivatives.[4c,7] Obviously, these compounds were fully aromatic, and factors other than loss of aromaticity were responsible for their high reactivity. We present here a number of representative examples of unusual reactions and discuss the factors involved.

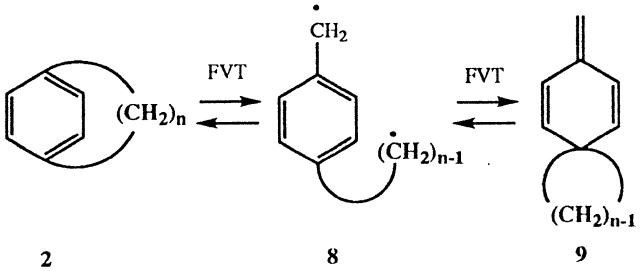
REACTIONS OF SMALL CYCLOPHANES

Thermal, catalytic and photochemical reactions

As expected, the thermal stability of cyclophanes decreases with decreasing bridge length. While [6]meta-

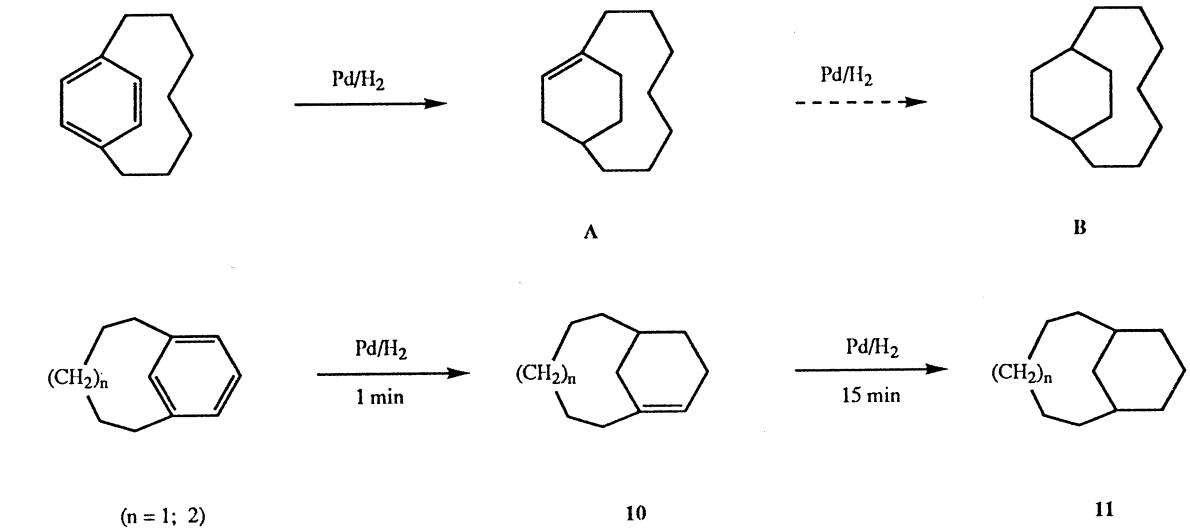


1 **7**

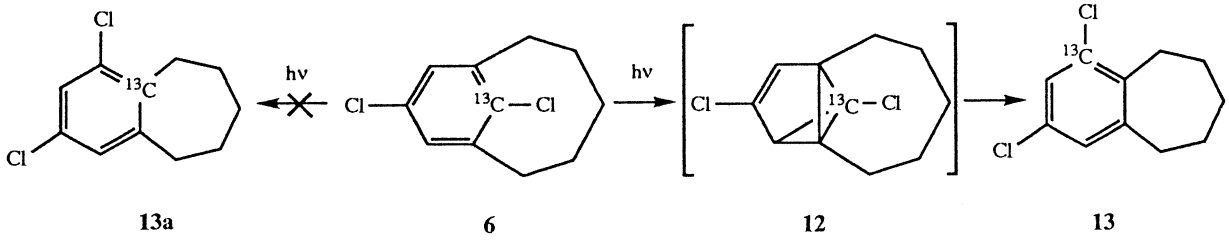


2 **8** **9**

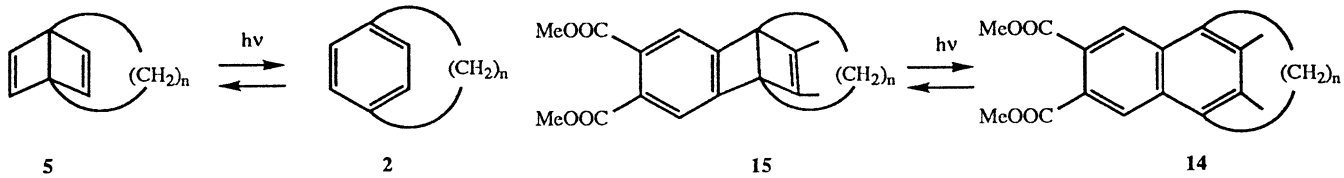
Scheme 3



Scheme 4



Scheme 5

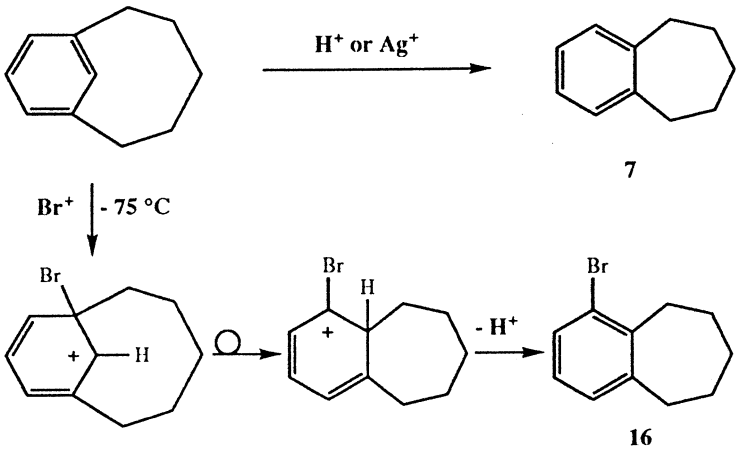


Scheme 6

cyclophane (Scheme 1: **1**, A = CH_2CH_2, X = H) is reasonably stable,[8] [5]metacyclophane (**1**, A = CH_2, X = H) slowly polymerizes on standing at room temperature,[9] and [4]metacyclophane (**1**, A = –) is too unstable to be isolated, so that its intermediacy could only be demonstrated by interception reactions.[10] Correspondingly, the [*n*]paracyclophanes **2** (*n* = 8 or 7) are stable under ordinary conditions; [6]paracyclophane is a borderline case; [5]paracyclophane must be kept below −20 °C;[11] [4]paracyclophane can be intercepted under special conditions[12] and is stable only at −196 °C;[13] and [3]paracyclophane is so unstable that attempts to prepare it by various methods have failed so far; instead, indanes were formed in some cases, but there is no solid evidence for the formation of [3]paracyclophane even as a fleeting intermediate.[14]

When heated in solution to 150 °C, [5]metacyclophane rearranged to its *ortho* isomer **7** (Scheme 3); the mechanism of this process has not been investigated. Under flash vacuum thermolysis (FVT) conditions at temperatures between 200 and 600 °C, the small paracyclophanes **2** undergo radical cleavage at the benzylic carbon–carbon bond of the bridge to form the intermediate diradical **8**, which closes the ring to form the spiro compound **9**; this process is reversible when $n \geq 7$, and as compounds **9** are easily prepared by other routes, this opens an attractive alternative access to the 'less small' members of **2**.[4c]

A reaction that clearly demonstrates the difference in stability between normal and bent benzene rings is catalytic hydrogenation. Other than alkenes, benzene is stable when treated with Pd/H_2; it requires a stronger catalyst such as platinum or ruthenium to be hydrogenated. In contrast, small cyclophanes are readily hydrogenated



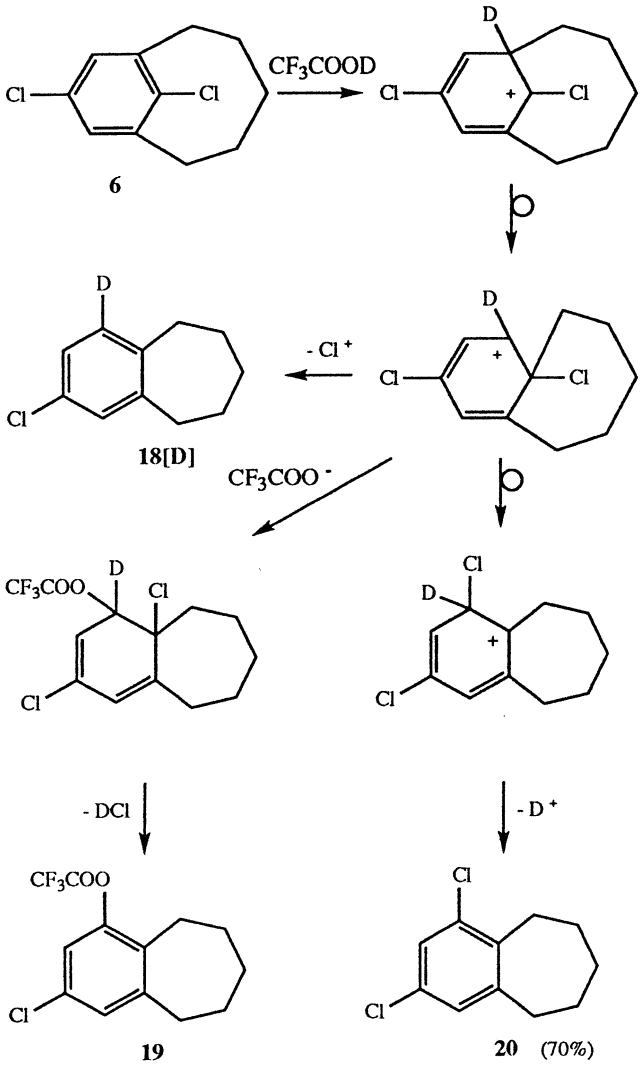
Scheme 7

with Pd/H_2 at room temperature.[15] Thus, Li and Jones[15a] reported that [7]paracyclophane is reduced to the stage of the (very) hyperstable olefin **A**; further reduction to **B** is extremely slow (Scheme 4). Recently, we discovered that if the hydrogenation of [6]- or [5]metacyclophane is performed under very mild conditions (room temperature, hydrogen at atmospheric pressure and a reaction time of 1 min), the reaction can be stopped at the intermediate stage of the hyperstable olefins **10**; after about 15 min, complete reduction to the perhydro derivatives **11** is achieved (Scheme 4).[15b] This again underlines the extreme reactivity of this type of bent benzene ring.

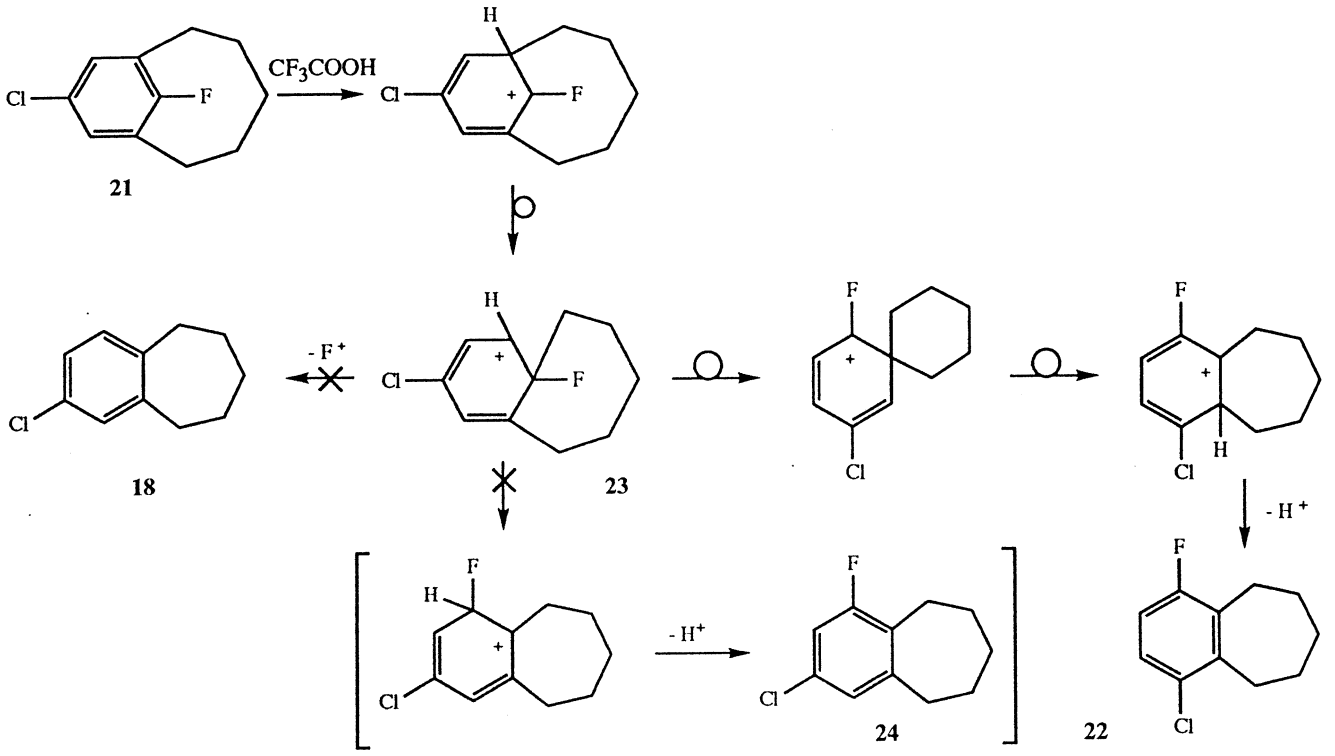
Not only in the thermal behavior, but also on irradiation, there appears to be a dichotomy between **1** and **2** (Scheme 5). As in the thermal reaction, the preferred process on irradiation of [5]metacyclophane is rearrangement to the *ortho*-isomer **7**.[16] Labeling studies in the case of 8,11-dichloro[5]metacyclophane **6** indicated that this photochemical rearrangement apparently proceeds via the benzvalene intermediate **12**, as in the rearranged product **13**, the chlorine substituent remained attached to the labeled carbon atom, whereas in an ionic (electrophilic) process (*cf.* Schemes 7 and 8), the two would have been separated as shown in **13a**.[16]

In contrast, the irradiation of small [*n*]paracyclophanes **2** leads to the establishment of a photodynamic stationary state between **2** and its Dewar isomer **5**, the position of which seems to be related to the strain: high strain disfavors **2**. Thus, for **2** ($n = 6$), the stationary state lies at a ratio **2**:**5** = 75:25,[17] whereas for $n = 5$, it is as low as 7:93 (Scheme 6).[4c,11] In the case of the [5](1,4)para-naphthalenophane **14** with its more flexible aromatic nucleus, the aromatic system suffers less from strain and consequently, in the photodynamic stationary state, the **14**:**15** ratio is 35:65, the highest observed so far for a [5]paracyclophane.[18a]

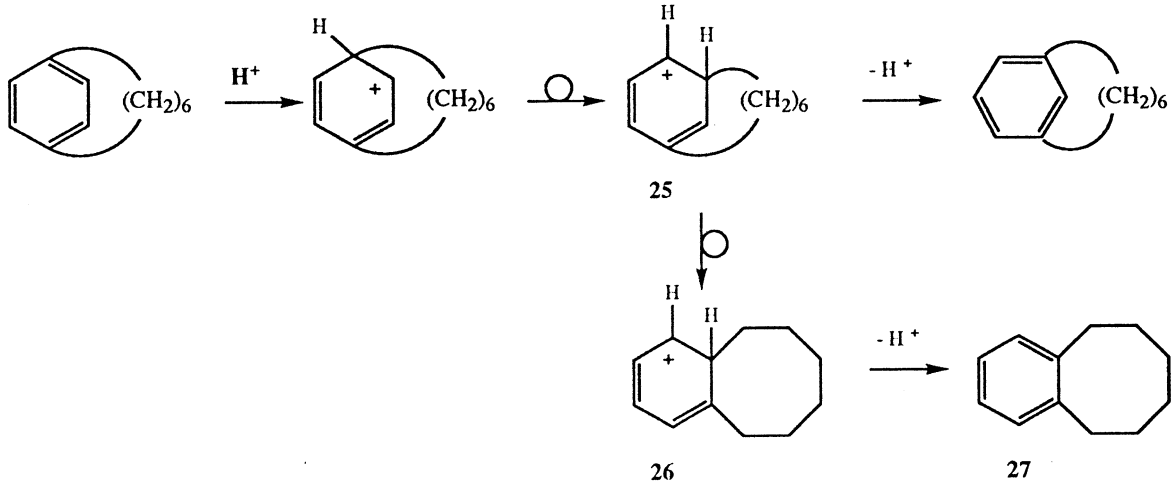
Two remarkable aspects of this photochemistry should be pointed out. First, the approach from the Dewar isomer, unfavorable as the photostationary ratio may be, has in fact so far been the *only* synthetic pathway to [5]paracyclophanes. Second, although photochemical conversions of aromatic compounds into Dewar isomers have been known for some time, the ease and extent with



Scheme 8



Scheme 9



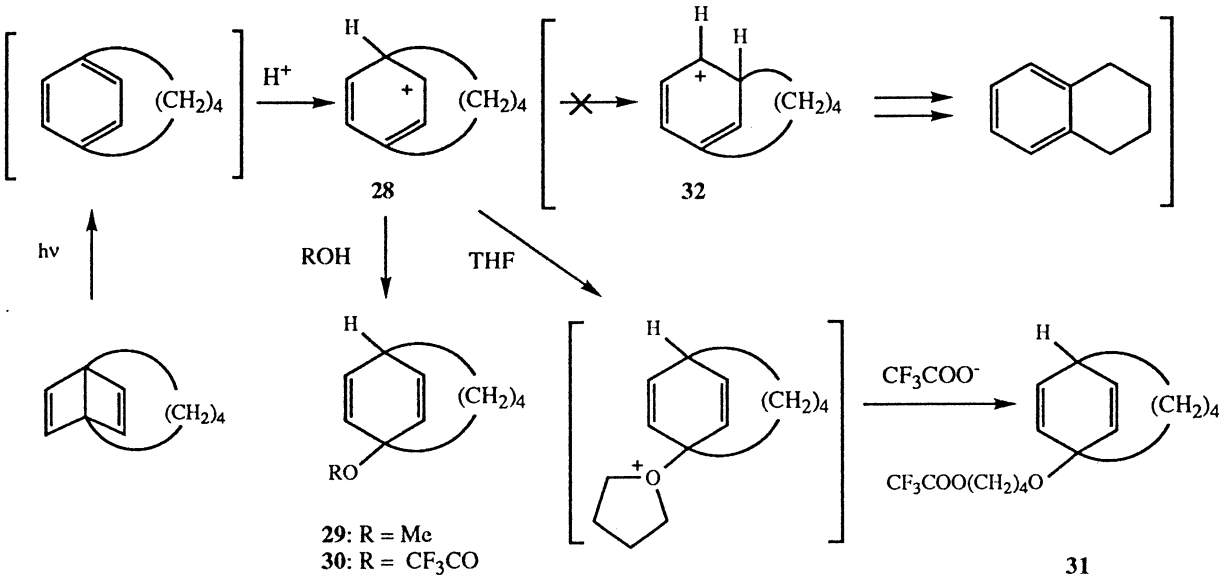
Scheme 10

which the [5]paracyclophanes can be converted into their Dewar isomers are without analogy in the photochemistry of *planar* aromatic compounds; it obviously reflects the high strain in the aromatic isomer, because the Dewar form is not more strained than ordinary Dewar benzenes, since the bridge can be attached to the 1,4-positions without (much) additional strain.

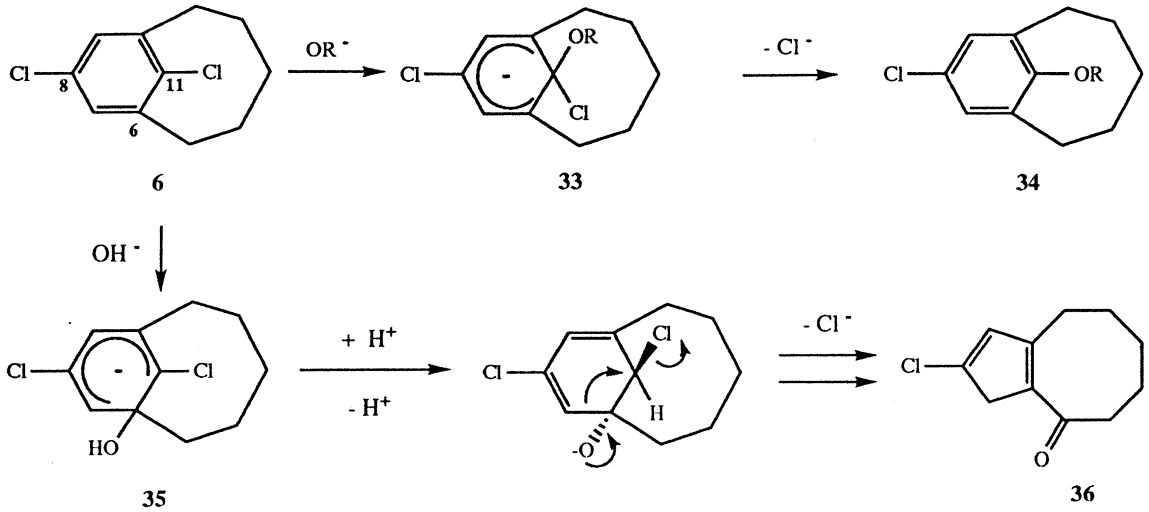
Reactions with electrophiles

Whereas [6]metacyclophane seems to be relatively stable towards rearrangement after electrophilic attack,[19] [5]metacyclophanes are sensitive; thus, protons or silver ions cause rearrangement of [5]metacyclophane to its *ortho* isomer **7**,[20] and bromination occurs surprisingly mildly without a catalyst and at −75 °C, but again occurs with (Wagner–Meerwein type) rearrangement to the brominated *ortho* isomer **16** (Scheme 7).[14b]

The mechanism proposed in Scheme 7 is supported by the product formation from the trifluoroacetic acid treatment of **6**. Owing to the electron-withdrawing effect of the chlorine substituents, this reaction proceeded more slowly than that of the unsubstituted parent compound (at room temperature: 3 h and 1 min, respectively) and gave rise to the three *ortho* annelated products **18**–**20**; with



Scheme 11



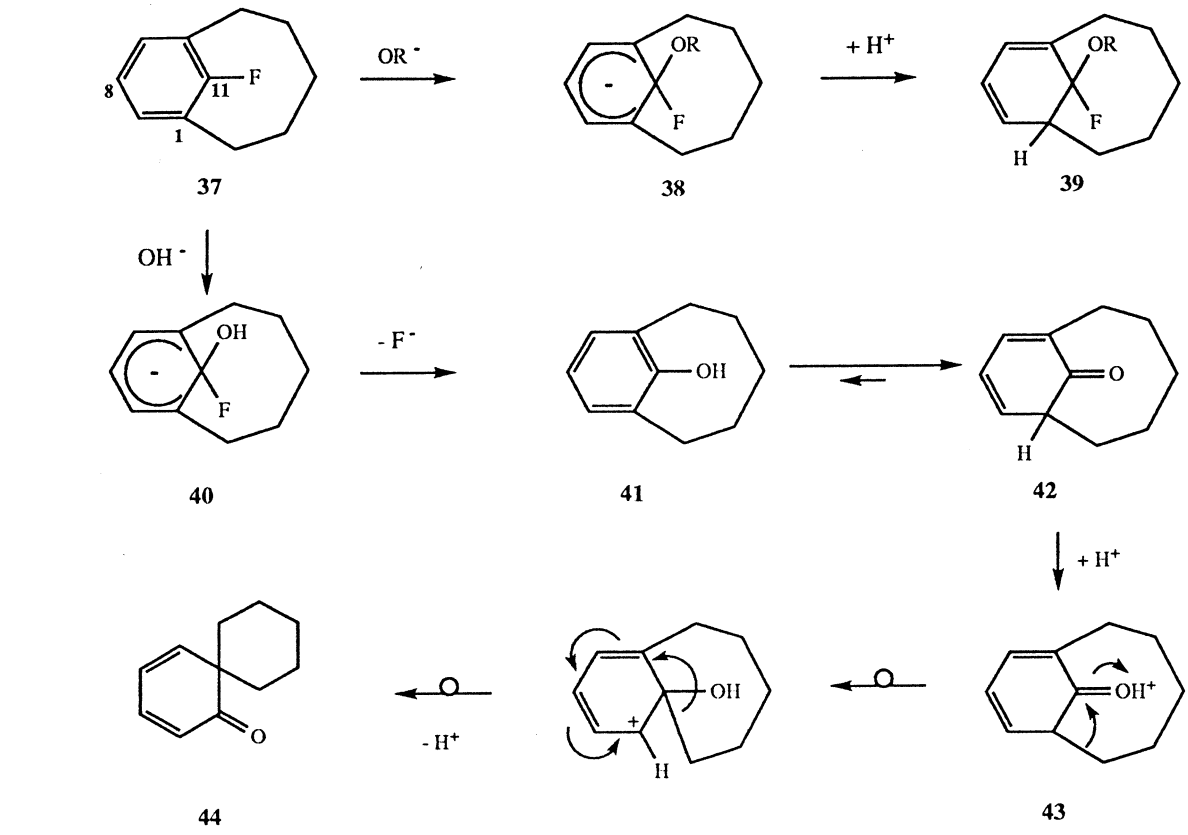
Scheme 12

deuterotrifluoroacetic acid, [D]**18** was obtained instead of **18** (Scheme 8).[20]

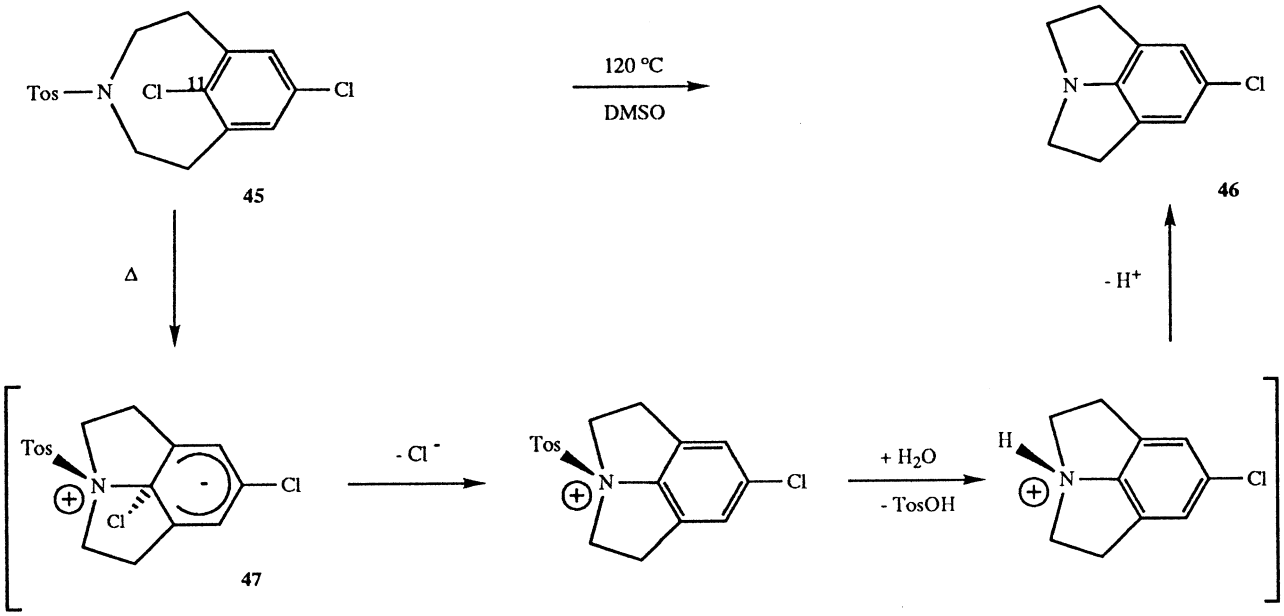
A different substitution pattern in the rearranged *ortho* isomer is observed when the (at first sight minor) change is made of replacing the Cl-11 in **6** by fluorine as in **21**. Acid treatment of **21** leads to **22** (Scheme 9), involving a triple Wagner–Meerwein shift of the alkyl bridge.[14c] The reason for this deviating behavior apparently stems from the inability of fluorine in the intermediate rearranged cation **23** either to migrate in a 1,2-shift, eventually leading to the originally expected **24** (*cf.* **20** in Scheme 8), or to depart as a (formal) fluorine cation which would have furnished **18**.

[*n*]Paracyclophanes have an analogous tendency to rearrange on protonation to the less strained *meta* and/or *ortho* isomers. Thus, [6]paracyclophane gave a 1:3 mixture of its *meta* and *ortho* isomers (Scheme 10), presumably because at the intermediate stage of **25**, deprotonation to the relatively unstrained [6]metacyclophane competes with a second Wagner–Meerwein rearrangement to **26** which on deprotonation yields benzocyclooctene (**27**).[19]

Surprisingly different is the course of reaction when [4]paracyclophane, obtained by irradiation of its Dewar isomer, is intercepted by acid (Scheme 11).[13,21] Instead of an analogous rearrangement to the *ortho* isomer tetralin, 1,4-addition products were observed, as illustrated by the reaction with trifluoroacetic acid in methanol or THF which, via the intermediate carbonium ion **28**, led to the adducts **29** or **30**/**31**, respectively; apparently, the reactivity of **28** is so high that it accepts any base from the solvent rather than undergo a second

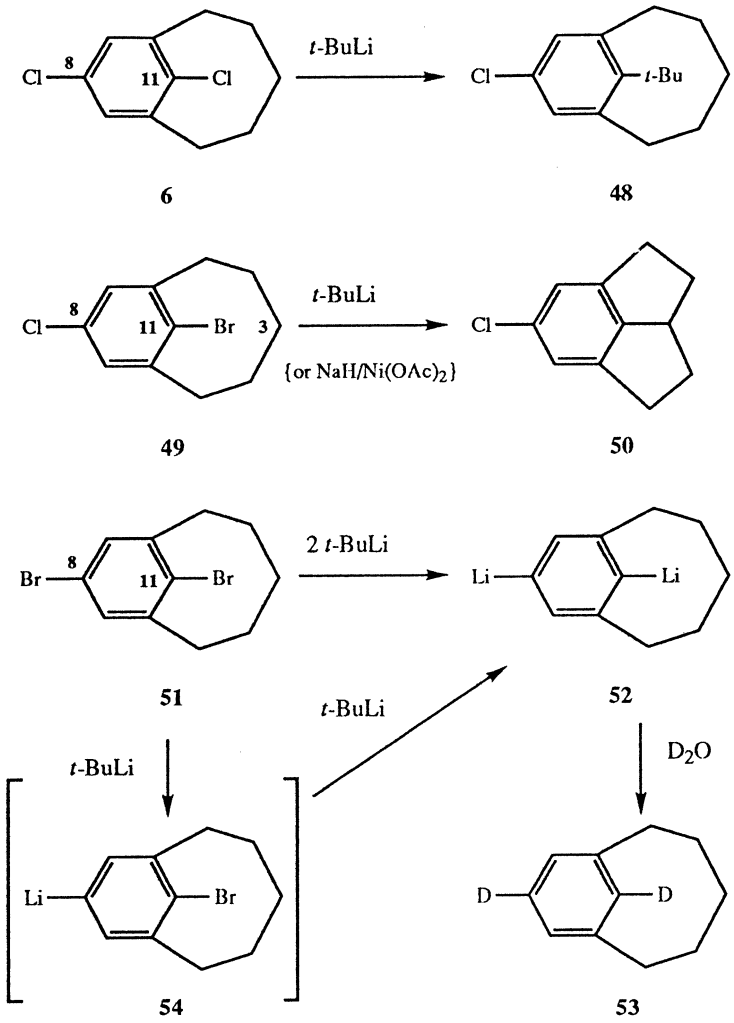


Scheme 13



Scheme 14

Wagner–Meerwein shift to **32**, which would rearrange and be deprotonated to give tetralin. A detailed calculational analysis[21] revealed that the susceptibility of [4]paracyclophane to protonation is extremely high, as expressed by the calculated pK_A = 51 for **28**, which, of course, is not the result of any special basicity of the π-system of [4]paracyclophane, but rather a (symbolic!) measure of the large gain in energy on protonation which changes the hybridization of a bridgehead carbon from (ideal) sp^2 to sp^3 and leads to concomitant relief of bridge



Scheme 15

strain in **28**. [5]Paracyclophane shows an intermediate behavior in yielding both 1,4-adducts and the *ortho* isomer benzocycloheptene.[21]

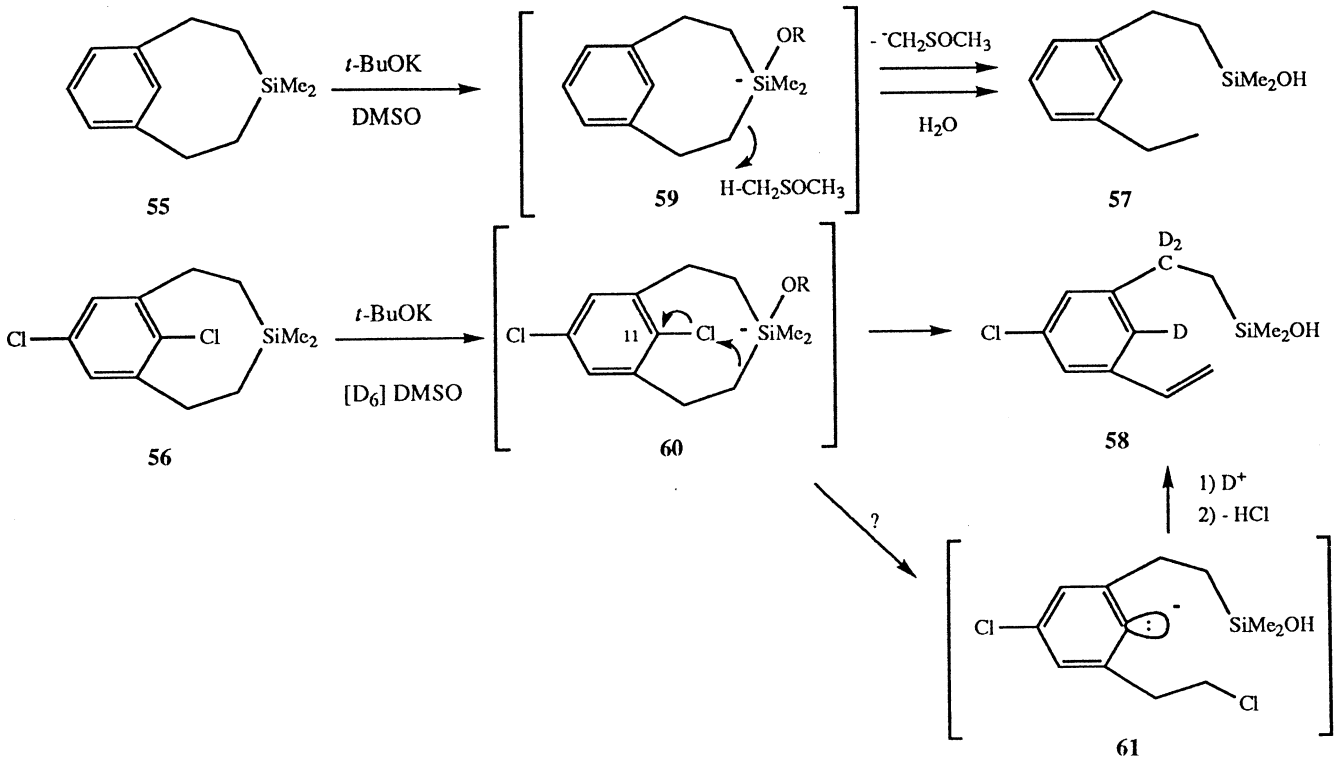
Reactions with nucleophiles

In this category, a diverse group of reactions will be described which, each in its own right, has no counterpart in the chemistry of planar aromatic analogues.

It is a classical experience in aromatic chemistry that nucleophilic substitutions, in contrast to their electrophilic counterparts, do not occur unless the aromatic nucleus is activated by strongly electron-withdrawing groups such as the nitro group. However, **6** is readily attacked by alkoxide ions at the *ipso* carbon atom 11 to give the Meisenheimer complex **33** and hence the substitution products **34**. Hydroxide ion attacks at the bridgehead carbon atom 6 to furnish **35**, which is converted into **36** as shown in Scheme 12.[4c,16,22]

The reaction is slower when the electron-withdrawing chlorine at position 8 is missing, and it is facilitated when the halogen at position 11 is fluorine, which is in line with the proposal that the reaction proceeds by a direct S_N2(Ar) mechanism (Scheme 12).[4c,16,22] In the latter case, a wealth of unexpected reactions was encountered,[14c] of which only a selection can be presented here. Thus, **37**, like **6**, reacted with alkoxides by addition at C-11 to furnish **38**, but the subsequent course of the reaction was different: whereas **33** 'finished' the Meisenheimer substitution by extrusion of chloride ion to give **34** (Scheme 12), the corresponding intermediate **38** added a proton to give the 1,2-adduct **39** (Scheme 13).

Even more surprising was the reaction of **37** with hydroxide ion. In contrast to **6**, **37** was attacked *not* at the bridgehead carbon C-1, but at C-11 (Scheme 13). The intermediate **40** *did* expel fluoride ion (possibly after deprotonation) leading to the highly strained phenol **41**, which rearranged to give **42**. Apparently, the strain in **41** is higher than the loss of aromatic resonance energy on tautomerization to **42**, which makes the couple **41**/**42** one of the few examples where the keto form is more stable

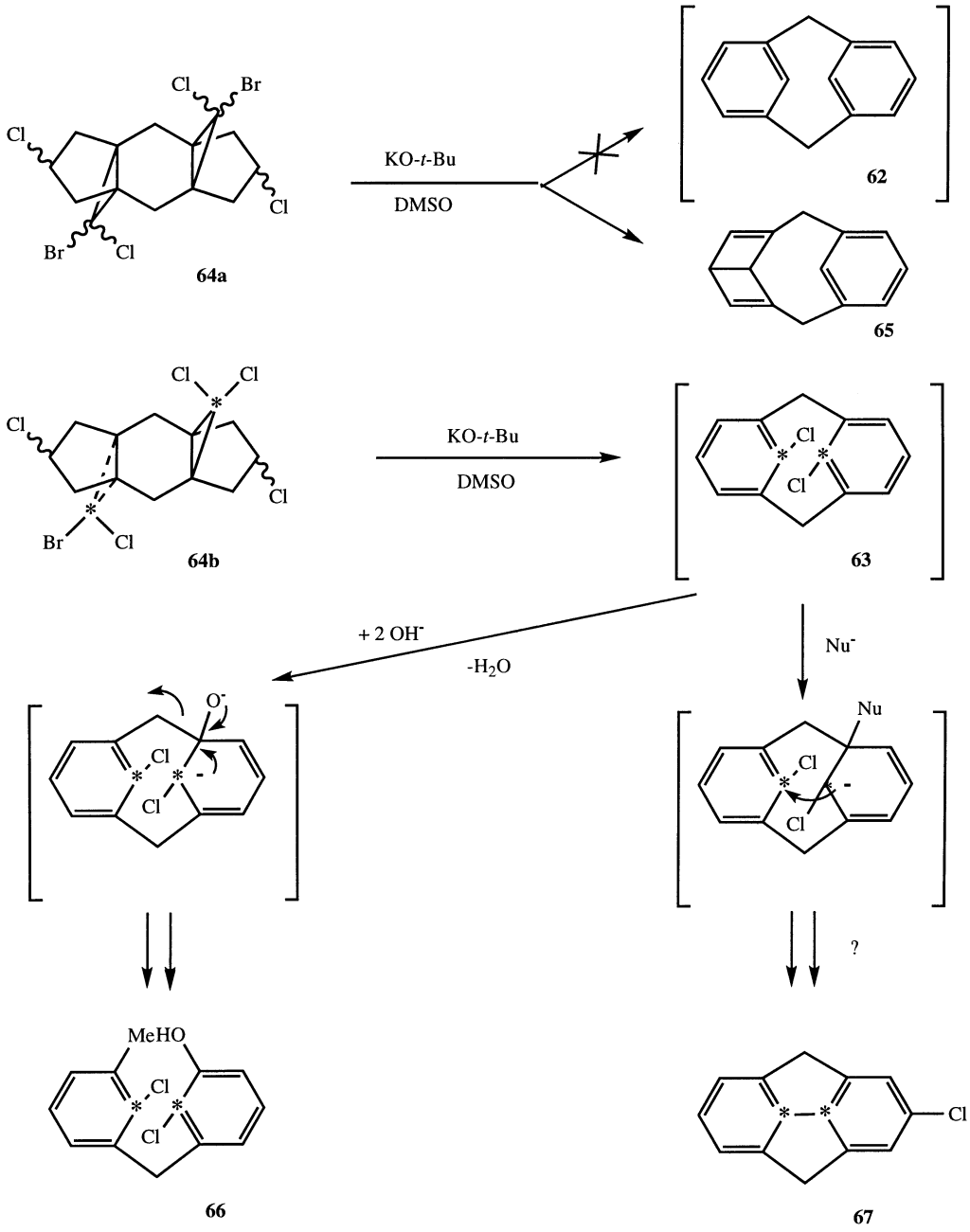


Scheme 16

than the corresponding phenol.[14c] Although the transformation to **42** reduces the strain considerably, the compound is certainly not strain-free; this explains why on standing in contact with water, and more rapidly under acid catalysis, **42** underwent a spectacular rearrangement to the spirodienone **44**, which is rationalized as shown to proceed by protonation to **43**, followed by two consecutive Wagner–Meerwein-type alkyl shifts.[14c]

Another example of the unprecedented susceptibility of [5]metacyclophanes to undergo nucleophilic attack at the benzene ring is the transformation of the 3-aza[5]metacyclophane **45**[18b] to the strained, tricyclic dihydroindole derivative **46** on heating in DMSO at 120 °C (Scheme 14).[18c] It is suggested that the first step in this transformation is the nucleophilic attack of the tosylamide nitrogen on the *ipso* carbon C-11 to form **47**; in view of the extremely weak basicity of this nitrogen lone pair, the reaction is remarkable indeed. Subsequent hydrolysis of **47** yields **46**, which has some interest of its own as being an aniline derivative with a nitrogen lone pair forced into an orientation parallel to the π-system of the benzene ring; incidentally, the ring system of **46** is a nitrogen analogue of a strained hydrocarbon first reported by Rapoport and Pasky[23] (*cf.* **50** in Scheme 15).

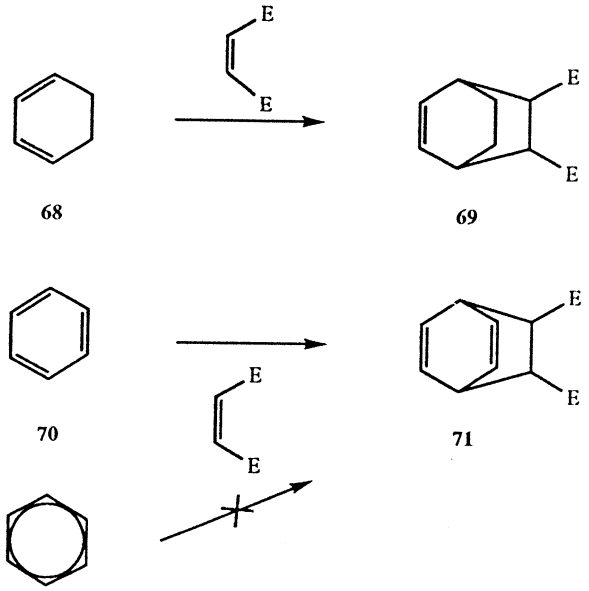
Organolithium reagents are also nucleophiles but often show a reactivity different from that of normal nucleophiles. Their behavior towards halogen-substituted [5]metacyclophanes depends in a dramatic fashion on the nature of the halogen as shown in Scheme 15. With **6**, a direct substitution of the chlorine at C-11 by a *tert*-butyl group occurs with formation of **48**; this reaction is unusual for organolithiums, but parallels the behavior of the alkoxides depicted in Scheme 12 and is believed to follow the same direct $S_N2(Ar)$ mechanism.[16] Replacing the chlorine at C-11 by bromine as in **49** leads to ring closure with formation of **50**, which is the all-carbon analog of **46** (Scheme 14) and the chloro derivative of Rapoport and Pasky's hydrocarbon.[23] This reaction probably proceeds by a radical pathway; in support of this interpretation, the same conversion was achieved with NaH–$Ni(OAc)_2$, a reagent which reduces aromatic halides via aryl radical intermediates.[24] When both chlorines of **6** are replaced by bromine as in **51**, the expected normal bromine–lithium exchange occurs, and it does so even twice with formation of **52**; it is of interest that **52** was deuterated to give **53**, the ^2H NMR spectrum of which furnished compelling evidence for the intact ring current of its bent benzene system.[7] The difference in behavior between **49** and **51** has been tentatively explained as follows:[16] with **49**, obviously a single electron transfer/radical mechanism is operative leading to an intraannular radical attack at C-3 followed by radical ring closure to give **50**, whereas with **51**, first the easily accessible bromine at C-8 undergoes the normally very fast bromine–lithium exchange reaction with formation of **54**; the negative charge associated with the organolithium functionality in **54** counteracts a rapid single electron transfer to the benzene ring so that the second bromine–lithium exchange has a chance to proceed as normal, resulting in the formation of **52**.



Scheme 17

Finally, two examples of base-induced reactivity from two different classes of [5]metacyclophanes may serve to demonstrate further the unforeseen but often rewarding chemistry one may encounter in this area. First, ring opening reactions of the 3-sila[5]metacyclophanes **55** and **56** to form **57** and **58**, respectively,[14c] are remarkable insofar as (cyclic) silanes are normally stable towards base attack unless the ring is small and strained, as in silacyclobutanes.[25] Scheme 16 shows a tentative mechanism starting with attack of the strong base on silicon to furnish the pentacoordinated silicate intermediates **59** or **60**. Whereas **59** opens the heterocyclic ring to yield a primary β-phenylethyl carbanion *in statu nascendi*, which is protonated by DMSO to give **57** and a dimsyl anion, the analogous ring cleavage in **60** creates a corresponding anionic center in the vicinity of the chlorine subsituent which may be abstracted with the formation of a new anionic center at C-11 and a β-chloroethyl substituent to form **61**, which finally is transformed to **58** as shown (the introduction of two deuteriums at the benzylic position of **58** is a subsequent, normal base-catalyzed exchange reaction).[14c]

A second case of nucleophilic attack on a bent benzene ring of a [5]metacyclophane intermediate was presumably encountered in an attempt to synthesize the dichloro derivative **63** of [1,1]metacyclophane **62**; note that **62** and

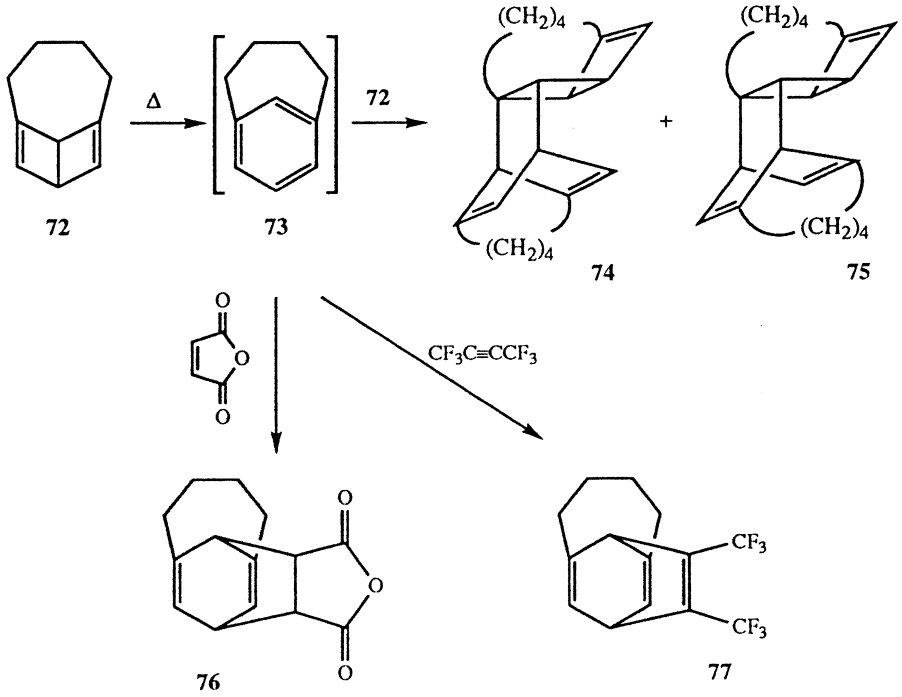


Scheme 18

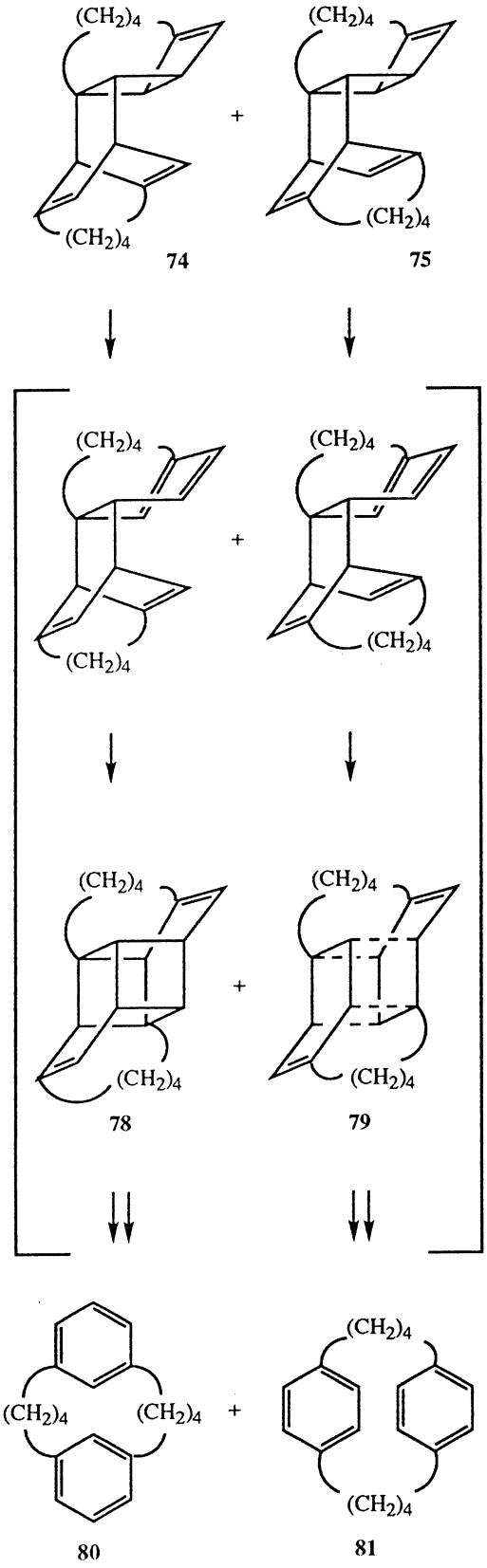
63 comprise two [5]metacyclophane units (Scheme 17). A previous attempt to obtain the unsubstituted parent compound **62** from **64a** with potassium *tert*-butoxide in DMSO had furnished **65**, the mono-Dewar isomer of **62**, instead.[26] It was expected that **64b** would lead to **63**, and as previous experience had shown that chlorine substitution stabilizes [5]metacyclophanes,[4c,16] we had hoped that **63** might prove to be isolable. Probably **63** was indeed formed, but under the reaction conditions it did not survive because it was further transformed by the strong base to give **66** and **67** in about 10% yield.[27] The formation of **66** can easily be explained as shown in Scheme 17: attack of base, *in casu* inevitable traces of OH^-, at one of the bridgehead positions (*cf.* the transformation **6** → **35** in Scheme 12), followed by ring opening and formation of a benzylic carbanion eventually gives **66**; on the basis of this mechanistic reasoning, the structure of **66** forms good evidence for the intermediacy of **63**. The rationalization of the formation of **67** is more speculative. Labeling of **64b** with carbon-13 (*) at the positions indicated in Scheme 17 proved that the two central carbons retained the positions expected in **63**, *i.e.* they were connected by the central carbon–carbon bond; obviously, it is not carbon but the chlorine substituent which (somehow) underwent a (formal 1,4) shift. Whatever the exact mechanism may be, most likely the central bond is formed in a nucleophilic attack by the negative charge in one ring on the other ring, as indicated in Scheme 17.[27]

Diels–Alder reactions

1,3-Dienes, and in particular cyclic derivatives such as cyclopentadiene or cyclohexadiene (**68**), are classical substrates for the Diels–Alder [4+2] reaction; in analogy with the transformation **68** → **69**, one would expect a (localized) cyclohexatriene **70** to undergo a Diels–Alder reaction to give **71** (Scheme 18). In the absence of special steric effects (which are known to influence the reactivity strongly), the very fact that benzene is inert towards



Scheme 19



Scheme 20

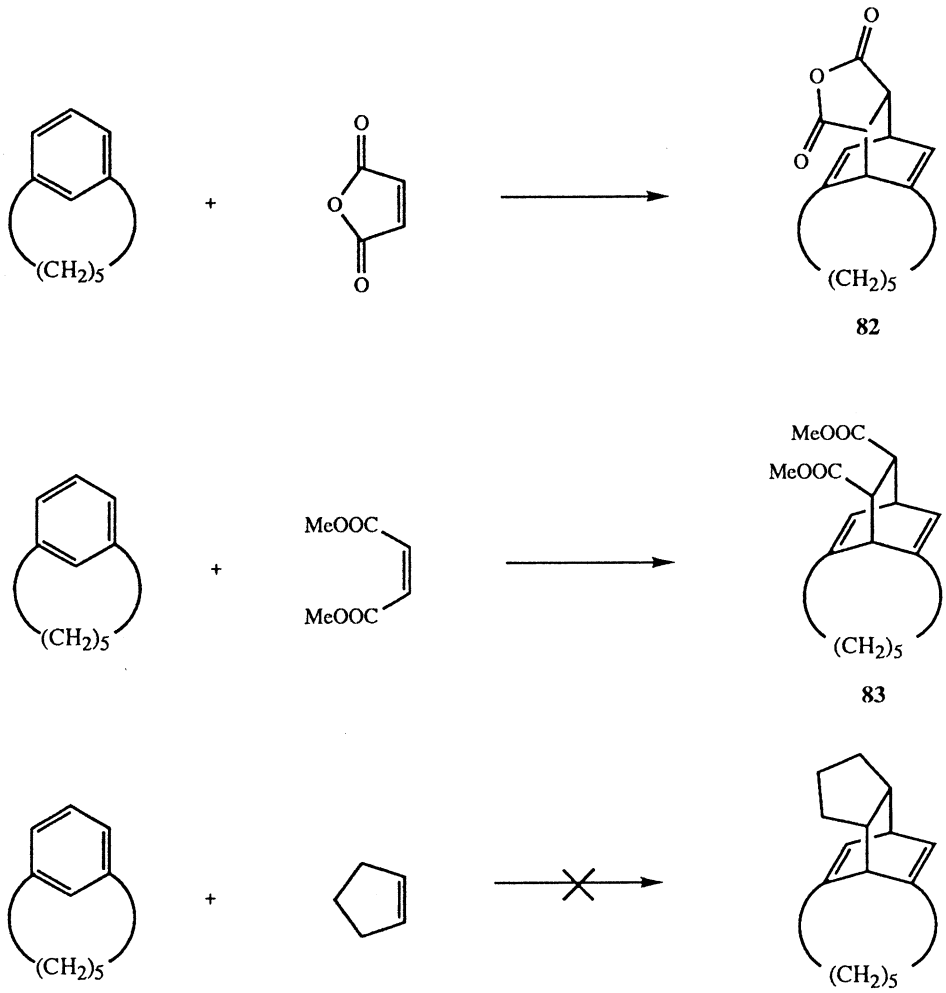
Diels–Alder reactions, unless highly reactive dienophiles or drastic conditions are applied,[28] is generally considered to be a consequence of the stabilization associated with its non-cyclohexatriene-like, delocalized nature.

Again, strained metacyclophanes react with unprecedented ease, even with relatively unreactive dienophiles; as briefly mentioned in the Introduction, this phenomenon initially gave rise to the hypothesis that with decreasing bridge length, bent benzene rings gradually were forced to give up the delocalized aromatic structure in favor of cyclohexatriene-like localization.[3] The most reactive member of the metacyclophane series is [4]metacyclophane (**73**), which was too unstable to be isolated, but instead was intercepted by its Dewar precursor **72** under the conditions of its generation in an ampoule in pentane solution at about 150 °C (Scheme 19).[10,29] The primary products were **74** and **75**, differing only in the relative orientation of the bridges in the Diels–Alder reaction; note that the formation of **74** and **75** involves a Diels–Alder reaction of a benzene ring as diene with the completely unactivated double bond of a Dewar benzene as dienophile! In the presence of maleic anhydride or hexafluoro-2-butyne, the adducts **76** or **77**, respectively, were obtained instead.

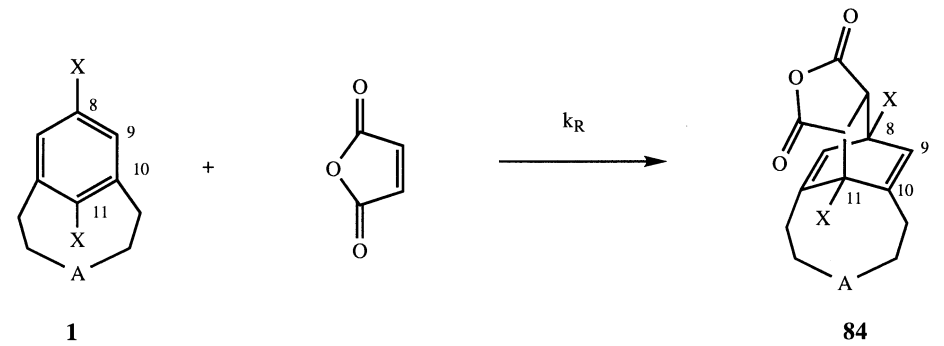
In addition to **74** and **75**, and depending on the reaction conditions, a number of other products were also formed in low yield, of which **80** and **81** are the most noteworthy (Scheme 20); in particular, **81**, a [4,4]paracyclophane, is astounding at first sight: how can a paracyclophane be formed from *meta* precursors such as **72** or **73**? A thorough discussion of the details of the mechanism is beyond the scope of this review; suffice it to say that a consistent rationalization can be found as briefly indicated in Scheme 20 by assuming that starting from **74**/**75**, consecutive ring opening and intramolecular Diels–Alder reaction lead to the cage compounds **78** and **79**, respectively; two corresponding retro-Diels–Alder reactions involving the alternative, horizontal bonds of the central cage (dotted in **79**) finally yield **80** and **81**, respectively,[10,29] which are stable end-points with strain-free, planar benzene rings.

In comparison with [4]metacyclophane, the Diels–Alder reactivity of [5]metacyclophane is clearly reduced, but in comparison with normal aromatic compounds, it still is spectacular. With 'standard' dienophiles such as maleic anhydride, it reacts *instantaneously* to give **82** (Scheme 21). With the less reactive dimethyl maleate, 77% of **83** was obtained after 25 h at 65 °C; only with cyclopentene, the non-activated double bond of which may be similarly unreactive as that in **72** (Scheme 19), did a reaction not occur.

Within the group of [5]metacyclophanes **1**, the propensity to undergo a Diels–Alder reaction decreases in the order A = CH_2 > NTos > C=O ≫ $SiMe_2$, as shown in Scheme 22 for the reaction with maleic anhydride; several other dienophiles have been investigated and the results support these trends. The relative rates k_R are



Scheme 21



Relative rates k_R: A = CH_2 > NTos > C=O >> $SiMe_2$

X = H >> Cl

Scheme 22

qualitative in the sense that they are based on total reaction times or competition experiments. In general, the experimentally observed order is in line with expectation: strain and high electron density in the benzene ring increase the reaction rate. Thus, the dichloro-substituted derivatives (**1**, X = Cl) react more slowly than their parent compounds (**1**, X = H),[3b,18b,c,d29] because the chlorine substituents withdraw electron density and lower the HOMO energy; this experimental observation indicates that the Diels–Alder reactions described here belong to the class of normal electron demand reactions. Furthermore, it is evident that strain plays a major role in activating the benzene ring, probably for two reasons. First, the strain-induced bending of the benzene ring

raises the HOMO and increases electron density and orbital coefficients in the hollow region of the boat, which is the side where the dienophile attacks.[14b,16,22] Second, the strain is considerably reduced in the Diels–Alder adducts which have less severe anti-Bredt character at the bridgehead position. This can be visualized by the (admittedly incorrect) oversimplification of considering the benzene ring in its cyclohexatriene representation: the 'anti-Bredt double bond' C-10—C-11 in **1** has been replaced by the double bond C-9—C-10 in **84**; although the latter is also at a bridghead position, it is much more comfortable being *trans* in a 10-membered ring. The concomitant release of strain will undoubtedly be operative in the transition state and help to increase the reaction rate.

However, when looking at closer details, the order of reactivity does pose some puzzles. Not surprisingly, the larger bridge length in **1** (A = $SiMe_2$), which stems from the two long C—Si bonds, confers properties on this compound which make it more similar to [6]metacyclophane than to [5]metacyclophane (**1**, A = CH_2), so that the Diels–Alder reactivity is considerably reduced.[14c] The same holds to a lesser extent for **1** (A = C=O).[18d] On the one hand, its bridge is shorter owing to the two *sp*3–*sp*2 bonds to the carbonyl carbon at position 3, but on the other, the naturally larger sp^2 angle of 120° at this position makes the bridge 'wider' and reduces the angle strain; apparently, the latter factor is dominant, as indicated by the reduction of the reaction rate by a factor of about 20 compared with **6**. Even less clear is the situation for the 3-aza[5]metacyclophane **1** (A = NTos, X = Cl). In comparison with [5]metacyclophane, it has two shorter C— N bonds in the bridge instead of two C—C bonds, which will increase the strain; indeed, the x-ray crystal structure, revealing a slightly more bent benzene ring, and theoretical calculations indicate the molecule to be more strained. Nevertheless, the aza derivative is 5–10 times less reactive than **6**.[18b] This indicates that for the fine tuning of the reactivity, additional factors, which are not well understood at the moment, must also play a role.

CONCLUSION

From the chemical behavior of small, strained cyclophanes, two special aspects emerge. The first is a rich, diverse reactivity full of surprises which appears to be utterly untypical of aromatic compounds. Second, all structural and spectroscopic criteria and theory testify of the truly aromatic character of these compounds.

Both aspects seem contradictory at first sight, but can be reconciled by considering that the considerable strain in these compounds, about 180 kJ mol^{-1} in [5]metacyclophane (MNDO,[16,20b,22] density functional calculations[15]), is largely released in all the reactions considered, be they hydrogenation, addition of electrophiles or nucleophiles to the one-carbon bridge (position 11) or Diels–Alder reactions (positions 8 and 11). This holds not only for the (primary) products of the reactions, where the formal sp^2 hybridization is changed to sp^3, which makes bridge attachment easier, but also for the transition states preceding them, which causes these reactions to proceed rapidly and to completion. One of the additional factors is the deformation of the π -electron cloud of the benzene ring, which raises the HOMO, lowers the LUMO and causes a high electron density at the inner, concave side of the benzene ring, thus facilitating attack from this side.

Finally, an old lesson has proven to be true once again: (lack of) reactivity is not necessarily a reliable indicator of the ground-state structure of a molecule!

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