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A Remarkably Specific π-Mediated Rearrangement of Benzocyclobutenylfluorocarbene

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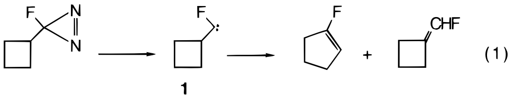
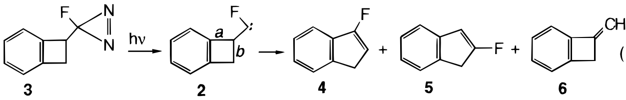
Laser flash photolysis (LFP) has engendered a renaissance in the study of alkyl-substituted carbenes.[1] We have focused on rearrangements of alkylhalocarbenes, where singlet ground states simplify the products and kinetic analysis.[1a,2] Of particular interest is cyclobutylfluorocarbene (**1**), where 1,2-C and 1,2-H rearrangements are competitive, respectively affording cyclopentenyl- and methylenecyclobutane products in a ratio of 3.4:1 and in >90% yield (eq 1).[2a,b] LFP afforded the absolute rate constants $k_c = 1.8 \times 10^6\ s^{-1}$ and $k_H = 5.3 \times 10^5\ s^{-1}$ for these processes.[2a,b]



(1)

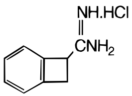
The present investigation began with a seemingly simple inquiry: how would benzannelation of **1** affect the competitive rearrangements, noting as well that benzocyclobutenylfluorocarbene (**2**) has two available distinct 1,2-C migrations (eq **2**)?



(2)

Thus, carbene **2** could undergo a "phenyl" 1,2-C shift (bond a) to **4**, a "benzyl" 1,2-C shift (bond b) to **5**, or a 1,2-H shift to **6**. In the event, 1,2-H migration is suppressed and the residual rearrangement is strongly dominated by the "phenyl" 1,2-C process, a specificity that we attribute to mediation by the phenyl π orbitals on the basis of ab initio calculations.

Diazirines. 1-Cyanobenzocyclobutene[3,4] was converted to amidine **7** in 70% yield by reaction with HCl/EtOH to yield the imidate salt, followed by ammonolysis (NH_3/EtOH).[5] Benzocyclobutenylchlorodiazirine (**8**) was obtained in 50% yield by oxidation[6] of **7** with 12% aqueous NaOCl, saturated with NaCl, in a LiCl−DMSO/pentane mixture at 30−35 °C. The diazirine was purified by chromatography on silica gel (pentane elution) and characterized by NMR and UV spectroscopy.[7a]



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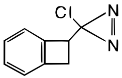

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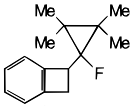

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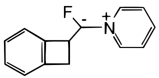

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Treatment[8] of **8** with n-$Bu_4N^+F^-$ afforded a complex decomposition mixture rather than **3**. The latter diazirine could be obtained, however, from a "modified" Graham oxidation of **7** (30−35 °C), in which the aqueous NaOCl oxidant was saturated with KF and the DMSO reaction medium was "loaded" with 0.77 M LiF.[9] This reaction afforded a variable mixture (ranging from 9:1 to 2:1) of **8** and **3** in 50% overall yield, which was separated by 3-fold repetitive chromatography on silica gel with pentane.[7b]

Product Studies. Photolysis of diazirine **3** at 25 °C gave fluoroindenes **4** and **5** in >90% yield and in a ratio of 95.3:4.7 as determined by capillary GC on a 30 m Cp-sil 5 CB or HP-1 column. Equal GC response factors were assumed for **4** and **5**. The 1,2-H shift product **6** appeared to be absent. The structure of **4** was verified by GC-MS, NMR, and comparison to an authentic sample[10] synthesized by the conversion of 1-indanone to 1,1-difluoroindan with diethylaminosulfur trifluoride (DAST),[11] followed by HF elimination over alumina.[12] The assignment of **5** is more tentative, however, and rests on a GC-MS parent ion and a vinyl-H NMR absorption at δ 6.10.

Photolysis of diazirine **3** in the presence of tetramethylethylene afforded the expected carbene trapping product **9**, characterized by NMR and high-resolution MS. A correlation of the product ratio **9**/**4** [Add/Re] vs the concentration of tetramethylethylene was *linear* (Supporting Information, Figure S-1), indicating that **4** was derived very largely from carbene **2**; excited diazirine **3** was not significantly involved.[1a,c,2a,13,14] The yield of **5**, however, was *independent* of [tetramethylethylene] from 0.24 to 3.6 M olefin, suggesting that the 4−5% yield of **5** is most likely derived from excited **3** and not from carbene **2**.[15]

Thermolyses of **3** at 100 °C (48 h) and 138 °C (36 h) gave **4** and **5** in distributions of 98.1:1.9 and 96.8:3.2, respectively, somewhat more specific results than the photolytic distribution (95.3:4.7). The a/b specificity of the 1,2-C migrations of carbene **2** therefore exceeds 20 (*hν*, 25 °C) and is as high as 51.6 at 100 °C. Note that we implicitly assume that both **4** and **5** arise only from carbene **2** in thermal decompositions of **3**.

Kinetics. The absolute rate constant for the rearrangement

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[1] For reviews, see: (a) Moss, R. A. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 1, pp 59ff. (b) Platz, M. S.; Modarelli, D. A.; Morgan, S.; White, W. R.; Mullins, M.; Celebi, S.; Toscano, J. P. *Prog. React. Kinet.* **1994**, *19*, 93. (c) Liu, M. T. H. *Acc. Chem. Res.* **1994**, *10*, 287. (d) Jackson, J. E.; Platz, M. S. in ref 1a (Brinker), pp 89ff.

[2] (a) Moss, R. A.; Ho, G.-J. *J. Phys. Org. Chem.* **1993**, *6*, 126. (b) Moss, R. A.; Ho, G.-J.; Liu, W. *J. Am. Chem. Soc.* **1992**, *114*, 959. (c) Moss, R. A.; Ho, G.-J. *Tetrahedron Lett.* **1990**, *31*, 1225. (d) Moss, R. A.; Fantina, M. E.; Munjal, R. C. *Ibid.* **1979**, 1277.

[3] We followed a procedure analogous to that of Hart. Hart, H.; Oku, A. *J. Org. Chem.* **1972**, *37*, 4269.

[4] Kirchoff, R. A. U.S. Patent 4540763, 1985.

[5] Dox, A. W.; Whitmore, F. C. In *Organic Syntheses*, 2nd ed.; Gilman, H., Blatt, A. H., Eds.; Wiley: New York, 1941; Collect. Vol. I pp 5ff. Amidinium salt **7** had a mp of 138−140 °C; NMR (δ, DMSO-d_6) 3.3−3.7 (m, 2H, CH_2), 4.59 (m, 1H, CH), 7.2−7.4 (m, 4H, aryl), 9.08 (s, 4H, NH).

[6] Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

[7] (a) For **8**: NMR (δ, $CDCl_3$) 3.17−3.26, 3.38−3.40 (d/AB, 2H, CH_2), 4.11 (m, 1H, CH), 7.02−7.30 (m, 4H Ar); UV (pentane) λ 346, 362 nm. (b) For **3**: ^1H NMR (δ, $CDCl_3$) 3.23−3.50 (m, 2H, CH_2), 4.11−4.19 (m, 1H, CH), 7.01−7.32 (m, 4H, Ar); ^{19}F NMR (δ, $CFCl_3$, $CDCl_3$) −143.04 (d, $J_{HF} = 8$ Hz); UV (pentane) λ 330, 346, 362 nm.

[8] Moss, R. A.; Terpinski, J.; Cox, D. P.; Denney, D. Z.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1985**, *107*, 2743. See also: ref 2b.

[9] We thank Prof. W. Sander, Ruhr-Universitat, Bochum, for the fluorodiazirine procedure. The mechanism of this reaction is presently uncertain.

[10] ^1H NMR (δ, $CDCl_3$) 3.28 (d of d, $J_{HH} = 2$, $J_{HF} = 5.8$ Hz, CH_2), 5.78 (t, $J = 2$ Hz, 1H, CH), 7.24−7.39 (m, 4H Ar); ^{19}F NMR (δ, $CFCl_3$, $CDCl_3$) −134.3 (t, $J = 5.8$ Hz). The small H−F coupling at the vinyl H in fluorocyclopentenes has been noted previously.[2b,12]

[11] Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

[12] Strobach, D. R.; Boswell, G. A., Jr. *J. Org. Chem.* **1971**, *36*, 818.

[13] LaVilla, J. A.; Goodman, J. L. *Tetrahedron Lett.* **1990**, *31*, 5109. White W. R., III; Platz, M. S. *J. Org. Chem.* **1992**, *57*, 2841. Modarelli, D. A.; Morgan, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7034. For an alternative interpretation of reactions attributed to excited diazirines, see: Bonneau, R.; Liu, M. T. H.; Kim, K. C.; Goodman, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 3829 and references cited therein.

[14] The inverse correlation of Re/Add vs 1/[alkene] was linear with an intercept of 0.011, indicating, at most, 1% involvement of excited **3**[1a,2a] (see Supporting Information, Figure S-2).

[15] Similarly strict carbene/diazirine product partition has been encountered with *tert*-butylchlorocarbene: Moss, R. A.; Liu, W. *J. Chem. Soc., Chem. Commun.* **1993**, 1598.

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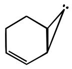
of carbene **2** to 3-fluoroindene (**4**) was determined by LFP[16] using the pyridine ylide methodology.[1d,17] LFP at 351 nm and 24 °C of a pentane solution of diazirine **3** ($A_{368} = 0.8$) in the presence of pyridine afforded a strong absorption of ylide **10** at 390 nm. A correlation of the apparent rate constants for ylide formation (4.84×10^7 to 1.01×10^8 s^{-1}) vs pyridine concentration (6.1−36 mM) was linear (5 points, $r = 0.999$) with a slope of 1.8×10^9 M^{-1} s^{-1}, equivalent to the rate constant for ylide formation from **2** and pyridine, and a *y*-intercept of 3.75×10^7 s^{-1} (see Supporting Information, Figure S-3). The latter value can be equated with k_{re} for **2** → **4**, the process that destroys >95% of the carbene in the absence of pyridine.

The **2** → **4** rearrangement is thus 21 times faster (42 times faster on a per bond basis) than the rearrangement of **1** to 1-fluorocyclopentene ($k_{re} = 1.8 \times 10^6$ s^{-1})[2a,b] and 71 times faster than the H shift of **1** to fluoromethylenecyclobutane, suggesting that **2** accesses a lower energy (C shift) pathway and a more stabilized transition state. We propose that this pathway is π orbital mediated and that the **2** → **4** transformation can be formulated as an electrophilic attack of the carbenic carbon on the aromatic ring. Indeed, the present rearrangement is reminiscent of the Skattebøl rearrangement of (e.g.) cyclopropylidene **11** to 7-norbornenylidene (**12**)[18] and of the rearrangement of **12** to diene **13**.[19] These processes cannot conclude in cyclopropanations because the products would be too highly strained; therefore the carbenes can be classified as "foiled methylenes."[20]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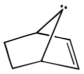
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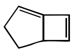
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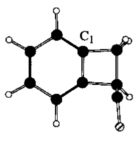
Ab initio calculations support our qualitative view of the **2** → **4** rearrangement. Two low-energy conformations of the singlet fluorocarbene **2** were located and subjected to complete geometry optimizations and normal mode analysis at the HF/6-31G* level of theory.[21] Geometry optimizations were carried out at the MP2/6-31G* level and led to an energy difference of 1.2 kcal/mol between the conformers of **2** after correction using HF calculated zero-point energy (ZPE) differences. Next, the two transition structures **15** and **16** corresponding to the a and b 1,2-shift processes were located and subjected to similar analyses.[22] In agreement with the experimental results, the phenyl shift transition structure **15** was found to be 4.9 kcal/mol lower in energy than that for the benzyl shift structure **16** (ZPE-corrected MP2/6-31G*). The calculated activation energies relative to the lower energy conformer of fluorocarbene **2** (**14**) are 2.8 and 7.7 kcal/mol, respectively.[23]



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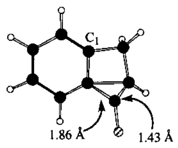

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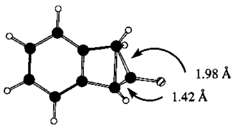

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The geometry of structure **16** is consistent with typical carbene rearrangement transition structures having a long bond between the carbene center and the reaction site.[24] Furthermore, the calculated changes in charge distribution as structure **15** develops from **14** are consistent with our depiction of this reaction as an electrophilic attack on benzene by the carbenic carbon. For example, the net charge on the carbene center of **2** is highly positive (+0.42) due to the inductive effect of the fluorine atom. As the reaction progresses to the transition structure, interaction with the π system results in a reduction of positive charge by 0.16 units to +0.26. At the same time, the carbons and hydrogens of the benzene ring become more positive, the greatest changes being associated with the carbons ortho and para to the point of attack (e.g., the charge on C_1 becomes more positive changing from −0.020 to −0.008).

We conclude by noting that the selective rearrangement of carbene **2** to 3-fluoroindene (**4**) is a representative rather than an isolated reaction. Thus, the photogenerated acetoxycarbene analogue of **2** rearranges to 3-acetoxyindene in >99% yield with $k_{re} = 8.5 \times 10^6$ s^{-1} at 25 °C,[25] whereas the thermally generated (78 °C) chlorocarbene analogue affords a 92:7:1 distribution of the chloro analogues of **4**, **5**, and **6**, respectively.[26] Details of these reactions will appear in due course.

Acknowledgment. We are grateful to the National Science Foundation for financial support, and to Professors K. Krogh-Jespersen and S. Knapp for helpful discussions.

Supporting Information Available: Figures S-1−S-3; see text (3 pages). See any current masthead page for ordering and Internet access instructions.

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(16) For a description of our LFP system, see: Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341.

(17) Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Liu, M. T. H. *J. Am. Chem. Soc.* **1988**, *110*, 5595.

(18) For a brief review, see: Moss, R. A.; Jones, M., Jr. In *Reactive Intermediates*; Jones, M., Jr., Moss, R. A., Eds.; Wiley: New York, 1981; Vol. 2, pp 113ff.

(19) Moss, R. A.; Ho, C.-T. *Tetrahedron Lett.* **1976**, 3397. Moss, R. A.; Dolling, U.-H.; Whittle, J. R. *Ibid.* **1971**, 931.

(20) Gleiter, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 5457.

(21) All optimizations utilized Gaussian94. Gaussian 94, Revision B.1; Frisch, M. J.; Trucks, G.W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R. L.; Martin R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gorden, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc.; Pittsburgh, PA; 1995. Charge calculations utilized natural population analysis methodology.

(22) Transition structures **15** and **16** were characterized as first-order saddle points by normal coordinate analyses at the HF/6-31G* level (one negative frequency). Zero-point energies were scaled by 0.9646 as suggested by Pople, J. A.; Scott, A. P.; Wong M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345.

(23) For comparison, the experimentally determined activation energy for the 1,2-C shift of cyclopropylfluorocarbene to cyclobutene is 4.2 kcal/mol; cf., ref 2b.

(24) Moss, R. A.; Liu, W.; Krogh-Jespersen, K. *J. Phys. Chem.* **1993**, *97*, 13413.

(25) The usual 1,2-acyl migration of acetoxycarbenes is suppressed, see: Moss, R. A.; Xue, S.; Liu, W. *J. Am. Chem. Soc.* **1994**, *116*, 1583.

(26) Xue, S. Unpublished Work. Photolysis of the chlorodiazirine analogue of **3** leads to carbene reactions that are grossly contaminated with excited state diazirine chemistry.