Inner-Phase Stabilization of Reactive Intermediates

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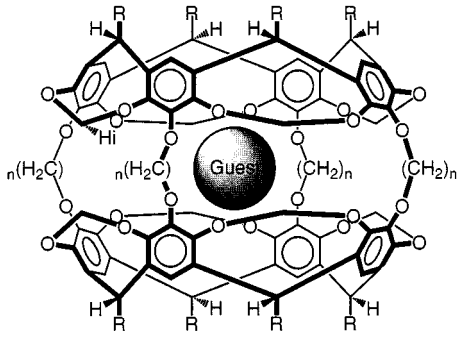
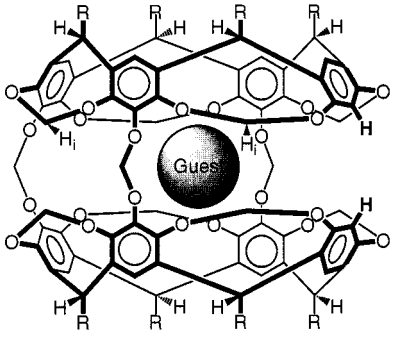
Molecular container compounds are spherical, hollow molecules with inner cavities (inner phases) that are large enough to accommodate a single guest molecule. These inner phases are superb environments for the stabilization and spectroscopic investigation of important reactive intermediates. The surrounding host protects the incarcerated reactive intermediate from dimerization or from a reaction with bulk-phase reactants that are too large to enter the inner phase by passing through a portal in the host shell.

Introduction

The taming of reactive intermediates and their spectroscopic investigation has always been a special challenge for the chemical and physical experimentalist. In the past decades, different approaches have been developed, the most common of which is matrix isolation. The reactive intermediate is photochemically generated from a stable precursor molecule embedded in a solid inert-gas matrix under cryogenic conditions.[1] The stabilization of virgin, chemically unmodified intermediates in solution is more difficult to achieve, but has been successfully mastered for carbocations.[2] Incarceration in the inner phases of molecular container compounds represents a novel and very powerful method for the stabilization and investigation of molecules that have a fleeting existence under normal working conditions.[3−6] The concept of molecular container compounds was developed by Donald J. Cram.[7] Molecular container compounds are spherical, hollow molecules with inner cavities that can accommodate a single guest molecule. The guest is held inside by constrictive binding,[8] a new binding phenomenon that arises when the openings



1⊙Guest n = 1
2⊙Guest n = 4
R = $CH_2CH_2C_6H_5$



3⊙Guest

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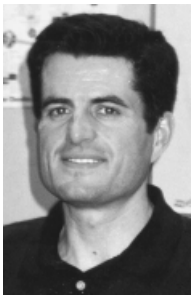

Ralf Warmuth was born in Leverkusen, Germany. He studied chemistry at the University of Cologne, Germany, and received his Diploma in biochemistry (1989) under the guidance of Professor Ernst Bause. He carried out his thesis work at the Max-Planck Institute for Biophysics in Frankfurt/M., Germany, and at the Institute Le Bel of the Université Louis Pasteur in Strasbourg, France, with Dr. Ernst Grell, Professor Jean-Marie Lehn, and Professor Gerhard Quinkert as his advisors and obtained his Ph.D. from the Johann-Wolfgang-Goethe-University in Frankfurt/M. in 1992. After postdoctoral work in the research groups of Dr. Mark Mascal at the University of Nottingham, U.K. (1992–1994) and of Professor Donald J. Cram and Professor Ken N. Houk at the University of California, Los Angeles (1994–1997, Feodor Lynen fellow), he joined Kansas State University as an Assistant Professor in 1997. His research focuses on inner-phase chemistry, protein structure, and protein folding.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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(portals) in the host shell are too narrow, preventing guest escape. Complexes such as **1** ⊙Guest, whose constrictive binding energy prevents guest escape without cleavage of covalent host bonds, permanently incarcerate their guests and are referred to as *carceplexes*. The name carceplex is derived from the word *carcer* (Latin for prison).

Hemicarceplexes **2** ⊙ Guest and **3** ⊙ Guest allow guest exchange at elevated temperatures through an enlarged portal in the host shell (Figure 1).[9] Cram coined the term "inner phase" for the interior of a container compound since the properties of an incarcerated guest molecule are different from those in the bulk phase. Incarcerated guests can freely rotate and translate inside their molecular prison, but are protected by the host from dimerization or from reacting with bulk-phase reactants that are too large to enter the inner phase through a size-restricted opening in the host shell.

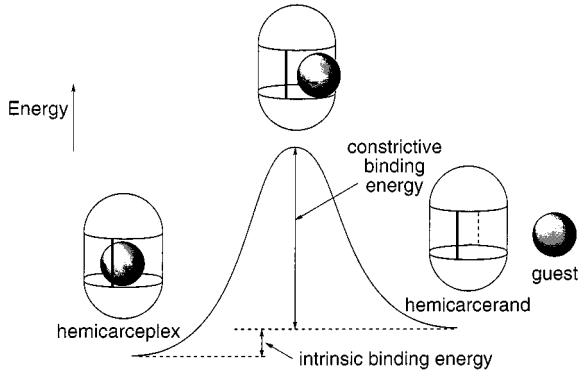


Figure 1. Both intrinsic and constrictive binding contribute to the high thermal stability of hemicarceplexes[7,8]

Cyclobutadiene

Cram and co-workers introduced this novel approach with the room-temperature stabilization of one of the most interesting and extensively studied reactive intermediates, namely cyclobutadiene (**4**), the "Mona Lisa of organic chemistry" (Figure 2).[3] Cyclobutadiene is the prototypical example to verify the theory of aromaticity.[10,11] It has transient existence under normal working conditions and is stable only in cryogenic matrices at 8 K, under which conditions Orville L. Chapman recorded its FT-IR spectrum.[12]

The inner-phase stabilization of cyclobutadiene is not only highly impressive, but also demonstrates unique features of hemicarceplexes that are prerequisites for such a venture:

- *Stable guest molecules of appropriate size can be thermally incarcerated in inner phases by mass law.*

Cram and co-workers synthesized the tris(bridged) hemicarcerand **3**, in which the enlarged equatorially located opening allows guest entrance and exit at elevated temperatures.[13] Thus, simply heating empty **3** and the known photochemical cyclobutadiene precursor α-pyrone (**5**) in refluxing chlorobenzene overcomes the constrictive binding energy to form hemicarceplex **3** ⊙ **5**, which is stable at room temperature.[3]

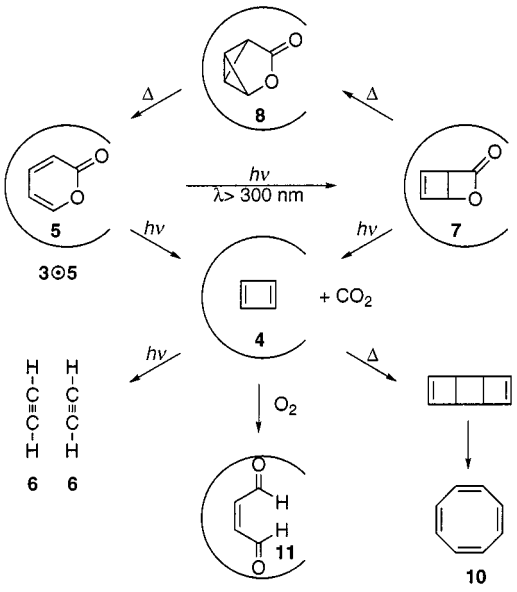


Figure 2. Inner-phase generation and chemistry of cyclobutadiene (**4**);[3] the semicircle symbolizes hemicarcerand **3**

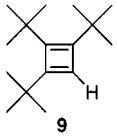
- *Incarcerated guests are photochemically and thermally manipulable.*

Photolysis of **3** ⊙ **5** with the unfiltered light of a xenon arc lamp generated incarcerated cyclobutadiene and CO_2. The latter was subsequently expelled from the inner phase of **3**. On prolonged photolysis of **3** ⊙ **5**, **5** was cleaved into two acetylene (**6**) molecules, which escaped from the inner phase and could be precipitated as red copper(I) acetylide.

In order to elucidate the mechanism of the inner-phase generation of **2**, Cram and co-workers selectively photolyzed **3** ⊙ **5** with filtered light ($\lambda > 300$ nm), which yielded photopyrone **3** ⊙ **7**. As a solid, **3** ⊙ **7** underwent thermal rearrangement at 90 °C into **3** ⊙ **8**. At higher temperatures, **3** ⊙ **8** quantitatively reverted to **3** ⊙ **5**. The efficient formation of **3** ⊙ **7** is understandable considering the low absorptivity of the surrounding **3** above 300 nm. However, the short-wavelength photolysis (200−250 nm) of incarcerated guests, which is required for the formation of **4** from **5** and its degradation to acetylene, poses the question as to how the photon reaches the guest through the strongly absorbing shell of the host. Cram and co-workers suggested the possibility of photosensitization.

- *Hemicarceplexes and carceplexes exist in the solid, solution, and gaseous phases, which allows the investigation of hosts and their guests using common solid-phase, liquid-phase, and gas-phase spectroscopic techniques.*

The high stability of incarcerated **4** allowed its first NMR-spectroscopic investigation in solution. A sharp singlet was observed at $\delta = 2.27$, which is 3.03 ppm upfield from the chemical shift of the ring proton of **9**[14] as a result of the shielding effect of the aryl units of the surrounding host.



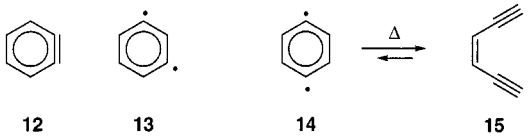
The sharpness of the signals attributable to the inward-pointing methylene protons of **3** proved the singlet ground state of **4**. These host proton resonances are significantly broadened in hemicarceplexes with guests that have a triplet ground state such as **3** ⊙ oxygen.[15]

- *The surrounding hemicarcerand protects the guest from bulk-phase reactants that are too large to enter the inner phase through an opening (portal) in the hemicarcerand shell.*

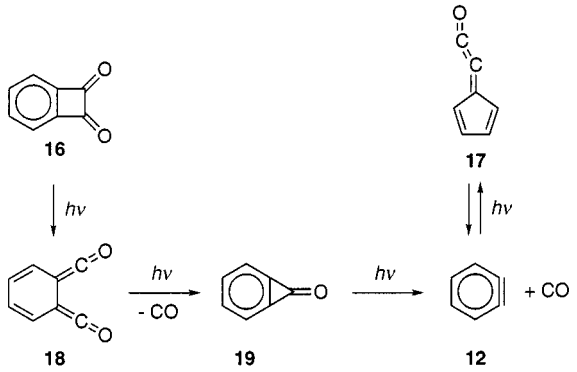
In the absence of oxygen in the reaction mixture, cyclobutadiene proved to be stable up to 60 °C! When a solution of **3** ⊙ **4** was heated in a sealed tube at high temperatures for a short period, the guest escaped from the protective shelter and dimerized to give cyclooctatetraene (**10**), which was noticeable by its characteristic odor on opening the tube. When dioxygen, whose size allows passage through the enlarged portal of **3** at room temperature,[15] was passed through a solution of **3** ⊙ **4**, **4** was oxidized in the inner phase to malealdehyde (**11**). Cram proposed that inner phases can be envisaged as eventually allowing the stabilization and examination of many other highly reactive species containing bent acetylenes and allenes, anti-aromatic rings, radicals, and carbenes.

Benzocyclopropenone and *o*-Benzyne

Almost half a century after Georg Wittig postulated didehydrobenzene (**12**)[16] and John D. Roberts unequivocally proved its existence by means of ^{14}C-labeling studies,[17] this reactive intermediate was stabilized by incarceration (Figure 3).[5] Since its discovery, *o*-benzyne has received much attention from the scientific community as a versatile intermediate in organic synthesis[18] and because of its unusual structural and electronic properties.[19,20] The recent elucidation of the mode of action of the highly potent enediyne anticancer drugs,[21] which involves a rearrangement of enediyne **15** to *p*-benzyne (**14**), known as Bergman cycloaromatization after its discoverer Robert G. Bergman,[22] led to a renaissance for all three benzyne isomers **12**−**14** and an even greater interest in their electronic and spectroscopic properties.[23−25]



o-Benzyne has been investigated in detail in cryogenic matrices by UV/Vis[26] and FT-IR spectroscopy[27] and by gas-phase microwave spectroscopy.[28] Chapman first matrix-isolated *o*-benzyne in argon at 8 K by photolyzing benzocyclobutenedione **16** (Scheme 1).[27a] A photochemical equilibrium between *o*-benzyne and cyclopentadienylidene ketene (**17**) in the presence of carbon monoxide led initially to an erroneous assignment of a ketene stretching frequency to the important triplet bond stretching mode of *o*-benzyne.[26,29]



Scheme 1

The correct stretching frequency was later identified at 1857 cm^{-1},[27d] which is consistent with predictions from Leopold and Lineberger's photodetachment studies.[30] A recent solid-state ^{13}C NMR spectrum of doubly ^{13}C-labeled [1,2-$^{13}C_2$]-*o*-benzyne at 20 K in argon allowed Grant and co-workers to determine the triple bond length of *o*-benzyne.[31] However, stabilization of *o*-benzyne in solution has only been achieved through coordination of the reactive triple bond to metal ions.[32] The author's group has photochemically generated *o*-benzyne (**12**) in the inner phase of hemicarcerand **2**, where it is sufficiently stable to allow recording of solution ^1H and ^{13}C NMR spectra.[5a]

The benzocyclobutenedione hemicarceplex **2** ⊙ **16** served as a precursor for the generation of incarcerated *o*-benzyne **2** ⊙ **12**. Photolysis at $\lambda > 400$ nm yielded the highly strained benzocyclopropenone (**19**). The latter had previously been studied in solution below −78 °C.[33] However, protected from hydrolysis by the surrounding host shell, it proved to be stable at room temperature, allowing its X-ray crystal structure analysis.[34] In the solid state, the C_2 axis of the guest **19** is parallel to the long polar axis of **2**, as shown schematically in Figure 3. This orientation correlates well with the preferred orientation in solution and provides an explanation for the high stability of the incarcerated guest.

When **2** ⊙ **16** was photolyzed in solution, even small amounts of water present in the bulk phase efficiently trapped the transiently formed bis(ketene) **18** to yield the hydroxyphthalide hemicarceplex **2** ⊙ **20** (Figure 3).[34] In the crystal structure of **2** ⊙ **16**,[34] one carbonyl group is aligned along the long axis of **2**, while the second one points towards a portal of the hemicarcerand as shown in Figure 3. Assuming that guest orientation is slow in the excited state of **16**, one ketene carbonyl group of **18** will most likely protrude through a portal of **2**, which would explain its efficient reaction with water in the bulk phase. The importance of the guest's functional group alignment with respect to the host's portals in through-shell reactions was recognized earlier by Cram and co-workers in relation to through-shell alkylation and isotope-exchange reactions.[35]

Further photolysis of **2** ⊙ **19** with filtered UV light at 280 ± 10 nm resulted in the extrusion of CO and the generation of **12**, the solution ^1H NMR spectrum of which could be recorded at −75 °C.[5a] The assignment of the two

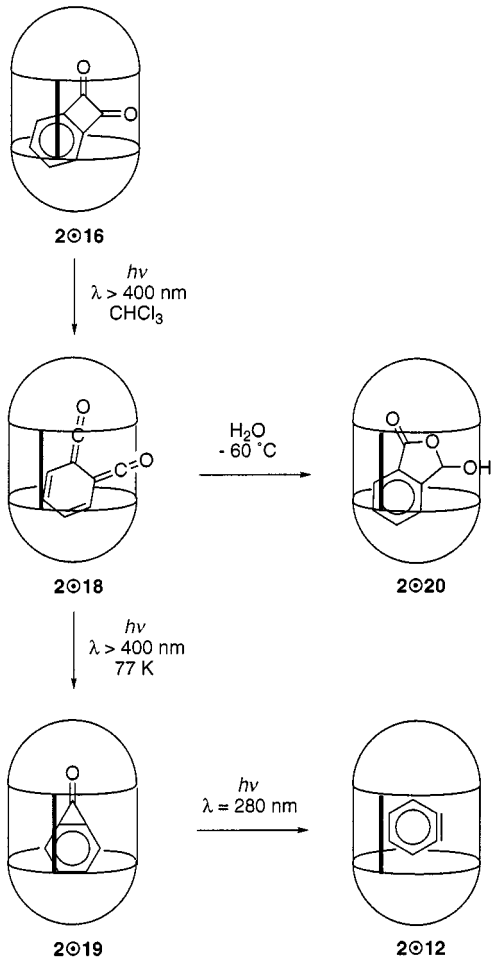


Figure 3. Photochemical generation of incarcerated *o*-benzyne inside hemicarcerand **2**;[5] the preferred inner-phase guest orientations of **16**, **19**, and **20** are shown

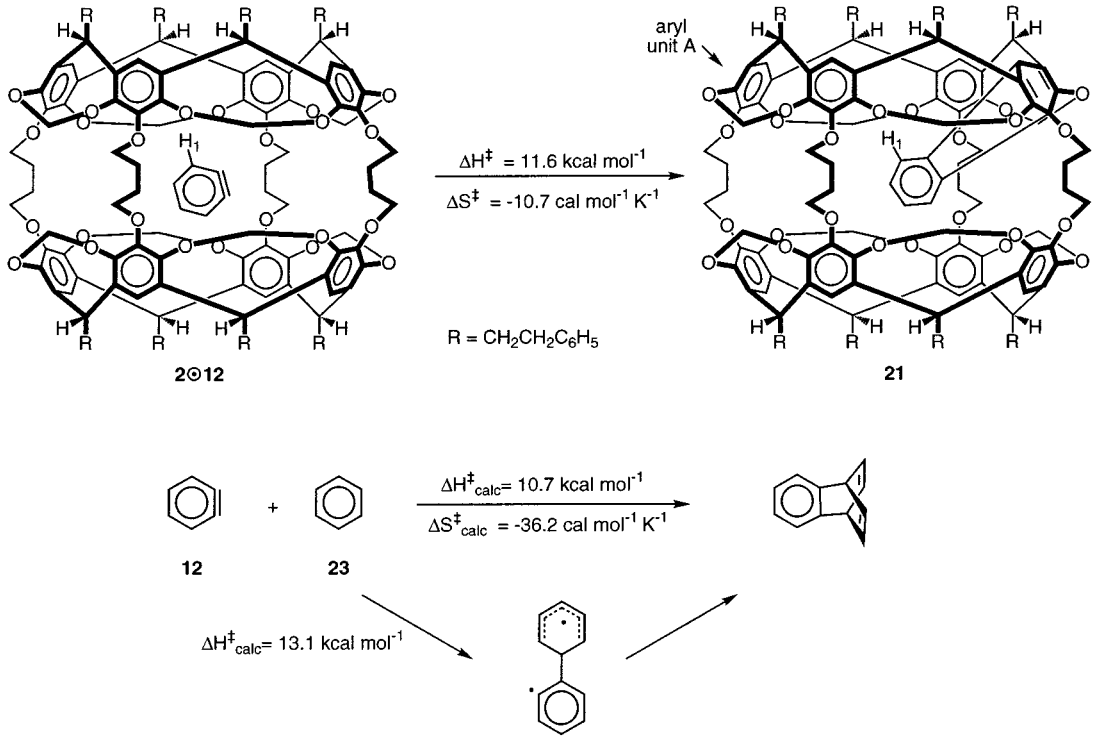
guest proton signals at δ = 4.99 and 4.31 could be achieved by the use of deuterium-labeled [3-D]-*o*-benzyne. As already mentioned for the guest protons of incarcerated cyclobutadiene **3** ⊙ **4**, the ^{1}H chemical shifts of **12** are significantly upfield shifted by the surrounding host. With the assumption that the *o*-benzyne protons are subject to the same shielding by the surrounding host **2** as the protons of the structurally similar benzene,[36] the chemical shifts of "free" *o*-benzyne were estimated to be δ = 7.0 and 7.6. Jiao et al. calculated the chemical shifts at the SOS-DFPT-PW91/III level of theory.[36] The small deviations of Δδ = 0.1 and 0.3, respectively, between experiment and theory demonstrate the high quality of this computational method.

Much less relatively upfield shifted are the guest ^{13}C signals. Hence, they should provide more insight into the electronic properties of *o*-benzyne and allow better comparison between calculation and experiment. The ^{13}C NMR spectrum of fully ^{13}C-labeled incarcerated *o*-benzyne was recorded at −98 °C in [D_8]THF.[5a] The measured chemical shift for the quaternary carbon atom of **12**, δ = 181.33, is within the experimental error of the average of the three chemical shift tensor principle values, δ = 193 ± 15, of matrix-isolated ^{13}C-enriched **12** at 20 K in argon.[31] The ^{13}C NMR spectrum of incarcerated *o*-benzyne also offered information regarding the ^{13}C-^{13}C coupling. Comparison of the experimental ^{13}C-^{13}C coupling constants with those of model compounds suggested a cumulenic character for *o*-benzyne, which, however, contradicts the results of the most recent ab initio calculations.[19] These show no evidence for the pronounced bond-length alternation necessary for a cumulenic structure. From their calculation of the magnetic properties of *o*-benzyne, Jiao et al. concluded that the system is aromatic on the basis of its geometric, energetic, and magnetic properties, and that the in-plane π-bond induces a small amount of bond localization resulting in acetylenic character.[19]

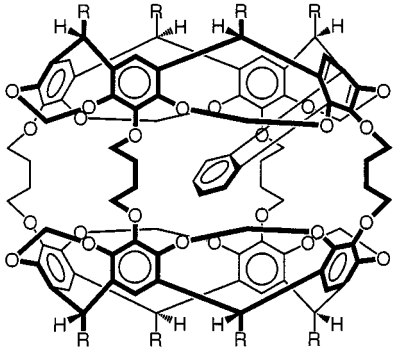
Innermolecular Diels−Alder Reaction of *o*-Benzyne

The high reactivity of *o*-benzyne led to a Diels−Alder reaction with the surrounding host **2** (Scheme 2).[5b] This Diels−Alder reaction is sufficiently slow below −75 °C (half-life of 205 s)[5a] to allow the recording of the ^{1}H NMR spectrum of *o*-benzyne, but it reduces the guest's lifetime at room temperature to approximately 7 ms. Such a bimolecular reaction, where one reactant is completely encapsulated within the other, is referred to as an *innermolecular* reaction.[5b,37] Although undesired if one's goal is the stabilization of a reactive intermediate, there are interesting aspects associated with innermolecular reactions, which are important with regard to understanding reactivity in rigid environments (matrix effects).[38] Innermolecular reactions take place at the concave inner surface of one reactant and are expected to be subject to significant steric effects. Furthermore, the surrounding hemicarcerand restricts the mobility of the guest. This will have consequences regarding entropy contributions to the activation barrier of an innermolecular reaction compared to a reaction in the liquid or gas phase. The reaction of incarcerated *o*-benzyne is very selective. *o*-Benzyne adds exclusively across the 1,4-positions of one aryl unit of **2**.[5b] The selective formation of **21** rather than **22** is a result of the large difference in stabilities of these regioisomers.[39] The MM3* minimum-energy conformer of the *o*-benzyne hemicarceplex also shows a significant preorganization of the reactive triple bond for the observed Diels−Alder reaction, with distances of 4.53 Å and 4.05 Å between the reacting *o*-benzyne carbon atoms and the corresponding aryl carbon atoms of **2**.[39] An analysis of the temperature dependence of the observed *o*-benzyne proton chemical shifts[5b] suggests a similar orientation, which also explains why *o*-benzyne reacts very rapidly with an aryl ring of the host above −75 °C, but does not react with water of the bulk solvent phase.

The high degree of pre-organization of the guest for the innermolecular reaction is reflected in the measured activation entropy, $\Delta S^{\ddagger}_{expt}(298\ K) = -10.7$ cal mol^{-1} K^{-1},[5b] which compares well with the activation entropy of the electrocyclization of hexatriene [$\Delta S^{\ddagger}_{expt}(298\ K) = -6.05$ cal mol^{-1} K^{-1}][40] or intramolecular Diels−Alder reactions.[41] Beno et al. calculated the activation parameters for the Diels−Alder reaction between *o*-benzyne (**12**) and benzene (**23**) at the Becke3LYP/6-31G* level of theory (Figure 9).[39] Interestingly, the calculated $\Delta H^{\ddagger}_{calcd.}$ was found to be slightly



Scheme 2



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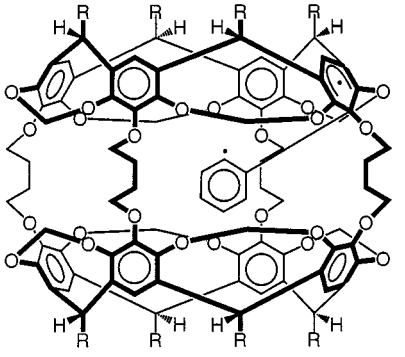
R = $CH_2CH_2C_6H_5$



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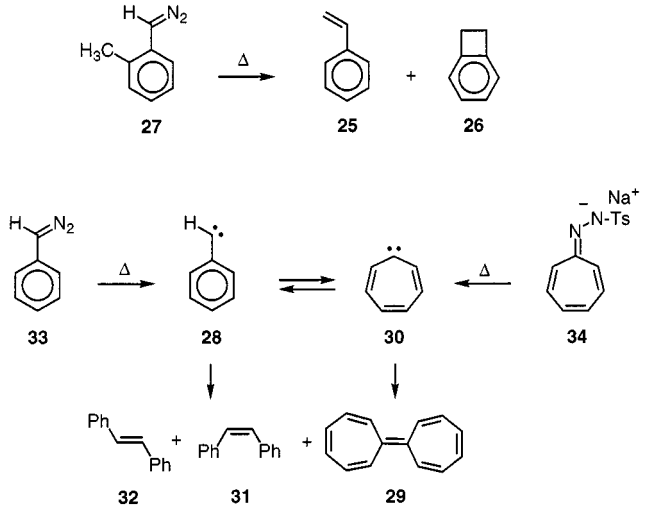
smaller than the experimental $\Delta H^{\ddagger}_{expt}$ of the innermolecular reaction, despite the increased reactivity of the aryl unit of **2** due to the electron-donating substituents. This suggests that the increased reactivity of **2** must be compensated by steric repulsion in the transition state leading to **21**. The MM3*-optimized structure of **21** reveals the origin of such steric repulsion.[39] Although the phenylene unit is not located in an overcrowded environment compared to that in the regioisomer **22**, the phenylene-H(1) in **21** experiences some repulsive interaction with the aryl unit A, which should also be felt in the transition state (Scheme 2).

In addition, Beno et al. calculated the activation barriers for a stepwise Diels−Alder reaction between *o*-benzyne and benzene.[39] The stepwise $\Delta H^{\ddagger}_{stepwise}$ was found to be only 2.4 kcal mol^{-1} higher than that for the concerted pathway (Scheme 2). The above-mentioned repulsive interactions in the innermolecular reaction transition state should be more pronounced for a concerted pathway than for a stepwise pathway involving the intermediate formation of biradical **24**. This suggests that the steric perturbation imposed by the surrounding host might change the reaction mechanism in the inner phase from a concerted to a stepwise pathway. This hypothesis awaits further experimental and computational efforts.

Phenylcarbene Rearrangement

In 1998, the author's group began a systematic investigation of phenylcarbene rearrangement inside molecular container compounds. The phenylcarbene rearrangement is one of the most important and fascinating carbene rearrangements, and has received much attention since its discovery in the late 1960s.[42] In pioneering work, Vander Stouw and Shechter reported the formation of styrene (**25**) and benzocyclobutene (**26**) upon pyrolysis of *o*-tolyldiazomethane (**27**) (Scheme 3).[43] Shortly thereafter, Jones et al. observed that phenylcarbene (**28**) undergoes ring expansion in the gas phase to yield heptafulvalene (**29**).[44] They pro-



Scheme 3

posed cycloheptatrienylidene (**30**) as an intermediate. The formation of identical carbene dimerization products − heptafulvalene, *cis*- and *trans*-stilbenes (**31** and **32**) − upon thermolysis of either phenyldiazomethane (**33**) or the sodium salt **34** of tropone tosylhydrazone demonstrated the reversibility of the phenylcarbene rearrangement.[45] This led Baron et al. to predict the formation of styrene and benzocyclobutene as rearrangement products of the three isomeric *o*-, *m*-, and *p*-tolylcarbenes (**35**−**37**), which they confirmed experimentally.[46]

Possible Mechanism

In the originally formulated Baron mechanism, the three isomeric tolylcarbenes interconvert reversibly through bicycloheptatriene and cycloheptatrienylidene intermediates (Figure 4).[46] Gasper et al. proposed an alternative norcaradienylidene walk mechanism (Figure 4).[42c]

The rationale for this mechanism is the inability of the Baron mechanism to account for the different styrene/benzocyclobutene ratios produced from the isomeric tolylcarbenes and to explain the formation of 2,6-dimethylstyrene as a minor product in the gas-phase pyrolysis of 3,4,5-trimethylphenyldiazomethane. The norcaradienylidene walk mechanism provides a route for the rearrangement of *p*- and *m*-tolylcarbenes to styrene without the intermediate formation of *o*-tolylcarbene (Figure 4). In recent pyrolysis studies of deuterated tolyldiazomethanes, Chapman and coworkers observed identical styrene/benzocyclobutene ratios for all isomeric tolyldiazomethanes. They suggested that the apparently anomalous styrene/benzocyclobutene ratio observed for *o*-tolyldiazomethane stems from a hydrogen atom transfer in the *o*-tolyldiazomethane prior to nitrogen loss and carbene formation.[47] This conclusion finds much support in the thermolysis and photolysis of other diazo compounds.[48]

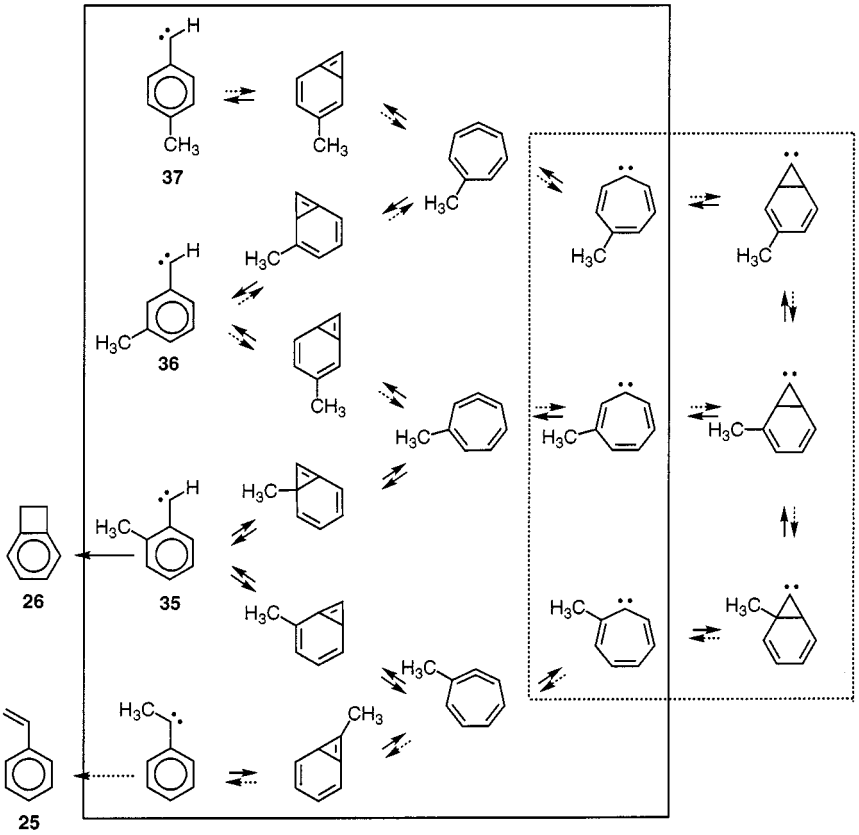
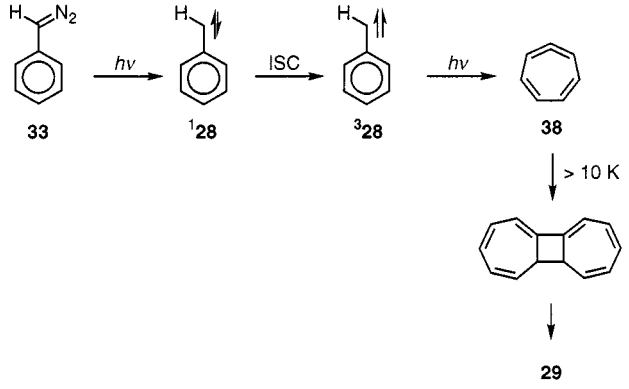


Figure 4. Thermal rearrangement of the three isomeric tolylcarbenes **35**−**37** leading to styrene (**25**) and benzocyclobutene (**26**); the "Baron" mechanism is highlighted in a closed-line frame;[46] the thermal transformation according to a "norcaradienylidene walk" mechanism is shown in a broken-line frame;[42c] the "norcaradienylidene walk" mechanism provides a route for the rearrangement of *m*-tolylcarbene (**36**) and *p*-tolylcarbene (**37**) to **25** without the intermediate formation of *o*-tolylcarbene (**35**) (broken arrows)

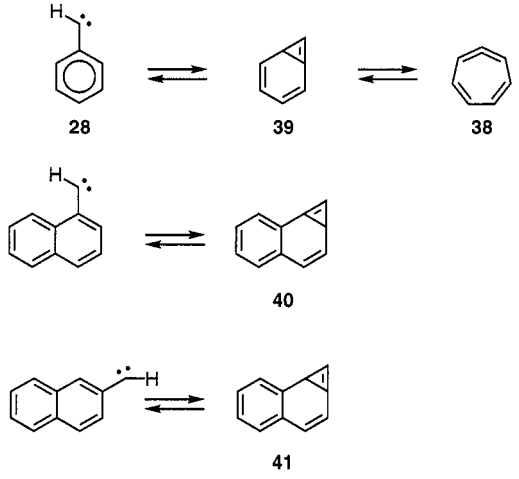
Matrix-Isolation Studies

The involvement of cycloheptatetraene (**38**) in phenylcarbene rearrangements is supported by matrix-isolation experiments.[49] Chapman and co-workers photolyzed matrix-isolated phenyldiazomethane (**33**) at 10 K in argon, which produced triplet phenylcarbene (^{3}**28**) (Scheme 4).[49a,49b] Excitation of ^{3}**28** ($\lambda > 416$ nm) led directly to the highly strained cycloheptatetraene, which was identified on the basis of its characteristic asymmetric allene stretches in the FT-IR spectrum.



Scheme 4

Matrix isolation of the pyrolysis products of phenyldiazomethane confirmed that cycloheptatetraene is the ground state on the C_7H_6 potential energy surface. Rapid dimerization upon warming the matrix prevented the drawing of any mechanistic conclusions regarding the equilibrium between cycloheptatetraene and cycloheptatrienylidene, which plays an essential role in the solution-phase chemistry of both intermediates.[50] The failure to observe spectroscopic evidence for bicycloheptatriene **39** poses questions as to its importance in the phenylcarbene-to-cycloheptatetraene rearrangement.[49b] Nevertheless, high-level ab initio calculations predict its intermediacy.[51] Conclusive spectroscopic evidence for the involvement of bicycloheptatrienes in arylcarbene rearrangements has hitherto only been provided for **40**−**41** in the related naphthylcarbene rearrangement (Scheme 5).[52]



Scheme 5

Inner-Phase Phenylcarbene Rearrangement

A constrictively stabilized cycloheptatetraene provides an opportunity to address some of the aforementioned aspects of the phenylcarbene rearrangement:

- How important is the norcaradienylidene walk in the phenylcarbene rearrangement?
- What is the role of the cycloheptatetraene−cycloheptatrienylidene equilibrium in the solution chemistry of both species?
- How reliable are the recent computational predictions?

Cycloheptatetraene was prepared by means of a photochemical phenylcarbene rearrangement inside the inner phase of hemicarcerand **2**, where it is stable at room temperature, its dimerization being prevented by the surrounding host shell (Figure 5).[6]

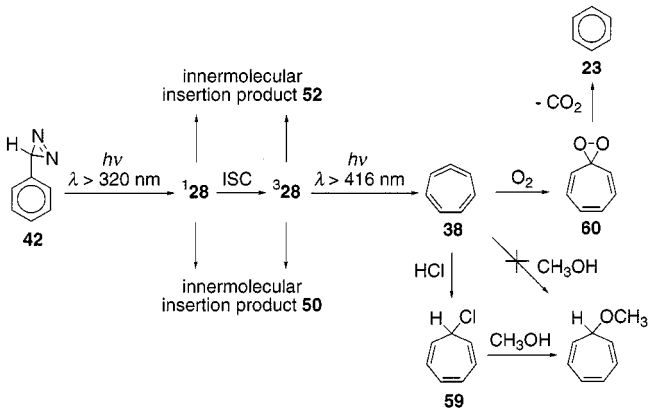
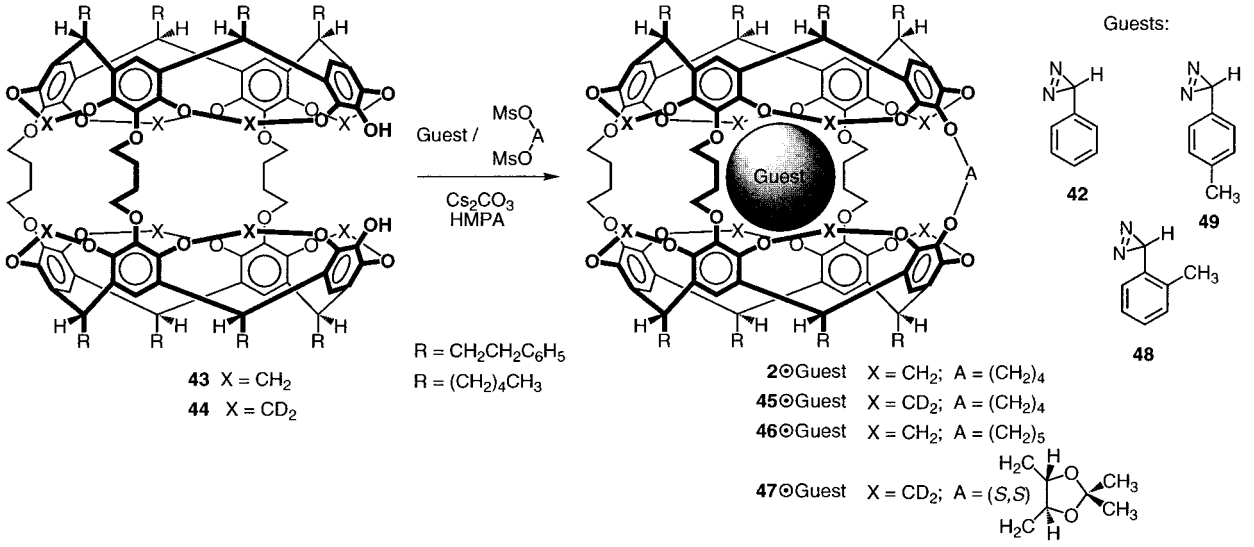


Figure 5. Cycloheptatetraene (**38**) was generated photochemically in the inner phase of hemicarcerands **2** and **45** through a photochemical phenylcarbene (**28**) rearrangement;[6] incarcerated **38** undergoes inner-phase reactions with dioxygen and hydrogen chloride; however, it does not react with bulk-phase methanol

The choice of phenyldiazirine (**42**) as a photochemical phenylcarbene precursor rather than the more frequently used and more easily synthesized phenyldiazomethane (**33**) stemmed from the higher thermal stability of diazirines compared to the diazomethanes. Nevertheless, thermal guest incarceration as described earlier proved to be unsuitable. An alternative procedure for the room-temperature incarceration of guest molecules has recently been developed by Cram and co-workers.[35,53] In this "sealing in" procedure, the tris(bridged) diol **43** is treated with a linker group in the presence of guest in the solvent HMPA, which is too bulky to template hemicarcerand formation. This method has allowed the preparation of several stable aryldiazirine hemicarceplexes, e.g. **2** ⊙ Guest and **45**−**47** ⊙ Guest (Scheme 6).[6,54] The kinked structure of *m*-tolyldiazirine prevented its incarceration to complete the series of isomeric tolyldiazirine hemicarceplexes.[54]

The photochemical generation of cycloheptatetraene from **42** involves the interconversion of three highly reactive intermediates.[49] Photochemical elimination of nitrogen



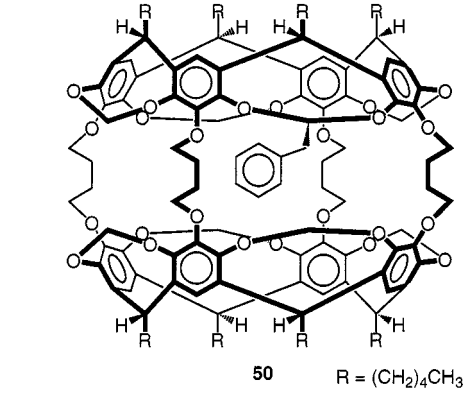
Scheme 6

yields singlet phenylcarbene (^{1}**28**), which undergoes intersystem crossing to give ground-state triplet ^{3}**28**.[56] Excitation of ^{3}**28** yields cycloheptatetraene. However, when a frozen solution of **2** ⊙ **42** was photolyzed at 77 K, the innermolecular insertion product **50** was formed quantitatively as a result of an insertion of transient **28** into an inward-pointing acetal C−H_i bond of **2**.[6]

The high regioselectivity is a consequence of the close proximity of these inward-pointing acetal C−H bonds and the carbene center, and of the high reactivity of these bonds. Thus, the lifetime of phenylcarbene must be rather short in the inner phase, preventing photoexcitation of triplet ^{3}**28**.

After partial deuteration of **2**, a small isotope effect increased the life-time of incarcerated **28** and consequently its probability of undergoing ring expansion, leading to the formation of incarcerated cycloheptatetraene **45** ⊙ **38** in yields of 12% and 30% at 77 K and 15.5 K, respectively. The yield of **45** ⊙ **38** increased further while the extent of C−D insertion decreased when the photolysis was carried out in the presence of a bulk-phase triplet sensitizer. This supports the hypothesis that singlet phenylcarbene preferentially undergoes innermolecular reactions. This is a reasonable assumption since ^{1}**28** is expected to be several orders of magnitude more reactive than ^{3}**28**.[38c]

Surprisingly, photolysis of the *p*-tolyldiazirine hemicarceplex **2** ⊙ **49** at 15.5 K resulted in substantially lower yields of incarcerated 5-methylcycloheptatetraene **2** ⊙ **51** (4%) as compared to **2** ⊙ **38** in the inner-phase phenylcarbene rearrangement (Scheme 7). It is possible that the *p*-methyl group of *p*-tolylcarbene (**37**) changes the inner-phase guest orientation such that the carbene center is closer to an acetal C−H bond. The distance between and the precise mutual orientation of the reacting groups must be very critical to the rate of the innermolecular insertion and hence indirectly to the yield of the ring expansion.



Scheme 7

The slower rate of C−D insertion inside **45** not only increased the yield of ring-expansion product, but also favored other reaction channels of **28**, such as the insertion into a linker C−H bond to yield **52** (Figure 6).[55] The formation of **52** is quite surprising, since the reacting C−H bonds are seen to be pointing away from the inner phase in all X-ray crystal structures of **2** ⊙ Guest and are apparently inaccessible to an incarcerated phenylcarbene on examination of a CPK model.[34,36] Thus, the linker groups must be either conformationally mobile at 77 K or different linker group conformations with partially exposed CH_2 groups are "frozen out" during the rapid cooling of solutions of **45** ⊙ **42** from room temperature to 77 K.

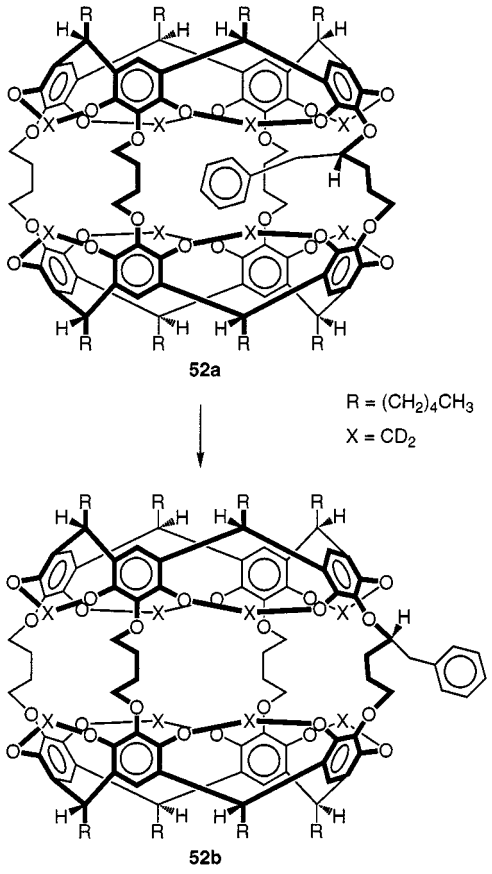
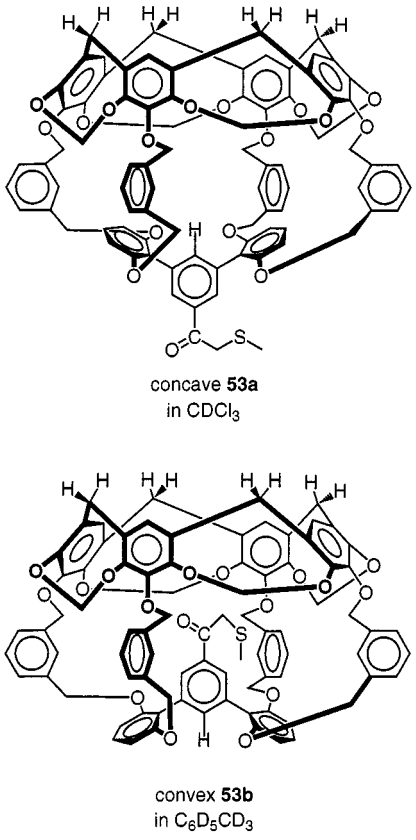
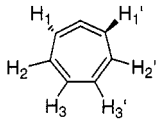


Figure 6. Schematic depiction of an "inside-out" rotation of the innermolecular phenylcarbene insertion product **52**, where the benzyl group rotates from the inner phase (**52a**) through a portal into the bulk phase (**52b**)



Scheme 8



38

Another interesting aspect of **52** is its conformational isomerization, in which the benzyl group undergoes an inside−outside rotation driven by the release of strain (Figure 6). Innermolecular reactions, such as those observed for incarcerated phenylcarbene, allow the covalent attachment of a functionality to the inner surface of a hemicarcerand, which is then constrictively protected. This innermolecularly fixed functional group can either occupy the inner phase as in **50** or can undergo a unimolecular inside−outside rotation as observed for **52**. This conformational isomerization is related to the solvent-dependent conformational isomerization observed for molecular lantern **53**[57] (Scheme 8) and provides an entry into the applications of hemicarcerands as sensory devices or molecular machines.[37]

NMR Characterization of Cycloheptatetraene (38)

One of the most important advantages of the inner-phase stabilization of reactive intermediates is the possibility of applying solution-phase NMR-spectroscopic techniques to characterize the incarcerated guest. The author's group has used 2-D NMR and variable-temperature NMR techniques to probe the guest geometry and dynamics. From the relative NOEs between H(2) and H(1) and H(2) and H(3) in NOESY NMR experiments, the H(1)−H(2)/H(2)−H(3) distance ratio was measured as 1.13 ± 0.01. This distance ratio is important since it provides a calibration point for recent geometry optimizations performed by other groups.[51]

For the same reason, the experimental determination of the relative energies of the postulated intermediates in the phenylcarbene rearrangement and the barriers associated with their interconversion is also important.[58] In particular, the energies of the five different spin states of cycloheptatrienylidene relative to cycloheptatetraene have received much attention (Figure 7).[51] Only one of these spin states has been spectroscopically characterized. Independently, Chapman's[59a] and Wentrup's group[59b] claimed to have observed triplet cycloheptatrienylidene by EPR spectroscopy. Both detected species were found to be metastable in argon below 21 K and disappeared upon warming the matrix, presumably due to a rearrangement of cycloheptatrienylidene to cycloheptatetraene.[51] Unfortunately, the relevant spectra did not match and clearly arose from different species. While the identity of the triplet species detected by Chapman's group has yet to be fully clarified, Wentrup's EPR spectrum shows all the features that one would expect for $^3B_2$-**30**. Of the four remaining spin states, the open-shell

singlet $^1A_2$ has been suggested as the transition state structure for the enantiomerization of chiral cycloheptatetraene.[60] CASSCF calculations predict an enantiomerization barrier of 20.5 kcal/mol,[51c] which is approximately half of the measured barrier for the enantiomerization of allene.[61]

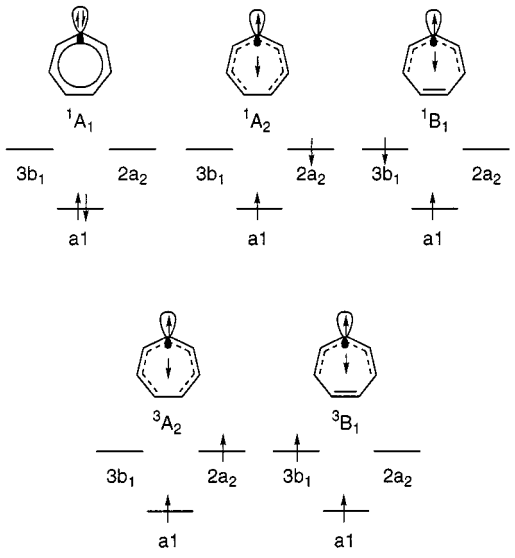
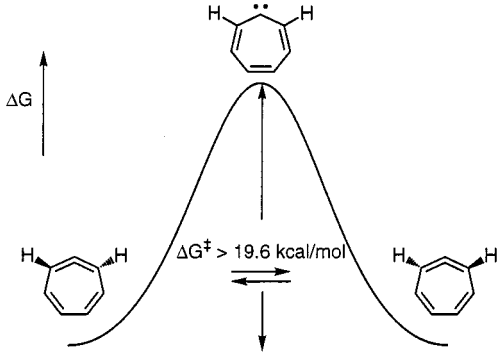


Figure 7. Different electron configurations of all five spin states of cycloheptatrienylidene (**30**);[51c] for clarity, only the HOMO and LUMO are shown; only $^3B_1$-**30** has been characterized spectroscopically[59]

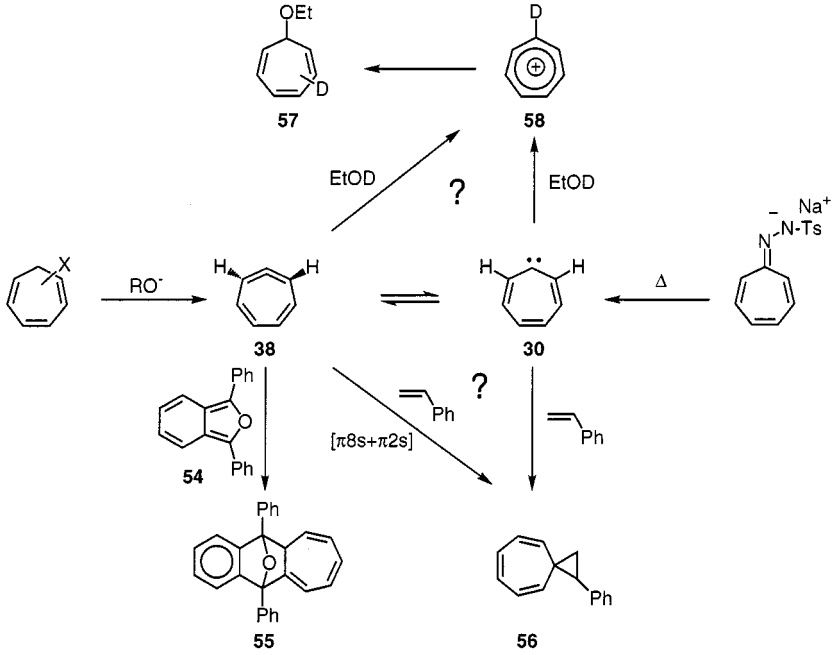
In order to measure this enantiomerization barrier, the author's group generated cycloheptatetraene in the chiral inner phase of hemicarcerand **47**.[55,62] Fortunately, both diastereomeric hemicarceplexes **47** ⊙ (+)-**38** and **47** ⊙ (−)-**38** formed in approximately equal amounts (2:3) and their guest protons H2 showed a small but discernible Δδ value, allowing their differentiation by NMR spectroscopy. Whether the diastereomeric excess results from asymmetric induction in the phenylcarbene ring expansion or from an inner-phase equilibration of the diastereomeric complexes is not clear and requires further investigation. Unfortunately, it proved impossible to induce coalescence of the two signals, even at 100 °C. The absence of line-broadening suggests that the barrier must be higher than 19.6 kcal/mol, which sets a lower limit in agreement with all current calculations (Scheme 9).[51] Although a precise determination of the barrier awaits further experimental investigation, it is remarkable that cycloheptatetraene is sufficiently stable at 100 °C to allow the recording of its ^1H NMR spectrum.



Scheme 9

Inner-Phase Chemistry

The lower limit of the enantiomerization barrier of cycloheptatetraene sheds light on the puzzling chemistry of cycloheptatetraene and cycloheptatrienylidene in solution.[50] Both species have been trapped with various reactants to yield identical trapping products, which is consistent with their rapid equilibration. However, the origin of the reacting species − cycloheptatetraene or cycloheptatrienyli-

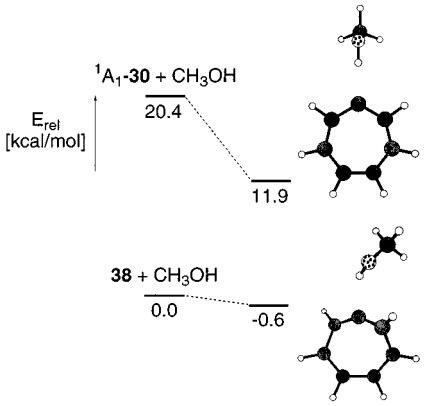


Scheme 10

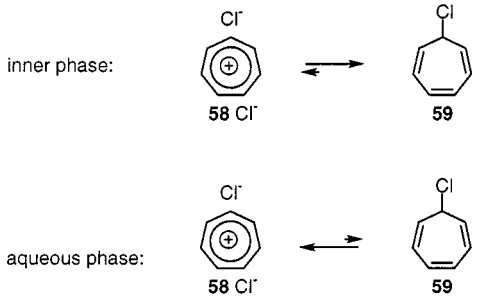
dene − in some of these reactions remains uncertain. This should be demonstrated with the following three examples (Scheme 10).

In the presence of the powerful enophile **54**, the Diels−Alder product **55** is formed, which clearly results from a reaction of cycloheptatetraene.[50a,63] Less clear-cut, however, is the origin of spirocyclopropane **56**, the styrene trapping product.[64,65] Formally, **56** could be formed through a carbene cyclopropanation or an allowed [π2s + π8s] cycloaddition.[66] The lack of optical activity of **56** when optically active cycloheptatetraene is trapped with styrene supports the carbene cyclopropanation route, although Jones et al. admitted that this evidence is weak.[50a] More convincing are the alcohol trapping studies of Kirmse et al.[50b] The formation of ether **57**, in which the deuterium is equally distributed over all seven positions of the ring, requires the intermediate formation of the tropylium ion **58**. Since strained cyclic allenes react with alcohols to yield vinyl ethers,[67] the formation of **57** seemed to give firm evidence for the protonation of **30** from an unfavorable equilibrium with cycloheptatetraene. This interpretation was recently questioned by Waali et al.[68] On the basis of their semiempirical calculations, which show a strong similarity between the HOMO of cycloheptatetraene and that of cycloheptatrienylidene, they believe that in all the reactions discussed above, cycloheptatetraene is the reacting species. The through-shell reaction studies with bulk-phase methanol performed in this laboratory clearly demonstrate that this is only partially true. In particular, alcohols are *not* sufficiently electrophilic to protonate cycloheptatetraene yielding **58**.[6] Incarcerated cycloheptatetraene does not react with bulk-phase methanol, even at elevated temperatures, despite the fact that methanol is small enough to react with incarcerated guests by passing through one of the equatorially located portals of **45** (Figure 5). How can one account for an instantaneous reaction of cycloheptatrienylidene despite the tremendous energetic barrier between cycloheptatrienylidene and cycloheptatetraene? Kirmse and Sluma have already pointed out that a polar medium strongly stabilizes the polar cycloheptatrienylidene as compared to the apolar cycloheptatetraene. The calculated dipole moments of cycloheptatetraene and cycloheptatrienylidene are 0.83 D and 4.03 D, respectively.[69] In ethanol or methanol, we can thus expect a strong stabilization of $^1A_1$-cycloheptatrienylidene. A hydrogen-bonding interaction might stabilize cycloheptatrienylidene even further such that it becomes close in energy to cycloheptatetraene.[70] In fact, DFT calculations predict a 7.9 kcal/mol decrease in the enantiomerization barrier upon formation of a hydrogen bond (Scheme 11).

The nucleophilicity of the HOMO of cycloheptatetraene is clearly demonstrated in the instantaneous reaction of **45** ⊙ cycloheptatetraene with HCl to yield **45** ⊙ cycloheptatrienyl chloride (Figure 5).[6] VT NMR studies of incarcerated cycloheptatrienyl chloride reveal a fast exchange of all seven guest protons at 120 °C in $CDCl_2CDCl_2$, leading to a single resonance at δ = 4.86. The exchange most probably takes place via transiently formed ionic **58**$^+$Cl$^-$, which is in an inner-phase equilibrium with **59** (Scheme 12).[71] In analogy to the marked shift of the inner-phase cycloheptatetraene/cycloheptatrienylidene equilibrium towards the non-polar cycloheptatetraene, the C−Cl bond in cycloheptatrienyl chloride (**59**) has covalent character in the inner phase as opposed to being ionic as in water.[72]



Scheme 11. Stabilization of cycloheptatrienylidene and of cycloheptatetraene upon formation of a hydrogen bond with methanol; relative energies (B3LYP/6-311++G** + ZPVE) are calculated for the BLY3P/6-311G** optimized geometries (**30**, **38**, and CH_3OH) and for the B3LYP/6-31G* optimized geometries (**30**···$HOCH_3$ and **38**···$HOCH_3$ complexes)

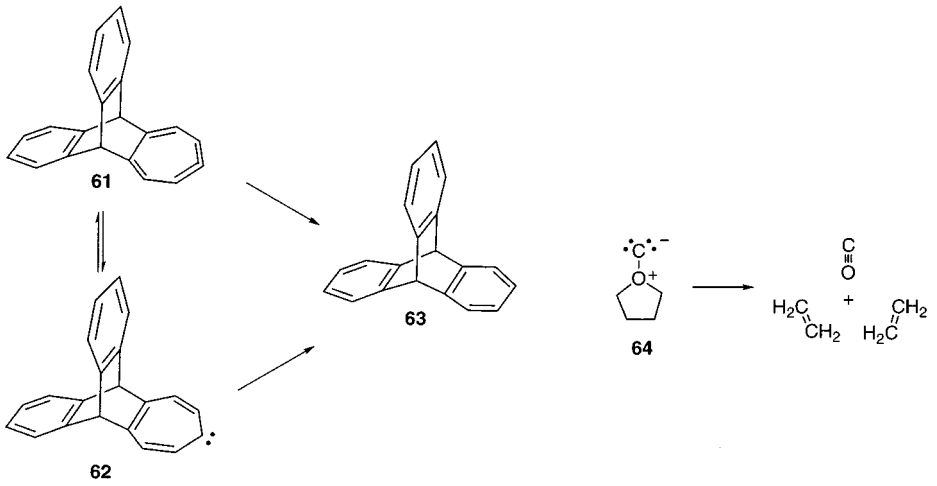


Scheme 12

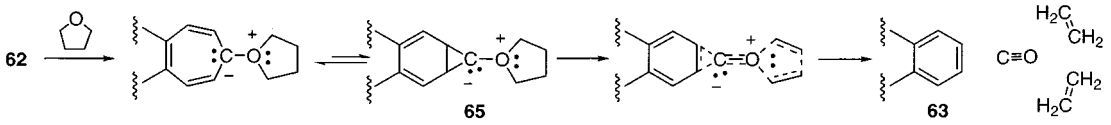
The quantitative formation of **45** ⊙ benzene when **45** ⊙ cycloheptatetraene is exposed to atmospheric oxygen is very surprising (Figure 5). Low-temperature ^{1}H NMR studies revealed the intermediate formation of the spirocyclic dioxirane **60**, which subsequently decomposes unimolecularly to give benzene **23** and CO_2.

Interestingly, Waali et al. reported a related transformation of cycloheptatetraene to arene.[73] When allene **61** or carbene **62** was generated in tetrahydrofuran, triptycene (**63**) was formed in substantial amounts along with other products (Scheme 13). The exact mechanism of this formal carbon extrusion is not clear. An analysis of the evolved gases revealed the presence of CO and ethylene. Waali et al. suggested the possibility of a carbon atom transfer to a nucleophilic THF oxygen atom to produce **64**, which subsequently decomposes with elimination of these gases.

Alternatively, **63**, CO, and ethylene could be formed through a concerted fragmentation of the THF−carbene adduct **65**.



Scheme 13



The inner-phase transformation of cycloheptatetraene to benzene clearly involves a different mechanism, with **60** playing a central role. Although the exact mechanism of the formation of **60** is not clear, two possible mechanistic scenarios will be outlined briefly (Figure 8).

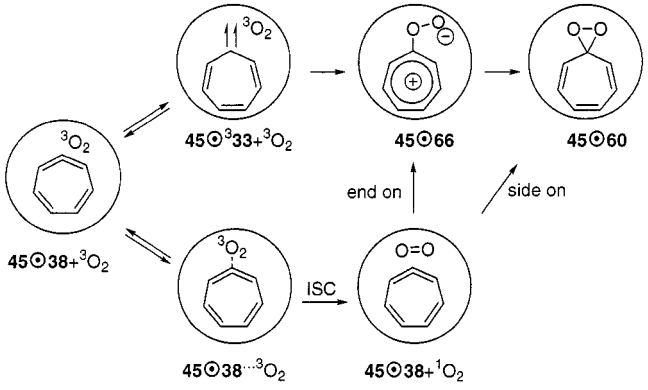
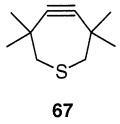
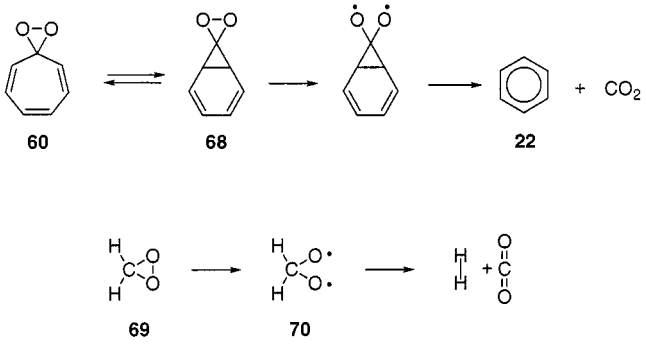


Figure 8. Two different mechanisms for the inner-phase addition of triplet oxygen to cycloheptatetraene (**38**) leading to dioxirane **60**

In the trimolecular hemicarceplex **45** ⊙ **38** + $^3O_2$, cycloheptatetraene could react with triplet oxygen to give tropone oxide **66** either through a pre-equilibrium with the highly reactive ^{3}**30** (e.g. $^3B_1$-**30**) or through a singlet-triplet surface-crossing mechanism. Subsequent thermal rearrangement of **66** would then yield **60**. Alternatively, efficient intersystem crossing of oxygen could take place in a charge-transfer complex **45** ⊙ **38**···$^3O_2$ between **38** and triplet oxygen to produce singlet oxygen, which would then add to **38** to give **60**. This type of thermal singlet oxygen generation was recently discovered by Krebs and Turro in a charge-transfer complex between triplet oxygen and the strained cycloheptyne **67**.[74]



The decarboxylation of **60** most probably involves homolytic cleavage of the O−O bond of norcaradiene followed by the concerted cheletropic extrusion of CO_2. This stepwise mechanism finds support in the similarity of the measured activation barrier for the decarboxylation of **60**[55] and the calculated barrier for the decarboxylation of dioxirane **68** via dioxymethane (**69**) (Scheme 14).[75]



Scheme 14

A key requirement for both of the outlined mechanisms is a sufficiently long lifetime of the trimolecular complex **45** ⊙ **38** + $^3O_2$ to allow a spin inversion of either of the guests. Using CPK models and a simple method for the estimation of the inner-phase volume of **45**, as recently described by Eid, Jr. and Cram,[76] the author's group has estimated an increase of the inner-phase occupancy from 35−45% in **45** ⊙ **38** to about 45−55% in **45** ⊙ **38** + $^3O_2$ upon addition of the second guest. The latter value is closer

to the fraction of occupied space in many solvents and to the optimal space occupancy for the favorable formation of self-assembled molecular capsules.[77,78] Hence, decreasing the inner-phase vacuum will have an entropic advantage that may partially compensate for the high tendency to expel the smaller guest ($^3O_2$) due to the high frequency of guest collisions (billiard-ball effect).[79]

Conclusion

Since their first synthesis by Donald J. Cram and coworkers,[80] molecular container compounds have become an important tool for the investigation of fundamental aspects of structural and mechanistic organic chemistry.[81] Perhaps the most impressive application of containers has been the stabilization of cyclobutadiene, *o*-benzyne, and cycloheptatetraene and the investigation of their properties in solution, as has been described in this review article. The high thermal stability of these imprisoned reactive intermediates demonstrates the advantageous application of inner phases for the stabilization and investigation of molecules with highly strained multiple bonds. One can readily envisage a wealth of reactive species, including cyclic alkynes, allenes, and cumulenes, investigation of which in inner phases should provide new insight into their properties and chemistry.

The concept of molecule protection by incarceration, which has been outlined for organic reactive intermediates, is also very important in nature, notably for the correct folding of many proteins. Evolution has led to a complex pathway for the folding of polypeptides involving chaperonins. Chaperonins such as GroEL provide a ''passive box'', creating an environment equivalent to infinite dilution for the polypeptide substrate inside their central cavities, thereby preventing non-productive aggregation of the substrates.[82] The ongoing investigation of man-made and natural containers and their guests, and the understanding of the interactions between them, will remain a great challenge for physical and organic chemists as well as for biochemists over the next decades and it will provide us with many answers to questions regarding structure and mechanism in both worlds.

Acknowledgments

The author would like to thank all of his co-workers for their efforts to advance this exciting research field. He warmly thanks the National Institute of General Medical Sciences, the Petroleum Research Fund administered by the American Chemical Society and Kansas State University for generous financial support of his research.

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