Ab Initio Study of Concerted Cycloadditions of Allene, Monofluoroallene, and 1,1-Difluoroallene with Diazomethane, Formonitrile Oxide, Cyclopentadiene, and Furane

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Received October 6, 1994®

Abstract: Structures and energetics of reactants and transition structures of cycloadditions of allene (A), monofluoroallene (MFA), and 1,1-difluoroallene (DFA) with diazomethane, formonitrile oxide, cyclopentadiene, and furane have been investigated with the use of ab initio molecular orbital calculations. Structure optimizations were performed with both RHF/3-21G and RHF/6-31G* calculations but were limited to RHF/3-21G for the reactions of cyclopentadiene and furane. For these reactions as well as for the reactions involving DFA electronic energies were computed to the MP3/6-31G* level, whereas the full MP4/6-31G* level was also explored for all the other reactions. Kinetic contributions to activation enthalpies and entropies and solvent effects were also considered. Electronic activation energies are found to be very sensitive to the treatment of electron correlation and fail to converge to values unaffected by further theoretical improvements; indeed, the inclusion of full fourth order correlation (MP4) decreases the activation energies by 5–8 kcal/mol with respect to the preceding level of correlation (MP3). In contrast, the reactivity sequences of A, MFA, and DFA as well as regio and diastereoselectivities attain, in general, stable predictions even at rather low levels of calculation and agree well with experimental trends. The increasing reactivities of A, MFA, and DFA appear to be bound to the decreasing energies requested for the geometry deformation toward their transition structures. As for diastereofacial selectivity in the cycloaddition of MFA, the syn-attack has been found to be strongly favored by the more facile anti- than syn-deformability of the allene moiety, foreshown by a small anti-bending or syn-pyramidalization of the π-atomic orbital of the C_2 carbon atom in the structure of the free MFA. Both syn-pyramidalization and the difference of syn/anti-deformability are traceable to the role of vicinal delocalizations between the C_2 C_3 π-bond (in the free MFA) or the new-forming bonds (in the transition structures) and the allylic C–H and C–F bonds at C_1. Differences in vicinal delocalizations are also found to be significant in affecting the regiochemistry of fluoroallenes, even though electrostatic interactions appear to play a major role in this type of selectivity.

In his recent Account[1] dealing with his elegant and impressive study of selectivity of fluoroallene cycloaddition, Dolbier concludes: "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 (1,1-difluoroallene) and MFA (monofluoroallene)... The results that have been presented on the regio- and stereochemical outcome 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... (appropriately substituted allenes) constitute ideal substrates for use in testing the theories of π-facial selectivity."

These conclusions are certainly stimulating, the more so as, from a theoretical point of view, fluorine-substituted allenes are small enough for the highest level of calculation so far proposed for these problems becomes feasible.

Regarding theoretical facilities for studying organic reactions, significant progress has been made in recent years both in understanding the nature of transition structures and in defining the level of ab initio theory required to reproduce experimental results. In particular, it has been established that the prototype of Diels–Alder reactions, *i.e.*, ethylene plus butadiene, and the prototypes of 1,3-dipolar cycloadditions, *i.e.*, ethylene plus formonitrile oxide or nitrone, have concerted mechanisms[2–4] and that, in the case of Diels–Alder reactions, calculated activation energies tend to converge to experimental values when fairly extended basis sets, including polarization, are used and electron correlation is extensively accounted for.[5] Very recently, in a theoretical study of Diels–Alder reactions of cyclopentadiene with substituted ethylenes[6] it was concluded that structure optimizations at the HF/6-31G* level, followed by single-point energy calculations at the MP3 level of electron correlation and by statistical evaluations of activation enthalpy contributions and entropies, could afford good agreement with experimental values; in addition, comparative treatment of many examples has established the ability of ab initio calculations to reproduce

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® Abstract published in *Advance ACS Abstracts*, April 1, 1995.

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Chart 1

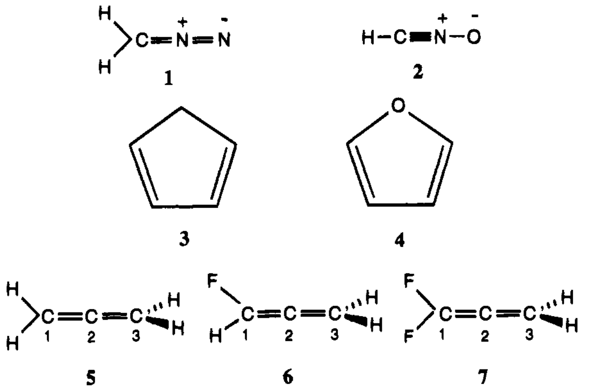
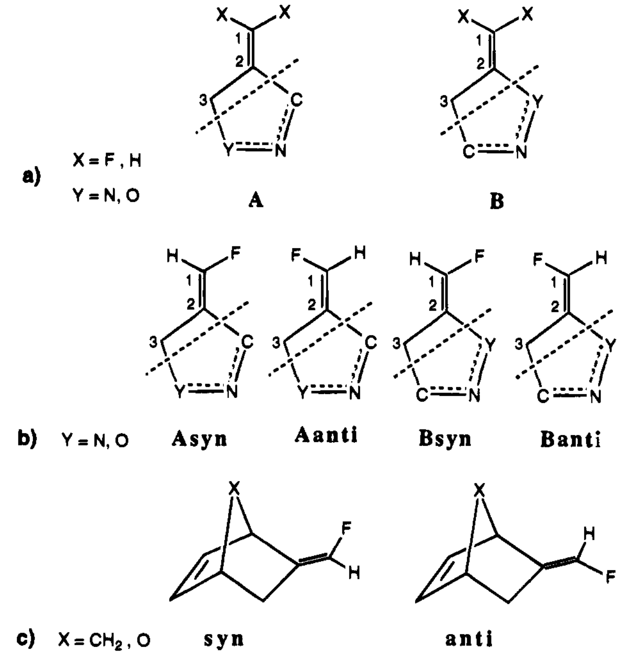


Chart 2



observed reactivity orders and stereoselectivities[7-11] of Diels–Alder reactions even at a more modest level of theory.

The performance of ab initio calculations in the field of 1,3-dipolar cycloaddition has not been investigated to anything like the same extent. In the cycloadditions of ethylene[2,12] and cyclobutene[12] with formonitrile oxide it has been shown that activation energies and reaction energies are severely affected by successive improvements of the theoretical model and that even the most extended feasible calculations produce unstable results. Fortunately, it has also been found[12] that many features of the results are affected by the procedure in a systematic manner and that, as a consequence of cancellation of systematic errors, differential results are much more stable than absolute values with respect to the increased completeness of calculations; as a matter of fact, the diastereofacial preferences of 1,3-dipolar cycloaddition to cis-3,4-disubstituted cyclobutenes, norbornene, bicyclo[2.1.0]pent-2-ene, and 2,3-dioxabicyclo[2.2.2]oct-5-ene are well accounted for at any level of theory.[12-16] By contrast, when the regioselectivity of 1,3-dipolar cycloadditions is considered, preliminary results[17] advocate caution in drawing conclusions from low level ab initio calculations and stress the need for test calculations in order to assess the convergence of results to values unaffected by theoretical improvements.

Accordingly, and in the context of our systematic theoretical study of the many facets of selectivity in 1,3-dipolar cycloaddition, we now report the results of ab initio calculations for 1,3-dipolar cycloadditions (with diazomethane (**1**) and formonitrile oxide (**2**)) and Diels–Alder reactions (with cyclopentadiene (**3**) and furane (**4**)) of allene (**5**), monofluoroallene (MFA) (**6**), and 1,1-difluoroallene (DFA) (**7**) (Chart 1), taking into account all the diastereofacial and regiochemical alternatives (Chart 2). In particular, A-regiochemistry arises from attack by the carbon atom of the 1,3-dipole to the central atom C_2 of allene dipolarophiles, and syn diastereoselectivity corresponds to the approach by the 1,3-dipole on the same side of the fluorine atom. In many cases, optimized transition structures up to HF/6-31G* and electronic energies up to MP4SDTQ/6-31G* have been produced. Activation enthalpies and entropies have been evaluated by including the kinetic contributions of the nuclear motions; solvent effects have been investigated in the approximation of the self-consistent reaction field,[18] as implemented in the context of ab initio molecular orbital theory.

Computational Methods

The ab initio molecular orbital calculations were performed using the GAUSSIAN 92 suite of programs[19] on a C220 Convex computer. Geometries for all structures were fully optimized at HF/3-21G and HF/6-31G* [20] utilizing analytical gradient techniques and default threshold for convergence. The searches were limited to concerted transition structures. Critical points were fully characterized as minima or first-order saddle points by diagonalizing the Hessian matrices of the optimized structures. Transition structures were found to have only one negative eigenvalue, the corresponding eigenvector involving the expected concerted formation of the two new bonds. Electron correlation was included *via* the Møller–Plesset perturbation theory up to the fourth order (MP4SDTQ/6-31G*); for the largest systems we had to limit ourself to HF/3-21G optimizations and third-order Møller–Plesset perturbation.

Vibrational frequencies, in the harmonic approximation, were calculated for all the optimized structures and used to compute zero-point energies, their thermal corrections, and the vibrational entropies. Although calculated vibrational frequencies are usually scaled for a more gratifying overall comparison with

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Table 1. Computed Kinetic Contributions to the Thermodynamic Properties of Reactants and Transition Structures[a]

		ZPVE		$\delta H(298)$		$S(298)$		$\delta G(298)$		$\delta(\Delta H^\ddagger)$		$(\Delta S^\ddagger)$		$\delta(\Delta G^\ddagger)$	
structure	stereo-regio	*b*	*c*	*b*	*c*	*b*	*c*	*b*	*c*	*b*	*c*	*b*	*c*	*b*	*c*
allene, A		37.56	37.30	40.40	40.17	57.28	60.13	23.33	22.24						
1-fluoroallene, MFA		33.26	33.08	36.39	36.22	65.47	65.49	16.87	16.70						
1,1-difluoroallene, DFA		28.29	28.23	31.74	31.67	68.66	68.60	11.27	11.22						
diazomethane, DZM		21.42	21.57	24.11	24.30	58.29	58.50	6.73	6.86						
formonitrile oxide, FNO		13.10	13.53	15.73	16.17	41.92	41.81	3.23	3.70						
cyclopentadiene, CP		62.80		65.81		65.81		46.18							
furane, FU		47.53		50.29		64.36		31.10							
allene-DZM	A	61.35	61.15	65.65	65.54	76.05	76.81	42.98	42.64	1.14	1.08	−39.52	−41.82	12.92	13.55
	B	61.67	61.50	65.91	65.81	75.48	76.06	43.40	43.15	1.42	1.35	−40.16	−42.57	13.39	14.04
MFA-DZM	Asyn	56.90	56.65	61.56	61.42	79.61	80.63	37.82	37.38	1.06	0.90	−44.15	−43.36	14.22	13.83
	Aanti	56.76	56.65	61.53	61.49	80.83	81.43	37.43	37.21	1.03	0.97	−42.93	−42.56	13.83	13.65
	Bsyn	57.05	56.95	61.73	61.68	80.11	80.99	37.85	37.53	1.23	1.16	−43.65	−43.00	14.25	13.98
	Banti	57.05	56.96	61.77	61.76	80.51	81.16	37.76	37.56	1.27	1.24	−43.25	−42.83	14.16	14.01
DFA-DZM	A	51.82	51.66	56.94	56.87	84.09	84.99	31.87	31.53	1.09	0.90	−42.86	−42.11	13.87	13.45
	B	51.93	51.89	57.08	57.12	84.67	85.57	31.84	31.61	1.23	1.15	−42.28	−41.53	13.84	13.53
allene-FNO	A	52.88	52.92	57.17	57.27	76.07	76.44	34.49	34.48	1.04	0.93	−23.13	−25.50	7.93	8.53
	B	52.69	52.75	57.00	57.08	76.28	76.42	34.26	34.30	0.87	0.74	−22.92	−25.52	7.69	8.35
MFA-FNO	Asyn	48.45	48.48	53.05	53.18	79.40	80.37	29.38	29.22	0.93	0.79	−27.99	−26.93	9.28	8.82
	Aanti	48.27	48.36	53.06	53.19	81.40	81.64	28.79	28.85	0.94	0.80	−25.99	−25.66	8.69	8.45
	Bsyn	48.19	48.37	52.85	53.07	80.04	80.32	28.99	29.12	0.73	0.68	−27.35	−26.98	8.89	8.72
	Banti	48.17	48.41	52.90	53.15	80.70	80.73	28.84	29.08	0.78	0.76	−26.69	−26.57	8.74	8.68
DFA-FNO	A	43.41	43.45	48.48	48.61	83.98	84.99	23.44	23.27	1.01	0.77	−26.60	−25.42	8.51	8.34
	B	43.12	43.41	48.21	48.52	84.13	84.43	23.12	23.35	0.74	0.67	−26.45	−25.97	8.19	8.42
MFA-CP	syn	98.12		103.22		84.39		78.06		1.03		−46.89		15.00	
	anti	98.05		103.23		85.07		77.87		1.04		−46.21		14.82	
MFA-FU	syn	82.25		87.17		83.23		62.35		0.49		−46.59		14.38	
	anti	82.19		87.18		83.93		62.16		0.50		−45.90		14.19	

[a] Harmonic approximation assumed; standard state (298 K) of the fugacity scale (pure perfect gas at 1 atm); energies in kcal/mol and entropies in eu (cal/mol·K); ZPVE: zero-point vibrational energy; $\delta H(298)$, $\delta G(298)$ are the kinetic contributions to molar enthalpy and free enthalpy (to be added to electronic energy); $S(298)$ is the molar entropy; $\delta(\Delta H^\ddagger)$ and $\delta(\Delta G^\ddagger)$ are the kinetic contributions to activation enthalpy and free enthalpy; $(\Delta S^\ddagger)$ is the activation entropy. [b] HF/3-21G calculations. [c] HF/6-31G* calculations.

experimental spectra, we are rather against the practice of an average scaling factor. As a matter of fact, most of the overestimation in the high frequency range is due to anharmonicity, whereas underestimations often occur in the low frequency range so that each frequency should be "corrected" according to its origin, *e.g.*, by using the scaling factor determined in parent molecules where the same normal mode occurs.[21] As far as zero-point energy is concerned, it has been shown that the values obtained from SCF harmonic frequencies appear to be significantly larger than experimental values and a scaling factor (0.91) has been suggested as a simple temporary solution for want of a better one.[22] However, one can easily verify from the unscaled zero-point energies of Table 1 that the use of the same scaling factor for reactants and transition structures does not affect the contribution of zero-point energy to the activation energy by more than a few tenths of a kcal/mol. Thermal corrections and vibrational entropies, on the other hand, are dominated by the population of the lowest lying excited vibrational modes and, in actual calculations at room temperature, only a limited number of low-frequency modes needs to be included: these frequencies fall just in the range within underestimations also occurring, and a frequency scaling could be ruinous. Our opinion is that no scaling, coupled with a sound awareness of the intrinsic deficiencies of the theoretical evaluation, is, in this context, the best choice.

The effect of the solvent on the electronic activation energies is evaluated using reaction field theory and the spherical cavity approximation.[18,19] The changes in geometry and in vibrational frequencies are not calculated. Owing to the limitations of this model where important contributions to the total solvation energy are neglected (multipole electrostatic terms, solvophobic effect, ...), the results are considered only for rough and qualitative comments.

Results and Discussion

The computed electronic energies for reactants and transition structures (TS) are provided as supplementary material. The structures for 1,3-dipolar cycloadditions are optimized up to HF/6-31G*, and electron correlation is taken into account in single-point energy calculations up to full fourth order (MP4SDTQ/6-31G*, frozen core) for MFA reactions, but only up to third order for DFA reactions; structures for Diels−Alder reactions are optimized only at HF/3-21G, and electron correlation is taken into account up to third order. Table 1 reports the contributions of nuclear motions (translational, rotational and vibrational) to the thermodynamic properties (H, S, G) of reactants and TSs and to the corresponding activation parameters ($\Delta H^\ddagger$, $\Delta S^\ddagger$, $\Delta G^\ddagger$). Both HF/3-21G and HF/6-31G* calculations are reported and found to involve only minor differences; the standard state adopted in this tabulation was that of a pure perfect gas at 1 atm (fugacity scale). Table 2 lists the computed activation parameters after zero-point energy and thermal corrections of Table 1 are included; electronic activation energies come from the MP4SDTQ/6-31G*//HF/6-31G* single-point calculations. When energies at the MP4 level were not calculated, electronic activation energies were assumed as the averages of MP2/6-31G* and MP3/6-31G* single-point energy calculations. The decision to average MP2 and MP3 values did not depend on theoretical arguments but only on the empirical finding that, in many examples, the full MP4 activation energy happened nearly to coincide with the aforesaid average[5,23] (see also the results of this paper for diazomethane reactions). For a more direct

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Table 2. Calculated Activation Parameters for the Cycloadditions of Diazomethane, Formonitrile Oxide, Cyclopentadiene and Furane to Allene and Fluoroallenes and Comparison between Calculated and Experimental Product Selection[a]

structure	stereo-regio	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	selectivity[d]	experimental product selection[e]		
allene-DZM	A	12.57	14.24 (+0.11)	−33.48	24.22 (+0.11)	0.00 (0.00)	0.00	ref 23	
	B	12.99	14.93 (−0.16)	−34.23	25.13 (−0.16)	0.91 (−0.27)	<1.53		
MFA-DZM	Asyn	4.10	5.59 (+0.98)	−35.02	16.03 (+0.98)	0.00 (0.00)	0.00[f]	0.00[g]	0.00[h]
	Aanti	7.44	9.00 (+0.11)	−34.22	19.20 (+0.11)	3.17 (−0.87)	1.17	0.28	−0.56
	Bsyn	8.41	10.16 (−0.69)	−34.66	20.49 (−0.69)	4.46 (−1.67)		1.30	−0.71
	Banti	7.72	9.55 (−0.68)	−34.49	19.83 (−0.68)	3.80 (−1.66)		0.05	−2.02
DFA-DZM[b]	A	3.30	4.79 (+0.70)	−33.77	14.86 (+0.70)	0.00 (0.00)	0.00[f]	0.00[g]	0.00[h]
	B	6.35	8.09 (−1.29)	−33.19	17.99 (−1.29)	3.13 (−1.99)	>2.70	0.26	−1.07
allene-FNO	A	11.31	12.83 (+2.69(	−17.16	17.95 (+2.69)	0.00 (0.00)	0.00[i]	0.00[l]	ref 30
	B	11.81	13.14 (+2.46)	−17.18	18.26 (+2.46)	0.31 (−0.23)	−0.98	0.24	
MFA-FNO	Asyn	5.47	6.85 (+4.12)	−18.59	12.40 (+4.12)	0.00 (0.00)	0.00[i]	0.00[l]	
	Aanti	8.55	9.94 (+3.85)	−17.32	15.10 (+3.85)	2.70 (−0.27)	−1.14	−1.59	
	Bsyn	9.28	10.55 (+2.09)	−18.64	16.11 (+2.09)	3.71 (−2.03)	−0.74	0.00	
	Banti	8.42	9.77 (+2.79)	−18.23	15.21 (+2.79)	2.81 (−1.33)	−1.24	−0.29	
DFA-FNO[b]	A	9.03	10.39 (+4.48)	−17.08	15.48 (+4.48)	0.00 (0.00)	0.00[i]	0.00[l]	
	B	11.10	12.36 (+2.08)	−17.63	17.62 (+2.08)	2.14 (−2.40)	0.14	>2.70	
MFA-CP[b,c]	syn	10.76	12.38 (+0.31)	−38.55	23.87 (+0.31)	0.00 (0.00)	0.00		
	anti	11.98	13.61 (−0.09)	−37.87	24.90 (−0.09)	1.03 (−0.40)	0.02		
MFA-FU[b,c]	syn	14.45	15.53 (+0.31)	−38.26	26.93 (+0.31)	0.00 (0.00)	0.00		
	anti	16.61	17.70 (−0.03)	−37.56	28.90 (−0.03)	1.97 (−0.34)	0.54		

[a] Electronic energy, $\Delta E^{\ddagger}$, from MP4(SDTQ)/6-31G*//HF/6-31G* calculation; kinetic contributions from HF/6-31G*; energies in kcal/mol, entropy in eu; standard state (298 K) of the molar concentration scale (gas in ideal mixture at 1 mol/L, $P = 1$ atm); solvent effects (in parentheses) according to SCRF ($\epsilon = 4.3$ for allene-DZM and allene-FNO, $\epsilon = 5.0$ otherwise). [b] Electronic energy as average of MP2 and MP3 values (see text). [c] Kinetic contributions from HF/3-21G calculations. [d] Relative free enthalpy and (in parentheses) relative solvent effect. [e] Product percentages converted into relative energy differences (kcal/mol); experimental data from refs 1 and 27, unless stated otherwise. [f] Diazomethane. [g] Diazopropane. [h] Diphenyldiazomethane. [i] Benzonitrile oxide. [l] Mesitonitrile oxide.

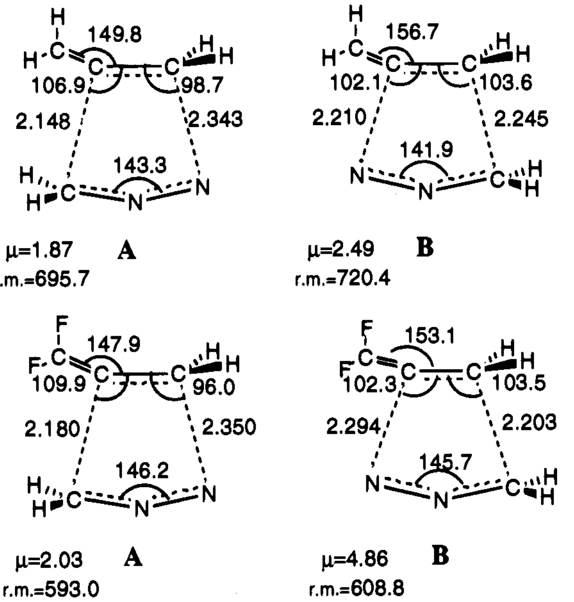

Figure 1. Optimized geometries (6-31G*) (Å and degrees) of the TSs for the reactions of allene and difluoroallene with diazomethane. (Dipole moments, μ, in Debyes and reaction modes, rm (imaginary frequencies) in cm^{-1}).

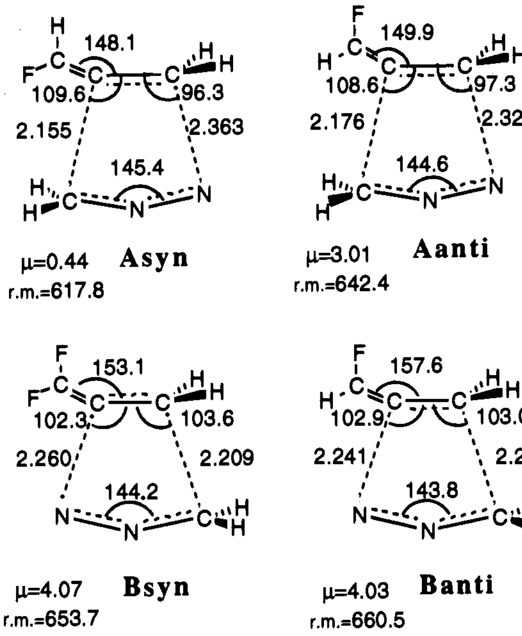

Figure 2. Optimized geometries (6-31G*) for the TSs for the reactions of monofluoroallene with diazomethane.

comparison of the computed $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ with experiment where concentrations are given in mol/L, the standard state of molar concentration (ideal mixture at 1 mol/L and 1 atm)[24] has been adopted in Table 2. Table 2 also contains the effect of the solvent polarity on the activation energy (kcal/mol, in parentheses), the theoretical selectivity between regio- (A/B) and diastereofacial (syn/anti) transition structures expressed in free enthalpy differences (kcal/mol), and the experimental product selection of the reaction in study (or of related reactions); the experimental product selection, usually expressed as a percentage of the detected product, has been converted into relative activation energy differences.

Figures 1−5 and Tables 3−5 contain theoretical information about the structure, dipole moment, and electronic activation energy at various levels of theory; these results will be useful for the discussion of the origin of regio- and diastereofacial selectivity and also for a general appraisal of the reliability of theoretical predictions.

Theoretical results for each reaction will first be discussed one at a time and compared with the available experimental

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[24] For conversion from 1 atm standard state to 1 mol/L standard state the following contributions need to be added to standard enthalpy, free enthalpy, and entropy, respectively: $-RT$, $RT \ln R'T$, $-R \ln R'T - R$, where R' is the value of the R constant given in L·atm/mol·K. For a reaction with A + B = C stoichiometry, the corrections for $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and $\Delta S^{\ddagger}$ are RT, $-RT \ln R'T$, $R \ln R'T + R$, respectively. Finally, at 298 K the corrections amount to 0.59 and −1.90 kcal/mol for $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ and 8.34 eu for $\Delta S^{\ddagger}$. To avoid misunderstanding, let us underline that the theoretical results are still intended for gas-phase reactions.

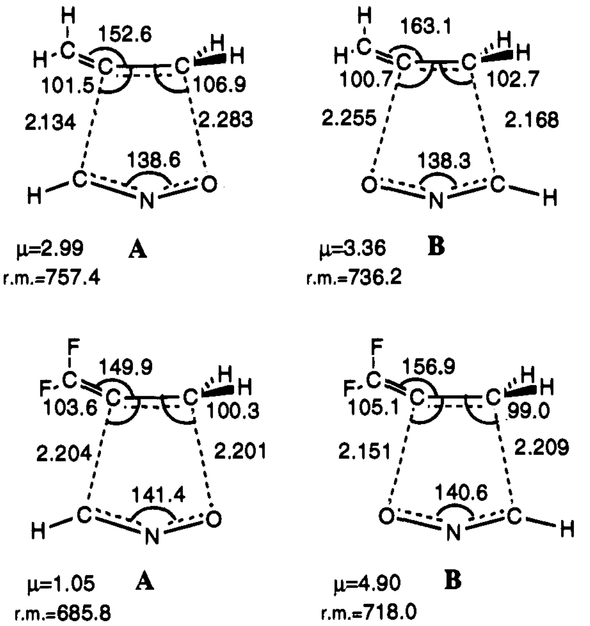

Figure 3. Optimized geometries (6-31G*) for the TSs for the reactions of allene and difluoroallene with formonitrile oxide.

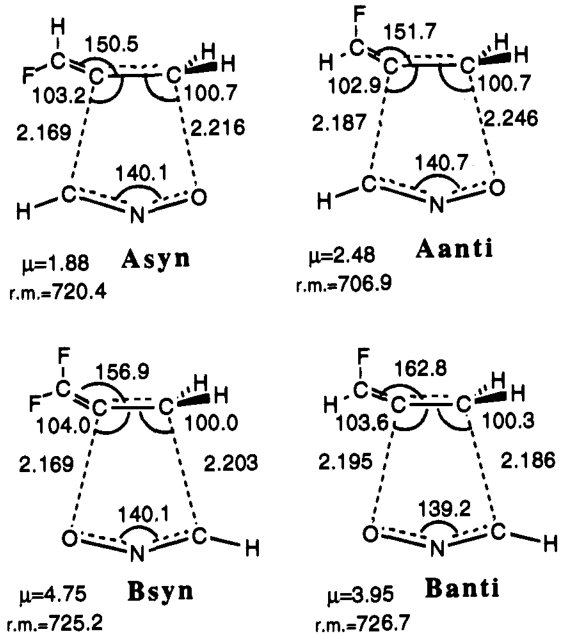

Figure 4. Optimized geometries (6-31G*) for the TSs for the reactions of monofluoroallene with formonitrile oxide.

Table 3. Electronic Activation Energies of the Cycloaddition of Allene and 1,1-Difluoroallene (DFA) to Diazomethane (DZM) and Formonitrile Oxide (FNO)[a]

	allene−DZM		allene−FNO	
	A	B	A	B
HF/3-21G opt	28.60	−0.55	28.22	−2.39
HF/6-31G* opt	35.50	+0.51	37.81	−2.12
MP2/6-31G*//[b]	8.19	+0.66	11.14	+0.96
MP3/6-31G*//[b]	17.80	+0.73	20.67	−0.43
MP4DQ/6-31G*//[b]	18.47	+0.72	21.19	−0.23
MP4SDQ/6-31G**//[b]	19.22	+0.53	18.92	−0.36
MP4SDTQ/6-31G*//[b]	12.57	+0.42	11.31	+0.50
	DFA−DZM		DFA−FNO	
	A	B	A	B
HF/3-21G opt	15.49	+2.64	14.56	+8.88
HF/6-31G*//[c]	26.20	+1.63	30.51	+3.53
MP2/6-31G*//[c]	0.27	+2.02	12.27	+2.54
MP3/6-31G*//[c]	9.76	+2.45	18.65	−0.20
HF/6-31G*opt	25.67	+2.00	28.93	+5.32
MP2/6-31G*//[b]	−1.57	+2.92	4.64	+1.32
MP3/6-31G*//[b]	8.17	+3.18	13.42	+2.81

[a] Energy in kcal/mol; energies of B-TSs are relative to A-TSs. [b] HF/6-31G* optimized geometry. [c] HF/3-21G optimized geometry.

data; general considerations about the origin of cycloaddition selectivity will be developed in the second part with the help of simple model calculations reported in Table 6 and Figures 6 and 7.

Diazomethane Cycloadditions. The theoretical study of the cycloadditions of allene, MFA, and DFA with diazomethane takes advantage of two features which are not common, for example, to formonitrile oxide cycloadditions. Firstly, the experimental reactions were carried out not only with substituted diazomethanes but also with the prototype diazomethane, whereas the reacted nitrile oxides were only benzonitrile and mesitonitrile oxide; this allows a direct comparison between calculated and experimental results, thereby avoiding any qualitative consideration of the differences introduced by the use of a 1,3-dipole different from that submitted to calculation. Secondly, selectivity predictions of diazomethane cycloadditions appear, in general, to be rather insensitive to the extension of the basis set and to the increased inclusion of electron correlation; moreover, the absolute values of the activation parameters, though not proven to converge toward definite values at increasing levels of theory applied in this study, yet seem to be close to the experimental values when electronic activation energies are calculated at the full MP4/6-31G* level.

Allene. The reaction of allene with diazomethane was studied experimentally and theoretically in a recent work of ours;[23] a few results are reported here for the sake of completeness (Table 3, Figure 1). Only one regioisomer, 4-methylene-1-pyrazoline (adduct A in our notation) had been previously detected by Crawford et al.,[25] whereas not less than 7% of the alternative regioisomer (adduct B) was found in the revised experiment;[23] in terms of energy difference, the revised regiochemistry places the TS of the unfavored regioisomer B at less than 1.53 kcal/mol above that of the favored one and significantly reconciles theoretical selectivity ($\Delta\Delta G^{\ddagger}$ = 0.91 kcal/mol) with the experimental finding (Table 2). It is interesting to recall that the adoption of MCSCF/3-21G optimized geometries together with full MP4/6-31G* single-point energy calculations leads to almost identical results[23] (12.9 and 13.5 kcal/mol for the electronic activation energies of A-TS and B-TS, respectively, $\Delta\Delta E^{\ddagger}$ = 0.6 kcal/mol, vs. the corresponding values 12.6 and 13.0 of Table 2).

When considering absolute activation parameters, we must recall that known experimental $\Delta H^{\ddagger}$ for diazomethane cyclodditions range from 7.5 ± 0.6 kcal/mol for the highly-reactive methyl acrylate to 13.2 ± 0.9 and 13.8 ± 0.8 kcal/mol for the less reactive norbornene and phenylbutadiene, respectively; for the same reactions, $\Delta S^{\ddagger}$ range from −33 ± 2 to −31 ± 3 and −29 ± 3 eu.[26] A rough comparison of reaction rates[23] indicates that activation enthalpy of allene reaction should resemble that of the less reactive dipolarophiles, in good agreement with the calculated value of 14.2 kcal/mol. The computed activation entropy (−33.5 eu) is also surprisingly plausible.

Solvent polarity has only minor effects on activation enthalpy and free enthalpy; in any case, it appears to favor the transition

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(25) Crawford, R. J.; Cameron, D. M.; Tokunaga, T. *Can. J. Chem.* **1974**, *52*, 4025.

(26) Huisgen, R. 1,3-Dipolar Cycloaddition. Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, pp 95−97.

structure with the higher dipole moment (B-TS) and to decrease the selectivity of the reaction.

Difluoroallene. Experimentally, DFA was found to be highly reactive with diazomethane, high-yield and totally site specific cycloaddition readily occuring at its C(2)−C(3) double bond; moreover, the reaction was found to be regiospecific[27] (adduct A). In contrast with the reaction with diazomethane, DFA's cycloadditions with substituted diazomethanes were not regiospecific but gave rise to increasing proportions of adduct B as the substituents became bulkier (*e.g.*, A:B = 61:39 and 14:86 for 2-diazopropane and diphenyldiazomethane, respectively).

The theoretical results of the reaction of DFA with diazomethane of Table 2 place the B-TS at more than 3 kcal/mol over the A-TS, thus agreeing with the experimental A-regiospecificity; the solvent effect, on the other hand, tends to favor the B-TS on account of its much higher dipole moment. The activation enthalpy, $\Delta H^{\ddagger}$, is much lower than that of the cycloaddition of allene (4.79 *vs.* 14.24 kcal/mol) and correctly accounts for the high reactivity conferred to allene by fluorine substitution. Notice how, as expected, activation entropies of the two TSs are similar to each other and to those of the reactions of diazomethane with allene and MFA. The regioselectivity observed with 2-diazopropane and diphenyldiazomethane can be simply accounted for by invoking, as suggested by Dolbier,[1] the role of steric effects in reversing the orientational preference of diazomethane.[27,28]

Figure 1 and Table 3 report the most important geometrical features of the transition structures together with their dipole moments and the electronic activation energies calculated at different levels of theory. It appears that absolute values, failing to converge on a definite value, are totally unreliable and become also unrealistic at the MP2 level of theory. Although we have chosen the average of the results of MP2 and MP3 calculations as representing an improved estimate of the absolute value (*viz.*, the value used in Table 2), the level of confidence certainly cannot be increased by such a procedure. The relative activation energy, *i.e.*, regiochemistry, on the other hand, is significantly independent of the level of calculation and can be taken as reliable.

Monofluoroallene. Diazomethane gave only one regioisomeric adduct (adduct A) in reacting with 1-fluoroallene (MFA);[27] when deuterium-labeled diazomethane was used, a strong syn selectivity was observed in the reaction,[28] revealed by the formation of Asyn and Aanti adducts in the ratio 88:12. In the cycloaddition of substituted diazocompounds with MFA, not only did regioisomer B become predominant as the substituents became bulkier but also the anti stereoisomer was seen to be dominant; in particular, the Asyn:Aanti:Bsyn:Banti ratios were 37.8:23.3:4.2:34.7 with 2-diazopropane and 2.7:6.9:8.9:81.5 with diphenyldiazomethane.

According to calculation in the reaction of diazomethane with MFA, (Table 2) the Asyn-TS is found to be the favored transition structure, followed by the Aanti-TS, whereas Banti-TS is favored over Bsyn-TS. The preference for A-TSs, however, is reduced by solvent effects which tend to favor B-TSs; furthermore, when bulky substituents in diazomethane hinder A-cycloadditions, Banti structure is left as the most favored one. These theoretical results appear to agree nicely to the experimental findings. Another interesting comparison of theory and experiment concerns the finding that the calculated activation enthalpy of the reaction of diazomethane with fluoroallene (5.59 kcal/mol) turns out to be intermediate between those of the reaction with allene (14.24 kcal/mol) and difluoroallene (4.79 kcal/mol), thus accounting for the experimental reactivity sequence.[1]

Table 4. Absolute and Relative Electronic Activation Energies of the Cycloadditions of 1-Fluoroallene to Diazomethane and Formonitrile Oxide[a]

	Asyn	Aanti	Bsyn	Banti
	Monofluoroallene−diazomethane			
HF/3-21G opt	17.59	+5.21	+4.66	+3.99
HF/6-31G*//[c]	27.58	+2.95	+3.63	+2.61
MP2/6-31G*//[c]	0.98	+3.19	+3.73	+3.13
MP3/6-31G*//[c]	10.76	+3.15	+4.07	+3.23
HF/6-31G* opt	27.12	+3.24	+3.85	+3.10
MP2/6-31G*//[b]	−0.50	+3.37	+4.22	+3.54
MP3/6-31G*//[b]	9.45	+3.32	+4.49	+3.69
MP4DQ/6-31G*//[b]	10.17	+3.32	+4.37	+3.67
MP4SDQ/6-31G*//[b]	10.77	+3.39	+4.41	+3.71
MP4SDTQ/6-31G*//[b]	4.10	+3.34	+4.31	+3.62
	Monofluoroallene−Formonitrile Oxide			
HF/3-21G opt	16.62	+6.60	+8.30	+6.52
HF/6-31G*//[c]	31.90	+2.02	+3.52	+1.16
MP2/6-31G*//[c]	12.24	+1.32	+0.07	−1.29
MP3/6-31G*//[c]	19.07	+1.95	+1.51	−0.37
HF/6-31G* opt	30.31	+3.27	+5.07	+3.20
MP2/6-31G*//[b]	4.61	+3.17	+3.34	+2.93
MP3/6-31G*//[b]	13.87	+3.38	+4.07	+2.87
MP4DQ/6-31G*//[b]	14.47	+3.36	+4.06	+3.00
MP4SDQ/6-31G*//[b]	12.51	+3.30	+4.22	+3.07
MP4SDTQ/6-31G*//[b]	5.47	+3.08	+3.81	+2.95

[a] Energies in kcal/mol; the Asyn is taken as the reference. [b] HF/6-31G* optimized geometry. [c] HF/3-21G optimized geometry.

Table 4 sets out results which can be useful for an appraisal of the reliability of theoretical forecasts. The major points are (i) the electronic activation energy could not be shown to converge to a stable value; (ii) the results at the MP4 level demonstrate that the MP3 level of electron correlation is largely insufficient for reliable absolute values; (iii) relative activation energies, *i.e.*, selectivity, appear to be reasonable at any level of theory, thus offering an encouraging example of error compensation; and (iv) optimized structure parameters are moderately affected by the extension of the basis set (from HF/3-21G to HF/6-31G*, as shown in supplementary material). In particular, as the level of theory rises, so the C···N bond lengthens and the C···C bond shortens; consequently, the TSs with A-regiochemistry become less synchronous and those with B-regiochemistry invert their bond length ratios. In any event, at the HF/6-31G* level the forming C···C bond is always shorter than the forming C···N bond, both in this reaction and in that with allene and with DFA (Figures 1 and 2).

Formonitrile Oxide Cycloadditions. Unfortunately, unlike the case of diazomethane, experimental results with the prototype formonitrile oxide are not available and difficult to produce, whereas the reactions of benzonitrile oxide (A:B = 56:44 with DFA, Asyn:Aanti:Bsyn:Banti = 4.0:35.8:16.7:43.5 with MFA) and mesitonitrile oxide (A:B > 99:1 with DFA, Asyn:Aanti:Bsyn:Banti = 4:85:4:7 with MFA), which have been used[28] as 1,3-dipoles, are theoretically unattainable because they are too large for the high level of calculations required. The comparison between calculated and experimental data regarding the reactions of nitrile oxides will be discussed after the results of the reactions of allene, DFA, and MFA have been introduced (Figures 3 and 4).

Allene. Benzonitrile oxide and acetonitrile oxide were reacted with allene to obtain the bis-adducts, 3,3′-diphenyl-5,5′-spiro-2,2′-diisoxazoline and 3,3′-dimethyl-5,5′-spiro-2,2′-diisoxazoline, respectively.[29] The formation of the above bis-adducts implies a B-regiochemistry for the first step but cannot

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[27] Dolbier, W. R., Jr.; Burkholder, C. R.; Winchester, W. R. *J. Org. Chem.* **1984**, *49*, 1518.

[28] Dolbier, W. R., Jr.; Purvis, G. D., III.; Seabury, M. J.; Wicks, G. E.; Burkholder, C. R. *Tetrahedron* **1990**, *46*, 7991.

exclude important fractions of the other regioadduct. In fact, we did repeat the experiment[30] and found mixtures of the two regioadducts, B-regiochemistry being prevalent with benzonitrile oxide (A:B = 16:84) and A-regiochemistry with mesitonitrile oxide (A:B = 60:40). Accordingly, final theoretical results (Table 2) point to a mixture where a slight preference for A-TS in the gas phase is counterbalanced by a slight preference for B-TS due to solvent effects. For comparison, electronic activation energies were also calculated with single-point MP4SDTQ/6-31G* calculations and MCSCF/3-21G geometries and found to be very similar[31a] to those reported in Table 2.

The most disappointing aspect of these calculations is apparent in Table 3 where, although in a very narrow range of values, the preferred regioselectivity (according to electronic activation energy) is found to be B at the HF level, A at the MP2 level, B at the MP3 level, and A at the MP4 level of calculation; moreover, the calculated absolute value of the negative activation entropy, $\Delta S^{\ddagger}$ in Table 2, is probably significantly underestimated (by, at least, 10 eu) with respect to the experimental values of similar reactions.[26]

Difluoroallene. The theoretical results, reported in Tables 2 and 3, can be read with reference to those of DFA plus diazomethane, it being noted that A regioselectivity ($\Delta\Delta G^{\ddagger}$ = 2.14 *vs.* 3.13 kcal/mol) is lower and the influence of solvent polarity higher on reversing the regiochemistry. The electronic activation energy used for the calculation of $\Delta H^{\ddagger}$ of this reaction (Table 2) is most probably systematically overestimated; as a matter of fact, the averages of MP2 and MP3 electronic activation energies of the reactions of allene and MFA with formonitrileoxide (for A and B regioadducts with allene and Asyn, Aanti, Bsyn, and Banti isomers for MFA) are higher than those of MP4 by 3.8−4.6 kcal/mol (see Tables 3 and 4), and the same occurs with other reactions involving formonitrile oxide.[31b] Let us note, however, that if an MP4 is "better" than an MP3 result, then the above average is every case "better" than the MP3 result: this is the reason why this average has also been taken for the cycloaddition of DFA and formonitrile oxide in Table 2; anyway, it must be stressed that the high reactivity of formonitrile oxide with DFA (by comparison with allene and MFA) can be accounted for only when the above reduction (3.8−4.6 kcal/mol) is made on the averaged values.

Monofluoroallene. The final calculated activation free-enthalpies (from full MP4/6-31G* electronic activation energy, Table 2) of the reactants of formonitrile oxide with MFA yielding Asyn, Aanti, Bsyn, and Banti isomeric adducts are similar to those of the reactions of diazomethane with MFA and follow the same pattern. In particular, Asyn-TS is foreseen to be the favored one, followed by Aanti, Banti, and Bsyn, the least favored TS, the whole range of values spanning only 3.7 kcal/mol. Solvent effect is high and in favor of B-adducts, thus further decreasing regioselectivity.

Table 4 yields further comments on the theoretical predictions. Once again, absolute energies appear to be unreliable because of lack of convergence on definite values with respect to increasing completeness of calculations; relative energies, on the other hand, appear to reach a more or less "stable" sequence of values.

The theoretical selectivity of the cycloaddition of the prototype nitrile oxide to allene, MFA, and DFA (Table 2) coupled with consideration of steric hindrance and dipole moments of phenyl- and mesityl-substituted nitrile oxides will be used to obtain a simple tentative explanation of the experimental regiochemistry and stereochemistry. Both solvent effects and steric effects between the phenyl substituent of the 1,3-dipole and the hydrogen or fluorine atoms of the C(1) carbon of the allene moiety operate against A-type cyloaddition and can easily reverse the very low *in vacuo* A-selectivity of the prototype reaction of allene (0.31 kcal/mol) and effectively mask that of DFA (2.14 kcal/mol). The experimental product selection of the reactions of MFA with benzonitrile oxide can be accounted for by the same effects. Starting from calculated selectivity, the Asyn-TS, favored in the prototype reaction, is ruled out by the same steric effects operating in the case of DFA, whereas the most disfavored Bsyn-TS can profit by a favorable solvent effect; as a consequence, Banti and Aanti-TSs appear as the preferred orientations in benzonitrile oxide cycloaddition where Bsyn also obtains a discernible presence.

The substitution of a mesityl for a phenyl group, on the other hand, systematically shifts regiochemistry toward an increased preference for A-cycloaddition; so, the regioisomeric ratio, A/B, changes from 0.2 to 1.5 with allene, from 0.7 to 8.1 with MFA, and from 1.3 to more than 20 with DFA. This behavior with allene dipolarophiles conforms to what seems to be a general trend with monosubstituted alkynes and, to a lesser extent, alkenes.[32] The general observation can be related to the fact that mesitonitrile oxide has a higher dipole moment than benzonitrile oxide (4.4 D *vs.* 4.0 D).[33] In the reactions in study an increased dipole moment of the nitrile oxide should disfavor B-cycloaddition and favor A-cycloaddition by further increasing the high dipole moment of the B-TS and by further decreasing the low dipole moment of the A-TS; the effect, obviously, should be higher in the reaction with DFA than in that with allene. Anyway, if one accepts that the relative energy of A and B-TSs is significantly bound to the difference between their dipole moments, one can except that substitution of mesitonitrile oxide for benzonitrile oxide can restore a high regioselectivity with DFA and reverse the sign of the selectivity with allene. Moreover, regarding MFA, the substitution of mesitonitrile oxide for benzonitrile oxide should have the effect of ruling out the highly polar Bsyn and Banti orientations and of leaving only Aanti as the dominant orientation.

As for the steric hindrance to A-cycloadditions of mesitonitrile oxide in comparison to benzonitrile oxide, one can argue that the two *ortho* methyl groups certainly increase steric congestion

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(29) (a) Stagno d'Alcontres, G.; Lo Vecchio, G. *Gazz. Chim. It.* **1960**, *90*, 1239. (b) Stagno d'Alcontres, G.; Gattuso, M.; Lo Vecchio, G.; Crisafulli, M.; Aversa, M. C. *Gazz. Chim. It.* **1968**, *98*, 203.

(30) The reaction of benzonitrile oxide (generated *in situ* from benzohydroximic acid chloride with triethylamine) and mesitonitrile oxide, respectively, with a large excess of allene (*e.g.*, 50 mg of the nitrile oxide in 10 mL of allene/ethyl ether 5:1) was carried out at room temperature in a sealed ampoule. After 20 h the excess of allene and diethyl ether was evaporated off, and the regioisomer ratio was evaluated by ^{1}H NMR analysis of the crude residue. In the case of mesitonitrile oxide the reaction product consisted of a mixture of 3-mesityl-4-methylene-2-isoxazoline (regioisomer A), 3-mesityl-5-methylene-2-isoxazoline (regioisomer B) and trace amounts of the bis-adduct derived from regioisomer B (A:B = 60:40, total yield ≥90%). In the reaction of benzonitrile oxide there was a complete isomerization of 3-phenyl-5-methylene-2-isoxazoline (regioisomer B) to 3-phenyl-5-methylisoxazole, whereas 3-phenyl-4-methylene-2-isoxazoline (regioisomer A) did not isomerize under the reaction conditions. Also in this latter reaction trace amounts of the bis-adduct to regioisomer B were detected (A:B = 16:84, total yield ≥85%). A mixture of regioisomers was also formed in the reaction of allene with acetonitrile oxide. Experimental details of these reactions will be published elsewhere.

(31) Rastelli, A.; Bagatti, M.; Gandolfi, R. Unpublished results: (a) The electronic activation energies of the reaction of allene with formonitrile oxide, according to MP4SDTQ/6-31G*//MCSCF/3-21G calculations, are 15.09 and 15.31 kcal/mol for A-TS and B-TS, respectively. (b) In the reaction of acrylonitrile with formonitrile oxide (MP4SDTQ/6-31G*//HF/6-31G*) the A-TS and B-TS electronic activation energies obtained as averages of MP2 and MP3 results are overestimated by 3.4 kcal/mol; in ref 31a, the averages for A-TS and B-TS are overestimated by 4.4 and 4.1 kcal/mol, respectively.

(32) Grunanger, P.; Vita-Finzi, P. *Isoxazoles*; Wiley-Interscience: New York, 1991; pp 185 and 494.

(33) Grundmann, Ch.; Grunanger, P. *The Nitrile Oxides*; Springer-Verlag: Berling-Heidelberg-New York, 1971; p 21.

Table 5. Absolute and Relative Electronic Activation Energies of the Diels–Alder Reactions of 1-Fluoroallene to Cyclopentadiene and Furane[a]

	MFA–cyclopentadiene		MFA–furane	
	syn	anti	syn	anti
HF/3-21G opt	24.46	+2.88	28.08	+3.68
HF/6-31G*//[b]	35.51	+0.86	37.26	+1.75
MP2/6-31G*//[b]	4.37	+1.27	8.97	+2.23
MP3/6-31G*//[b]	17.15	+1.16	19.94	+2.09

[a] Energies in kcal/mol; the syn-TS is taken as the reference. [b] HF/3-21G optimized geometry.

at the carbon atom of the CNO moiety with the result that the forming C···C bond at the TS (both the A-TSs and B-TSs) should be less advanced, *i.e.*, longer; owing to the low rigidity of TSs, the lengthening of the C···C bond, coupled with an eventual shortening of the C···O bond, can suceed in relieving strain at a low energy cost. Finally, if we consider that the *ortho* methyls cannot sterically interact with the hydrogen or fluorine atom at the C(1) carbon of the allene moiety in A-TSs, it is reasonable to conclude that steric hindrance against A-regiochemistry, with respect to B-regiochemistry, is similar for mesitonitrile oxide and benzonitrile oxide or even slightly lower in the former case.

Although the above explanation is new and could not have been obtained without explicit calculations of the relative activation properties of the reactions in question, we have to acknowledge Dolbier's intuition in foreseeing that electrostatic interactions were most likely to provide the missing link and explain the above regiochemical and stereochemical results.[1]

Diels–Alder Cycloadditions of Fluoroallene with Cyclopentadiene and furane. In these reactions, owing to the relatively large dimension of TSs, we had to be content with a modest level of calculation; so we made optimizations at the HF/3-21G level and single-point energy calculations only at the MP3/6-31G* level, adopting the average of MP2 and MP3 values as the final value of electronic energy.

Both difluoroallene (DFA) and monofluoroallene (MFA) exhibit considerably greater reactivity in Diels–Alder reactions than allene. While allene itself required vigorous conditions to afford a modest yield in its reaction with cyclopentadiene, MFA reacted slowly, at 0 °C, but with excellent yield, and DFA's reaction was virtually instantaneous at −20 °C.[1,34,35] Accordingly, the calculated activation enthalpy of the reaction of MFA reported in Table 2, namely 12.4 kcal/mol for the syn TS and 13.6 kcal/mol for the anti TS, is rather low and resembles the experimental value of the reaction of cyclopentadiene with acrylonitrile (12.6 kcal/mol in benzene).[36]

The most interesting theoretical aspect of this reaction, although one might not guess it from the experimental results which show equivalent amounts of syn and anti adduct to the fluorine substituent (syn:anti = 51:49), is precisely its propensity for the contrasteric syn addition, which is small (1.0 kcal/mol in the final results of Table 2), but evident at any level of calculation (Table 5).

Further interest comes from comparisons with the reactions of MFA with furane. The observed syn selectivity with furane (syn:anti = 70:30)[1,26] is much more manifest than that with cyclopentadiene, whereas its reactivity is known to be lower; accordingly, the calculated selectivity (2.0 *vs.* 1.0 kcal/mol) and activation enthalpy (15.5 *vs.* 12.4 kcal/mol for the syn orientation), at the same level of calculation, are larger.

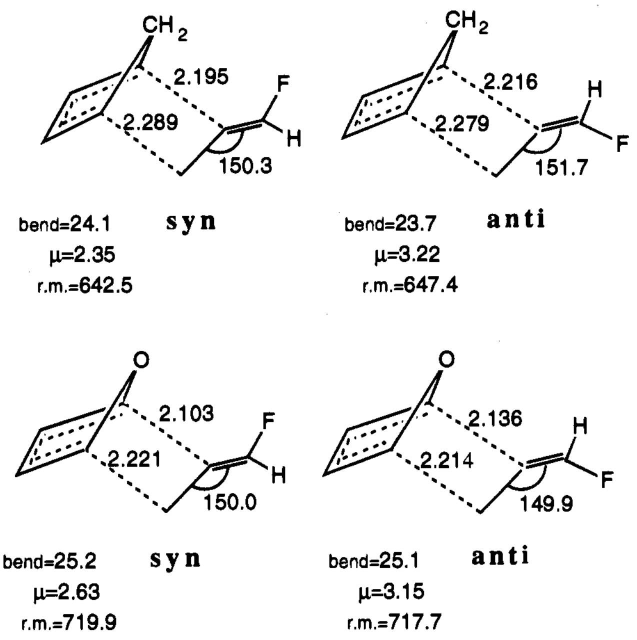

Figure 5. Optimized geometries (3-21G) for the TSs for the reactions of monofluoroallene with cyclopentadiene and furane (Bending angles, *bend*, of CH_2 and O out of the plane of the diene moiety).

Information on transition structures is given in Figure 5 for further discussion on the origin of stereoselectivity in these Diels–Alder reactions.

Model Calculations for Diastereofacial and Regiochemical Selectivity. Although the theoretical results at the present level of theory predict differences in activation parameter fairly accurately when simple prototype reactions are compared, so that relative reaction rates and product selectivities are correctly reproduced, these calculations cannot furnish, *per se*, a rationale of the experimental behavior. However, the problem of obtaining explanations of experimental trends is certainly simplified by the favorable results of calculations, for now one is left with the simpler problem of explaining theoretical trends.

In a recent series of papers[12,15,37] a procedure for the analysis of intramolecular interactions was introduced and extensively applied to the explanation of conformational preference,[37a,c,d] double bond pyramidalization,[37b] diastereofacial selectivity in 1,3-dipolar cycloadditions,[12,15] and the regiochemistry of the 1,3-dipolar cycloaddition of methyl vinyl ether.[37e] The procedure, which rests on the intuitive concepts of classical steric-electrostatic repulsions and of vicinal delocalizations, and makes use of an orthogonal set of hybrid atomic orbitals (OHAO) for their evaluation, leads to a consistent picture of the effect induced by single intramolecular interactions (or selected groups thereof) and also afford insight into the role of specific interactions in determining particular aspects of the ground-state and transition-state molecular structures. In particular, a detailed analysis of the transition structures of syn/anti cycloadditions of a group of dipolarophiles (norbornene, *cis*-3,4-dichlorocyclobutene, bicyclo[2.1.0]pent-2-ene and 2,3-dioxabicyclo[2.2.2]oct-5-ene) with formonitrile oxide has revealed

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(38) The role of dipole–dipole interactions in governing, at large distances, the approach between 1,3-dipoles and dipolarophiles in concerted cycloadditions has also been discussed by Firestone several years ago: Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181.

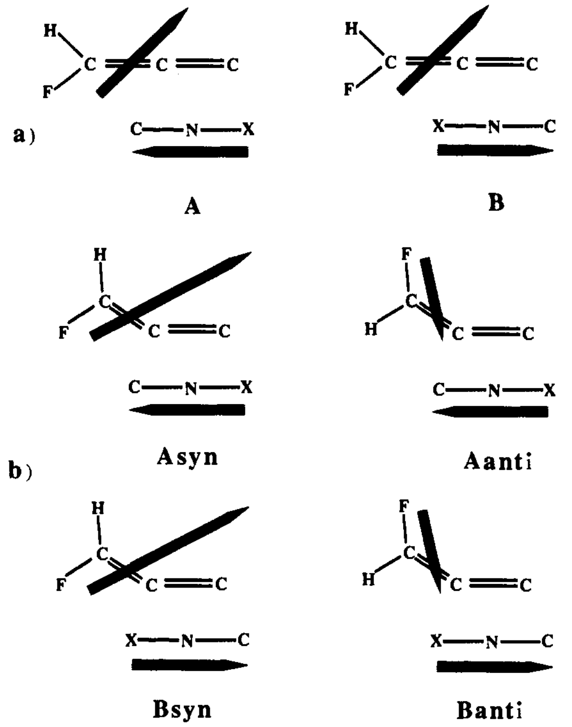


Figure 6. Schematic dipole moment orientations in A/B regiochemical and syn/anti diastereochemical approaches of the 1,3-dipole and MFA: (a) undeformed and (b) deformed MFA.

the factors that control facial diastereoselectivity. Although steric and electrostatic repulsions, the deformation energies of dipolarophiles and 1,3-dipoles (from ground-state geometry to the geometry assumed in the transition structure), the incipient bond energies and the vicinal delocalizations between incipient bonds and allylic bonds all participate in the complex energy balance which determines the geometry and energy differences between the syn/anti TSs, the ultimate factors appear to be the classical steric-electrostatic interactions between the deformed reactants and the vicinal interactions involving the forming bonds and the bonds at the allylic positions. Regiochemistry has not been explored with this procedure to anything like the same extent,[37e] but it appears reasonable that the controlling factors are the same, though with a higher relevance of electrostatic effects.

A detailed analysis of individual transition structures along the lines of the above procedure would be out of place in this report; we prefer to limit discussion, mainly at a qualitative level, to certain major aspects common to all the reactions under consideration. In particular, the role of electrostatic effects and vicinal interactions will be illustrated, in the following, with the support of qualitative arguments and model calculations.

To avoid misunderstandings, let us underline that, in our approach to explanation, the finding that a specific effect conforms to the experimental or theoretical trend to be explained does not necessary implies that it controls the selection mechanism, but only that it can concur in producing that trend.

Electrostatic Effects. Figure 4 illustrates the possible consequences of dipole orientations and also the changes (orientation and intensity) of the dipole moment of MFA when forced to bend by the incoming 1,3-dipole according to Asyn, Aanti, Bsyn, and Banti approaches. The A-regiochemistry of MFA cycloaddition appears to be largely favored by dipole orientations at large distances,[38] where only long range interactions operate and reactant geometries are not perturbed significantly (Figure 6a); a fortiori, the A-regiospecificity of DFA takes advantage of the same effect, whereas the preference for A-regiochemistry of the reaction of allene with diazomethane cannot. At closer distances, selectivities could be largely affected by the electrostatic interactions depicted in Figure 6b; here it is shown that the changes of dipole orientation bound up with MFA bending largely favor the Asyn orientation and disfavor the Bsyn one, whereas the anti approaches appear to be less differentiated. One can see that the trends of TS's overall dipole moments and of electronic activation energies are precisely those foreseen. Whereas the effect of Figure 6b could also be claimed to slightly support the preference for A-regiochemistry (A-TS is less polar than B-TS) of the reaction of allene with diazomethane, the small syn preference of Diels–Alder addition of cyclopentadiene and furane to MFA could not be accounted for by this argument.

Deformability and Vicinal Interactions. Allene and fluoroallenes as well as 1,3-dipoles and cyclic dienes undergo important structural changes on passing from their states of isolated molecules to bimolecular concerted TSs, the C(1)–C(2)–C(3) angles reported in Figures 1–5 being suitably representative of the extent of deformation. One can see that (i) the bending angles (supplementary to those reported in Figures 1–5) of allene and fluoroallenes are around 30° and that (ii) A-TSs and syn-TSs attain bending angles higher than B-TSs and anti-TSs, respectively. Now, since dipolarophile (dienophile) deformation involves a major contribution to activation energy, the noticed trend suggests that differences of deformation energy could be closely bound to regio- and diastereoselectivities of the reactions in question. The results in Table 6 help in the discussion of this suggestion.

Deformability is defined as the energy of a deformed structure over the energy of the optimized structure, being linear for allene and DFA and slightly bent (−1.55°) for MFA; the deformed reference structure is one where the allene moiety is rigidly bent by 30°, other geometrical parameters being kept fixed. As expected,[12,14,37b] the negative small bending found in the optimized structure of MFA forecasts asymmetric (±30°) deformability with negative easier than positive bending (7.21 *vs.* 8.89 kcal/mol). Since, by definition, bendings are negative when subsidiary to syn approaches, the preference for syn stereoselectivity in MFA cycloadditions can well be supported by the greater ease of bending. A second trend of calculated deformabilities shows that bending is easier for DFA than for MFA and has the highest cost for allene, in perfect agreement with the sequence of experimental reactivities and of theoretical activation enthapies, deformability reveals itself to be an interesting property of fluorine substitution.

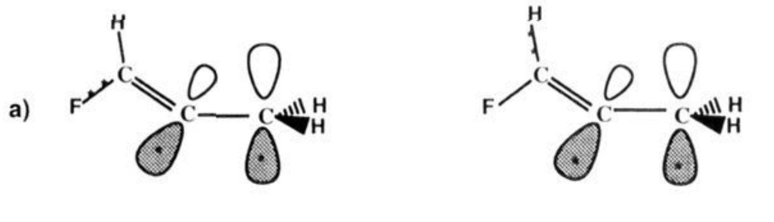
The above qualitative trends are by no means bound to high quality calculations; in fact, they are well reproduced by HF/STO-3G calculations. This check is important because it legitimates the minimal basis set calculations reported in the second part of Table 6. These calculations aim at tracing back variable deformability to the changes in intramolecular interactions between the C(2)=C(3) π-bond and the vicinal C–H, C–F σ-bonds at C(1). The π-atomic orbitals of the C(2)=C(3) bond are coplanar with the σ-bonds of the C(1) atom and, owing to their large overlap, interact strongly and produce broad stabilization; according to the model calculations of vicinal interactions,[37c] stabilization amounts to 25.98 kcal/mol for allene and 27.52 kcal/mol for DFA. When the molecules are rigidly bent by 30°, vicinal stabilization decreases by 3.13 kcal/mol in allene and only 0.80 kcal/mol in DFA, thus explaining the lower deformation energy in the latter case. Similarly, vicinal stabilization decreases by only 0.56 kcal/mol when MFA is rigidly bent by −30°, instead of 2.60 kcal/mol when it is bent in the opposite direction. Table 6 also shows that stabilizations

Table 6. Model Calculations on Allene, Fluoroallene (MFA), and 1,1-Difluoroallene (DFA)

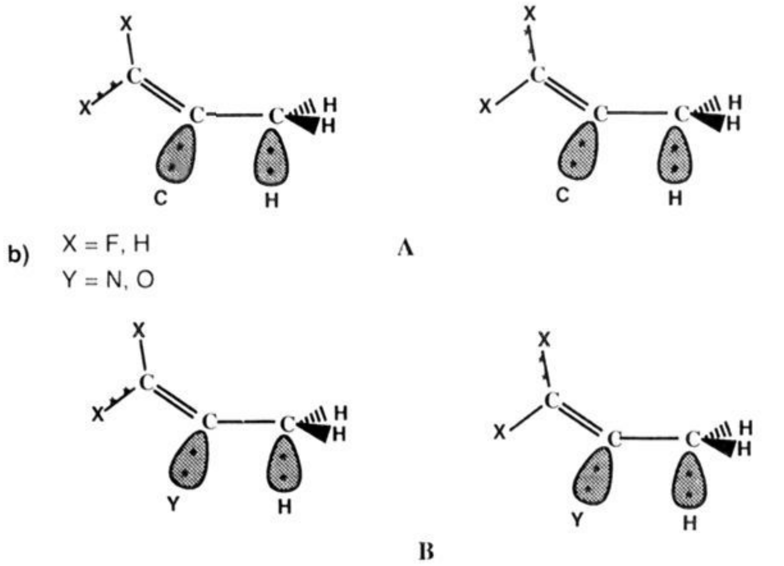
deformability (kcal/mol)[a]	HF/6-31G*	HF/STO-3G	deformability (kcal/mol)[a]	HF/6-31G*	HF/STO-3G
allene (±30°)	10.54	11.47	MFA (−30°)[b]	7.21	9.76
MFA (linear)	0.03	0.01	MFA (+30°)	8.89	10.17
MFA (−1.55°, opt)[b]	0.00	0.00	DFA (±30°)	6.93	9.11

vicinal interactions (kcal/mol)[c]	total	synperiplanar	antiperiplanar
allene (linear, opt.)	−25.98 (0.00)	π-CH −12.99	π-CH −12.99
allene (±30°)	−22.85 (3.13)	π-CH −8.48	π-CH −14.37
MFA (linear)	−25.83 (0.07)	π-CF −12.73	π-CH −13.11
MFA (−1.55°, opt.)	−25.90 (0.00)	π-CF −12.62	π-CH −13.28
MFA (−30°)	−25.34 (0.56)	π-CF −10.84	π-CH −14.50
MFA (+30°)	−23.29 (2.60)	π-CH −9.21	π-CF −14.08
DFA (linear, opt.)	−27.52 (0.00)	π-CF −13.76	π-CF −13.76
DFA (±30°)	−26.72 (0.80)	π-CF −12.24	π-CF −14.47
DFA (±30°, A)[d]	−25.88 (0.00)	C···C-CF −12.40	C···C-CF −13.48
DFA (±30°, B)[e]	−24.81 (1.07)	N···C-CF −11.65	N···C-CF −13.16
DFA (±30°, B)[f]	−25.02 (0.86)	O···C-CF −11.82	O···C-CF −13.20
allene (±30°, A)[d]	−19.66 (0.00)	C···C-CH −6.63	C···C-CH −13.03
allene (±30°, B)[e]	−20.26 (−0.59)	N···C-CH −6.93	N···C-CH −13.33
allene (±30°, B)[f]	−21.38 (−1.72)	O···C-CH −7.60	O···C-CH −13.78

[a] Deformability is the energy (kcal/mol) of the structure where the allene moiety is rigidly bent by 30° over the energy of the optimized structure which is linear for allene and difluoroallene and slightly bent (−1.55°) for monofluoroallene. [b] Negative angles denotes bent structures where the C−F and the C(2)=C(3) bond are trans with respect to the C(1)=C(2) bond. [c] Vicinal interactions with respect to the C(1)=C(2) bond; these are the stabilizing delocalizations between the C(2)=C(3) π-bond and the C−X (X = H, F) σ-bonds of the carbon C(1); in bent structures C−X can be either synperiplanar or antiperiplanar to the coplanar pyramidalized π-orbital of the carbon C(2); in parentheses relative stabilization energies with respect to the optimized structures. [d] Vicinal interactions in a model system, mimicking an A-TS, where a forming C···C bond (2.0 Å) is substituted for the π-orbital of the carbon C(2) and a forming C···H bond (2.0 Å) for the π-orbital of the carbon C(3). [e,f] Same as *d* but with forming N···C and O···C bonds (2.0 Å, mimicking a B-TS) at the carbon C(2). See also Figure 7.



Syn-periplanar π-CF interaction   Anti-periplanar π-CH interaction



Syn and anti-periplanar new bond-CX interactions

Figure 7. Schematic representation of model vicinal interactions: (a) four-electron interactions, in the deformed (−30°) MFA, supporting syn attack and (b) 6-electron interactions supporting A and B regiochemical approaches.

between antiperiplanarly-oriented vicinal interactions increase on bending, whereas those between synperiplanar interactions decrease; the favored negative bending of MFA depends on the fact that synperiplanar π−CF interactions (Figure 7a) decrease less than synperiplanar π−CH interactions when equivalent bendings are forced. In a previous work[37c] we had already shown that the synperiplanar interaction between the CF bond and the nitrogen lone-pair in the fully-eclipsed structure of fluoromethylamine is large and responsible for the high relative stability of that structure.

The final comment on the results of Table 6 concerns the possible role played by vicinal interactions in the regioselectivity of the reactions of fluoroallenes with diazomethane and formonitrile oxide (Figure 7b). The A-type TS is mimicked by placing a carbon atom in the direction of the π-type hybrid orbital of the C(2) atom of bent DFA at a distance of 2.0 Å; for the B-type TS a nitrogen atom or an oxygen atom is used (at the same distance and orientation) to mimic the formation of N···C and O···C bonds. The results of Table 6 show that vicinal interactions between the C···C forming bond and the CF bonds (A-regiochemistry) are more stabilizing than those involving Y···C new bonds (B-regiochemistry), whereas the reverse happens with allene where the interactions involve CH instead of CF bonds. It follows that vicinal interactions are favorable to A-regiochemistry in DFA cycloadditions, but support B-regiochemistry in allene cycloadditions. It is worth recalling that vicinal interactions were already shown to have an important role on the regiochemistry of the cycloaddition of methyl vinyl ether with diazomethane and formonitrile oxide.[37e]

Conclusions

As expected, from the results and discussion here presented one can draw conclusions concerning different aspects of the problem in study. Firstly, one can comment on the ability of calculations (i) to provide *quantitative* estimates of the enthalpies and entropies of activation and (ii) to accurately predict *relative* reactivities and *selectivities* (diastereo- and regioselectivities) for typical prototype concerted cycloadditions. Then (iii) one can underline the peculiarities of the cycloaddition of allene and fluoroallenes with 1,3-dipoles and dienes also in view of the effects which are supposed to *control* selectivities.

The absolute values of the activation parameters are unreliable at the present level of theory. The main reason is that electronic activation energies at the MP4(SDTQ)/6-31G* level do not show convergence to definite values, *i.e.*, to values unaffected by further theoretical improvements. As a matter of fact, the inclusion of full fourth order correlation (MP4) decreases the activation energy of 1,3-dipolar cycloaddition of allene and MFA by more than 5 kcal/mol with diazomethane and by more than 8 kcal/mol with formonitrile oxide, with respect to the preceding level of approximation (MP3). Although not checked in our reactions, Diels–Alder cycloadditions do not appear to elude this trend; in fact, the results on the reaction of butadiene plus ethylene, presented by Bach *et al.*,[5] show that the decrease amounts to 5.14 kcal/mol. Whether, and in which cases, the MP4 level of correlation will be sufficient for reliable predictions of activation energies would require the inclusion of higher levels of correlations in order to assess the convergence of results. Moreover, the quantitative estimates of activation parameters require the calculation of the kinetic contributions to thermodynamic functions; present calculations suffer by the well-known deficiencies mainly connected with the harmonic approximation adopted in the frequency calculations; fortunately, the kinetic contribution to activation enthalpy is small in our reactions, so that the problems concern mainly activation entropy. Lastly, the chosen treatment of solvent effects can be given only a qualitative value. The comparison of calculated and experimental activation parameters for the reactions in study is impossible because of lack of experimental data; however, by comparison with similar reactions, it does appear that activation ethalpies calculated at the MP4 level of correlation are rather close to experimental values, whereas the negative activation entropies are, most likely, overestimated by 8–10 eu in formonitrile oxide cycloadditions and Diels–Alder reactions and in the right range of values in diazomethane cycloadditions.

Relative reactivities of allene, MFA, and DFA as well as regio- and diastereoselectivities are, in general, rather insensitive to the extension of the basis set and to the increased inclusion of electron correlation; formonitrile oxide cycloadditions need a higher level of calculation than diazomethane cycloadditions and Diels–Alder reactions when results of comparable quality are requested. Relative reactivities and selectivities agree well with the available experimental trends; moreover, theoretical selectivities of the reactions of allene, MFA, and DFA with diazomethane and formonitrile oxide, coupled with consideration of steric hindrance and dipole moments of substituted 1,3-dipoles, are able to account for the peculiar experimental behavior of allene and fluoroallenes toward cycloaddition.

Although steric and electrostatic repulsions, deformation energies, incipient bond energies, and vicinal delocalizations all are supposed to participate in the energy balance determining reactivities and selectivities, the role of deformation energies, and of electrostatic interactions has been discussed in detail also with the use of model calculations. The increasing reactivities of A, MFA, and DFA appear to be bound to the decreasing energies requested for their geometry deformation toward the transition structures. As for diastereofacial selectivity in the cycloaddition of MFA, the syn-attack has been found to be strongly favored by the more facile anti- than syn-deformability of the allene moiety. The favored anti-deformability is foreshown by the small anti-bending (1.6° in the optimized structure of the free MFA) or syn-pyramidalization of the π-atomic orbital of the C_2 carbon atom. Both syn-pyramidalization and the difference of syn/anti deformability are traceable to the role of vicinal delocalizations between the C_2-C_3 π-bond (in the free MFA) or the new-forming bonds (in the TS) and the allylic C–H and C–F bonds at C_1. Vicinal interactions between the new-forming bonds and the allylic C–H and C–F bonds are found to be significant orienting factors also for regiochemical alternatives; however, electrostatic interactions are suggested to play a major role in the regiochemical control of 1,3-dipolar cycloadditions of allene and fluoroallenes.

Acknowledgment. We thank MURST and CNR for financial support and CICAIA (University of Modena) for computer facilities.

Supplementary Material Available: Selected geometrical data and absolute eneriges at the levels of calculations cited in the present paper (4 pages). This material is contained in many liabraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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