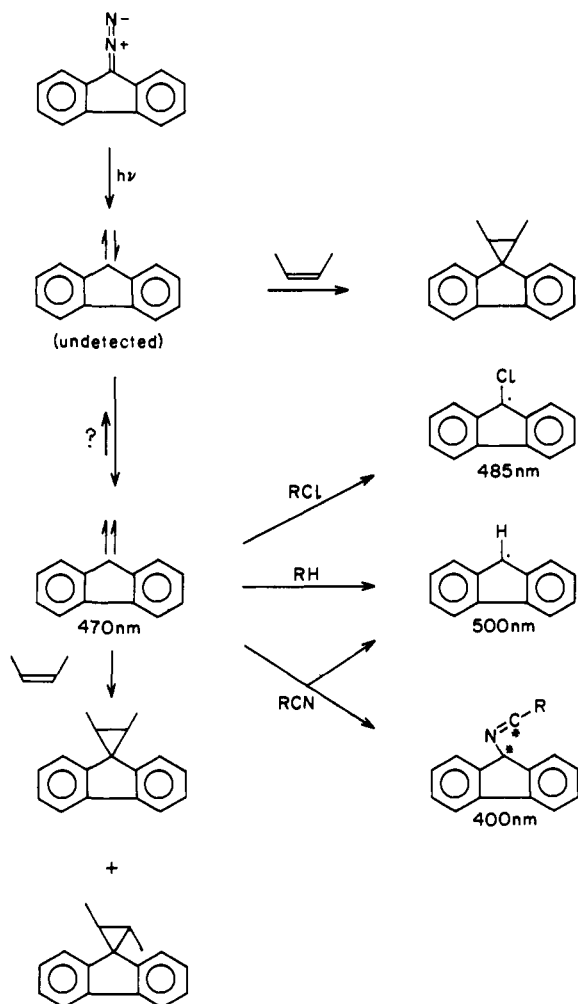


Scheme I



The above interpretation is supported by product studies (using GC-MS analysis) that show two major products on similar yields (ca. 20% each). One was 9-fluorenylacetonitrile, expected from radical recombination following abstraction from the solvent. The second product incorporates the acetonitrile moiety bonded at the nitrile center and indicates direct attachment of the carbene on the solvent. The mass spectrum of a third and minor product indicates incorporation of two acetonitrile moieties, in excellent agreement with the mechanism recently proposed by Kende et al.¹³ Thus, nitriles should be regarded as highly reactive rather than "inert" solvents as was originally suggested.² The revised mechanism proposed for the reactions of fluorenylidene is shown in Scheme I.

Further confirmation that transients at 400 nm were nitrile ylides was obtained from olefin quenching experiments. Thus, fumaronitrile quenches the acetonitrile ylide with $k_q = (5.7 \pm 0.4) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. By contrast, when pivalonitrile was used, we obtained $k_q = (1.5 \pm 0.2) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ under the same conditions.¹⁴

Thus, fluorenylidene is a highly reactive carbene that reacts with solvents containing hydrogen or chlorine to give the 9-fluorenyl radical and with ketones or nitriles to form ylides. Since ylides typically have singlet ground states, the interesting question arises as to whether they can be formed directly from the triplet carbene. Although simple mechanism ultimately leading to the

singlet ylide can be advanced for such a process, it is possible that singlet and triplet fluorenylidene are in equilibrium.¹⁶ However, our results require that for $^1\text{Fl} \rightleftharpoons ^3\text{Fl}$, $K \geq 10$ and that quenching by *cis*-4-methyl-2-pentene was competitive with intersystem crossing.

The above reassignments fit all of the available data and the behavior of the carbene conforms to the normally accepted reaction mechanisms. They account for (i) nonstereospecific additions to olefins,⁴ (ii) radical-like behavior in atom abstractions,³ giving good yields of cage escape, (iii) spectral similarities between the 470-nm band and the 9-fluorenyl radical,³ (iv) dramatic enhancement of the lifetime measured at 470 nm at 77 K, (v) buildup of transients at 400 nm only when nitriles were present and with their ylide-like properties such as preferred reaction with electron deficient olefins,¹¹ and (vi) formation of several products containing acetonitrile moieties in the photolysis of DAF in acetonitrile.

Finally, most of the data in earlier reports can be reinterpreted on the basis of this revised mechanism. Results involving the 400-nm transient should be assigned to a nitrile-ylide. Time-resolved data for the 470-nm species correspond to triplet fluorenylidene or species (singlet?) in equilibrium with it. Conclusions concerning carbene intersystem crossing should be ignored. Results based on a reduction of the quantum yield of the formation of the 400-nm transient (earlier assigned to singlet fluorenylidene) should be treated cautiously; such a reduction may reflect quenching of the singlet, triplet, or both, before or after equilibration.

(16) A condition that is believed to be met in the case of diphenylcarbene.^{17,18}

(17) Closs, G. L.; Rabinow, B. E. *J. Am. Chem. Soc.* **1976**, *98*, 8190.

(18) Eisenthal, K. B.; Turro, N. J.; Aikawa, M.; Butcher, J. A., Jr.; DuPuy, C.; Hefferon, G.; Hetherington W., III; Korenowski, G. M.; McAuliffe, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 6563. DuPuy, C.; Horenowski, G. M.; McAuliffe, M.; Hetherington W. M., III. Eisenthal, K. B. *Chem. Phys. Lett.* **1981**, *77*, 272. Wang, Y.; Sitsmann, E. V.; Novak, F.; DuPuy, C.; Eisenthal, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3238.

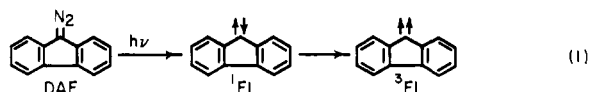
Irradiation of Diazofluorene on a Picosecond Time Scale and at Very Low Temperature: A Reassignment of Transient Structures

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Irradiation of 9-diazafluorene (DAF) leads to loss of nitrogen and eventual formation of products characteristic of the reactions of singlet fluorenylidene (^1Fl) and triplet fluorenylidene (^3Fl); eq 1).¹ Irradiation of DAF with a 10-ns light pulse permits detection



of transient products. Three significant products are observed in acetonitrile solution at room temperature.^{2,3} The first is produced during the pulse, absorbs at 470 nm, and decays with a half-life of 17 ns. The second product grows in as the first decays, absorbs at 400 nm, and has a half-life of about 100 μs . Also, a small amount of 9-fluorenyl radical ($\text{FlH}\cdot$), which has a unique absorption at 500 nm, appears as the first product decays.³ Previously we assigned the 470- and 400-nm absorbing products to ^1Fl and ^3Fl , respectively.² Irradiation of DAF in cyclohexane solution with a 10-ns pulse shows only $\text{FlH}\cdot$.^{2,3} Herein we report

(13) Kende, A. S.; Hebeisen, P.; Sanfilippo, P. J.; Toder, B. H. *J. Am. Chem. Soc.* **1982**, *104*, 4244.

(14) Our earlier measurements¹⁵ of these rate constants were repeated to ensure the match of experimental conditions with the experiments described below.

(15) Wong, P. C.; Griller, D.; Scaiano, J. C. *Chem. Phys. Lett.* **1981**, *83*, 69.

(1) Jones, M., Jr.; Rettig, K. R. *J. Am. Chem. Soc.* **1965**, *87*, 4013; 4015.

(2) Zupancic, J. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1980**, *102*, 5958.

(3) Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 5934.

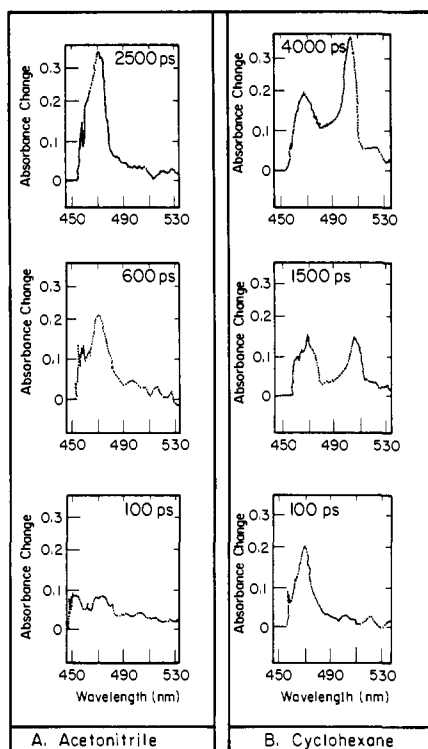
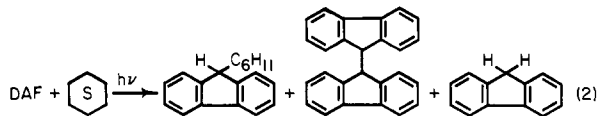


Figure 1. (A) Absorption spectra taken 100, 600, and 2500 ps after irradiation of a solution of DAF in CH_3CN with a ca. 30-ps laser pulse. Each spectrum is an average of ca. 30 laser shots and is smoothed according to the quartic procedure.¹⁷ (B) Absorption spectra taken 100, 1500, and 4000 ps after irradiation of DAF in cyclohexane.

investigations of the photolysis of DAF on a picosecond time scale and its irradiation at ca. 10 K in a glassy matrix. These experiments lead to changes in the assignment of the structures of some of the transients.

Photolysis of a 3.3×10^{-3} M solution of DAF in acetonitrile with a ca. 30-ps pulse at 355 nm from a mode-locked Nd:YAG laser⁴ results in formation of the transient product that absorbs mainly at 470 nm. Time-resolved absorption spectra are shown in Figure 1a. It is evident that the species responsible for this absorption is not formed instantaneously on this time scale but grows in after the laser pulse with a half-time of 0.28 ± 0.09 ns. This finding indicates that there is an unobserved precursor to the species absorbing at 470 nm.

Photolysis of DAF in cyclohexane solution leads eventually to products characteristic of the formation of $\text{FIH}\cdot$ (eq 2).⁵ Irra-



diation with the 30-ps pulse reveals rapid formation of the product absorbing at 470 nm. As this absorption decays, it is replaced by the spectrum of $\text{FIH}\cdot$ (Figure 1B). The rates of growth of $\text{FIH}\cdot$ and decay of the initially formed 470-nm absorbing product are the same within our ability to measure them and correspond to a half-time for reaction of 1.4 ± 0.6 ns. These results show that the transient product absorbing at 470 nm is formed in both acetonitrile and hydrocarbon solvents and that this product, or some species in rapid equilibrium with this product, reacts in cyclohexane to become $\text{FIH}\cdot$ and in acetonitrile to become the product absorbing at 400 nm. Irradiation of DAF in spiro[2.2]pentane⁶ gives results that are qualitatively identical with

(4) Details of this laser system will be reported in the forthcoming full paper.

(5) Kirmse, W.; Horner, L.; Hoffman, H. *Justus Liebigs Ann. Chem.* **1958**, 614, 19.

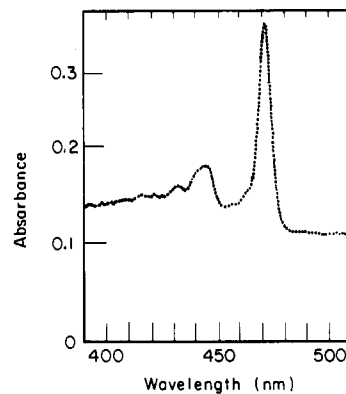


Figure 2. Absorption spectrum of stable product obtained by irradiating DAF in a 2-methyltetrahydrofuran glass at ca. 10 K. The concentration of DAF at room temperature is 6.5 ± 10^{-4} M.

those obtained in cyclohexane. However, the half-time for reaction of the product absorbing at 470 nm in this solvent is increased to 29 ± 6 ns.

Photolysis of DAF in a glass at ca. 10 K strongly supports assignment of the transient product with absorption maximum at 470 nm to ^3Fl . The EPR spectrum generated by photolysis of DAF at 77 K has been unambiguously assigned to ^3Fl .⁷ In hydrocarbon glasses the EPR signal is not stable at this temperature but decays with complex kinetic behavior characteristic of site-dependent reactivity.⁸ Our earlier effort² to measure the absorption spectrum of ^3Fl in methylcyclohexane at 77 K gave a product with an apparent absorption maximum at ca. 400 nm. However, irradiation of DAF at 10 K in a 2-methyltetrahydrofuran glass, where both the EPR signal and the absorption spectrum are stable, does not give a significant absorption at 400 nm, but absorptions with maxima at 470 and 442 nm are formed (Figure 2). These experiments show that the absorption observed in acetonitrile at 400 nm by laser spectroscopy is not due to ^3Fl .⁹ Instead, the absorption observed in acetonitrile, or hydrocarbon, solution at 470 nm by laser spectroscopy corresponds to the stable spectrum obtained at 10 K in the glass. Due to the inherent, and unknown, difference in sensitivity of the EPR and the optical absorption techniques, it is not possible to be absolutely unequivocal in the assignment of the absorption at 470 nm to ^3Fl . However, the weight of the circumstantial evidence encourages us to make this assignment.

It is generally agreed that alcohols react with singlet carbenes to give ethers.¹⁰ Irradiation of DAF in the presence of methanol gives methyl 9-fluorenyl ether in ca. 90% isolated yield.² When low concentrations of ethanol are included in the spiro-pentane solution of DAF, both $\text{FIH}\cdot$ and ^3Fl can still be detected after irradiation. Addition of the alcohol causes the rate of decay of ^3Fl and the rate of growth of $\text{FIH}\cdot$ to increase concomitantly but does not significantly alter the amount of ^3Fl present at extrapolated time equals zero (Stern-Volmer slope = 0.87 ± 0.7 M⁻¹).¹¹ However, the amount of $\text{FIH}\cdot$ formed is reduced by addition of ethanol (Stern-Volmer slope = 5.7 ± 1.5 M⁻¹). These findings give an apparent rate constant for reaction of the carbene with ethanol of $2.0 \pm 0.4 \times 10^8$ M⁻¹ s⁻¹, and appear to indicate that

(6) Applequist, D. E.; Fanta, G. F.; Henrikson, B. W. *J. Org. Chem.* **1958**, 23, 1715.

(7) Trozzolo, A. M.; Murray, R. W.; Wasserman, E. *J. Am. Chem. Soc.* **1962**, 84, 4990.

(8) Lin, C.-T.; Gaspar, P. P. *Tetrahedron Lett.* **1980**, 3553. Senthilnathan, V. P.; Platz, M. S. *J. Am. Chem. Soc.* **1980**, 102, 7637.

(9) The structure of the 400-nm absorbing transient structure is not revealed by these experiments. One possibility, suggested initially by M. Jones of Princeton University (private communication with the author), is an acetonitrile ylide.

(10) Kirmse, W. In "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971. Moss, R. A.; Jones, M., Jr. *Carbenes* **1975**, 1, 2.

(11) The magnitude of this slope is in fact statistically indistinguishable from zero. However, in the event that the decrease in the apparent amount of ^3Fl at zero time is real, reaction of ^3Fl with the alcohol before equilibration is complete (as discussed above) seems like a reasonable explanation.

^3Fl is responsible for both hydrogen atom abstraction and for formation of the ether products.

The reaction of DAF in acetonitrile with methanol can be sensitized with triplet thioxanthone. Irradiation of an 8×10^{-4} M solution of thioxanthone containing 9.2×10^{-4} M DAF and 0.5 M methanol at 380 nm gives the ether in 92% yield. When 0.05 M 2,5-dimethyl-2,4-hexadiene is included in the reaction mixture as a quencher of thioxanthone triplet, the formation of the ether is slowed by a factor of ca. 40, indicating that the diene and DAF are competing for the sensitizer triplet. These findings also appear to show that ^3Fl is responsible for formation of ethers from alcohols.

The dilemma generated by the observation of singlet reactivity from a carbene that appears to be a triplet can be resolved if at room temperature ^3Fl is in very rapid equilibrium with the as yet unseen ^1Fl .¹² The rate of equilibration between the two spin states in this model is faster than any reaction we have yet examined in relatively dilute acetonitrile or spiropentane solution. Assuming that reaction of the singlet carbene with methanol can be no faster than diffusion controlled, the kinetics suggest that the equilibrium mixture in acetonitrile at room temperature contains at least 5% ^1Fl . Equilibration between a singlet and triplet carbene has been suggested previously to account for the chemistry of diphenylmethylene.¹³

These new findings necessitate a reinterpretation of the chemical properties attributed earlier to ^1Fl and ^3Fl .^{2,3,14-16} The previous assignments of ^1Fl and ^3Fl rested in large part on the analysis of competition reactions between methanol and various olefins for the carbene. These studies confirmed that a species generated prior to the one responsible for the 400-nm absorption in acetonitrile formed products appropriate for ^1Fl with the anticipated yields. The present results indicate that there are at least two species preceding the one that absorbs at 400 nm, the triplet carbene and its unseen precursor and companion, which is presumably the singlet. The competition experiments reported earlier, although confirming the measured rate constants, cannot indicate which spin state is responsible for the observed products if their equilibration is more rapid than their reaction. Indeed, in this circumstance the observed chemical properties of the carbene may simply reflect the nature of the reagent used as the probe. Alcohols react with the singlet carbene and drain the equilibrium from that side, and hydrocarbons react with ^3Fl to give free radical products. At high concentration a very reactive probe may intercept the precursor to ^3Fl before equilibration has been achieved. In this case spin-specific reactivity might be observed.¹

Acknowledgment. This work was supported by grants from the National Science Foundation and from the National Institutes of Health. We particularly wish to thank Cynthia Teeters for her help with the low-temperature optical spectroscopy and M. Hendrich and Dr. P. DeBrunner of the Physics department for their assistance with the low-temperature EPR spectroscopy. We also thank Drs. D. Griller and J. Scaiano of NRC, Canada, and M. Platz of Ohio State University for discussion of this work and for sharing with us their results prior to publication.

Registry No. DAF, 832-80-4; FIH, 2762-16-5; H, 1333-74-0; ethanol, 64-17-5; methanol, 67-56-1; thioxanthone, 492-22-2; 2,5-dimethyl-2,4-hexadiene, 764-13-6; cyclohexane, 110-82-7.

(12) Another possibility, suggested by D. Griller and J. C. Scaiano of NRC, Canada, is that the alcohols react with ^3Fl to give the observed ether products.

(13) Closs, G. L.; Rabinow, B. E. *J. Am. Chem. Soc.* **1976**, *98*, 8190. Eisenthal, K. B.; Turro, N. J.; Aikawa, M.; Butcher, J. A., Jr.; DuPuy, C.; Heferson, G.; Hetherington, W.; Korenowski, G. M.; McAuliffe, M. *J. Ibid.* **1980**, *102*, 6563. Gaspar, P. P.; Whitsel, B. L.; Jones, M., Jr.; Lambert, J. B. *Ibid.* **1980**, *102*, 6108. DuPuy, C.; Korenowski, G. M.; McAuliffe, M.; Hetherington, W. M.; Eisenthal, K. B. *Chem. Phys. Lett.* **1981**, *27*, 272.

(14) Zupancic, J. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1981**, *103*, 944.

(15) Zupancic, J. J.; Grasse, P. B.; Schuster, G. B. *J. Am. Chem. Soc.* **1981**, *103*, 2423.

(16) Wong, P. C.; Griller, D.; Scaiano, J. C. *Chem. Phys. Lett.* **1981**, *83*, 69.

(17) Wilson, P. D.; Edwards, T. H. *Appl. Spectrosc. Rev.* **1976**, *12*, 1.

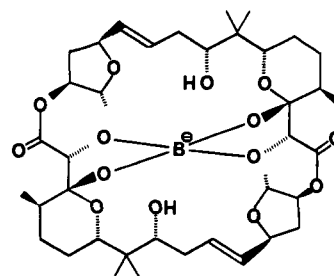
Total Synthesis of Aplasmomycin. Stereocontrolled Construction of the C(3)–C(17) Fragment

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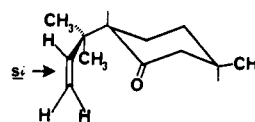
Aplasmomycin, isolated from a marine-derived strain of *Streptomyces griseus*, is a boron-containing antibiotic ($\text{C}_{40}\text{H}_{60}\text{O}_{14}\text{BNa}$) that exhibits activity against Gram-positive bacteria and also Plasmodia.¹ It belongs to the family of borate-bridged macrocycles of which boromycin was the first known member.² X-ray crystallographic analysis of aplasmomycin silver salt revealed a beautifully symmetrical C_2 structure composed of two identical subunits bound together as indicated in formula 1.³ The



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unique structure and biological activity of aplasmomycin distinguish this molecule as an unusually interesting target for synthesis. Reported in this and the following paper is the first total synthesis of aplasmomycin. In overall outline the synthesis was conducted by the construction of precursors corresponding to the C(3)–C(10) fragment (starting with inexpensive commercial (+)-pulegone) and the C(11)–C(17) fragment (starting from D-mannose). Coupling of these intermediates and chain extension with dimethyl oxalate formed the entire C(1)–C(17) chain of the aplasmomycin subunit, from which the antibiotic was obtained by coupling, macrolactonization, adjustment of functionality, and introduction of borate.

Reaction of (+)-pulegone with the reagent from 2.5 equiv of vinylmagnesium bromide and 1.25 equiv of cuprous iodide in tetrahydrofuran (THF) at -30°C for 1 h afforded after extractive isolation a 1:1 mixture of *trans*- and *cis*-5-methyl-2-(1,1-dimethylallyl)cyclohexanones (88%), which was equilibrated by exposure to 0.1 equiv of sodium methoxide in methanol to an 85:15 *trans*-*cis* mixture.⁴ Chromatography on silica gel using a Waters Associates Model 500 preparative machine with 1% ether in hexane for elution readily afforded the pure *trans* isomer (2) as



2

a colorless oil.⁵ In the next step a crucial 1,3-stereorelationship was established by taking advantage of the sizeable steric inter-

[†] Formerly written as Pan Pei-Chuan.

(1) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176.

(2) Dunitz, J. D.; Hawley, D. M.; Mikloš, D.; White, D. N. J.; Berlin, Y.; Marušič, R.; Prelog, V. *Helv. Chim. Acta* **1971**, *54*, 1709.

(3) Nakamura, H.; Sitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *J. Antibiot.* **1977**, *30*, 714.

(4) Reactions involving air-sensitive reagents, intermediates, or products were conducted under dry argon.

(5) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each stable intermediate by using chromatographically purified and homogeneous samples.