Cycloadditions of Fluoroallene and 1,1-Difluoroallene

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It was not so long ago that cycloadditions, as a class of reactions, were considered mechanistically obscure. Today, however, the high level of mechanistic understanding of these reactions along with their acknowledged unique regiochemical and stereochemical characteristics combine to make them among the most highly used and indispensible tools of the practicing chemist. Nevertheless, there are aspects of these reactions that continue to intrigue and inspire the current generation of physical organic chemists.

Cycloadditions are processes in which two ore more reactants combine to form a stable cyclic molecule, during which σ bonds are formed at the expense of π bonds and wherein no small fragments are eliminated.[1] Such reactions may be pericyclic in nature, that is, "reactions in which all first order changes in bonding relationships take place in concert on a closed curve",[2] or they may be reactions in which the two σ bonds are formed stepwise, that is, via a first σ-bond-forming step to produce a transient intermediate, usuallly a diradical, which cyclizes in a second step to form the product.

Allenes. Allenes as a class are considerably more reactive in undergoing cycloaddition reactions than are other alkenes with isolated, nonactivated double bonds. One of the reasons for this is that, on the basis of heats of hydrogenation, there is an effective "strain" of 10–11 kcal/mol associated with cumulated double bonds, a strain that is usually relieved when the allene undergoes any kind of addition reaction, including cycloadditions.

Perturbational molecular orbital theory indicates that, in general, the rates of *concerted* cycloadditions such as Diels–Alder and 1,3-dipolar cycloadditions of allenes are largely dependent upon the relative energies of the frontier molecular orbitals of the dienes or dipoles and those of the dienophilic or dipolarophilic allene.[3] Usually this means that the rates of such allene cycloadditions are greatly dependent upon the energy of the LUMOs of the allene addends; i.e., the *lower*, the better. Substitution of one of the double bonds of allene by a σ and π acceptor, such as CO_2Me or CHO, will enhance that bond's reactivity in Diels–Alder and 1,3-dipolar cycloadditions. In contrast, substitution of allene by a σ acceptor, π donor substituent, such as halogen (specifically in our case fluorine) or alkoxy leads to a lowering of the energy of the LUMO at the *non*substituted double bond, which thus activates that bond toward reaction.[4]

Allene also readily undergoes stepwise [2 + 2] cycloadditions,[5] with initial bond formation at the C_2 carbon of the allene leading to the intermediacy of a stabilized allylethyl diradical. As a result and in contrast to concerted cycloadditions, the overall regiochemistries of *non*concerted cycloadditions of an allene, as exemplified by the example below,[6] are not fully determined in their rate-determining steps, but also partially in their second, product-determining steps.

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(2) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* 1968, 1, 17.
(3) Houk, K. N. *Acc. Chem. Res.* 1975, 8, 361.
(4) Domelsmith, L. N.; Houk, K. N.; Piedrahita, C. A.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* 1978, 100, 6908.
(5) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* 1959, 81, 2723.
(6) Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* 1982, 104, 3670.
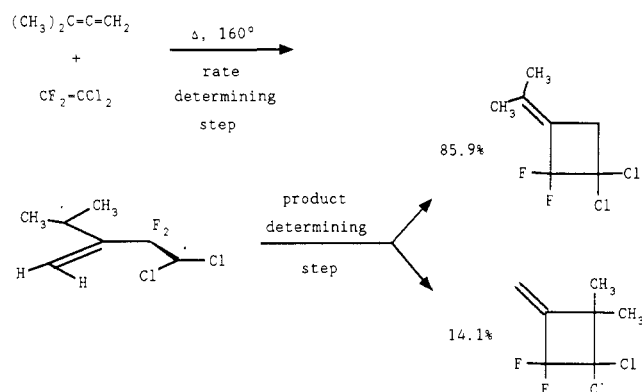
Fluorine as a Substituent. The fluorine substituent has many characteristics that make it uniquely useful in mechanistic studies.[7,8] In spite of its high electronegativity, fluorine is the best π donor of the halogen substituents because of the good match of its p orbitals with those of carbon. The high electronegativity and effective orbital overlap also give rise to a C–F σ bond which is both strong and short. With an A value of 0.11 (compared, for example, to A values of 1.8 for a methyl substituent and 0.7 for a chlorine substituent),[9] the fluorine substituent is the smallest of all non-hydrogen substituents, and as such it rarely exerts a steric influence on the outcome of a reaction. The considerable thermodynamic advantage (5–7 kcal/mol) for geminal fluorine substituents to be located on an sp^3-hybridized carbon in preference to an sp^2-hybridized carbon[10] also constitutes an important potential factor in determining the outcome of cycloadditions of fluorine-substituted olefins.

Fluorinated Allenes. Ab initio calculations carried out on 1,1-difluoroallene (DFA) and fluoroallene (MFA) indicate clearly that their LUMOs are their C_2–C_3 π^* orbitals, and their HOMOs are their C_1–C_2 π orbitals.[4,11,12] In MFA and DFA, the electron-donating and
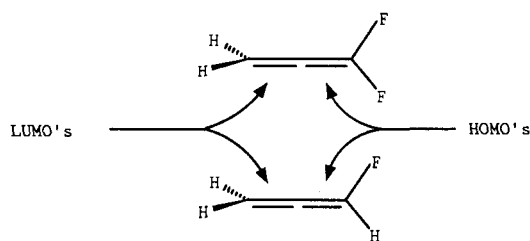

-withdrawing characteristics of fluorine operate in different ways on their two orthogonal π bonds. Only the C_1–C_2 substituted double bonds can be influenced by the electron-donating properties of the fluorine lone pairs, and empirically this effect appears to be canceled by the inductive withdrawing effect of fluorine on this π bond. This phenomenon has been called the "perfluoro effect" by Brundle et al.[13] In contrast, the

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(9) Hirsch, J. A. *Top. Sterochem.* 1967, *1*, 199.
(10) Dolbier, W. R., Jr.; Medinger, K. S.; Greenberg, A.; Liebman, J. F. *Tetrahedron* 1982, *38*, 2415.
(11) Dolbier, W. R., Jr.; Piedrahita, C. A.; Houk, K. N.; Strozier, R. W.; Gandour, R. W. *Tetrahedron Lett.* 1978, 2231.
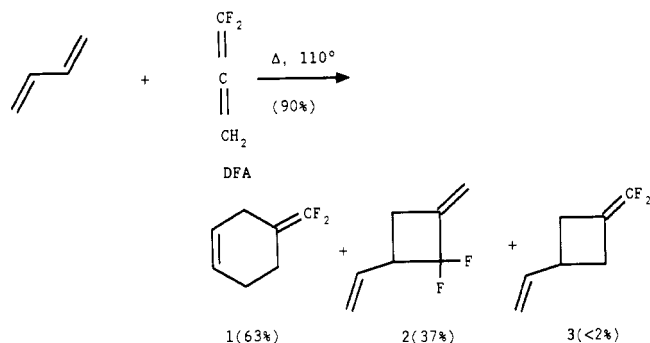(12) Dixon, D. A.; Smart, B. E. *J. Phys. Chem.* 1989, *93*, 7772.
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perfectly aligned, allylic fluorine substituent lowers the π and π^* orbital energies of the unsubstituted, C_2–C_3 double bond both through inductive withdrawal and through "negative hyperconjugation". This distinctly different effect of the fluorine substituents on the two π bonds of MFA and DFA, combined with the thermodynamic factors discussed above, gives rise to the unique and mechanistically diagnostic behavior of these allenes in cycloadditions. In this report the cycloaddition chemisty of 1,1-difluoroallene and fluoroallene will be summarized and discussed, with an emphasis being placed upon those reactions which are considered to be *pericyclic* in nature.

In 1960, Knoth and Coffman published a brief but interesting report of a number of cycloadditions of DFA including its reactions with cyclopentadiene and acrylonitrile.[14] Their work hinted at the diversity and richness of the chemistry of fluorine-substituted allenes which would be encountered 20 years later in the course of our comprehensive examination of the cycloadditions of DFA and MFA.

Cycloadditions of Difluoroallene

Consistent with the discussions above, both MFA and DFA exhibited considerably greater reactivity in Diels–Alder and 1,3-dipolar cycloadditions than allene. While allene itself required vigorous conditions to give a modest yield in its Diels–Alder reaction with cyclopentadiene, MFA reacted slowly in excellent yield at 0 °C, and DFA's reaction with cyclopentadiene was virtually instantaneous at –20 °C.[11,14,15] A similar trend in reactivity was observed in their respective 1,3-dipolar cycloaddition reactions with diazomethane.[16]
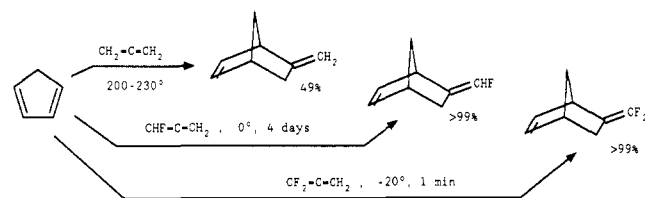
These early experiments evolved into a detailed investigation of the regiochemistry of DFA's reactions with 1,3-dienes. This study provided unexpected rewards because it was found that DFA underwent [2 + 2] cycloadditions with these dienes in competition with its expected Diels–Alder reactions, with the two competing processes exhibiting dramatically different regiochemistries.[11]

Diels–Alder Reactions. As indicated above, the reaction with 1,3-butadiene produced significant amounts of both Diels–Alder and [2 + 2] adducts. As in the cyclopentadiene reaction, this and all other Diels–Alder reactions of DFA were found to be totally regiospecific with respect to the allene, with cycloaddition occurring *only* with its non-fluorine-substituted C_2–C_3 π bond, in this case to form adduct 1. In contrast, the major competitively formed [2 + 2] adduct (2) was found to be that which derived from cycloaddition to the fluorine-substituted double bond. Moreover, unlike the [2 + 4] process, the [2 + 2] process

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DFA

1(63%)   2(37%)   3(<2%)

was not regiospecific since traces (<2%) of the alternate regioisomer **3** were observed in the crude product mixture. Most of DFA's [2 + 2] reactions were not nearly so regioselective as this one, but they all gave as the major product the isomer with the CF$_2$ incorporated in the ring.[15] The [2 + 2] cycloaddition chemistry of DFA itself provided significant mechanistic insight, but this subject is beyond the scope of this Account.[17]

By means of DFA's reactions with unsymmetrically substituted 1,3-dienes such as isoprene, the regioselectivities of the observed [2 + 4] and [2 + 2] cycloadditions *with respect to the diene* were examined. As seen below, the observed regioselectivities are quite different for the [2 + 4] and the [2 + 2] cycloadditions, with little selectivity seen for the putative concerted Diels–Alder reaction, while relatively high selectivity is observed for the [2 + 2] reactions. The significant preference for formation of [2 + 2] adduct **6** over adduct **7** is, of course, consistent with its having a more stable diradical intermediate as its precursor.

4(29%)   5(35%)

6(26%)   7(10%)
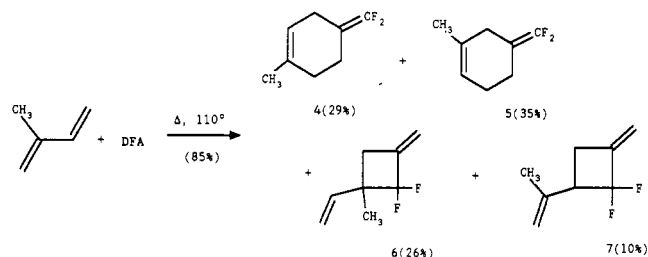
With a common intermediate not a viable alternative, due to the very different regiochemistries observed, the simplest rationale for the results is that a concerted [2 + 4] process takes place in competition with a nonconcerted [2 + 2] process. While the [2 + 2] results are completely consistent with the competitive involvement of two diradical intermediates, the Diels–Alder results can themselves be nicely rationalized in terms of a concerted process using the frontier molecular orbital theory of cycloadditions.[3] Moreover, calculations indicate that the LUMO coefficients, 0.73 at C$_2$ and –0.78 at C$_3$, of DFA are nearly identical,[4,11] consistent with the observed lack of selectivity in formation of adducts **4** and **5**.

These initial results indicated that the simple regiochemistry of DFA's cycloadditions might well provide unambiguous mechanistic insight, with concerted and nonconcerted reactions being able to be distinguished by mere identification of products. The results that were to be obtained in our subsequent work certainly enhanced the credibility of this hypothesis.

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1,3-Dipolar Cycloadditions.

Like the Diels–Alder reaction, 1,3-dipolar cycloadditions are 4π + 2π one-step multicenter reactions wherein the 1,3-dipoles play the role of the 4π system. As such, 1,3-dipolar cycloadditions are allowed by the Woodward–Hoffmann rules to occur by a concerted, suprafacial–suprafacial cycloaddition mechanism. The factors that govern the reactivity and regioselectivity of 1,3-dipolar cycloadditions are the same as those that govern the Diels–Alder reaction.[6,18] However, 1,3-dipolar cycloadditions tend to exhibit much more regioselectivity than their Diels–Alder counterparts. The types of 1,3-dipoles that we will be discussing, such as nitrones, diazo compounds, and nitrile oxides, are all species that react especially well with electron-deficient dipolarophiles, and thus the important frontier molecular orbital interaction in such cycloadditions is expected to be HOMO (dipole)–LUMO (dipolarophile).[6]

1,1-Difluoroallene was found be highly reactive with 1,3-dipoles, and it underwent facile, high-yield, and totally regiospecific cycloaddition to its C$_2$–C$_3$ double bond with all 1,3-dipolar reagents that were investigated. Generally, it was found that a *single* orientation of the 1,3-dipole was also highly, if not exclusively, favored in such cycloadditions, quite unlike the observations for DFA's reactions with 1,3-dienes, which showed little if any orientational selectivity.

In DFA's reactions with nitrones, for example, a *single* regioisomeric product was obtained in all cases,[19,20] as the reaction with C-phenyl-N-methylnitrone demonstrates. Likewise, DFA's reaction with diazomethane was found to be totally regiospecific.[21]

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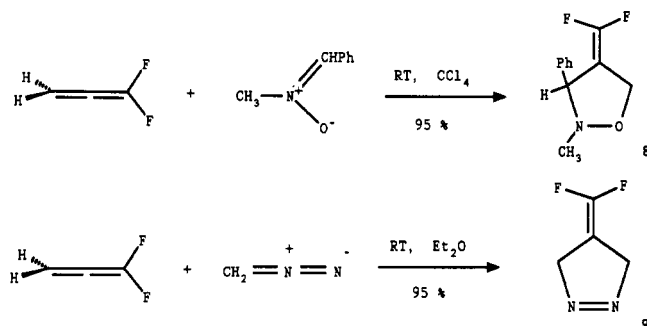
Further 1,3-Dipolar Results and Discussion. In contrast to its reaction with the parent diazomethane, DFA's cycloadditions with *substituted* diazomethanes (**10**) were *not* regiospecific, but led to two adducts, **11** and **12**, these deriving from the two possible orientations of the dipole with respect to the C$_2$–C$_3$ π bond of DFA.[21] It can be seen that as the substituents on the

            11   12

10-a   R = R' = Me   61%   39%

b   R = R' = fl =   28   72

c   R = R' = Ph   14   86
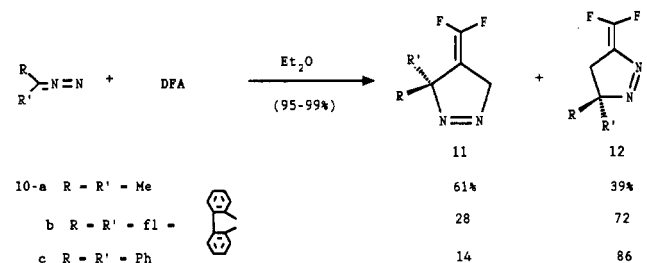
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(19) Dolbier, W. R., Jr.; Burkholder, C. R. *Isr. J. Chem.* **1985**, *26*, 115.
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diazo compound become increasingly bulky, adduct 12 becomes more favored as the product. Thus, as the substituents increase in size, steric effects would appear to intervene in determining the regiochemistry of the reaction.

Nitrile oxides are a classic type of 1,3-dipole. DFA's reactions with benzonitrile oxide and 2,4,6-trimethyl-benzonitrile oxide were investigated, as shown.[19,20] Interestingly, *both* regioisomeric adducts were formed in the reaction with benzonitrile oxide, but not with 2,4,6-trimethylbenzonitrile oxide. Obviously this variation in behavior cannot be due to a differential steric effect, since the more sterically hindered transition state should be that one leading to adduct 14.

|					
13-a	R = Phenyl	1 h(75%)		56%	44%
13-b	R = Mesityl	12 h (94%)		>99%	
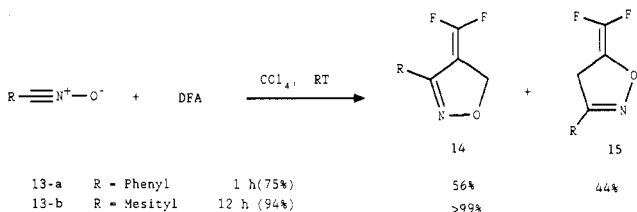
Cycloadditions of Fluoroallene

As discussed earlier in relation to its reactions with cyclopentadiene and diazomethane, fluoroallene is also quite reactive, being intermediate in dienophilic and dipolarophilic reactivity between allene and DFA.

The Issue of π-Faciality. Although one might not guess it from the cyclopentadiene results shown,[15] the
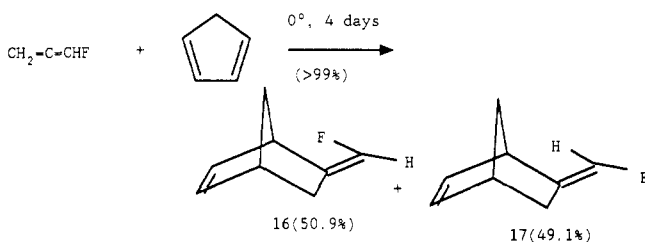

most interesting aspect about the cycloaddition reactions of MFA has to do with the fact that there is a *stereochemical* element to these reactions, since the two products, such as 16 and 17, which derive from C_2-C_3 addition, must necessarily have derived from cycloaddition either syn or anti to the fluorine substituent.
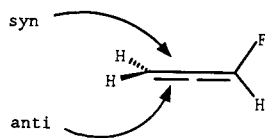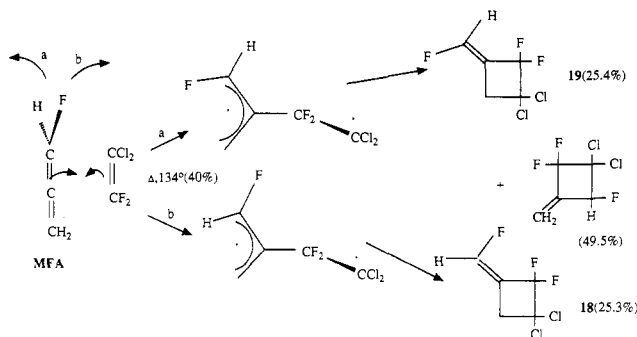

In recent years one has seen an increasing interest in what has come to be known as the *π-facial diastereoselectivity* of additions to unsymmetrically substituted π systems, particularly with regard to the effect of diastereotopically disposed *allylic* substituents.[22-24] Indeed, face selectivity in additions to trigonal carbon systems of all types is a truly fundamental question which is at the core of virtually all stereogenesis. It is therefore also of fundamental significance in organic synthesis as well as being of great portent to physical

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(23) Chung, W. S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* 1988, *110*, 7882.
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organic chemists. In fluoroallene, one has an excellent vehicle with which to probe the nature of π-facial selectivity in pericyclic reactions. First, in MFA the allylic fluorine substituent is perfectly aligned for either syn or anti electronic interaction. Secondly, the fluorine substituent of MFA, unlike *any* other substituent (other than deuterium, of course), is unlikely to exert a *steric* influence on the reactions being investigated. The only other systems that can compare with it regarding potential utility for probing π-facial selectivity are the 5-substituted adamantane derivatives being studied by le Noble and his co-workers.[23] Indeed, le Noble has found that the fluorine substituent is also the most advantageous for these studies.

Diels–Alder Reactions. MFA's Diels–Alder reactions are just as regiospecific with respect to the selectivity of addition to its C_2-C_3 π bond as are the Diels–Alder reactions of DFA.[15] With regard to *stereo*selectivity, our initial examination of MFA's reaction with cyclopentadiene did not indicate a significant preference for either syn or anti addition, but when MFA's additions to butadiene and furan were examined, a much more obvious, although certainly not dramatic, syn selectivity was observed.
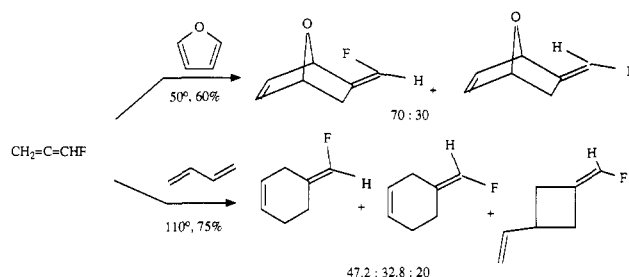
In a reaction of particular significance to the issue of π-faciality, the reaction of MFA with 1,1-dichloro-2,2-difluoroethylene, it can be seen from the ratios of products 18 and 19 that there is virtually *no* preference observed for syn or anti addition in this [2 + 2] cycloaddition.[15] The factors that determine π-facial selec-

tivity for a multistep, diradical mechanism should be very different from those that determine such in a concerted, pericyclic process. In a stepwise process, initial bond formation should be to C_2 of the C_1-C_2 π bond, with the net stereochemical outcome of this reaction being determined by whether the fluorine substituent, in rotating into allylic conjugation, prefers to rotate toward or away from the attacking reagent. The results indicate that, for a substituent of such small steric demand as fluorine, *no* apparent rotational preference is observed. This is in marked contrast to related studies of monoalkylallenes wherein a definite preference for net anti addition has been reported and

a steric rationale proposed.[25]

Thus, in a nonpericyclic cycloaddition of MFA, in which diradical intermediates are involved, no syn selectivity is observed. The observation of such selectivity in Diels–Alder and, as we will see below, 1,3-dipolar cycloadditions is therefore a strong indication that such selectivity derives from the pericyclic nature of the mechanism.

1,3-Dipolar Cycloadditions. Since cycloadditions of 1,3-dipoles are generally more orientationally selective than Diels–Alder reactions, it was expected that greater syn/anti selectivity might also be observed for these reactions. This indeed proved to be the case.

Nitrone Cycloadditions. MFA proved to be very reactive with nitrones, diazo compounds, and nitrile oxides, although of course not as reactive as was DFA.[20,26,27] MFA's reaction with *N-tert*-butylnitrone, for example, was complete after 5 days at room temperature while the analogous reaction with DFA required only 16 h. More significantly, it was found that this reaction occurred with greater syn selectivity (78:22) than had the Diels–Alder reaction.[20] Other nitrone cycloadditions occurred with even greater selectivity.[26,27]
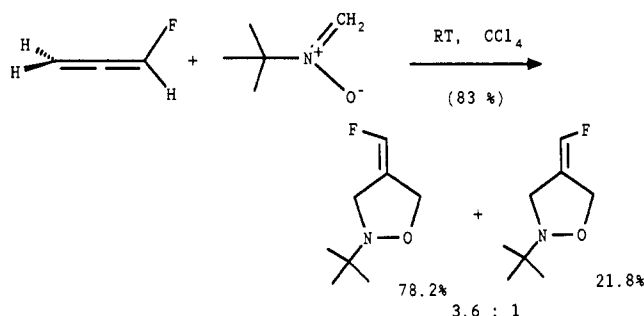

The observed remarkable preference for syn addition of nitrones to MFA is in marked contrast to similar additions of nitrones to methoxyallene and phenoxyallene wherein anti adducts were the major products.[28] Such results were explained in terms of steric effects. Since a fluorine substituent would be expected to exert little if any steric effect, the observed syn preference in these reactions of MFA must derive from other, more subtle influences.

Even though an 80:20 ratio is significant in terms of relative quantities, it nevertheless does not reflect a large difference in free energy of activation for the competitive processes. Activation parameters for the reaction of MFA with *N*-methyl-*C*-phenylnitrone were determined in three solvents[26] with no obvious insights being obtained, but it was indeed found that a difference of less than 1 kcal/mol in free energy of activation was sufficient to explain all of the stereoselectivities reported in this Account. One must then be very careful in attributing a unique factor as the source of such an observed effect.

A study of solvent polarity effects gave results that were consistent with Huisgen's classic studies of solvent effects on nitrone cycloadditions.[29] In fact, where

common solvents were used in Huisgen's and our work, a very similar trend was observed. Our activation energies were also consistent with those reported by Huisgen. Such comparisons indicate that the fluoroallene–nitrone cycloadditions should not be considered mechanistically different from other nitrone–alkene cycloadditions. As for the effect of solvent polarity on the syn:anti ratio, a definite trend toward less selectivity was observed with solvents of increasing polarity.[26]

Diazoalkane Cycloadditions. The cycloaddition chemistry of MFA with diazoalkanes very much resembled the complex behavior of DFA with diazoalkanes. As with DFA, diazomethane itself gave *only* a single regioisomeric adduct in reacting with MFA.[16] When deuterium-labeled diazomethane was used, a strong syn selectivity was observed in the reaction.[20]
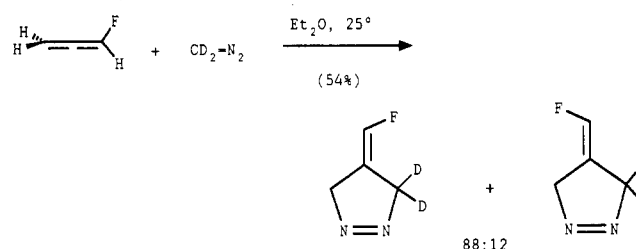
Cycloadditions of substituted diazo compounds with MFA provided even more intriguing results than those that were discussed earlier for DFA, wherein not only do the sterically favored regioisomers become predominant as the substituents become bulkier, but the anti stereoisomers **21** and **23** also are seen to predominate,[20] as exemplified by the reaction of MFA with diphenyldiazomethane (**10c**).
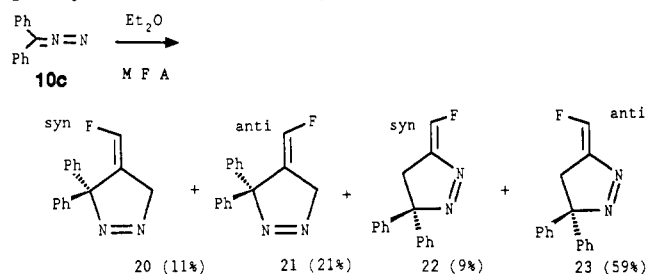
General Discussion

According to a perturbational theory analysis of molecular interactions,[30,31] *three* forces are potentially operative in the determination of the regiochemistry of bonding in any cycloaddition reaction: (1) electron density on one reactant interacting repulsively with that on the other (nonbonded, steric repulsion); (2) occupied molecular orbitals on one reactant mixing with unoccupied orbitals on the other (frontier MO interactions); (3) atoms in one reactant with net positive charge attracting atoms in the other with net negative charge and repelling atoms with net positive charge (electrostatic interactions). The importance of molecular orbital interactions in determining reactivity and regioselectivity in cycloadditions has been discussed by Houk,[6] while the potential significance of electrostatic interactions in the determination of regiochemistry of concerted cycloadditions has been discussed by Hehre.[32]

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Regioselectivity. In evaluating the various possible sources of consequential interaction in the above-discussed reactions, we have concluded that while frontier molecular orbital effects are undoubtedly important in determining regioselectivity with respect to relative π-bond reactivity for the allenes, and such effects probably are the most important factors in determining total regiochemistry of the observed Diels–Alder reactions, they are probably *not* of primary importance in the determination of the regiochemistry of 1,3-dipolar cycloadditions to DFA and MFA.[31]

Steric effects may well play a role in reversing the orientational preference observed in the addition of diazomethane to DFA and MFA when bulkier substituents than hydrogen are on the carbon. However, in the addition of nitrones the single observed orientation of addition is clearly contrary to what would be expected on the basis of steric effects, and the nitrile oxide results are also contrary to a steric effect rationale.

With MO and steric effects not providing clear-cut understanding of the regiochemical results for the 1,3-dipolar cycloadditions of DFA and MFA, it may be that electrostatic potential interactions will eventually provide a reasonable rationale. Electrostatic interactions essentially reflect the first-order Coulombic interactions of charged or polar reactants. The interaction "energy" is the energy arising from attraction or repulsion of the net partial charges associated with each atom in the transition state. Depending upon the charge and orientation of the reactants, the electrostatic energy may be negative (a net attraction) or positive (a net repulsion). In a reaction such as a 1,3-dipolar cycloaddition, all other things being equal (which they seem to be as far as steric and MO considerations are concerned), one would expect electrostatic interactions to play an important role. Electrostatic interactions between polar molecules are important both because they dominate at long distances and because they are large in the transition-state region. Clearly an evaluation of the electrostatic interaction energy is essential to the interpretation of all reactions of polar species.

Indeed, preliminary calculations of electrostatic potentials for DFA and the nitrone model $CH_2=NH^+-O^-$ indicate that the negative ends of these molecules are the CF_2 end of the allene and the O atom of the nitrone,[20,33] and the favored approach of the two reactants toward a reaction transition state was found to be that which would lead to that single regioisomer which is observed in all of the nitrone cycloadditions of DFA and MFA.

At this point the analogous predictions with respect to the cycloaddition reactions of diazo compounds or nitrile oxides are not clear, although preliminary calculations are, for example, not inconsistent with products **8** and **9** deriving from electrostatically favored transition states. There actually seems to be nothing yet published regarding the influence of electrostatic potential interactions in 1,3-dipolar cycloadditions.

π-Facial Diastereoselectivity. Similar factors should come into play in determining the favored approach of the 1,3-dipole to either the syn or the anti C_2-C_3 π face of MFA. Any preference for syn addition is of course by its nature contrary to any possible steric effect that might be exerted by the fluorine substituent.

According to a computational analysis,[20,33] the electrostatic interaction of the nitrone's O with MFA's CH_2 carbon will be favorable from either a syn or an anti approach. However, the electrostatic interaction of the nitrone CH_2 carbon with MFA's F substituent would be favorable for the hypothetical syn π-facial approach, while there would be no such favorable interaction in the hypothetical anti approach. There has also been an analysis of the diazoalkane/MFA results which indicates that electrostatic interactions are likely playing an important role in these syn/anti selectivities,[20] although one must await a definitive theoretical analysis of this and related systems. Nevertheless, at this point it appears probable that evaluations of electrostatic interactions will contribute importantly to our eventual understanding of the syn π-facial preference for 1,3-dipolar cycloadditions to MFA.

There is another factor, one that presumably falls into the category of a "secondary orbital effect", which also needs to be considered. This effect has been referred to by Cieplak,[22] le Noble,[23] and others[24] as the "hyperconjugation factor". Simply stated, this factor predicts that "both nucleophiles *and* electrophiles [should] approach trigonal carbon from the direction anti parallel to the electrorichest [allylic] single bond."[34] This prediction derived from the principle that an antiperiplanar σ bond should be able to delocalize into the newly developing σ^* orbital (created in our case upon bond formation at C_2 of the allene). le Noble, moreover, found that Diels–Alder reactions adhered to this prediction,[23] which when applied to cycloadditions of MFA would certainly predict syn π-facial selectivity since an antiparallel C–H σ bond should definitely be better hyperconjugating than a C–F σ bond.

Lastly, the results may be related to the observation by Gandolfi and DeMicheli of preferential syn addition of 1,3-dipoles to *cis*-3,4-dichloro- and *cis*-3,4-diacetoxycyclobutene.[35] In evaluating these results, calculations on *cis*-3,4-difluorocyclobutene by Caramella and Houk suggested that pyramidalization of the alkene carbons by the allylic fluorine substituents could influence the molecule's π-facial selectivity.[36] Indeed they suggested that the energetic effects of such interactions would be accentuated as the dipolarophile pyramidalizes to attain the transition-state geometry. Interestingly, in their ab initio calculations Dixon and Smart found the carbon skeleton of fluoroallene to be slightly bent.[12]

Conclusions

From the results and discussion here presented, it should be apparent that allenes, particularly fluorine-substituted allenes, are very effective addends for use in probing the subtleties of mechanisms of cycloaddition reactions. At this point *no* definitive answer can be given as to the cause of the regiochemical and stereochemical results that have been presented in this Account on the cycloadditions of DFA and MFA. While electrostatic interactions seem to have the best chance

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to close the gap and explain the regiochemical and stereochemical results, the theory of such interactions, particularly with respect to 1,3-dipolar cycloadditions, has not been adequately developed to allow one to reach any firm conclusions at this time. Other factors including those discussed above may also play a significant role.

The main thrust of the work that has been described in this Account was experimental. The results that have been presented on the regio- and stereochemical outcome of cycloadditions of difluoroallene and fluoroallene will be pertinent to any further theoretical rationale that is presented to explain the effect of substituents on this broad class of reactions. Moreover it should be evident that appropriately substituted allenes, with their perfectly aligned allylic bonds, constitute ideal substrates for use in testing the theories of π-facial selectivity.

Sponge Phospholipids[†]

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Sponges are simple cell aggregates that have thrived since the Cambrian Age in virtually all aquatic environments: marine and freshwater, from the equator to the poles, from shallow waters to enormous depths.[1] What is special about these ancient cells and their boundaries? What adaptive biochemical features exist in these oldest of the metazoans?

At a time when cell membrane biochemistry is gaining widespread attention, the discovery of well over 100 unprecedented sterols in sponges[2–5] followed by over 50 phospholipids[6] with unique structures and biosynthetic origins seems to have mystified further the riddle of membrane sterol–phospholipid interaction.[7–14] Are these sponge lipids indeed cell membrane components? What is their functional significance? In this Account we will attempt to unify the diverse findings on sponge phospholipids of the diacylglycerol type from comparative and evolutionary perspectives. Ether phospholipids, such as the plasmalogens, will not be considered.

Background

Our interest in sponge phospholipids is traceable to the earlier research on marine sterols.[2–5] In contrast to the monotony of terrestrial sterols (Figure 1), marine sterols show complex variations in both the tetracyclic nucleus and the side chain (Figures 2 and 3). The sterol mixtures of some sponges are composed entirely of the unique A-nor and 19-nor nuclei;[3] in others the isooctyl side chain of cholesterol is extended by alkyl branches and three-membered rings at various positions (Figure 3).[3–5] These structural oddities have attracted intensive biosynthetic studies.[2] The deliberate production of special lipids has, however, made even more puzzling their biological role in the organisms.

Sponges typically contain mixtures of the 24-alkyl sterols found in plants and cholesterol. However, a significant number of sponges possess substantial amounts of novel sterols, which prompted our early speculation[5a] that they were cell membrane components. Cholesterol is a membrane stabilizer:[8–13] it maintains the integrity of animal cell membranes by reducing the effective area of phospholipids (known as the condensing effect) and adjusting the flexibility and permeability of the latter. To achieve these ends the sterol molecule in general should have a rigid planar nucleus, a 3β-hydroxy group, C-18 and C-19 angular methyls, 17β and $20R$ configurations, and a C_6–C_{10} side chain (Figure 1).[5,8,9,14] Some sponge sterols contradict this rule (Figures 2 and 3):[5,9] the A-nor stanols have no 3β-hydroxyl function; the 19-nor stanols have no methyl group at C-19; and sterols with extended side chains interact poorly with the phospholipids in mam-

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