Reactivity and Stereochemical Studies of the [2 + 2] Cycloaddition of 1,1-Difluoroallene and Styrene

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Abstract: Difluoroallene and styrene undergo clean cycloaddition to form two adducts: 2,2-difluoro-3-phenyl-1-methylenecyclobutane (major) and 3-phenyl-1-(difluoromethylene)cyclobutane. Similar experiments with *p*-nitro- and *p*-methoxystyrene gave relative reactivities of 2.1 and 1.3, respectively. Cycloaddition with (*Z*)-β-deuteriostyrene gave the two products with *Z*:*E* ratios of 59:41 and 79:21, respectively, at 70 °C. A mechanism involving two kinetically distinguishable diradicals is proposed to rationalize the results.

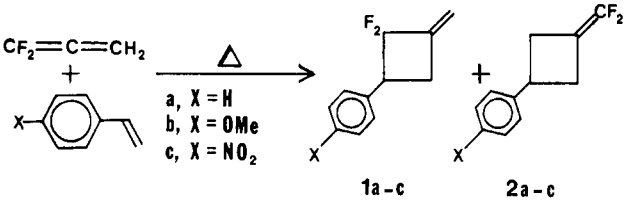
The mechanism of allene [2 + 2] cycloadditions has received considerable attention over the years[1] with early excitement being generated by Moore's 1,2-cyclononadiene dimerization studies[2] and Hoffmann's related conjecture that allenes could well act as antarafacial cycloaddends.[3] Early stereochemical studies,[4-6] while lending credibility to the concerted mechanism, did not provide unambiguous evidence for it while other, kinetic studies[7] provided strong evidence for the involvement of diradicals in such reactions.

In spite of an interesting theoretical exercise which reasserted the issue of concertedness,[8] recent work,[9,10] including two detailed stereochemical studies on the reactions of fumarate and maleate esters with 1,1-dicyclopropylallene[11] and 1,1-dimethylallene,[12] have been uniformly consistent with nonconcerted mechanisms generally being operative.

It was our intention, using a particularly clean allene cycloaddition which was also relatively free of potentially complicating steric effects, to obtain relative reactivity factors as well as unambiguous stereochemical information about these uniquely informative [2 + 2] reactions.

Results

The reaction chosen for study was that of the very reactive 1,1-difluoroallene (DFA)[13] with styrene. When the cycloaddition was carried out neat under vacuum in a sealed Pyrex tube with a tenfold excess of styrene containing hydroquinone inhibitor only



two adducts, 2,2-difluoro-3-phenyl-1-methylenecyclobutane (**1**) and 3-phenyl-1-(difluoromethylene)cyclobutane (**2**), were obtained in a 5.6:1 ratio (at 60 °C) in 59% yield. The reaction was very clean, with *no* 2:1 or higher adducts being observed. The lack of a higher yield was undoubtedly due to the observed inevitable, competitive but unobtrusive oligomerization of the highly self-reactive DFA. Products **1** and **2** were, moreover, shown to be noninterconverting as well as stable to further cycloadditions with either DFA or styrene under the reaction conditions.

A slight temperature dependence in the ratio of **1a**:**2a** was observed with the greatest selectivity being observed at the lowest temperature. The ratio diminished from 5.6:1 to 4.5:1 in raising the temperature from 60 to 100 °C, as seen in Table I.

In addition to the reaction of DFA with styrene itself, its reactions with *p*-methoxy- and *p*-nitrostyrene were examined with

Table I. Reactions of DFA with Para-Substituted Styrenes; Yields and Product Ratios

X	conditions[a]	product ratio (**1**:**2**)[b]	yield (%)[c]
H	100 °C, 2 h	81.8:18.2	58
H	80 °C, 8 h	83.1:16.9	60
H	60 °C, 32 h	84.9:15.1	59
OCH_3	100 °C, 2 h	83.5:16.5	58
OCH_3	80 °C, 8 h	84.7:15.3	58
OCH_3	60 °C, 32 h	86.2:13.8	57
NO_2	100 °C, 2 h	83.5:16.5[d]	72
NO_2	80 °C, 8 h	84.5:15.5[d]	74

[a] Styrene:allene = 10:1, hydroquinone or 4-*tert*-butylcatechol used as free radical inhibitor. [b] Error ±0.2%. [c] Error ±2%. [d] Error ±0.5%.

Table II. Reactions of DFA with Para-Substituted Styrenes; Competition Studies

run[a]	styrenes used	product ratios[b]	yields (%)[b]	reactivity ratio
1	**1b** (OCH_3)	83.1:16.9	38	1.3
	1a (H)	81.4:18.6	28	
2	**1c** (NO_2)	83.3:16.7	47	2.1
	1a (H)	81.7:18.3	22	

[a] Conditions: 100 °C, 2.0 h; styrenes:DFA ratio = 5:5:1. [b] Determined by ^{19}F NMR.

Table III. Reaction of DFA with (*Z*)-β-Deuteriostyrene; Stereochemistry and Product Ratios

styrene:DFA	conditions	product ratio[a] (**3**:**4**)	stereochemical[b] ratios **3**-*Z*:**3**-*E* and **4**-*Z*:**4**-*E*	yield (%)
1.0:2.8	100 °C, 3 h	81:19	57:43 79:21	22[c]
2.2:1	80 °C, 7.5 h	82:18	58:42 79:21	32[c]
6.8:1	70 °C, 15.5 h	83:17	59:41 79:21	58[d]

[a] Error 1%. [b] Error 2%. [c] Isolated yields. [d] GLC yield.

(1) Hopf, H. "The Chemistry of Allenes"; Landor, S. D., Ed., 1982; Vol. 2, pp 525-562.
(2) Moore, W. R.; Bach, R. D.; Ozretich, T. M. *J. Am. Chem. Soc.* **1969**, *91*, 5918.
(3) Hoffmann, R., Twenty-first Organic Chemistry Symposium of the American Chemical Society, Salt Lake City, Utah, June 1969, Abstracts, pp 110-129.
(4) Kiefer, E. F.; Okamura, M. Y. *J. Am. Chem. Soc.* **1968**, *90*, 4187.
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(6) Gajewski, J. J.; Black, W. A. *Tetrahedron Lett.* **1970**, 899.
(7) Dolbier, W. R., Jr.; Dai, S. J. *J. Am. Chem. Soc.* **1968**, *90*, 5028; **1972**, *94*, 3946.
(8) Pasto, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 37.
(9) Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3670.
(10) Pasto, D. J.; Heid, P. F.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3676.
(11) Komiya, Z.; Nishida, S. *J. Org. Chem.* **1983**, *48*, 1500.
(12) Pasto, D. J.; Yang, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 152.
(13) (a) Dolbier, W. R., Jr.; Piedrahita, C. A.; Houk, K. N.; Strozier, R. W.; Ganmdour, R. W. *Tetrahedron Lett.* **1978**, 2231. (b) Dolbier, W. R., Jr.; Burkholder, C. R. *J. Org. Chem.* **1984**, *49*, 2381.

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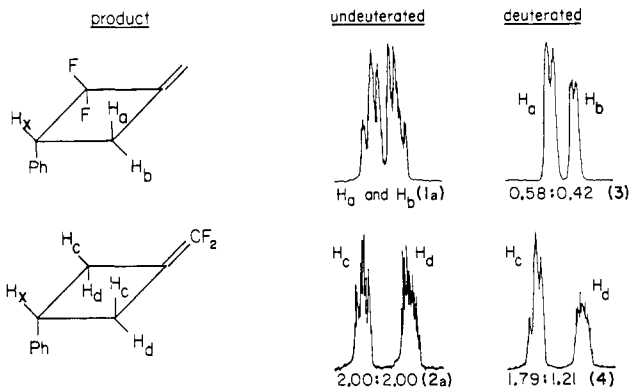


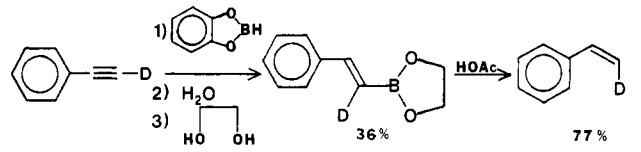
Figure 1. ^1H NMR (300 MHz) expansions of the ring methylene protons.

the product ratios and yields being summarized in Table I. Similar temperature dependencies for the **1**:**2** ratios were observed in these cases.

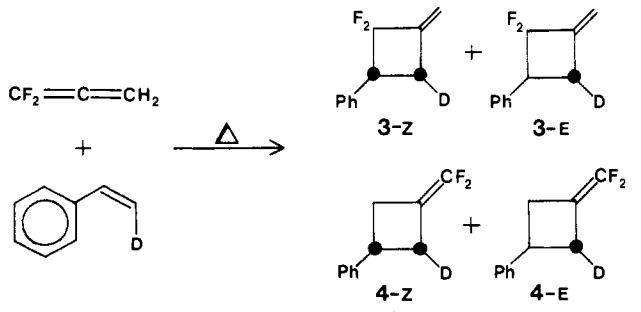
Products **1a–c** and **2a–b** were characterized by ^1H, ^{13}C, and ^{19}F NMR and IR spectra, low resolution and high resolution MS, and in the cases of **1a–c** and **2a**, combustion analyses. **2c**, due to isolation difficulties, was characterized only by ^1H and ^{19}F NMR.

Reactivity Study. By using equimolar mixtures of pairs of styrenes, the relative reactivities of each were determined as shown in Table II. Since all of the fluorine resonances of the four products observed in each competitive study could be resolved at 282 MHz, the product ratios and yields were determined via ^{19}F NMR with *m*-bromo(trifluoromethyl)benzene as an internal standard. The reactivities of *p*-nitro- and *p*-methoxystyrene relative to styrene were found to be 2.1 and 1.3, respectively.

Stereochemical Study. (*Z*)-β-Deuteriostyrene was prepared with 99.3% isotopic purity and >99% *Z* by the procedure shown below, which is a modified procedure of Brown.[14] Its reaction with DFA



was carried out generally as were those reactions described above, but with smaller ratios of styrene:DFA, which resulted in lower yields. The results are given in Table III. Again, stability of the products under the reaction conditions was demonstrated. Stereochemical ratios were also found to remain unchanged after resubjection to reaction conditions. Unreacted (*Z*)-β-deuteriostyrene was also able to be recovered with *complete* retention of stereochemical integrity. *No* cycloreversion of **3** or **4** to the starting materials was observed under the reaction conditions.

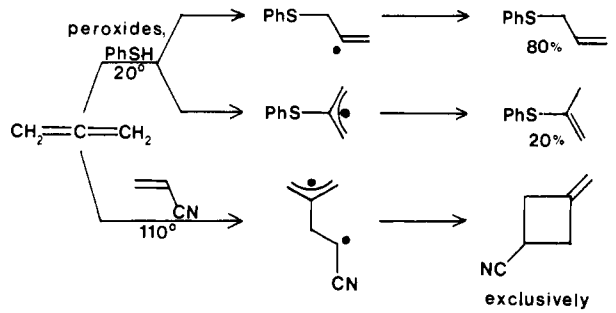


The critical *Z*:*E* ratios were determined by quantitative integration of the cyclobutane-ring methylene protons in the 300-MHz proton spectra of **3** and **4**. Base line resolution of H_a and H_b and of H_c and H_d in the spectra of **3** and **4**, respectively, enabled precise determinations of these ratios as shown in Figure 1. The assignment of the methylene protons to a particular chemical shift was made on the basis of difference NOE experiments.[15] (Difference NOE experiments can currently be performed so that Overhauser enhancements of less than 1% can be detected and accurately quantified).[17] Irradiation of H_x in **2a** gave an enhancement of 0.6% at the downfield methylene peak assigned H_c. Irradiation of H_c gave enhancements of 0.8% at H_x and 2.0% at H_d. Finally, irradiation of H_d gave enhancements of 0.6% at H_x and 1.7% at H_c. Thus, the results were internally consistent with the proton assignments given in Figure 1. Difference NOE was less successful for the structure elucidation of **1a**, perhaps due to the proximity of the geminal fluorines in **1a**. It was noted, however, that **2a** was an excellent model compound for the assignment of the resonances in the spectra of **1a** and **3**. Thus, the resonances were assigned in an analogous manner. Worth noting is the fact that the assignment of resonances by NOE experiments is in agreement with what one would expect to observe when the cycloaddition is performed with (*Z*)-β-deuteriostyrene. The largest methylene peaks in the spectra of **3** and **4** are from the resonance of proton(s) in the *Z*-deuterated adducts.

Discussion

While evidence continues to accumulate indicating the stepwise nature of [2 + 2] cycloadditions in general, and allene [2 + 2] reactions in particular, little is really known about the mechanistic details of such reactions. Little theoretical effort has been directed at [2 + 2] reactions.[18] Not much more is known about factors which drive such reactions than the general rules espoused in Roberts and Shart's classic review of all known such reactions in 1962.[19] The [2 + 2] reactions do not appear to be driven by HOMO–LUMO (donor–acceptor) interactions since many if not most of the best [2 + 2]'s are dimerizations. In general, classic factors seem to promote [2 + 2] reactivity, that is relief of strain and/or the presence of radical-stabilizing or olefin-destabilizing substituents.

Allenes are especially interesting, indeed unique addends in [2 + 2] cycloadditions. While free radical additions to allenes occur at both terminal and central carbons,[20,21] [2 + 2] cycloadditions



of allenes proceed virtually exclusively via initial central carbon attack.[1] The contrast in regiochemistry for these superficially similar processes can be understood in terms of the differences in energetics for the two processes. The addition of radicals to allene is generally an exothermic process with a very low activation energy and with little temperature dependence on regiochemistry being observed. Steric effects have been shown to play a dominant

(14) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249.

(15) The coupling of the methyne proton, H_x, to the ring methylene protons in both **1a** and **2a** was not helpful in the assignment of the asymmetric protons to a particular chemical shift. The coupling constant J_{AX} was shown to be nearly equal to J_{BX} by decoupling experiments. Similarly, $J_{CX} = J_{DX}$. This problem has been encountered before in the adduct of styrene and diphenylketene.[16]

(16) Baldwin, J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4874.

(17) (a) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Sanders, J. K. M.; Mersh, J. D. *Prog. NMR Spectrosc.* **1983**, *15*, 353. (c) Neuhaus, D.; Sheppard, R. N.; Bick, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 5996.

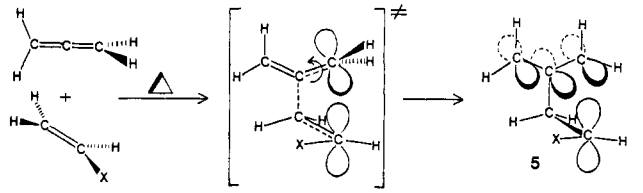
(18) Epiotis, N. E. *J. Am. Chem. Soc.* **1972**, *94*, 1924, 1935.

(19) Roberts, J. D.; Sharts, C. *Org. React. (N.Y.)* **1962**, *12*, 1.

(20) Heiba, E. I. *J. Org. Chem.* **1966**, *31*, 776.

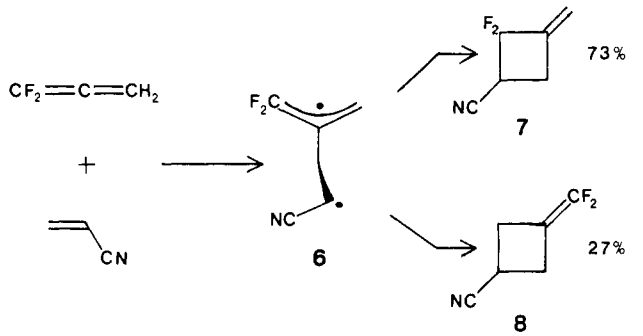
(21) Jacobs, T. L. "The Chemistry of Allenes"; Landor, S. D., Ed., 1982; Vol. 2, pp 399–416.

role in determining the regiochemistry of such reactions.[21] In contrast, the initial step in a [2 + 2] cycloaddition of allenes is endothermic with a significant activation energy. This, combined with the regiospecificity observed in initial bond formation, leads one to conclude that the transition state for this first step likely has undergone *significant rotation* of the terminal methylene of the reactive double bond, giving the transition state considerable stabilizing allyl radical character.[22] Moreover, once intermediate



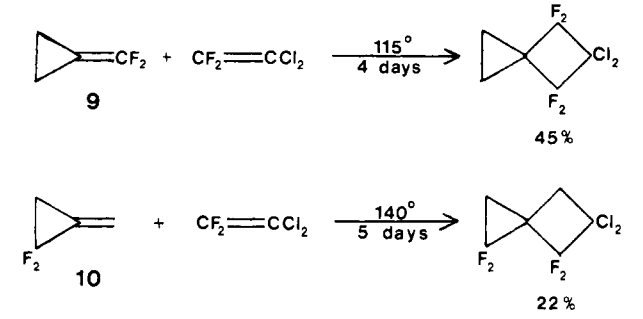
5 is formed only rarely has it been observed to revert to starting materials,[12] unlike the usual [2 + 2] diradical intermediates, because of the necessity that this same allyl radical stabilization be lost prior to such cleavage. We have indeed observed *no* reversibility of this initial bond formation under conditions of cycloaddition in any of our studies of the [2 + 2] reactions of allene or fluorine-substituted allenes.[7,13]

Another unique aspect of allene [2 + 2] cycloadditions is the fact that unlike virtually all other [2 + 2] addends, its regiochemistry of reaction is *not* totally determined by initial bond formation. For example, intermediate **6**, in the reaction of DFA with acrylonitrile, can cyclize to form either adduct **7** or **8**, with **7** in this case being significantly predominant.[13] Such a partitioning provides one with greater opportunity for mechanistic probing, as seen in the present stereochemical study.



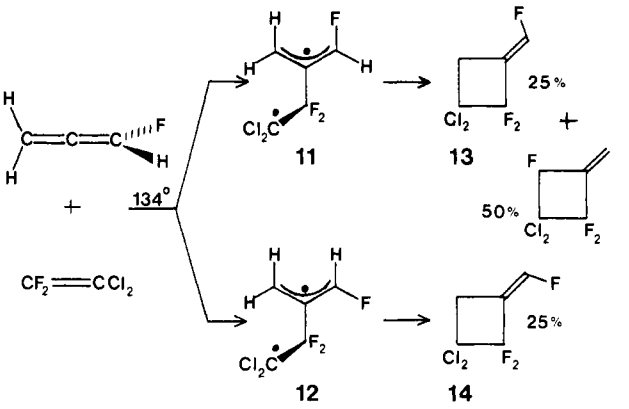
The DFA–styrene reaction is an *ideal* system for kinetic and stereochemical study. The high reactivity of DFA in [2 + 2] reactions ensures that high temperatures will not be required, hence minimizing the possibility of side reactions or thermal isomerizations of either starting materials or products.

Unlike the uncertainty present for most other allenes, one can be reasonably assured that the initially reactive π-bond of DFA is the fluorine-substituted one. This assumption derives from the observation that fluorine-substituted olefins are much more reactive in [2 + 2] reactions than hydrogen-substituted ones.[19] Especially significant is the comparison of the [2 + 2] reactivities of methylenecyclopropanes **9** and **10**. **9** and **10** are essentially

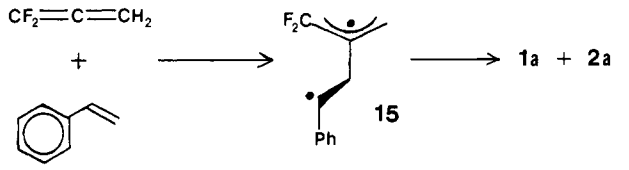


"homoallenes" and should be considered excellent models of the fluorine-substituted and the hydrogen-substituted π-bonds, respectively, of DFA.[23] Thus in the DFA–styrene reaction, we will assume initial reaction to be with the C_1–C_2 π-bond.

Steric effects should also be minimal for the DFA–styrene system with only the phenyl substituent making significant steric demand. The fluorine substituents of DFA have been previously demonstrated to exert little if any steric demand in [2 + 2] or [2 + 4] cycloadditions. A clear example of this lack of steric demand for fluorine is provided in the reaction of fluoroallene with 1,1-dichloro-2,2-difluoroethylene wherein products **13** and **14** are formed in equal amounts.[13b] Thus diradicals **11** and **12**, formed by the two modes of CHF rotation, were likely formed in near equal amounts.



The DFA–styrene reaction is best understood as involving the allyl–ethyl diradical system **15**. The intervention of HOMO–LUMO or charge-transfer interactions seems unlikely in view of the competition results (Table II) where both an electron-rich styrene (p-OCH_3) and an electron-deficient one (p-NO_2) are seen to undergo cycloaddition more rapidly than styrene itself. While



these results are consistent with expectations on the basis of a previous substituent effect study on thermal rearrangements of 2-aryl-3,3-dimethyl-1-methylenecyclopropanes,[24] the present results comprise to our knowledge the first example of a Hammett-type study of a [2 + 2] reaction.

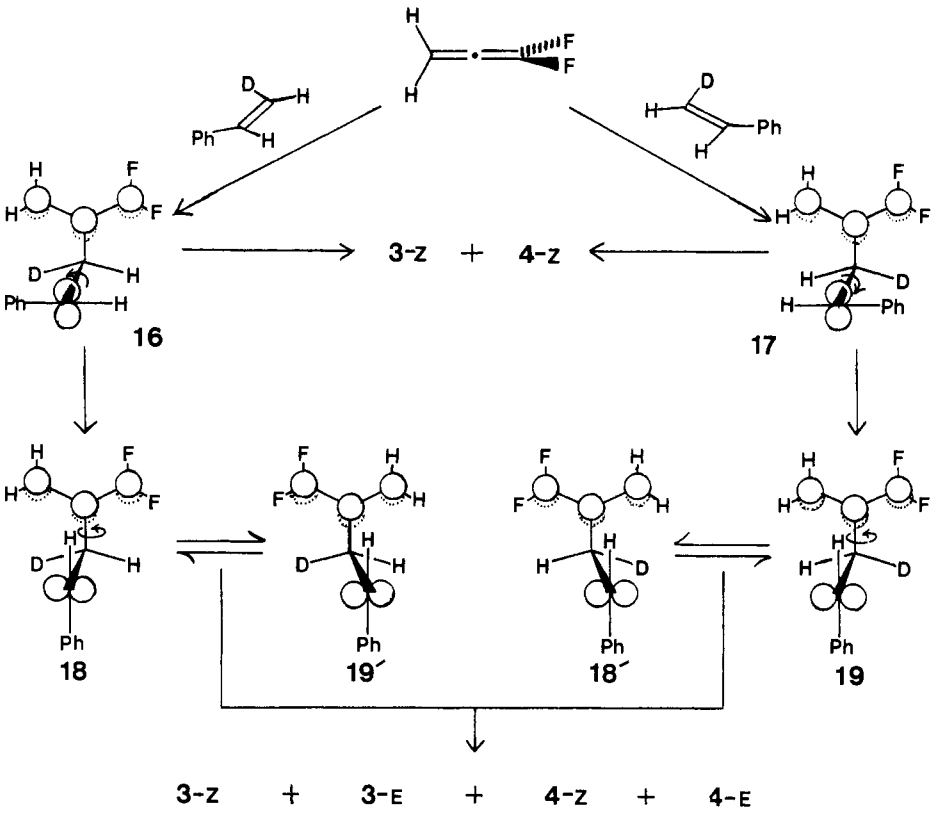
The stereochemical results in Table III allow one to begin to dissect the rather inscrutable intricacies of this complex mechanism. Pasto, in his related stereochemical study of the reactions of 1,1-dimethylallene with diethyl fumarate and diethyl maleate, reached similar conclusions in a *much* more complex reaction system.[12]

In order for a diradical mechanism to quantitatively rationalize the stereochemical results in Table II wherein the minor product **4** is formed with greater retention of stereochemistry than the major product **3**, it is necessary to invoke at least *two kinetically distinct* intermediates in the reaction. The first, short-lived intermediate or intermediates should be nonregioselective but highly stereoselective in cyclizing to **3** and **4**, and they must also convert to a more stable intermediate before being able to undergo much cyclization. This second intermediate should be much longer lived, should essentially randomize stereochemically before cyclizing, and should be much more highly regioselective in forming the more stable product **3** vs. **4**. Scheme I gives a reasonable mechanistic sequence of events which could indeed give rise to the above expectations. Assuming a lack of steric effect due to deuterium or fluorine substituents, **16** and **17** should be formed at similar

(22) A recent isotope effect study is consistent with such rotation occurring in the transition state.[10]

(23) Dolbier, W. R., Jr.; Daly, D.; Smart, B. E., unpublished results.
(24) Creary, X. *J. Org. Chem.* **1980**, *45*, 280.

Scheme I



rates and should have similar kinetic stability, rotating at similarly rapid rates to alleviate likely steric effects due to the phenyl substituent and forming the presumably more-stable diradicals **18** and **19**. Because of their likely reactivity, it is reasonable to assume a lack of selectivity for **16** or **17** in their cyclizations at the CH_2 or CF_2 termini, although one might expect that **16**, due to its likely mode of rotation to **18**, might prefer cyclization to **4**-*Z* while **17** might to a similar extent prefer cyclization to **3**-*Z*. Diradicals **18** and **19** should themselves be more stable kinetically due to the relative lack of proximity of their benzyl radical orbitals to the termini of their allyl radical systems. The allyl radical systems of **18** and **19** could potentially rotate as shown to form **19′** and **18′**, respectively, the enantiomeric forms of **19** and **18**. The two radical systems **18** $\rightleftharpoons$ **19′** and **19** $\rightleftharpoons$ **18′** are not interconvertible, but each should lead to identical, fully stereorandomized mixtures of **3** and **4**. Therefore the viability of Scheme I is independent of the relative rate of formation of **16** and **17**.[25]

Remarkably, such a simple picture for the reaction allows excellent correlation of the experimental results. For example, assuming that *all* excess *Z* (i.e., retained stereochemistry) products derive from cyclization of **16** and **17**, the results at 100 °C can be quantitatively reproduced having the mixture of **16** and **17** cyclize to 11.3% **3**-*Z* and 11.0% **4**-*Z* with the rest (77.7%) converting to the mixture of diradicals **18** and **19** which stereochemically equilibrate before undergoing regioselective (9:1) cyclization to completely randomized mixtures of *Z* and *E* **3** (69.7%) and **4** (8.0%). Such a kinetic scenario exactly reproduces the experimental *Z*:*E* ratios for **3** (57:43) and **4** (79:21).

Consistent with expectations, application of the same assumptions to the lower temperature reactions shows an increase in selectivity of closure of **16** and **17** at the lower temperatures, with 15% of **3**-*Z* being required vs. 10% of **4**-*Z* in order to exactly fit the experimental results at 70 °C.

Conclusion

Thus the stereochemical results in the reaction of (*Z*)-β-deuteriostyrene with DFA can be rationalized nicely if one invokes a highly reactive initially formed intermediate (or intermediates) which cyclizes relatively nonselectively to products **3** and **4** with high stereospecificity, but which mostly converts to a more stable diradical system. This system then cyclizes much more regioselectively to more stable products **3** over **4**, but with virtually complete loss of stereochemistry.

It is assumed, for lack of a better hypothesis, that the proposed diradicals or systems of diradicals are simply conformational isomers, such as those depicted specifically above. However, there is *no direct evidence* for the structures of the specific species actually involved, nor is it even necessary that the two modes of reaction be sequentially related. They could be parallel pathways. The stereochemical results merely require two pathways to products **3** and **4**, a minor pathway which is nonregioselective and stereospecific and a major pathway which is more regioselective but stereorandom.

It finally should be stated, however, that the specific mechanistic scheme presented in the discussion is one which is consistent with everything that is presently known about allene [2 + 2] cycloaddition reactions.

Experimental Section

Infrared spectra were determined as films between KBr plates. NMR chemical shifts for ^1H and ^{13}C spectra are reported in parts per million downfield from internal Me_4Si in $CDCl_3$ solution. Chemical shifts for ^{19}F spectra are reported in parts per million upfield from internal $CFCl_3$ in $CDCl_3$. Mass spectra and exact masses were determined at 70 eV. Elemental analyses were performed by Atlantic Microlabs. The product ratios for the deuterated work were obtained on a Varian Aerograph A90-P3 gas chromatograph with a thermal conductivity detector. Other product ratios and percent yields were determined as an average of three injections on a Hewlett-Packard 5790A gas chromatograph (FID) with a recording integrator or by ^{19}F NMR.

(*Z*)-β-Deuteriostyrene. A solution of 40.2 g (0.335 mol) of catecholborane and 36.2 g (0.351 mol) of phenylacetylene-d_1[26] was stirred under nitrogen at 10 °C for 20 min. During slow warming with an oil bath, an exothermic reaction took place at 55 °C. It was controlled by periodic application of an ice-water bath. After the mixture was stirred

(25) An enantiomeric scheme would result from attack from above the DFA.

(26) Wood, J. F.; Arney, J. S.; Cortes, D.; Berson, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 3855.

for 2.0 h at 70 °C, 700 mL of distilled water was slowly added and the milky white mixture was stirred at 89 °C for 4.0 h. Upon cooling the mixture, the filtered solid was washed with hexane and recrystallized from water with hot filtration. In this way, 36.0 g of white plates were collected. These were dried at 60 °C, in vacuo, overnight to afford 20.0 g (50.9 mmol) of the trimer of α-deuterio-β-phenylethenylboronic acid (45.6%): mp 150–153 °C; ^{1}H NMR (acetone-d_6) δ 7.50 (m); M$^+$ 393.1982 ± 0.0025 (6.4 ppm), calcd for $C_{28}H_{18}D_3B_3O_3$ 393.1958, deviation −0.00238 (6.1 ppm); MS, *m/e* (relative intensity) 393 (100), 131 (38.5), all others <15% relative intensity.

The trimer (20.0 g, 0.134 mol), 8.38 g (0.135 mol) of ethylene glycol, and 275 mL of toluene were heated at reflux with the azeotropic removal of water for 20 h. The solvent was removed by rotary evaporation at 20 torr to leave a liquid, which crystallized upon refrigeration. Recrystallization from *n*-hexane with hot filtration afforded 18.7 g (0.107 mol) of white needles (79.9%) of 2-((*Z*)-α-deuterio-β-phenyl)ethenyl-1,3,2-dioxaborolane: mp 47.5–49.0 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.50 (m, 6 H), 4.24 (s, 4 H).

To a melted solution of 18.5 g (0.106 mol) of the boronic ester and 100 mg of 4-*tert*-butylcatechol at 65 °C under nitrogen was added 67.1 g (1.12 mol) of freshly distilled (29 °C, 4.2 torr) glacial acetic acid dropwise. After the mixture was stirred at 90 °C for 1.5 h, the cooled solution was poured onto a 200 mL ice/100 mL pentane mixture, and after vigorous stirring, the water layer was extracted with pentane. The combined organic extract was washed with 0.5 N KOH solution and distilled water and dried, and the solvent was removed by rotary evaporation at 200 torr. Removal of the last traces of pentane by a stream of dry nitrogen followed by vacuum transfer of the colorless residue gave 8.52 g (0.0810 mol) of *cis*-deuteriostyrene (76.5%). The product was stored under nitrogen at −10 °C with approximately 50 mg of 4-*tert*-butylcatechol added. The 300-MHZ ^{1}H NMR spectrum agreed with the published spectrum[25] and *none* of the trans deuterated isomer was detected. A comparison of the mass spectrum of styrene at 12 eV with that of the cis deuterated material suggested an isotopic purity of 99.3 ± 0.7%.

2,2-Difluoro-3-phenyl-1-methylenecyclobutane (1a) and 3-Phenyl-1-(difluoromethylene)cyclobutane (2a). Into each of three 30-mL Pyrex bulbs, each containing 2.75 mL (24.0 mmol) of doubly degassed styrene, was condensed 15.3 mmol of previously degassed DFA.[27] After being sealed under vacuum, the bulbs were placed into a stirred oil bath at 97–99 °C. The bulbs were removed, cooled, and opened at the end of 3.0, 6.3, and 8.3 h. The regioisomer ratio **1a**:**2a** was determined to be 81.8:18.2 (±0.3) for each bulb by GLC with a $^1/_4$ in. × 20 ft. 10% DNP column at 128 °C, and the reaction was shown to be essentially complete within 3.0 h by a comparison of the chromatograms. Further examination of the 3.0-h reaction by TLC, GLC, and ^{19}F NMR demonstrated that there were no other products other than the oligomers of DFA.[13b] The excess styrene was removed from the 3.0-h reaction mixture by rotary evaporation at reduced pressure, and the products were separated by flash chromatography on a 40-mm column with 15 cm of 230–400 mesh silica gel with 25-mL fractions and hexane as the eluant. In this way, 0.54 g (3.0 mmol) of **1a**, which was further purified by preparative GLC at conditions similar to those given above, and 0.04 g (0.2 mmol) of **2a** were each isolated as colorless, sweet-smelling oils in a combined isolated yield of 21%.

1a: IR, 3070, 3038, 2938 (w), 1500 (s), 1454, 1432, 1276 (vs), 1155 (vs), 1113 (s), 1050 (vs), 927 (vs), 724 (vs), 694 (vs) cm^{-1}; ^{1}H NMR δ 7.32 (m, 5 H), 5.60 (m, 1 H), 5.30 (m, 1 H), 3.99 (d of virtual quartets, 1 H, J_{HF} = 13.4 Hz, J_{HF} = 10.2 Hz, J_{HH} = 10.2 Hz demonstrated by decoupling experiments), 2.87 (m, 2 H); ^{19}F NMR φ 91.4 (dddd, 1 F, J_{FF} = 209.1 Hz, J_{HF} = 13.6 Hz, J_{HF} = 5.1 Hz, J_{HF} = 2.5 Hz), 107.4 (dd, 1 F, J_{FF} = 209.1 Hz, J_{HF} = 10.5 Hz); ^{13}C NMR δ 144.1 (t, J_{CF} = 20.7 Hz, C_1), 135.2 (Ph), 128.5 (Ph) 128.1 (Ph), 127.4 (Ph), 119.0 (dd, J_{CF} = 286.6 Hz and J_{CF} = 278.4 Hz, CF_2), 112.2 (olefinic CH_2), 49.9 (t, J_{CF} = 21.6 Hz, CHPh), 29.1 (dd, J_{CF} = 14.3 Hz, J_{CF} = 4.0 Hz, aliphatic CH_2); MS, *m/e* 180 (55), 165 (66), 152 (25), 140 (43), 129 (100), 115 (28), 104 (100), 89 (16), 78 (49), 63 (21), 51 (39), 39 (35); M$^+$ 180.07466 ± 0.00103 (5.7 ppm), calcd for $C_{11}H_{10}F_2$ 180.07506, deviation −0.00039 (2.2 ppm); Anal. C, H.

2a: IR 3070, 3034, 2969,2931 (s), 1782 (vs), 1496, 1450, 1241 (vs), 1139 (s), 1096 (vs), 749 (vs), 694 (vs) cm^{-1}; ^{1}H NMR δ 7.25 (m, 5 H), 3.58 (virtual pentet, 1 H, *J* = 8.3 Hz), 3.08 (m, 2 H_{trans}), 2.79 (m, 2 H_{cis}); ^{19}F NMR φ 97.3 (m); ^{13}C NMR δ 150.8 (t, J_{CF} = 282.3 Hz, CF_2), 144.7 (Ph), 128.6 (Ph), 126.5 (Ph), 126.4 (Ph), 84.0 (t, J_{CF} = 26.2 Hz, C_1), 36.1 (CHPh), 31.7 (CH_2); MS, *m/e* 180 (33), 165 (36), 159 (31), 152 (19), 140 (11), 129 (73), 115 (20), 104 (100), 91 (12), 78 (60), 63 (17), 51 (42), 39 (23); M$^+$ 180.07468 ± 0.00099 (5.5 ppm), calcd for $C_{11}H_{10}F_2$ 180.07506, deviation −0.00038 (2.1 ppm); Anal. C, H.

Similarly prepared samples were heated at 70 °C for 1, 2, 3, and 6 h with the ratios (**1a**:**2a** = 83.1:16.9 ± 0.2) remaining constant for all times of reaction.

2,2-Difluoro-3-(4-methoxyphenyl)-1-methylenecyclobutane (1b) and 3-(4-Methoxyphenyl)-1-(difluoromethylene)cyclobutane (2b). In a manner similar to that above, sealed tubes containing 1.50 mL (11.2 mmol) of *p*-vinylanisole, 29 mg of hydroquinone, and 4.4 mmol of DFA were heated at 61–63 °C for 16 h. The regioisomeric ratio **1b**:**2b** was determined to be 86.1:13.9 by GLC with a $^1/_4$ in. × 10 ft diisodecylphthalate column at 150 °C. Product isolation as above provided 121 mg of **1b** and 8.0 mg of **2b** for an isolated yield of 14%.

1b: IR 3007 (w), 2970, 2947, 2847, 1615 (s), 1587, 1517 (vs), 1467, 1445, 1278 (vs), 1252 (vs), 1221 (s), 1182 (s), 1160 (s), 1122 (s), 1080 (Ph), 1053 (vs), 1037 (s), 933 (s), 835 (s), 812, 782, 745 cm^{-1}; ^{1}H NMR δ 7.17 and 6.87 (AB pattern, 4 H, J_{HH} = 8.9 Hz), 5.57 (m, 1 H), 5.25 (m, 1 H), 3.90 (d of virtual quartets, 1 H, J_{HF} = 13.5 Hz, H_{HF} = 9.8 Hz, J_{HH} = 9.8 Hz), 3.77 (s, 3 H), 2.80 (m, 2 H); ^{19}F NMR φ 91.8 (dddd, 1 F, J_{FF} = 208.9 Hz, J_{HF} = 13.5 Hz, J_{HF} = 5.2 Hz, J_{HF} = 2.5 Hz), 107.7 (dd, 1 F, J_{FF} = 208.9 Hz, J_{HF} = 10.3 Hz); ^{13}C NMR δ 158.9 (Ph), 144.2 (t, J_{CF} = 20.8 Hz, C_1), 129.1 (Ph), 127.2 (Ph), 119.0 (dd, J_{CF} = 286.3 Hz and J_{CF} = 277.7 Hz, CF_2), 113.8 (Ph), 112.0 (olefinic CH_2), 55.2 (OCH_3), 49.2 (t, J_{CF} = 21.3 Hz, CHAr), 29.3 (dd, J_{CF} = 14.7 Hz and J_{CF} = 4.9 Hz, aliphatic CH_2); MS, *m/e* 210 (100), 195 (31), 179 (22), 170 (11), 159 (23), 134 (77), 119 (47), 91 (23), 84 (31), 77 (11), 65 (11), 51 (10); M$^+$ 210.08649 ± 0.001179 (5.6 ppm), calcd for $C_{12}H_{12}F_2O$ 210.08562, deviation +0.00087 (4.1 ppm); Anal. C, H.

2b: IR 2965, 2934, 2840 (w), 1785 (vs), 1613, 1512 (vs), 1461, 1442, 1290, 1250 (vs), 1227, 1179 (s), 1140, 1112, 1096 (s), 1038 (s), 826 (s) cm^{-1}; ^{1}H NMR δ 7.18 and 6.90 (AB pattern, 4 H, J_{HH} = 8.9 Hz), 3.80 (S, 3 H), 3.58 (virtual pentet, 1 H, J_{HH} = 8.3 Hz), 2.91 (m, 4 H); ^{19}F NMR φ 97.4 (m); ^{13}C δ 158.2 (Ph), 150.7 (t, J_{CF} = 282.0 Hz, CF_2), 136.8 (Ph), 127.3 (Ph), 113.9 (Ph), 83.9 (t, *J* = 26.2 Hz, C_1), 55.3 (OCH_3), 35.4 (CHAr), 31.9 (CH_2); MS, *m/e* 210 (100), 195 (26), 179 (18), 159 (22), 134 (100), 119 (61), 91 (41), 84 (44), 77 (11), 65 (22), 49 (53), 39 (12); M$^+$ 210.08584 ± 0.001695 (8.1 ppm), calcd for $C_{12}H_{12}F_2O$ 210.08561, deviation +0.00024 (1.0 ppm).

2,2-Difluoro-3-(4-nitrophenyl)-1-methylenecyclobutane (1c) and 3-(4-Nitrophenyl)-1-(difluoromethylene)cyclobutane (2c). Similarly, pyrolysis reactions of 0.50 mL (3.6 mmol) of *p*-nitrostyrene, 0.32 mmol of DFA, and 20 mg of *tert*-butylcatechol were carried out at 102 °C, with isolation of **1c** by flash chromatography and additional though incomplete purification of **2c** by GLC providing a total isolated yield of 26%.

1c: IR 3085 (w), 2940 (w), 1600 (s), 1514 (vs), 1438, 1348 (vs), 1272 (s), 1218, 1200, 1155 (s), 1119 (s), 1108 (s), 1076 (s), 1048 (s), 930 (s), 850 (s), 730 (s), 692 cm^{-1}; ^{1}H NMR δ 8.20 and 7.43 (AB pattern, 4 H, J_{HH} = 8.91 Hz), 5.65 (m, 1 H), 5.36 (m, 1 H), 4.10 (d of virtual quartets, 1 H, J_{HF} = 12.7 Hz, J_{HF} = 9.8 Hz, J_{HH} = 9.8 Hz), 2.92 (m, 2 H); ^{19}F NMR φ 90.8 (dddd, 1 F, J_{FF} = 209.7 Hz, J_{HF} = 12.9 Hz, J_{HF} = 5.0 Hz, J_{HF} = 2.5 Hz), 106.4 (dd, 1 F, J_{FF} = 209.7 Hz, J_{HF} = 10.1 Hz); ^{13}C NMR δ 147.2 (Ph), 142.9 (t, J_{CF} = 20.75 Hz, C_1), 142.6 (Ph), 129.0 (Ph), 123.5 (Ph), 118.4 (dd, J_{CF} = 288.09 Hz and J_{CF} = 278.32 Hz, CF_2), 113.2 (olefinic CH_2), 49.6 (t, J_{CF} = 21.97 Hz, CHAr), 28.9 (dd, J_{CF} = 13.43 Hz and J_{CF} = 4.88 Hz, aliphatic CH_2); MS, *m/e* 225 (7), 209 (17), 208 (98), 185 (5), 179 (74), 178 (100), 177 (50), 164 (42), 160 (25), 159 (86), 149 (22), 146 (19), 128 (74), 119 (60), 103 (60), 91 (33), 77 (72), 63 (20), 51 (28), 43 (66), 39 (24), 32 (32); M$^+$ 225.06213 ± 0.00045 (20 ppm), calcd for $C_{11}H_9F_2NO_2$ 225.06013, deviation +0.00199 (8.87 ppm); Anal. C, H.

2c: ^{1}H NMR δ 8.19 and 7.41 (AB pattern, 4 H, J_{HH} = 8.91 Hz), 3.75 (virtual pentet, 1 H, J_{HH} = 8.25 Hz), 3.01 (complex m, 4 H); ^{19}F NMR φ 96.4 (m).

Quantitative Individual and Competitive Olefin + DFA Experiments. For each of the individual olefin + DFA experiments, 0.50 mL of an olefin was placed into a 5-mL bulb with either 10 mg of hydroquinone or, in the case of *p*-nitrostyrene, 20 mg of 4-*tert*-butylcatechol. After the olefin had been degassed twice, enough previously degassed DFA was condensed into the bulb so that an olefin:DFA mole ratio of 10:1.0 was maintained. The bulb was sealed under vacuum and placed into a well-stirred oil bath at the reaction conditions shown in Table I. The bulb was cooled and opened, and the regioisomer ratio and percent yield were determined by GLC and/or ^{19}F NMR integration of the reaction mixture. The method used for the competition experiments was similar except that all reactions were carried out at 100 °C for 2.0 h and the styrene:variable olefin:DFA mole ratio was 5:5:1 with 0.250 mL of styrene and used in each run. The results are given in Table II.

Examinations of these product mixtures by ^{19}F NMR, TLC, and GLC indicated no products other than DFA oligomers were formed. Yields were determined by comparison of each mixture of a known composition

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of purified major isomer **1** in its respective styrene as an external standard. Each reaction mixture and standard-containing solution was analyzed by GLC ($^1/_8$ in. × 10 ft, 20% DNP) 3–5 times, with the average being reported.

For all the reactions involving *p*-nitrostyrene and for the styrene/*p*-methoxystyrene competitive olefin experiment, the regioisomer ratios were determined by 282-MHz ^{19}F NMR in $CDCl_3$. Use of *m*-bromobenzotrifluoride as an internal standard allowed calculation of the percent yields. The samples were all degassed and sealed under vacuum. A T_1 population inversion experiment showed that the longest $T_1 \leq 6$ s for these compounds, and thus a 10-s pulse delay was used. The error in these results was estimated to be 2%.[28]

(*E*)- and (*Z*)-4-Deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane (3) and (*E*)- and (*Z*)-2-Deuterio-3-phenyl-1-(difluoromethylene)cyclobutane (4). A representative procedure for the deuterated runs is given below. Into a clean, dry, 30-mL, Pyrex bulb containing a doubly degassed mixture of 2.00 mL (17.2 mmol) of 99.3% (*Z*)-β-deuteriostyrene and 41 mg of hydroquinone was condensed 7.9 mmol of previously triply degassed DFA. After being sealed under vacuum, the bulb was placed in a stirred oil bath at 79–81 °C for 7.5 h. The bulb was cooled and opened, and the regioisomer ratio **3**:**4** was determined by GLC with a $^1/_4$ in. × 10 ft 10% DNP column at 140 °C. The excess (*Z*)-β-deuteriostyrene was removed by vacuum transfer at 12 torr, along with some **4**.

Crude separation of the residue by flash chromatography with a 45 mm diameter column with 14 cm of 230–400 mesh silica gel with 25-mL fractions and hexane as the eluant afforded 77 mg (0.42 mmole) of **4** followed by 378 mg (2.09 mmol) of **3** for a combined isolated yield of 32%. The ratios of *Z* to *E* isomers of **3** and **4** were determined by 300-MHz ^{1}H NMR with a pulse delay of 30 s to ensure relaxation of the protons integrated. In this way the stereochemical ratios for the deuterium *Z* vs. *E* to the phenyl ring were determined to be 58:42 for regioisomer **3** and 79:21 for **4**. Analysis of each isolated regioisomer by GLC at conditions similar to those given above showed a single peak. Examination of the recovered (*Z*)-β-deuteriostyrene, which was also purified by flash chromatography, by 100-MHz ^{1}H NMR demonstrated that there was no isomerization of the starting material under the reaction conditions.

An additional control whereby 19.5 mg of **4** was heated in heptane at 100 °C for 6 h showed *no* isomerization of **4** to the more stable **3** and no change in the *Z* to *E* ratio of recovered **4**.

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Registry No. 1a, 96245-32-8; **1b**, 96245-33-9; **1c**, 96245-34-0; **2a**, 96258-18-3; **2b**, 96245-35-1; **2c**, 96245-36-2; (*E*)-**3**, 96245-37-3; (*Z*)-**3**, 96245-38-4; (*E*)-**4**, 96245-39-5; (*Z*)-**4**, 96245-40-8; (*Z*)-PhCH=CHD, 21370-59-2; PhC≡CD, 3240-11-7; DFA, 430-64-8; α-deuterio-β-phenylethenylboronic acid trimer, 96245-41-9; 2-((*Z*)-α-deuterio-β-phenyl)ethenyl-1,3,2-dioxaborolane, 96245-42-0; catecholborane, 274-07-7; ethylene glycol, 107-21-1; styrene, 100-42-5; *p*-vinylanisole, 637-69-4; *p*-nitrostyrene, 100-13-0.

Stereodynamics of Intramolecular Triplet Energy Transfer in Carotenoporphyrins

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Abstract: Carotenoporphyrins, consisting of carotenoid polyenes linked covalently to porphyrins, are known to mimic both the antenna function and the photoprotection from singlet oxygen damage provided by carotenoids in photosynthetic organisms. A series of carotenoporphyrins whose conformations, as determined from ^{1}H NMR studies, range from folded (with the carotenoid π-electron system stacked over that of the porphyrin) to extended (with the chromophores widely separated) has been prepared. Time-resolved spectroscopic studies have revealed intramolecular triplet energy transfer from porphyrin to carotenoid. Two distinct pathways for such transfer (presumably occurring via an electron-exchange mechanism) were observed: (a) static transfer which does not require significant intramolecular motions; (b) dynamic transfer mediated by intramolecular motions. The relative importance of these pathways is a function of molecular structure and dynamics. The results for this series of carotenoporphyrins help define the photochemical and photophysical requirements for protection from singlet oxygen damage both in photosynthetic organisms and in other biological systems.

Two of the important functions of carotenoid polyenes in photosynthetic organisms are protection from singlet oxygen damage and antenna function. Antenna function involves absorption of light by carotenoid polyenes and transfer of singlet excitation to chlorophyll where it can be used for photosynthetic work. Photoprotection, which is vital for the survival of the organism, involves limiting singlet oxygen damage by either quenching singlet oxygen or preventing its formation. Because singlet oxygen is produced by energy transfer from a chlorophyll triplet-state sensitizer, one of the most effective photoprotective mechanisms is the quenching of the chlorophyll triplet by carotenoids prior to any interaction with oxygen.

It has been well established that carotenoporphyrins, which consist of carotenoid polyenes covalently linked to porphyrins or chlorophyll derivatives, can mimic both the photoprotective and antenna functions of carotenoids.[1-5] Because photoprotection

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