

Intramolecular Reactions of Fluorophenylcarbene inside a Hemicarcerand

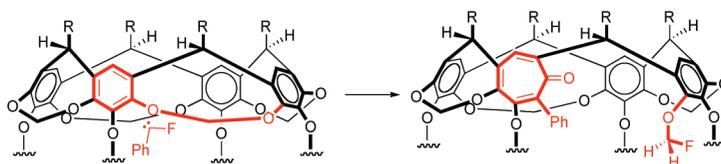
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ABSTRACT

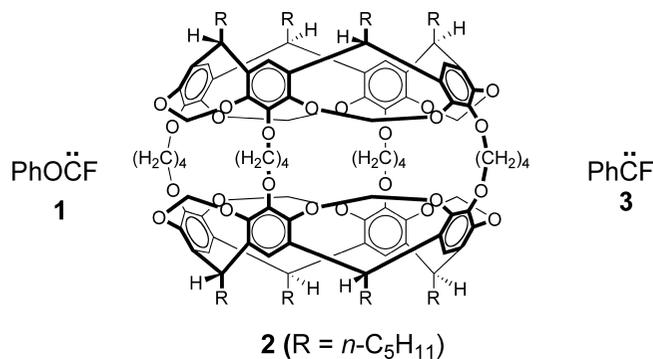


Photolysis of fluorophenyl diazirine, incarcerated in hemicarcerand **2**, affords fluorophenylcarbene, which attacks an aryl unit of the host, leading (after rearrangement) to a fluoromethoxy/phenyltropone derivative of the hemicarcerand. The incarcerated carbene is probably unstable at temperatures above 100 K.

Molecular incarceration can alter the chemistry and lifetimes of reactive intermediates in solution at ambient temperature.¹ Cyclobutadiene,² *o*-benzyne,³ and cycloheptatetraene⁴ are among the evanescent species rendered persistent by entrapment within molecular containers. In the case of carbenes, cyclodextrins, zeolites, and hemicarcerands have been studied as agents of reactivity control. Brinker and Rosenberg, in particular, have focused on cyclodextrins,⁵ observing chemospecific intramolecular reactions of, e.g., adamantanylidene⁶ and chlorophenylcarbene⁷ with their α -cyclodextrin hosts. Cozens and Moya-Barrios found that the lifetimes and reactivity of arylchlorocarbenes generated within the cavities

of alkali metal cation-exchanged zeolites depended on the identity of the zeolite's charge-balancing cations.⁸

In 2005, we reported that the otherwise fleeting fluorophenoxycarbene (**1**)⁹ was persistent and stable for days at ambient temperature when generated inside hemicarcerand **2**, thus permitting detailed NMR studies.¹⁰ Incarceration not only prevented the dimerization of **1** but altered its conformation and reactivity toward water as a consequence of a substantially lowered basicity inside the rigid hydrophobic container molecule **2**.¹⁰



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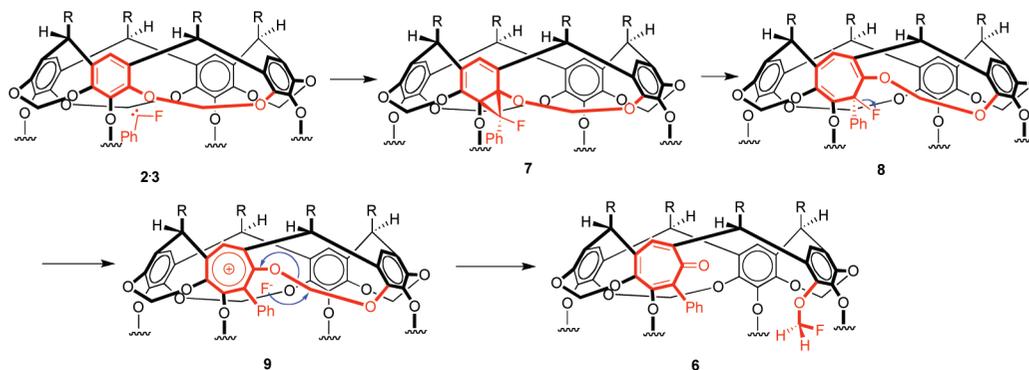
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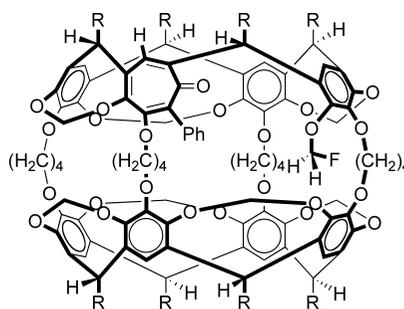
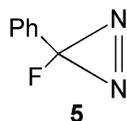
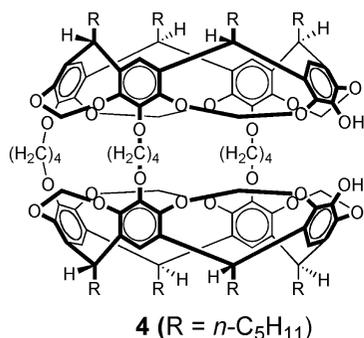
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Scheme 1. Conversion of Hemicarceplex **2**⊙**3** to Product **6** ($R = n\text{-C}_5\text{H}_{11}$)



Kirmse notes that “Taking carbene incarceration to its limits will be a fascinating endeavor.”¹¹ Here we explore the effect of changing the carbene’s substituents on the efficacy of carbene incarceration. Relative to methylene (CH_2), PhOCF (**1**) is stabilized by 59.7 kcal/mol by its PhO and F substituents.¹¹ “Excision” of the oxygen atom converts **1** to fluorophenylcarbene (**3**), where the stabilization relative to CH_2 is reduced by 14 to 45.7 kcal/mol.¹¹ Will the less stable **3** also be persistent when generated within hemicarceplex **2**, or will it undergo innermolecular reactions with its molecular “prison”?

Treatment of diol **4**^{4a} and excess 3-fluoro-3-phenyldiazirine (**5**)¹² with $\text{MsO}(\text{CH}_2)_4\text{OMS}$ ($\text{Ms} = \text{SO}_2\text{Me}$) and Cs_2CO_3 in HMPA gave the hemicarceplex **2**⊙**5** in 28% purified yield.¹³



Photolysis of diazirine **5** in CH_2Cl_2 or 3-methylpentane at 77 K with light of $\lambda > 320$ nm gave the deep blue PhCF , $\lambda_{\text{max}} = 547$ nm,¹⁴ but the color disappeared upon continued irradiation. However, in ethereal solvents such as anisole,

2-methyltetrahydrofuran, or diethyl ether, the color was stable to extended irradiation at 77 K. Similarly, photolysis of the colorless hemicarceplex **2**⊙**5** in CH_2Cl_2 at 77 K gave a deep blue-colored material, presumably **2**⊙**3**. The color was stable to further irradiation but bleached upon warming to ~ 100 K. We interpret these results to suggest the formation of transient complexes between PhCF and oxygen-containing solvents or hemicarceplex **2**, which deactivate the carbene’s excited state and render it photostable at temperatures below 100 K. The insolubility of **2**⊙**5** in common low temperature organic glasses prevented detailed spectroscopy of **2**⊙**3**.

¹H, ¹³C, and ¹⁹F NMR studies at -80 °C or above gave no evidence for the incarcerated carbene **2**⊙**3**. Instead, the spectra support compound **6** as the product of the reaction of PhCF with hemicarceplex **2**.¹³ The reaction conducted at 77 K, followed by warming to ambient temperature, gave **6** in 55% isolated yield; the NMR yield was similar.

A mechanistic rationale for the formation of hemicarceplex derivative **6** is presented in Scheme 1. The incarcerated PhCF of **2**⊙**3** adds to one of the tris-alkoxy activated aryl units of **2**, yielding the norcaradiene derivative **7**, which opens to the cycloheptatriene unit of hemicarceplex **8**.¹⁵ Next, ioniza-

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(13) See Supporting Information for experimental details and spectra.

(14) Similar observations of PhCF ($\lambda_{\text{max}} = 550$ nm at 13 K in a nitrogen matrix) have been reported: Zuev, P. S.; Sheridan, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 9381.

(15) Calculations at the B3LYP/6-31G(d) level indicate that the addition of PhCF to 1,2,3-trimethoxybenzene (a model for hemicarceplex **2**) at the C(1)–C(2) “double bond” requires 14.7 kcal/mol of activation energy and affords the corresponding norcaradiene with an exothermicity of 27.6 kcal/mol. Further reactions of the norcaradiene afford a tropone with an additional exothermicity of 16.1 kcal/mol. A reaction/enthalpy scheme appears in Supporting Information.

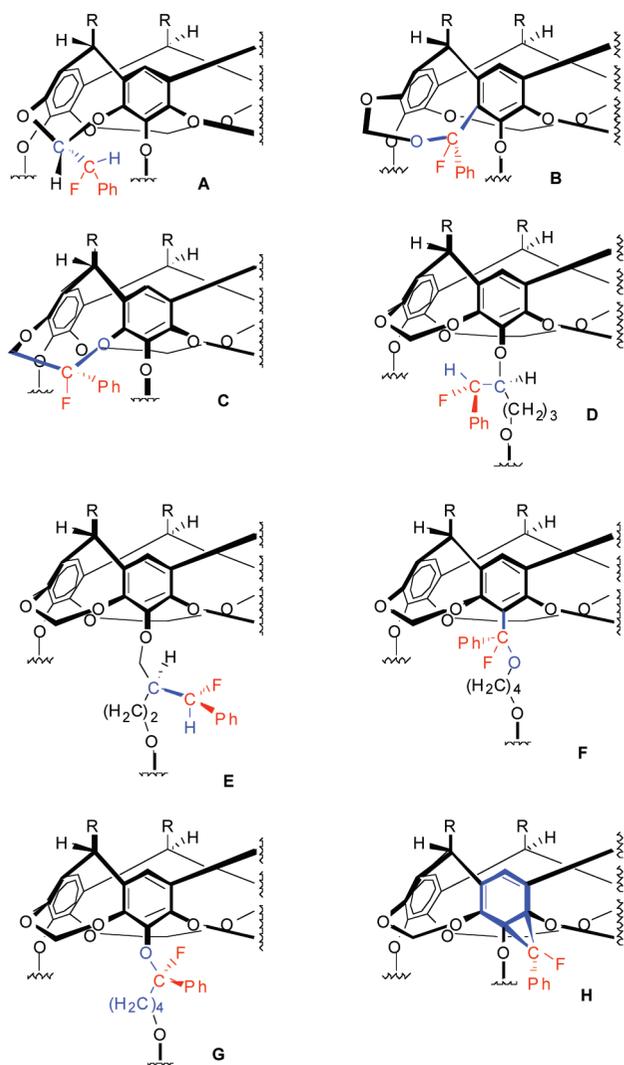


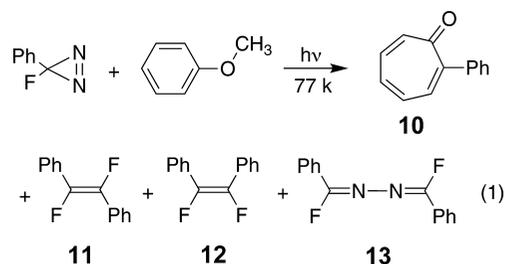
Figure 1. Partial structures of all possible primary reaction products between incarcerated PhCF and hemicarcerand **2**: C–H insertions (**A**, **D**, **E**), C–O insertions (**B**, **C**, **F**, **G**), and aryl cyclopropanation (**H**). The carbene fragment and the reactive functional group of **2** are highlighted in red and blue, respectively.

tion affords the tropylium ion derivative **9** and fluoride ion as a tight ion pair. Subsequent S_N2 attack of the fluoride at an adjacent dioxymethylene unit furnishes the tropone hemicarcerand derivative **6**, which also bears a fluoromethoxy substituent. Alternatively, there may be a more or less concerted process that does not involve complete ionization.

To elucidate the structure of **6** and its mode of formation, we first note that PhCF can react with **2** in only eight different ways (see Figure 1), of which several have been observed in other carbene hemicarceplexes.^{4a,b,d} These are insertions into C–H (**A**), $C_{\text{aryl}}\text{--O}$ (**B**), or $C_{\text{acetal}}\text{--O}$ (**C**) bonds of the spanners; insertions into $C_{\alpha}\text{--H}$ (**D**), $C_{\beta}\text{--H}$ (**E**), $C_{\text{aryl}}\text{--O}$ (**F**), or $C_{\alpha}\text{--O}$ (**G**) bonds of the linkers; or cyclopropanation of an aryl unit (**H**), which as one of us has shown earlier^{4d} is only possible at the C1–C2 or C1–C6 bond. Other reactions are impossible due to the rigidity of the host.

Each of the possible innermolecular reaction products will show a few unique NMR-spectroscopic features that may be used to uncover its identity and to exclude other possibilities. We employed the following observations in this analysis: (1) The ^1H and ^{13}C NMR spectra of **6** are consistent with a C_1 symmetric product. (2) In the ^{19}F NMR, the fluorine of **6** resonates at $\delta_{\text{F}} = -150.55$ ppm as a doublet of doublets ($^2J_{\text{HF}} = 57.4, 51.7$ Hz) and couples to two diastereomeric methylene protons, H_1 and H_2 . The latter give cross correlations to each other in the TOCSY of **6** but not to other host protons (see Supporting Information). This automatically excludes C–H insertions (**A**, **D**, **E**), $C_{\text{aryl}}\text{--O}$ insertions (**B**, **F**), and linker $C_{\alpha}\text{--O}$ insertion (**G**) as possible reaction modes of incarcerated PhCF. (3) The ^{13}C NMR spectrum shows a uniquely downfield shifted signal at $\delta_{\text{C}} = 190.27$ ppm, which we assign to the tropone carbonyl of **6** and which cannot be rationalized with a linker $C_{\alpha}\text{--O}$ insertion product. This leaves cyclopropanation (**H** in Figure 1) as the only reaction channel for PhCF, consistent with the observed reactivity of *p*-tolylcarbene inside the same hemicarcerand.^{4d} Cyclopropanation by PhCF is then followed by rearrangement to **6**, as detailed in Scheme 1.

Precedent for this sequence can be found in the dichlorocarbene-induced transformations of methoxy-aromatics to chlorotropones.¹⁶ Moreover, in a model reaction, photolysis of diazirine **5** in anisole at 77 K, followed by warming to 25 °C, gave 17% of 2-phenyltropone (**10**),¹⁷ as well as carbene dimers **11** (4%) and **12** (6%), and azine **13** (6%, from attack of PhCF on diazirine **5**); cf. eq 1.



The conversion of anisole to 2-phenyltropone upon reaction with photogenerated PhCF can be rationalized by a mechanism analogous to that of Scheme 1. As expected, the carbene dimers and azine **13** were the only products obtained when diazirine **5** was photolyzed in CH_2Cl_2 or pentane in the *absence* of anisole.

The attack of incarcerated PhCF on its hemicarcerand host, which proceeds rapidly even at very low temperatures, stands in dramatic contrast to the stability of similarly incarcerated PhOCF, which persists for days at ambient temperature.¹⁰ Clearly, the 14 kcal/mol reduction in substituent stabilization of PhCF relative to PhOCF has a major impact. PhCF is too reactive to persist within hemicarcerand **2**, whose walls are constructed of alkoxy-activated aryl units.¹⁸ Combined with the results of an earlier investigation of the innermolecular

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chemistry of tolylcarbenes, our work suggests that singlet carbenes prefer addition to the aryl units of hemicarcerand **2**, whereas triplet carbenes preferentially attack the inward pointing C–H bonds.^{4a,b,d} Perhaps an “umpolung” of the electronic properties of the cavitands, e.g., through metalation of the outer arene faces,¹⁹ might afford carcerands with greater resistance to attack by singlet carbenes.

From the viewpoint of effective carbene incarceration, the substituent change of PhO to Ph, which converts PhOCF to PhCF, results in an excessive decrease in carbenic stability and an unacceptable increase in carbenic reactivity. An alternative substituent change for PhOCF would be F to Cl, i.e., PhOCF to PhOCl. The stabilization energy of PhOCl relative to CH₂ can be calculated¹¹ as 53.6 kcal/mol, only ~6 kcal/mol less than the stabilization energy of PhOCF. The possible persistence of PhOCl inside hemicarcerand **2** thus becomes a matter of future experimental interest.

(18) Not surprisingly, the even less stabilized phenylcarbene (PhCH) also attacks the hemicarcerand; cf. ref 4.

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In conclusion, photolysis of fluorophenyldiazirine, incarcerated in hemicarcerand **2**, affords fluorophenylcarbene, which attacks an aryl unit of the host, leading (after rearrangement) to a fluoromethoxy/phenyltropone derivative of the hemicarcerand. From our NMR studies, the incarcerated carbene **2**⊙**3** is definitely unstable at temperatures above –80 °C, while the color bleaching experiment reported above suggests that **2**⊙**3** is probably unstable at temperatures above 100 K.

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Supporting Information Available: Preparative details for hemicarceplex **2**⊙**5**, photolysis experiments and product studies, enthalpy scheme and computational studies, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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