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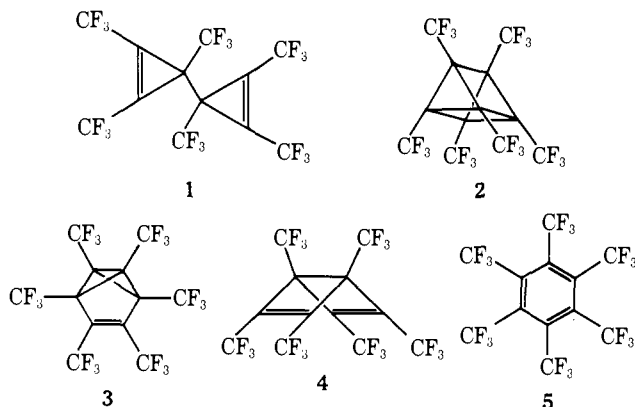
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Perfluorohexamethylbicyclopropenyl

Sir:

We wish to describe a synthesis and some chemistry of the title compound (**1**), the final member of the first complete set of benzene valence isomers.^{1,2} This family is shown below, numbered in order of diminishing energy content.^{2b,3}

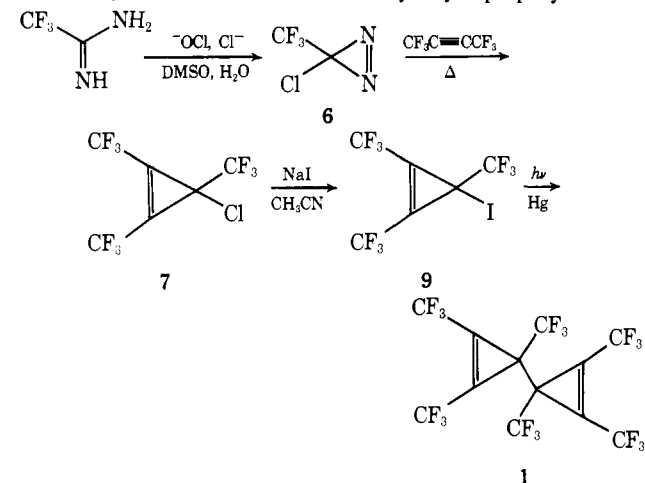


The synthetic strategy entailed coupling of a suitably functionalized perfluoro-1,2,3-trimethylcyclopropene, prepared in turn via addition of a carbene to perfluoro-2-butyne (PFB).

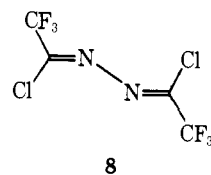
Dehydration⁶ of trifluoroacetamide followed by addition of ammonia⁷ to the resulting trifluoroacetonitrile gave trifluoroacetamidine.⁸ Oxidative cyclization of trifluoroacetamidine by the method of Graham⁹ (hypochlorite and chloride ion in aqueous dimethyl sulfoxide) gave diazirine **6** in 45% overall yield from trifluoroacetamide (Chart I). Chlorotrifluoromethyl-1-diazirine¹⁰ is a gas (bp -19 to -18°) with the following spectroscopic features:¹¹ ir 1590, 1290, 1210, 960, 730 cm^{-1} ; uv¹¹ 318 nm; NMR δ 18.37 (singlet); MS 114. The corresponding bromodiazirine was prepared in similar fashion by substitution of bromide for chloride ion in the Graham reaction.

When the chlorodiazirine¹³ was decomposed in the gas phase at 120° in a large excess of PFB, two products resulted. That of shorter glc retention time was the desired chlorocyclopropene **7** (bp 42° ; ir 1890, 1300, 1230, 1200, 1180, 1040, 910, 790, 730 cm^{-1} ; NMR δ 7.59 (quartet) and 18.58 (septet), $J = 0.7$ Hz; MS 278). The product of longer

Chart I. Synthesis of Perfluorohexamethylbicyclopropenyl



retention time (ir 1630, 1270, 1220, 1180, 1010, 990, 750 cm^{-1} ; NMR δ 17.16 (singlet); MS 260) proved to be the azine **8**, formed probably by carbene attack on diazirine.¹⁴ Since the azine was a major product even in the presence of



a 30-fold excess of PFB, it is clear that addition of the electron-deficient carbene to the electron-deficient acetylene is not a facile process. To solve this problem, a stirred gas-phase reactor operating at 200° was charged with PFB (~ 0.5 atm), and diazirine was bled in very slowly from a reservoir maintained at ~ 1 atm with a carbon tetrachloride slush bath. The diazirine decomposed rapidly at 200° , with the result that its steady-state concentration in the reactor remained very low. Consequently, the azine/cyclopropene ratio dropped to ~ 0.05 with PFB/diazirine ratios of ~ 4 . With this technique, pure **7** was obtained in 56% yield after GLC purification.

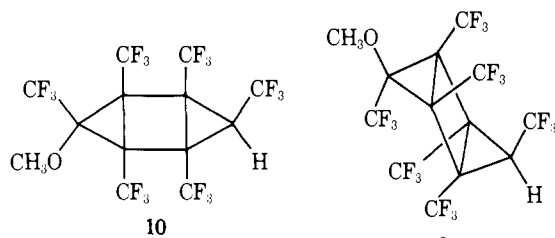
For coupling attempts to make the bicyclopropenyl, the iodocyclopropene (**9**) offered distinct advantages over its chloro counterpart. Nucleophilic displacement of the chlorine of **7** by iodide ion took place rapidly in solution at room temperature; the reaction also proceeded quite cleanly when gaseous chlorocyclopropene was contacted at 150° with excess sodium iodide supported on Chromosorb W. The last fact, together with the observation that methanolysis of **7** was fast even in dilute cyclohexane solution, argues strongly against the intermediacy of perfluorotrimethylcyclopropenium ion.¹⁶ Displacement by iodide ion presumably occurs via an $\text{SN}2'$ process or even via a carbanion intermediate.¹⁷ The iodocyclopropene, prepared in acetonitrile in 77% yield (GLC purified), was characterized by these properties: bp 71° ; ir 1900, 1300, 1280, 1230, 1200, 1180, 1030, 870, 780, 710 cm^{-1} ; uv 256 nm; NMR δ 8.39 (quartet, 6 F) and δ 15.45 (septet, 3 F), $J = 0.8$ Hz; MS 370.

Photolysis of **9** in the presence of mercury¹⁸ in the gas phase at $\sim 100^\circ$ with a Pyrex-filtered medium-pressure mercury arc gave **1** in 84% yield after GLC purification. The fluorocarbon sublimes readily, yielding beautiful colorless radial clusters, mp 72.5 – 73.5° (ir 1890, 1290, 1230, 1220, 1200, 1180, 1160, 1050, 1010, 900, 820, 790, 700, 690 cm^{-1} ; uv < 190 nm;¹⁹ NMR δ 6.01 (septet, 12 F) and δ 13.10 ("tridecal",²⁰ 6 F), $J = 1.6$ Hz; MS 486²¹).

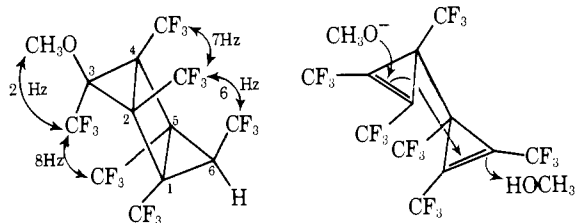
The thermal stability of perfluorohexamethylbicyclopropenyl is remarkable: it aromatizes cleanly with $t_{1/2} \geq 2$

h at 360°. ²² Hence the thermodynamically least stable member of the valence isomer set is by a wide margin the most stable kinetically. ^{1,2} Gas-phase photolysis of **1** with the full mercury arc produces a mixture containing all five of the valence isomers, ²³ together with unidentified by-products.

In the presence of triethylamine, methanol adds to **1** extremely rapidly, yielding a single stereoisomer of structure **10**. (GLC separation gave colorless rhombs, mp 135.0–136.5°, with the following spectral characteristics: ν_{IR}^{24} 1350, 1280, 1250, 1170, 1120, 1010, 990, 970 cm^{-1} ; NMR ²⁵ δ 2.70 (septet, 3 F), δ 2.49 (doublet of septets, 3 F), δ 6.56 (quartet, 6 F), and δ 11.31 (quartet, 6 F), *J*'s shown below; MS 518. This adduct was assigned the configuration **10a** on the basis of NMR analysis, assisted by spin decou-



pling, and chemical considerations. Of the eight stereoisomers possible for **10**, the four incorporating *syn*-tricyclohexane geometry are eliminated by the small size of the coupling constant (<1 Hz) between the C₁ and C₂ (also C₄ and C₅) CF₃ groups. Endo,exo and exo,endo isomers having



the anti skeleton are ruled out by the fact that the C₃ and C₆ CF₃ groups are coupled to *different* pairs of CF₃'s. Our preference for exo,exo (**10a**) over endo,endo stereochemistry rests principally on the mechanistic argument that stereospecific twofold antarafacial addition across the double bonds of **1** is much more likely than the twofold suprafacial addition which would be required to create the endo,endo adduct. ²⁶ Formation of **10a** may, but need not, occur in a fully concerted manner as shown.

Simple addition of methanol across a single cyclopropene double bond is a highly exothermic transformation, but one can estimate that the reaction leading to **10a** releases roughly 20 kcal/mol *more* energy despite the formation of a new strained ring. ²⁷ Given the close proximity of the double bonds in a bicyclopropenyl and the favorable energetics of reactions which link them, we expect transformations of this type to become a salient feature of bicyclopropenyl chemistry. ²⁸ Surprisingly, this energy-rich class of compounds is still thinly populated, and exploration of its chemistry has only recently gathered momentum. ³¹

Acknowledgment. The authors are pleased to acknowledge very helpful discussions of NMR spectra with Professor Robert Ditchfield and generous financial support from both the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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- The strain energy of cyclopropene is 53 kcal/mol, ⁴ while that of prismane is estimated to be 106–110 kcal/mol. ⁵ When account is taken of the \approx 20-kcal/mol energy difference between an unstrained C–C double bond and two unstrained single bonds, it becomes clear that bicyclopropenyl should lie \approx 40 kcal/mol above prismane. Allowing generously for disparities between parent and perfluoroalkyl-substituted systems, one can still conclude that **1** has by far the highest energy content in the set.
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- The trifluoroacetamide was prepared by gaseous addition of trifluoroacetone to liquid ammonia, a modification of Brown's procedure, and used immediately after evaporation of the ammonia followed by three freeze (–30°)–pump–thaw cycles.
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- The diazirine deserves care in handling, as it has detonated on rare occasions.
- All ir and uv data are from gaseous samples, and the ¹⁹F NMR data are presented in ppm *upfield* from hexafluoro-2-butyne unless otherwise noted. MS data are parent ions. Mass spectral points of interest will be noted separately.
- The gas-phase uv spectrum exhibits a highly structured absorption band between 300 and 340 nm, the 318-nm maximum being the most intense.
- Another source of CF₃CCl has been described, viz. C₆H₅HgCClBrCF₃: D. Seyferth and D. C. Mueller, *J. Am. Chem. Soc.*, **93**, 3714 (1971).
- Pyrolysis of other diazirines, notably perfluorodimethyldiazirine, ^{15a} also affords azines. Since certain diazirines isomerize to diazo compounds, ^{15b} azine **8** might form via attack of carbene on the acyclic isomer. In the case of perfluorodimethyldiazirine, however, there is convincing evidence to the contrary. ^{15a}
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- In this regard, there is no evidence for equilibration of the CF₃ groups of either **7** or **9** on the NMR time scale even in acetonitrile (ϵ 38.5).
- For a discussion of the stability of highly fluorinated carbanions, see R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, Chapter 4.
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- End absorption tails out to \sim 220 nm.
- Only 11 of the 13 lines have been observed, but the outermost two should be only $\frac{1}{2}$ as intense as their weak nearest neighbors.
- A major feature in the mass spectra of the cyclopropene derivatives (**1**, **7**, and **9**) is an ion of *m/e* 243, presumably perfluorotrimethylcyclopropenium ion. Even diazirine **6** yields the corresponding ion C₂F₃N₂⁺, but there is less reason in this case to be confident that the ion is cyclic.
- For evidence regarding the mechanism of thermal aromatization of bicyclopropenyls, see R. Weiss and S. Andrae, *Angew. Chem., Int. Ed. Engl.*, **12**, 150, 152 (1973); G. B. Schuster, N.J. Turro, R. G. Bergman, K. J. Shea, and J. H. Davis, *J. Am. Chem. Soc.*, **97**, 4758 (1975), and references contained therein; K. J. Shea, J. H. Davis, and R. G. Bergman, submitted for publication.
- Photoisomerization of **1** is sufficiently sluggish that preliminary attempts to determine the sequence in which the other four members of the set appear have been unrewarding. For a discussion of the mechanism of photoaromatization of bicyclopropenyls, see R. Weiss and H. Kolbl, *J. Am. Chem. Soc.*, **97**, 3222, 3224 (1975).
- IR data were obtained in chloroform.
- The ¹⁹F NMR data, obtained in trichlorofluoromethane, are presented in ppm *downfield* from external trifluoroacetic acid. All of the remaining couplings for structure **10a** are small (less than 1 Hz).
- This reaction is, in a sense, a simple anionic counterpart of the highly stereoselective cationic polyolefin cyclizations studied by Johnson's group and others. See, for example, W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *J. Am. Chem. Soc.*, **96**, 3979 (1974).
- The strain energy of cyclopropene matches almost exactly that of bicyclopentane; ⁴ the \approx 20 kcal/mol is once again the bond energy disparity between C=C and 2(C–C). The fact that the heats of isomerization of hexamethylprismane and perfluorohexamethylprismane to the respective Dewar benzenes are virtually identical ^{2b} lends credence to the assumption that this \approx 20-kcal/mol disparity is characteristic of perfluoroalkyl-substituted systems as well as hydrocarbons.
- Indeed, such a cyclization was postulated by Breslow to explain the amide ion catalyzed aromatization of hexaphenyl- and 1,1',2,2'-tetraphenylbicyclopropenyl. ²⁹ Cationic attack (Ag⁺) on bicyclopropenyls normally leads to ring opening followed by solvent interception or rearrangement, ³⁰ but anionic and perhaps free radical attack should commonly result in linking of the three-membered rings.
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- In addition to references already cited, see I. J. Landheer, W. H. deWolf, and F. Bickelhaupt, *Tetrahedron Lett.*, 349 (1975); W. H. deWolf, I. J. Landheer, and F. Bickelhaupt, *ibid.*, 17 (1975); I. J. Landheer, W. H. deWolf, and F. Bickelhaupt, *ibid.*, 2813 (1974); R. Weiss and H. P.

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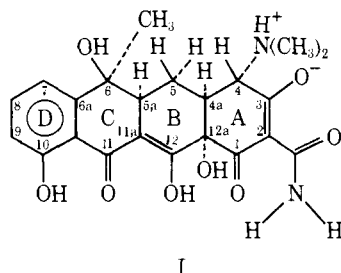
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Effect of Added Electrolyte on the Binding of Tetracycline to Paramagnetic Ion Probes. A ^{13}C and ^1H Nuclear Magnetic Resonance Study

Sir:

Previous investigations of the site of metal binding in tetracycline base (I, abbreviated TC) and its derivatives by proton^{1,2} and carbon-13³ NMR, using $\text{Me}_2\text{SO}-d_6$ as a solvent, strongly indicate binding occurs primarily at the tricarbonylmethane function of ring A. However, these results are not in agreement with a number of binding site studies on tetracycline carried out by others. For example, results of a carbon-13 NMR study of TC·HCl by Asleson⁴ in 50:50 (v/v) $\text{Me}_2\text{SO}-d_6$: D_2O in the pH range 8.0–9.5 suggests that binding involves the C_{11} – C_{12} β -diketone site. In Asleson's work TC·HCl was titrated with NaOH to the desired pH, thereby generating NaCl in a 1:1 mole ratio with TC. In an effort to resolve the apparent discrepancy, we have conducted experiments to determine what effect the solvent and/or the presence of electrolytes have on the nature of metal binding in TC.



Asleson and Frank have made complete assignments of the carbon-13 NMR spectra of TC and several of its derivatives in $\text{Me}_2\text{SO}-d_6$ and in D_2O .⁵ Spectra in $\text{Me}_2\text{SO}-d_6$ / D_2O mixtures show better signal separations than in either solvent alone, especially in the carbonyl region and in the aliphatic region at high field (see Figure 1A). In the present study a 70:30 (v/v) $\text{Me}_2\text{SO}-d_6$: D_2O solvent mixture was used. Solutions 0.3 M in TC can be prepared in this medium, thus enabling good spectra to be obtained in approximately 75 min.⁶ The apparent pH was maintained in the 7.0–7.5 range throughout the experiments by addition of small amounts of NaOH dissolved in the same solvent mixture.⁷ After recording the spectrum of TC, small portions of a 0.3 M solution of $\text{Nd}(\text{NO}_3)_3$ in the same solvent mixture were added to the sample tube such that Nd^{3+}/TC mole ratios were 0.018, 0.050, and 0.091. A spectrum was recorded at each of these ratios. Another series of spectra was recorded in the presence of $\text{La}(\text{NO}_3)_3$ at the same mole ratios to test for effects of a diamagnetic ion binding at the same site as Nd^{3+} .

As discussed previously,³ short-range dipolar interactions between the paramagnetic Nd^{3+} ion and ^{13}C nuclei of TC cause selective broadening for nuclei near the binding site. Examination of the differences in spectra recorded at the same Nd^{3+}/TC and La^{3+}/TC mole ratios reveal those per-

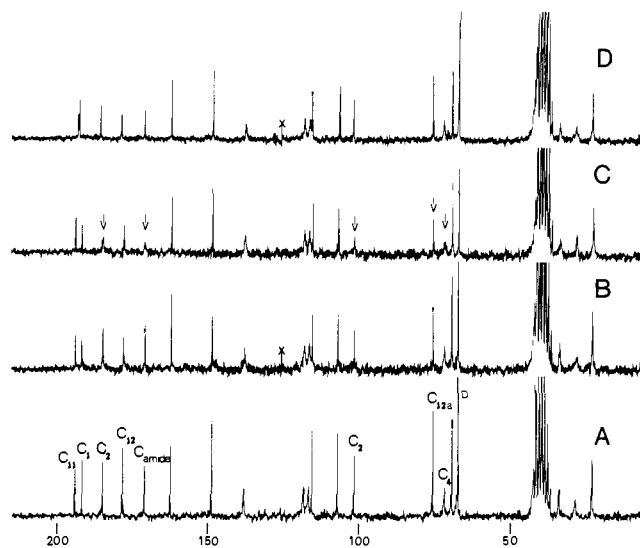


Figure 1. Carbon-13 NMR spectra of TC in 70:30 (v/v) $\text{Me}_2\text{SO}-d_6$: D_2O at pH 7.0–7.5. (A) No metal ion added; (B) $\text{La}^{3+}/\text{TC} = 0.05$; (C) $\text{Nd}^{3+}/\text{TC} = 0.05$; (D) $\text{Nd}^{3+}/\text{TC} = 0.05$ and $\text{Na}^+/\text{TC} = 1.0$. The scale is in ppm; the dioxane reference signal is labeled D; arrows point out signals selectively broadened.

Table I. Transverse Relaxation Times^a for Carbon-13 Resonance Signals in the Presence of Nd^{3+} and La^{3+}

Signal	T_2 , $\text{La}^{3+}/\text{TC} = 0.050$, s	T_2 , $\text{Nd}^{3+}/\text{TC} = 0.050$, s
C_3	0.081	0.025
C_{amide}	0.11	0.016
C_2	0.078	0.043
C_{12a}	0.099	0.060
C_4	0.026	0.020

^a Obtained from line width measurements on expanded-scale spectra. Errors are estimated to be 5–10%.

turbations arising solely from the paramagnetism of Nd^{3+} . Figures 1B and 1C compare spectra taken in the presence of Nd^{3+} and La^{3+} at $\text{M}^{3+}/\text{TC} = 0.050$. Selective signal broadening in the presence of Nd^{3+} occurs for resonances assigned to C_3 , the amide C, C_2 , C_{12a} , and to a slight extent for C_4 . The extent of broadening increases with increasing mole fraction of Nd^{3+} . Selective broadening of these signals may be shown quantitatively by comparing differences (Nd^{3+} vs. La^{3+}) in their T_2 values shown in Table I. These T_2 values were obtained from line-width measurements and include field inhomogeneity broadening. Signal shifts are all less than 0.3 ppm. Selective broadening of these same signals in the presence of Nd^{3+} occurs also for TC in 100% $\text{Me}_2\text{SO}-d_6$. It must be concluded that there is no significant solvent effect on the site of binding and that binding occurs primarily at the ring A tricarbonylmethane function, at least for lanthanide series ions under these conditions. The selective effect of Nd^{3+} on T_2 for C_{12a} is larger than expected for binding at this site and may indicate a contribution from scalar coupling. A more precise location of the metal ion would be possible using accurate T_1 values if contributions from ligand exchange and outer-sphere relaxation mechanisms could be determined.^{8,9}

The effects of the presence of NaCl were determined by dissolving a sufficient amount of NaCl in the solution having a 0.050 mole ratio of Nd^{3+}/TC to give a 1:1 mole ratio of $\text{NaCl}:\text{TC}$. The carbon-13 NMR spectrum of this sample is shown in Figure 1D. Comparison of Figures 1C and 1D shows that the addition of NaCl has a remarkable effect on the spectrum of TC in the presence of Nd^{3+} . Signals which were selectively broadened by Nd^{3+} sharpen to line widths