proportional to the coordination numbers of the atoms in the system, C. This repulsion energy is due to "Coulomb repulsion of the nuclei and the exclusion principle in the overlap of the atoms".[22] As has been shown by Friedel and Cyrot-Lackmann[23]

$$C = \alpha\mu_2 \equiv \alpha\int_{-\infty}^{\infty} E^2\,\rho(E,r)\,\mathrm{d}E$$

where $\rho(E,r)$ is the electronic density of states of the valence bands, which itself is (among other things) a function of the overall size of the system. We therefore find that the total energy E_T is

$$E_T = \alpha\int_{-\infty}^{\infty} E^2\,\rho(E,r)\,\mathrm{d}E + \int_{-\infty}^{E_F} E\,\rho(E,r)\,\mathrm{d}E$$

The first term on the right-hand side of the equation is the repulsive energy, $U(r)$, while the second term is the attractive energy, $-V(r)$. The term E_F refers to the Fermi energy for the system in question. We now follow the argument first discussed by Pettifor.[24] We consider two systems which we label 1 and 2. The terms E_{T1}, U_1, V_1, E_{T2}, U_2, and V_2 refer to the various energies of these two systems. We wish to perform calculations where $\Delta E = E_{T1} - E_{T2}$. It may be seen that

$$\Delta E = U_1(r_{1eq}) - V_1(r_{1eq}) - U_2(r_{2eq}) + V_2(r_{2eq})$$

where r_{1eq} and r_{2eq} refer to the respective equilibrium sizes of the two systems.

We use the fact that we are interested in equilibrium geometries in the following way. Note that near equilibrium E_{Ti} is constant. Therefore

$$U_2(r_{2eq}) - V_2(r_{2eq}) = U_2(r_{2eq}+d) - V_2(r_{2eq}+d)$$

In particular, we choose a value for d such that $U_2(r_{2eq}+d) = U_1(r_{1eq})$. We now find that

$$\Delta E = \int_{-\infty}^{E_{F1}} E\,\rho_1(E,r_{1eq})\,\mathrm{d}E - \int_{-\infty}^{E_{F2}} E\,\rho_2(E,r_{2eq}+d)\,\mathrm{d}E \quad (1)$$

We determine the value r_{1eq} from the true experimental size factor and $r_{2eq} + d$ from the equality

$$\int_{-\infty}^{\infty} E^2\,\rho_2(E,r_{2eq}+d)\,\mathrm{d}E = \int_{-\infty}^{\infty} E^2\,\rho_1(E,r_{1eq})\,\mathrm{d}E$$

This last expression is equivalent to stating

$$\mu_2(r_{2eq}+d) = \mu_2(r_{1eq}) \quad (2)$$

It may be seen that eqs 1 and 2 correspond exactly to the second-moment-scaling hypothesis.

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Empirical Force-Field Models for the Transition States of Intramolecular Diels-Alder Reactions Based upon ab Initio Transition Structures

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Abstract: A quantitative model based upon Allinger's MM2 force field has been devised to calculate the diastereoselectivity of intramolecular Diels-Alder (IDA) reactions. The parameters for the modified MM2 force field were derived whenever possible from ab initio calculations on the intermolecular transition structures for the Diels-Alder reactions of butadiene plus ethylene, acrolein, and acrolein coordinated to BH_3. The force field reproduces the ab initio 3-21G transition structures for the intramolecular Diels-Alder reactions of 1,3,8-nonatriene and 1,3,9-decatriene. The force field was developed for both thermal and acid-catalyzed reactions and provides insight into the origins of the diastereoselectivity in the IDA cycloaddition for a wide variety of nonatrienes and decatrienes. The flexibility of the transition structure and the conformational effects due to the chain connecting the two reacting moieties were shown to be of the greatest importance in determining the stereochemical outcome of these reactions. The use of the parameters in the new MM3 force field was tested.

Introduction

The Diels-Alder cycloaddition is among the most powerful tools in organic synthesis,[1,2] since it allows a direct access to cyclic, highly functionalized systems in a regioselective and stereocontrolled way. The reaction conserves the stereochemistries of the diene and alkene,[1,2] and a stereocenter on one or both the reactants is often able to influence the relative stereochemistry of the newly formed stereogenic centers in the products.[2] Thus, both the relative and the absolute configuration at all the stereocenters can be controlled in the synthesis of highly functionalized molecules, provided that the factors influencing the diastereoselectivity are known and predictable.

Even greater control is possible when both reactants are part of the same molecule: intramolecularity enhances the factors

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determining the cyclization stereoselectivity.[3] When the tether between the two reactants is relatively short, the regioselectivity is complete, even when this competes with the electronic directing effects usually found in the Diels-Alder reaction.[3-5] Because of its versatility, the intramolecular Diels-Alder (IDA) reaction has found wide use in the synthesis of complex natural products.[3,6] We have investigated IDA cycloadditions forming [4.4.0] and [4.3.0] bicyclic systems; these cover by far the bulk of the available experimental data.[3,6]

The goal of our research was to create a suitable force field for IDA reactions, in order to gain a predictive model for the diastereoselectivity of these cycloadditions. While the factors controlling the stereoselectivity of a given case often can be easily analyzed after the experiment has been performed, it is very difficult to predict the outcome of a reaction that incorporates several competing effects. We have attempted to create a transition-state model which is quantitatively reliable, computationally inexpensive, and easy to use. We began with Allinger's MM2 force field[7] and developed a set of additional parameters for the IDA transition states based on ab initio calculations on transition structures for various Diels-Alder cycloaddition reactions. This procedure has already been successfully employed for modeling various organic reactions[8] and has been called "transition-state modeling".[9]

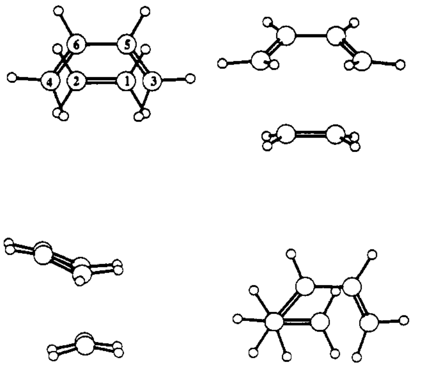

Figure 1. Butadiene plus ethylene 3-21G transition structure.

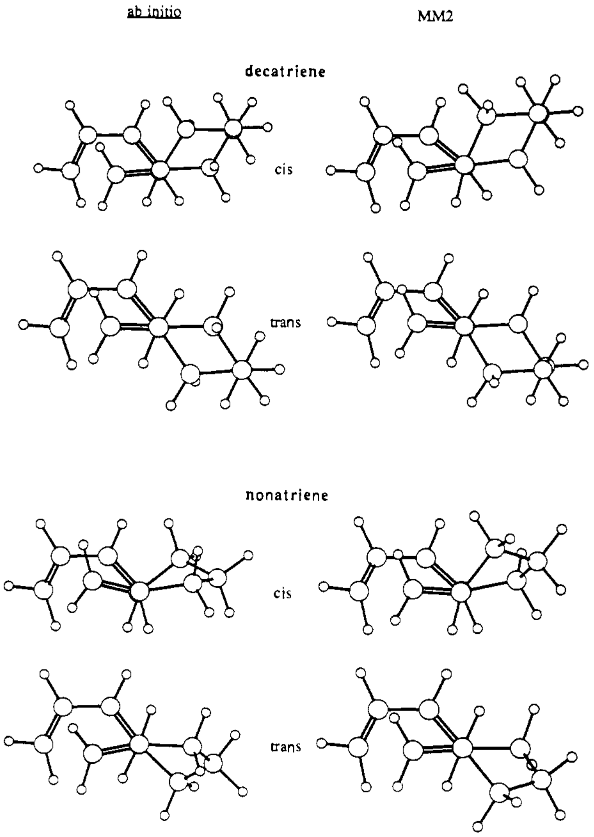

Figure 2. 1,3,9-Decatriene and 1,3,8-nonatriene: a comparison between 3-21G ab initio and MM2 transition structures.

Several IDA reactions have already been examined with force-field methods. Some authors correlated the experimental diastereomeric ratios with the relative stabilities of the products.[6k] Other approaches were based on transition-state modeling[6e,10-13] but were limited to the particular IDA reaction under examination. A complete study of all the IDA reactions by means of the same force-field method has never been attempted.

Extensive studies have shown that a simple transition-state model cannot reproduce simultaneously the stereoselectivities of intramolecular Diels-Alder reactions of unactivated and activated substrates. For that reason, the force-field parameters were tuned according to the different nature of the reacting moieties to account for substituent effects on the asynchronicity of bond formation. The presentation in this paper will follow the order of increasing

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complexity. We first present the results for IDA cycloadditions of unactivated trienes. Next, the thermal reactions of terminally activated trienes will be discussed. Activating groups on the tether raise some new problems concerning the preferred conformation for the connecting chain in the transition structures; these compounds will be discussed in the third section. Finally, Lewis-acid-catalyzed cycloadditions will be described.

Recently, a new molecular mechanics force field, MM3, has been developed by Allinger's group.[14] The equations that describe the potential surface have been significantly changed, but MM3 is similar to MM2 for the most part. In the absence of optimized MM3 parameters, the corresponding MM2 parameters are used. MM3 was still under development during the completion of this work, and its parametrization is in progress. However, the applicability of our parameters to the MM3 force field was tested and will be discussed in the last section of this paper.

Unactivated Alkenes

At levels of theory from RHF/STO-3G to MP2/6-31G* or MCSCF calculations, a concerted, synchronous transition structure for the butadiene plus ethylene cycloaddition is found to be most stable.[15] There are only minor variations in these transition structures with increasing the level of theory, and the predictions made on the basis of a STO-3G result[16] have been confirmed at higher levels. We chose to parameterize MM2 on the basis of 3-21G ab initio results;[17] for many Diels–Alder reactions, this is the highest level for which geometries are available. Most of the cited structures have been published, so they are not discussed here in detail. The 3-21G transition structure is shown in Figure 1.

The vibrational frequencies of the butadiene plus ethylene transition state show which distortions are relatively easy.[11,15c] The imaginary frequency corresponds to the synchronous motion along the reaction coordinate. The lowest energy real vibration is a twisting motion of the ethylene with respect to the butadiene. The second real vibration is the asynchronous motion.

Because of the ease of twisting, it was expected that a trimethylene connecting chain would impose a relatively high degree of what we call "twist mode asynchronicity" to the transition structures of these IDA reactions, with the internal forming bond acting as a pivot axis.[16] This expectation has been confirmed by the location of the ab initio transition structures for the IDA reaction of 1,3,8-nonatriene and 1,3,9-decatriene.[18]

The four transition structures are shown in Figure 2. The cis- and the trans-fused transition structures for the decatriene cycloaddition are almost undistorted by the tether and resemble closely the intermolecular butadiene–ethylene transition structure (cf. Figure 1). The tether assumes a favorable unstrained chairlike conformation in both. The lengths of the two forming bonds are slightly different, but the degree of asymmetry is very low. The calculations show an energy difference of 0.04 kcal/mol between the two 3-21G transition structures favoring the cis-fused one. Experimentally, the cis-fused decalin is favored by 0.1 kcal/mol;[19] the agreement of the calculated and the experimental data is excellent.

The situation is quite different for the cyclization of the 1,3,8-nonatriene. The forming five-membered ring forces the ethylene to twist around the internal forming CC bond. The direction of this motion was already correctly predicted.[16] The twisting motion of the reactants, of about 10–15°, prevails over the asymmetric stretch mode. The experimental preference for the cis-fused product is 1.0 kcal/mol, while the 3-21G calculations predict a preference of 0.7 kcal/mol.[18,19]

With these results in mind, we turned to the parameterization of the MM2 force field. We initially considered a completely rigid model analogous to the one that gave satisfying results for the intermolecular Diels–Alder reactions,[8d,e] for transannular Diels–Alder reactions,[13] and for other cycloadditions.[8a–c] In this model, the positions of the atoms of butadiene and ethylene were fixed at the values of the intermolecular transition state. The torsional parameters for the breaking and forming bonds were all set equal to zero, and the force constants for stretching and bending of the bonds and angles involving atoms attached to the butadiene or ethylene carbons of the transition state were fixed at product values. This gave reasonable values for the calculated steric energies. This model, however, did not allow for any asynchronicity in the transition structure; the results were rather promising for the IDA reactions of hydrocarbons,[8e] but the predictions made for trienes activated by substituents were unreliable. For this reason, the rigid model was soon abandoned.

A flexible model was then developed, using equilibrium bond lengths and angles from the ab initio 3-21G intermolecular transition structure. The critical features of the force field will be discussed here, while the complete list of parameters is given as supplementary material. The first critical choice concerned the atom type for the reacting units: the transition structure is an early one in terms of bond length changes, but the pyramidalization of the terminal carbons of the butadiene and ethylene groups is nevertheless significant (see Figure 1).[15] For this reason, the diene and ethylene terminal carbons were considered as sp^3 carbons. The two "inside" hydrogens on the reacting termini of the butadiene were made a new atom type: the geometries of these "inside" C–H bonds are in fact quite different from those of the two "outside" ones. The reference values for the bond lengths and angles were unchanged from those of the 3-21G transition structure. The stretching force constants were unchanged from the product-like values. The force constants for the two forming bonds were chosen empirically. The problems connected with the proper choice of the force constants for the two forming bonds in the IDA reaction was discussed by Coe;[10] in short, MMX[20a] allows a choice of the bond order between two atoms and assigns to this stretching motion a force constant based on Pauling's relationship.[20b,c] However, this choice does not allow enough flexibility to the molecule; consequently, the calculations for the nonatrienes were in disagreement with experiment. An empirical choice for the force constants for the two forming bonds seems to be more reliable.

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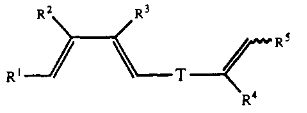
Chart I. Unactivated Trienes



TRIENE	T	R^1	R^2	R^3	R^4	R^5
1	$(CH_2)_3$	H	H	H	H	H
2	$(CH_2)_4$	H	H	H	H	H
3	$(CH_2)_4$	H	H	Me	H	H
4	$(CH_2)_4$	H	H	Me	Me	H
5	$(CH_2)_2$-C(=CMe_2)-CH_2	H	H	Me	Me	H
6	$(CH_2)_2$-N(Me)-CH_2	H	H	H	H	H
7	$(CH_2)_4$	H	Me	H	H	H
8	$(CH_2)_4$	Me	H	H	H	H
9	$(CH_2)_4$	H	H	H	Me	H
10	$(CH_2)_3$	H	H	Me	H	H
11	$(CH_2)_3$	H	H	H	Me	H
12	$(CH_2)_4$	H	H	H	H	E-Me
13	$(CH_2)_4$	H	H	H	H	Z-Me
14	$(CH_2)_3$	H	H	H	H	E-Me
15	$(CH_2)_3$	H	H	H	H	Z-Me
16	CH_2-CH(OH)-$(CH_2)_2$	H	H	H	H	H
17	CH_2-CH(OH)-$(CH_2)_2$	H	H	Me	H	H
18	CH_2-CH(X)-$(CH_2)_2$	H	H	Me	Me	H
19	CH(X)-$(CH_2)_2$	H	H	H	H	E-Me
20	$(CH_2)_2$-CH(X)	H	H	H	Me	H

The bending force constants were given values corresponding to those in the products but reduced to one-half of their default MM2 values in order to give the system more flexibility. The torsional parameters are more difficult to assign. To maintain the downward bending of the hydrogens or substituent at the internal carbons (C_5 and C_6, see Figure 1) of the butadiene moiety, as well as pyramidalization at C_5 and C_6, several new torsional parameters are necessary. The eclipsing between these two hydrogens was reproduced with V_2 = 15 kcal/mol for the H–C_5–C_6–H dihedral angle (the default value for the H—C=C—H dihedral angle in MM2). A value of V_2 = 15 kcal/mol also maintains the planar s-cis conformation of the diene unit (C_3–C_5–C_6–C_4). A torsional parameter was added in order to ensure the endo bending of hydrogens attached to C_5 and C_6. This was achieved by setting V_2 for H–C_5–C_3–C_1 and H–C_6–C_4–C_2 equal to −7.5 kcal/mol. The combination of these parameters leads to out-of-plane bending of approximately 10–15° for the two hydrogens or substituents at C_5 and C_6, in good agreement with the ab initio calculations.

A negative V_2 term was also used to control the position of the dienophile substituents. The C_3–C_1–C_2–H dihedral angle is close to 90° in the intermolecular butadiene–ethylene transition structure; a value of −10 kcal/mol for V_2 for C_3–C_1–C_2–H(R) maintains this angle but also allows some flexibility to the system. This parameter is implemented only for that forming single bond which becomes the bond common to both rings in the intramolecular reactions. This forces the terminal carbon of the dienophile to a more planar geometry than the internal one. With activated olefins, when the transition structure becomes more asynchronous, the internal forming bond is more strongly formed than the external one, and we can simply use the same torsional parameters.

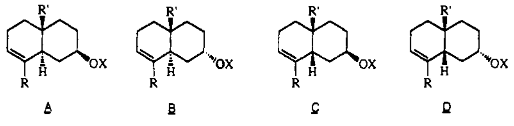
This choice of parameters was made in order to give satisfactory agreement with experimental data on stereoisomer ratios. We also compared the MM2 transition structures with the ab initio ones, with particular attention to the nonatriene transition structures. The ab initio and the MM2 intramolecular transition structures are compared in Figure 2. We also carried out test calculations where we slightly varied the parameters so as to be sure that the results are not drastically dependent on the exact parameters used. In this way we checked that our model does not accidentally reproduce a few isolated cases only.

Table I. Comparison of Experimental and Calculated Ratios of Stereoisomers in IDA Reactions of Unactivated Trienes[a]

entry	triene	exptl trans/cis ratios (ΔG_{c-t}, kcal/mol)	calcd trans/cis ratios (ΔE_{c-t}, kcal/mol)	T, K	ref
1	**1**	30:70 (-1.03)	26:74 (-1.29)	613	19
2	**2**	48:52 (-0.10)	55:45 (0.26)	613	19
3	3	>95:5 (>2.53)	86:14 (1.53)	433	22
4	4	>95:5 (>2.71)	86:14 (1.66)	463	22
5	**5**	>95:5 (>2.70)	92: 8 (2.21)	463	6a
6	6	48:52 (-0.07)	55:45 (0.20)	413	23
7	7	-	55:45 (0.18)	433	-
8	8	-	57:43 (0.23)	433	-
9	9	-	49:51 (-0.05)	433	-
10	10	-	47:53 (-0.11)	433	-
11	**11**	-	23:77 (-1.06)	433	-
12	**12**	-	55:45 (0.18)	433	-
13	13	-	64:36 (0.49)	433	-
14	**14**	-	29:71 (-0.77)	433	-
15	**15**	-	4:96 (-2.76)	433	-
16	16	55:45 (0.17)	60:40 (0.35)	433	25(b)
17	17	>95:5 (>2.53)	89:11 (1.80)	433	22(b)
18	**18**	95:5 (2.77; X=TMS)	90:10 (2.06; X=Me)	473	22(b)
19	**19**	33:67 (-0.73; Y=OTMS)	26:74 (-1.08; Y=OMe)	518	26(c)
20	**20**	50:50 (X=OTHP, OTBDMS)	24:76 (-0.99; X=OMe)	433	27(c)

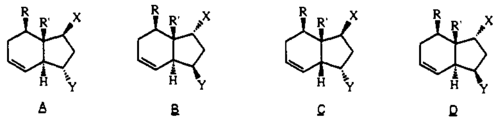
(a) Triene structures are given in Figure 3. We are comparing differences in steric energies with differences in free energies: the entropic term was not included in the calculated values since we are considering differences between the energies of two very similar transition structures; moreover, it is well known that the entropic contribution in a Diels-Alder reaction is negligible.[1,21]

(b)



R=R'=H (16)	-----	A:B:C:D (calc.)= 45:15:32:8
R=Me; R'=X=H (17)	A:B:C:D (exp.)= 58:42:0:0	A:B:C:D (calc.)= 68:21:10:1
R=R'=Me; X=Me,TMS (18)	A:B:C:D (exp.)= 58:37:5:0	A:B:C:D (calc.)= 63:27:10:0

(c)



R=Me; R'=X=H; Y=OMe (19)	------	A:B:C:D (calc.)= 21:5:47:27
R=Y=H; R'=Me; X=OMe (20)	------	A:B:C:D (calc.)= 23:1:65:11

Calculated stereoselectivities for the IDA reactions of the unactivated alkenes listed in Chart I are compared with experimental data in Table I. The cis-fused product is favored for 1,3,8-nonatriene, because the tether occupies the less crowded endo position in the corresponding transition structure. In the decatriene reaction, the diene moiety occupies an axial position on the forming cyclohexane ring in the cis-fused transition structure. The 1,3-diaxial interactions counteract the endo preference of the tether, resulting in no diastereoselectivity.[16] A 3-substituent on the diene increases this 1,3-diaxial destabilizing interaction to a very large extent, producing a strong preference for the trans-fused product (entries 3–5). This principle was already discovered and was used for synthetic purposes on the basis of empirical considerations.[6c,6d,24]

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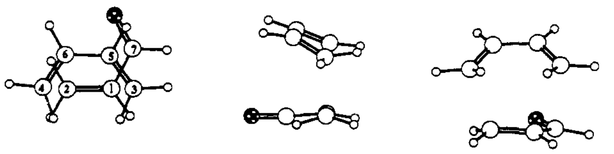


Figure 3. Butadiene plus acrolein s-cis endo 3-21G transition structure.

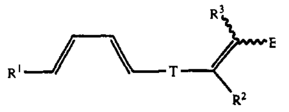
The force-field model allows us to predict the effects of substituents at all the positions on the transition structures and to clarify the factors producing stereoselection. That the 1,3-diaxial interactions are responsible for the diastereoselectivity in the decatriene reactions was demonstrated by the evaluation of the effect of a methyl at other positions of the diene unit; almost no difference was observed with respect to the unsubstituted decatriene reaction (compare entries 7 and 8 to entry 2). The same trend is evident for the nonatriene reactions, where a cis-selective reaction becomes almost an unselective one because of the substitution on C-3 of the diene (entry 10; cf. entry 1).

Substitution on the ethylene unit was also tested for both the decatriene and the nonatriene cyclizations. A methyl group on the junction of the two rings is predicted to have a minor influence on the stereochemical outcome of the decatriene cycloaddition (entry 9); in the trans-fused transition structure, the methyl group is in an unfavorable axial position but at the same time occupies the less hindered endo region. The two effects compensate almost perfectly, and the endo preference prevails over the equatorial preference to a small extent. The same factors are operating in the nonatriene reactions (entry 11).

Entries 12–15 evaluate the effect of alkyl substitution on the dienophile. In the decatriene series, neither a (*E*)-methyl nor a (*Z*)-methyl (entries 12 and 13) has much effect. For the nonatriene cycloadditions, the (*E*)-alkene is predicted to undergo the cyclization with slightly decreased cis selectivity, whereas the (*Z*)-alkene is predicted to have increased cis selectivity. In the twisted transition structures of the nonatriene reactions, the methyl group is in a more crowded position in the trans-fused one, due to the steric interactions with the inside hydrogens (Figure 2).

The presence of a substituent on the tether increases the complexity of the stereochemical outcome of the reaction, because four diastereoisomers can be formed. In Table I, some of the data were obtained for oxygenated compounds. A hydroxy or an alkoxy substituent in the homoallylic position does not have a significant effect on the diastereoselectivity of the cycloaddition reaction (compare entries 16–18 to 2–4). For an oxygenated substituent in the allylic positions, however, an effect is found. The existence of a stereoelectronic effect due to an allylic oxygen substituent has been experimentally demonstrated for intermolecular Diels–Alder reactions and studied theoretically.[28] The disagreement between the calculated and the experimental ratios is dramatic when the alkoxy group is allylic to the ethylene unit, while the position allylic to the diene seems to be less critical (entries 19 and 20). The anomalous result of entry 20 cannot be attributed to the presence of a methyl on the junction of the two forming rings, since this is not predicted to alter significantly the diastereomeric ratios (entry 11). Work is in progress for the ab initio evaluation of the conformational preference for oxygenated substituents in the Diels–Alder reaction.

Chart II. Terminally Activated Trienes



TRIENE	E	T	R¹	R²	R³
21	E-COOMe	$(CH_2)_3$	H	H	H
22	E-CHO	$(CH_2)_3$	Pr-i	H	H
23	E-COMe	$(CH_2)_3$	Pr-i	H	H
24	E-COOMe	$(CH_2)_3$	Pr-i	H	H
25	E-COOMe	$(CH_2)_4$	H	H	H
26	E-COOMe	$(CH_2)_2OCH_2$	H	H	H
27	E-CHO	$(CH_2)_4$	Pr-i	H	H
28	E-COMe	$(CH_2)_4$	Pr-i	H	H
29	E-COOMe	$(CH_2)_4$	Pr-i	H	H
30	Z-COOMe	$(CH_2)_3$	H	H	H
31	Z-COOMe	$(CH_2)_3$	Pr-i	H	H
32	Z-COOMe	$(CH_2)_4$	H	H	H
33	Z-COOMe	$(CH_2)_4$	Pr-i	H	H
34	E-COOMe	$CH(OH)\text{-}(CH_2)_2$	Pr-i	H	H
35	E-COOMe	$CH(OX)\text{-}(CH_2)_2$	Pr-i	H	H
36	E-COOMe	$(CH_2)_3\text{-}CH(Y)$	Me	H	H
37	E-COOMe	$(CH_2)_3\text{-}CH(Y)$	Me	H	H
38	E-COOMe	$CH(X)\text{-}(CH_2)_3$	Me	H	H
39	E-COOMe	$CH(X)\text{-}(CH_2)_3$	Me	H	Me
40	E-CHO	$CH(X)\text{-}(CH_2)_3$	H	H	Me
41	E-CHO	$CH(X)\text{-}(CH_2)_3$	Me	H	Me
42	E-CHO	$(CH_2)_3$	H	H	Me
43	E-CHO	$(CH_2)_3\text{-}CH(Me)$	H	H	H
44	E-CHO	$(CH_2)_3\text{-}CH(Me)$	H	Me	H

Terminally Activated Alkenes

As mentioned earlier, an increase in the asynchronicity of the transition structures is expected upon attachment of an activating substituent at the alkene terminus.[5,16] Several transition structures for the Diels–Alder intermolecular reaction of butadiene with asymmetric dienophiles have been located at the ab initio RHF level.[17,29] The transition structures found are indeed asynchronous but still concerted; the s-cis endo stereoisomer is both the lowest energy and the most asynchronous structure. The interaction of the acrolein with the diene reverses the conformational preference found in the ground state: the s-cis conformation is preferred in both the endo and the exo modes of approach, while the acrolein ground-state conformation is s-trans.[30] An increase of the theoretical level of the calculation causes an increased asymmetry for the s-cis endo transition structure; the geometry obtained at the 3-21G level is shown in Figure 3.

When the cycloaddition reaction involves a diene and an activated dienophile, the force-field parameters has to be slightly modified accordingly to the different nature of the reactants. The force constants for the two forming CC bonds were adjusted to

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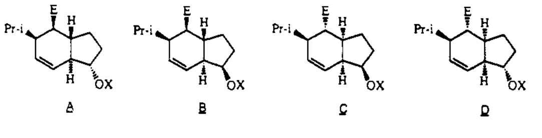
Table II. Comparison of Experimental and Calculated Ratios of Stereoisomers in IDA Reactions on Terminally Activated Trienes[a]

entry	triene	exptl trans/cis ratio (ΔG_{c-t}, kcal/mol)	calcd trans/cis ratio (ΔE_{c-t}, kcal/mol)	T, K	ref
1	**21**	60:40 (0.34)	64:36 (0.49)	423	31
2	**22**	89:11 (1.76)	82:18 (1.28)	423	32
3	**23**	85:15 (1.46)	77:23 (1.02)	423	32
4	**24**	72:28 (0.79)	65:35 (0.52)	423	33
5	**25**	51:49 (0.03)	60:40 (0.34)	428	34
6	**26**	60:40 (0.36)	62:38 (0.41)	443	35
7	**27**	75:25 (0.92)	77:23 (1.02)	423	32
8	**28**	67:33 (0.60)	73:27 (0.84)	423	32
9	**29**	50:50	70:30 (0.73)	433	36
10	**30**	65:35 (0.56)	17:83 (-1.41)	453	31
11	**31**	67:33 (0.64)	10:90 (-1.98)	453	31
12	**32**	51:49 (0.03)	50:50 (0.02)	428	34
13	**33**	55:45 (0.18)	42:58 (-0.27)	453	36
14	34	70:30 (0.71)	72:28 (0.79)	423	38(b)
15	**35**	82:18 (1.28; X=Bn)	75:25 (0.92; X=Me)	423	38(b)
	or	79:21 (1.11; X=TMS)			
16	**36**	53:47 (0.10)	60:40 (0.34)	428	39(c)
17	37	78:22 (1.04; Y=OTBDMS)	60:40 (0.34; Y=OMe)	413	39(c)
18	38	30:70 (-0.71; X=OTMS)	48:52 (-0.07; X=OMe)	423	34(c)
	or	41:59 (-0.31; X=OTMS)			
19	39	25:75 (-0.92; X=OTBDMS)	56:44 (0.20; X=OMe)	423	6j(c)
	or	28:72 (-0.79; X=OTBDMS)			34
20	40	60:40 (0.34; Y=OMOM)	57:43 (0.24; Y=OMe)	423	6j(c)
21	41	84:16 (1.39; Y=OMOM)	58:42 (0.27; Y=OMe)	423	6j(c)
	or	54:46 (0.14; Y=OTBDMS)			

(a) Trienes structures are reported in Figure 5. See also footnote (a) in Table 1.

(b)

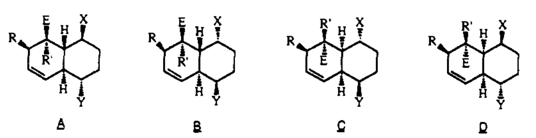


E = COOMe

X=H (**34**) A:B:C:D (exp.)= 37:33:26:4 A:B:C:D (calc.)= 48:23:19:10

X=Bn,TMS,Me (**35**) A:B:C:D(exp.; X=Bn)= 51:31:14:4 A:B:C:D (calc.)= 65:10:22:3
(X=TMS)= 31:48:17:4

(c)



E = COOMe

R=Me; R'=X=H; Y=OTMS, OMe(**36**) A*:B*:C*:D*(exp.)= 26:15:33:26
A:B:C:D (calc.)=36:12:42:10

R=Me; R'=Me; X=H; Y=OTBDMS, OMe(**37**)
A:B:C:D (exp.)= 15:13:27:53
A:B:C:D (calc.)= 49:7:37:6

R=Me; R'=Y=H; X=OH (**38**) A:B:C:D (exp.)= 41:12:47:0
A:B:C:D (calc.)= 43:17:26:14

R=Me; R'=Y=H; X=OTBDMS, Me (**39**) A:B:C:D (exp.)= 13:65:22:0
A:B:C:D (calc.)= 41:19:25:15

E = CHO

R=X=H; R'=Me; Y=OMOM, OMe (**40**) A:B:C:D(exp.)= 37:23:25:15
A:B:C:D (calc.)= 51:6:38:5

R=Me; R'=Me; X=H; Y=OMOM, OMe A:B:C:D(exp.)= 63:21:16:0
A:B:C:D(calc.) = 52:6:37:5
Y=OTBDMS (**41**) (exp.) = 27:27:13:33

0.5 and 1.5 mdyn/Å for the external and internal forming bonds, respectively, as compared to 1.0 mdyn/Å for both forming bonds in the unactivated case. The reduction of the stretching force constant for the external forming bond required elimination of the stretch–bend term in the MM2 force field and reduction of the cubic stretch term. This eliminates the potential spurious structure which arises from the minimum which is created by the force field for large bond lengths.[7] Another significant change is the reduction of some bending force constants; the largest reduction was for those involving the internal forming bond.

The dipole moments are always the default MM2 ones. The reacting termini of the diene are set equal to sp^3 carbons; consequently, MM2 assigns a small dipole moment to the C_3–C_5 and the C_4–C_6 bonds (see Chart II; μ = 0.3 D). These small dipole moments were also present in the hydrocarbon cases previously discussed, but since there was not a large dipole moment (as the one for the C=O bond, μ = 2.6 D) the dipolar interactions were not important in determining the final steric energies for the MM2 transition structures. In the case of the IDA reaction on activated alkenes, there is a favorable electrostatic interaction between the C=O dipole moment and the small C_4—C_6 dipole moment in the trans-fused transition structure, in which the electron-withdrawing group is located in the endo position. This interaction can account for the "electronic effect" that is often invoked to justify the endo preference experimentally found for this kind of substituent.[1]

Chart II shows the compounds studied, and Table II gives the calculated and experimental results. The agreement between the calculated and the experimental data is somewhat less satisfactory than in the pure hydrocarbon cases but is still quite good.

A closer examination of the data of Table II allows some interesting observations. The correct sense of diastereoselection is almost always calculated. It is difficult to reproduce the experimental trend found for the IDA reaction with different activating groups. Aldehyde reactions are in general more trans-selective than those of ketones, while the esters exhibit the lowest diastereoselectivity.[32] We made the choice to modify the CO–X dipole moments for the aldehydes and esters (X = H, OR) in order to tune the force field according to the different activating groups. No parameters were introduced for the ketone. This allowed us to obtain good agreement between the calculated and experimental ratios with these different dienophiles.

In the cycloadditions of (*E*)-nonatrienes and decatrienes, the trans-fused product is favored, although the stereoisomeric excess depends upon the particular substrate (Table II, entries 1–9). The preference cannot be attributed to steric reasons only, because when the substituent on the alkene occupies the more favorable endo position, the tether is forced into the less favorable exo environment. The evaluation of the steric effects only (Table I, entries 12 and 14; cf. entries 1 and 2) shows that in both cases (*E*)-olefins undergo the IDA reaction with stereoselectivity unchanged from the corresponding unsubstituted triene cases. The force field reproduces the endo preference in a satisfactory way, despite the fact that no special parameters were used to reproduce this "endo effect". The default MM2 dipole moments present on the carbonyl and the diene stabilize the endo, trans-fused transition structure.

Few experimental data are available for (*Z*)-alkenes, perhaps because of the generally low selectivity in the cycloaddition reactions of these compounds that makes their use synthetically inconvenient.[3] As discussed in the previous section, increased cis selectivity would be expected in the cyclization of (*Z*)-alkenes, at least of the nonatrienes, because the cis-fused transition structure will allow both the tether and the activating group to occupy the preferred endo position. This conformation is favored also on the basis of steric effects alone (Table I, entry 15); if present, ster-

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eoelectronic effects would reinforce the endoselectivity. We also noticed in the previous section that simple steric considerations give a surprising result for the cycloaddition of (*Z*)-decatrienes (Table I, entry 13), where the trans-fused cycloadduct is predicted to be slightly favored over the cis-fused one.

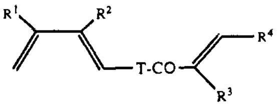
The experimental data available for the IDA reaction on activated (*Z*)-alkenes are even more puzzling: the trans-fused product is always favored (Table II, entries 10–13) despite the presence of both substituents in the exo position. Also other reactions of (*Z*)-α,β-unsaturated carbonyls or esters have an anomalous stereochemical outcome.[37] In the case of the decatriene IDA reactions (Table II, entries 12 and 13), the calculated diastereomeric ratios are in agreement with both the experimental data and the evaluation of the steric factors only (Table I, entry 13). The calculated ratios for the activated (*Z*)-nonatriene cycloaddition, on the other hand, are consistent with the "steric case" (Table I, entry 15) but diverge from the experimental data for (*Z*)-α,β-unsaturated esters (Table II, entries 10 and 11). Factors other than the steric interactions or secondary orbital overlap become important in the reactions of strained, electron-deficient (*Z*)-alkenes. The scarce availability of experimental data for the IDA reaction on (*Z*)-alkenes did not allow us to evaluate these factors more carefully.

Some results in Table II involve trienes bearing an oxygenated substituent in the allylic position. Sometimes the force field is satisfactory with the standard MM2 parameters for the heteroatoms, but some discrepancies are evident, particularly for entries 17–19 and 21. The experimental diasteromeric ratio for entry 18 is not completely clear. In the discussion, the authors report a cis/trans ratio of 70:30, but the data reported in the Experimental Section gave an overall cis/trans ratio of 59:41. The data for related compound **39** in entry 19 seem to support the 70:30 cis/trans ratio for the cycloaddition of triene **38** (entry 18); however, triene **37** has a methyl substituent geminal to the carbomethoxy group. It is well-known from studies of Diels–Alder cycloadditions of 1-substituted acrylates that a methyl group in the α position has an endo preference similar to that of the carbonyl or carbomethoxy groups.[1] The behavior of such 1-alkyl-substituted dienophiles in the intramolecular reaction is even more puzzling. Aldehydes **40** and **41**, structurally similar to ester **39**, are predicted to be trans-selective in the IDA reaction, in satisfactory agreement with the experimental data (entries 20 and 21). There is also a significant dependency of the diastereomeric ratio upon the nature of the ethereal substituent, as is evident from the two different experimental ratios reported in entry 21. A special feature of the trienes considered in entries 17, 19, and 21 is the presence of a TBDMS protecting group on the oxygen. Anomalous behavior of such ethers was pointed out by several authors in different reactions,[6k,38,39] where the OTBDMS group prefers the axial position on a cyclohexane ring. In both entries 17 and 19 in Table II, the experimentally favored diastereoisomer is axially substituted; obviously those are not the most stable ones in the force field, which favors the equatorial position for steric reasons. The presence of an oxygenated allylic substituent has a strong influence on determining the diastereoselection in these IDA reactions; work is in progress to evaluate quantitatively the effects involved.

IDA Reactions on Internally Activated Alkenes

Internally activated trienes generally undergo the thermal IDA cycloaddition with moderate to high cis selectivity, an experimental result that is usually ascribed to combined effects of secondary orbital overlap and of the endo preference for the tether. However, these effects do not control the terminally activated (*Z*)-trienes stereoselectivity, since they do not undergo the IDA reaction with strong cis selectivity. When we applied the parameters described above to the IDA reaction of 1,7,9-decatrien-3-one, almost no stereoselectivity (trans/cis ratio = 51:49 at 273 K) was calculated. By contrast, this compound is well-known to undergo the IDA cycloaddition at this temperature with 90% cis selectivity.[41]

Chart III. Internally Activated Trienes



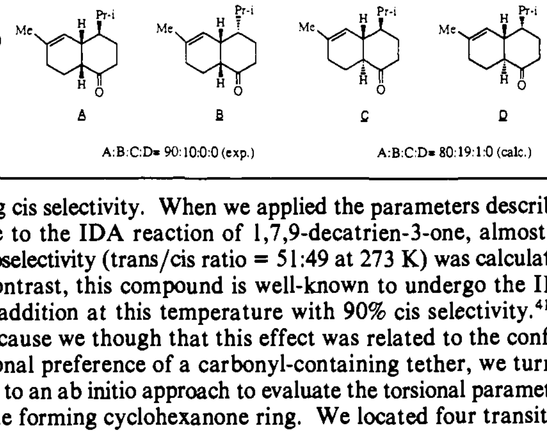
TRIENE	T	R^1	R^2	R^3	R^4
45	$(CH_2)_3$	H	H	H	H
46	$(CH_2)_2$	H	H	H	H
47	$(CH_2)_3$	H	H	H	E-Pr-i
48	$(CH_2)_3$	H	Me	H	E-Pr-i
49	CH(Pr-i)-$(CH_2)_2$	Me	H	H	Me
50	$(CH_2)_2$	H	H	Me	H
51	$(CH_2)_2$	H	Me	Me	H

Table III. Comparison of Experimental and Calculated Ratios of Stereoisomers in IDA Reactions of Internally Activated Trienes[a]

entry	triene	experimental trans/cis ratio (ΔG_{c-t},kcal/mol)	calculated trans/cis ratio (ΔE_{c-t},kcal/mol)	T (K)	reference
1	45	5:95 (-1.73)	6:94 (-1.61)	295	41
2	46	13:87 (-1.71)	14:86 (-1.62)	453	45
3	47	<5:95 (<-1.73)	4:96 (-1.86)	295	41
4	48	<95:5 (<-1.84)	17:83 (-0.99)	315	44
5	49	<1:99 (<-2.49)	1:99 (-2.49)	273	43[(b)]
6	50	30:70 (-0.78)	37:63 (-0.51)	463	46
7	51	31:69 (-0.74)	38:62 (-0.39)	463	47

(a) Trienes structures are reported in Figure 6. See also footnote (a) in Table 1.

(b)



A:B:C:D= 90:10:0:0 (exp.)

A:B:C:D= 80:19:1:0 (calc.)

Because we though that this effect was related to the conformational preference of a carbonyl-containing tether, we turned again to an ab initio approach to evaluate the torsional parameters for the forming cyclohexanone ring. We located four transition structures for the IDA reaction of 1,7,9-decatrien-3-one with the 3-21G basis set and full optimization of all the variables;[17] there are half-chair and twist-boat transition structures for both the endo and exo diastereomers. The result was disappointing: the calculated trans/cis diastereomeric ratio was only 40:60, as compared to the experimental value of 5:95. Even 6-31G* single-point calculations on the 3-21G transition structures did not improve the agreement with experiment. Nevertheless, an interesting feature is revealed at all levels of theory: for the exo transition structures, the half-chair conformation for the tether is preferred over the twist boat by 2 kcal/mol, while in the endo mode of approach the two conformers have almost the same energy, the chair being more stable by only 0.2 kcal/mol at the 3-21G level. Normally the twist-boat conformation is not taken into account for cyclohexanes, since it is approximately 5 kcal/mol higher in energy than the chair. However, when the cyclohexane ring includes two or more trigonal centers, the twist-boat con-

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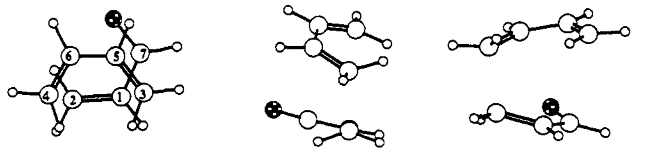


Figure 4. Butadiene plus acrolein-BH_3 complex s-cis endo 3-21G transition structure (the BH_3 moeity is not shown).

formation becomes comparable to, or even lower than, the chair.[42] Boatlike conformations for the tether have been invoked to rationalize the diastereomeric outcome of these reactions.[6e,43] Further computational or experimental studies will be required to resolve this issue.

To reproduce the experimental trans/cis rates for the reactions of 1,7,9-decatrien-3-one (**45**) and of 1,6,7-nonatrien-3-one (**46**) (Table III and Chart III), a torsional parameter (C_5–C_3–C_1–CO: $V_2 = -1$, $V_3 = -4$ kcal/mol) was introduced. This parameter stabilizes the twist-boat conformation more than the half-chair one for the cis-endo transition structure. In our MM2 force field, the cis-fused transition structure is 0.6 kcal/mol more stable in the twist-boat than in the half-chair conformation.

There is a barrier to rotation about the single bond of the enone, but there are no parameters in MM2 for such a bond. This was not important in the case of terminally substituted trienes, since the conformation of the exocyclic α,β-unsaturated moiety was not critical for the stereoselectivity of the reaction. Ab initio calculations were used to evaluate this barrier for acrolein in the ground state[30] and in the transition state of the butadiene–acrolein Diels–Alder reaction. That barrier was estimated to be 10 kcal/mol in both the endo and exo transition structures. This value was incorporated in the MM2 parameter list, distributing the barrier to its four main components ($H—C_1—C═O$; $C_2—C_1—C═O$; $H—C_1—CO—C$; $C_2—C_1—CO—C$); each one was assigned a value of $V_2 = 2.5$ kcal/mol.

The data for the internally activated IDA reactions are collected in Table III. The experimentally favored cis isomer in entry 5 arises from a twist-boat conformation for the tether that places the isopropyl group in a pseudoequatorial position; this conformation is favored over that with the substituent equatorial on a chairlike conformation.

Entries 6 and 7 demonstrate the introduction of a parameter for the geminal methyl group. In the intermolecular Diels–Alder cycloadditions of 1-substituted acrylates and related dienophiles, the methyl group occupies the endo position in preference to the carboxyl: the exo carbonyl isomer is consequently favored. Therefore, when we introduced a torsional parameter to account for the conformational preferences of a CO group relative to H, we also introduced a torsional parameter for the geminal methyl group. The subsequent agreement within the calculated and the experimental data is reasonable. Entry 4 demonstrates that the parameters assigned for the downward bending of the substituents on the diene internal carbons lead to qualitative agreement with the experimental ratios: this is apparent also in entry 7. It is interesting to note that, in these cases (entries 4 and 7), the calculated ratios favor the cis isomer less than the experimental results. The opposite was true in the all-hydrocarbon case (Table I, entries 3–5, 17, and 18), when the calculated data were less trans-selective than the experimental ones.

Acid-Catalyzed Reactions of Terminally Activated Alkenes

All the factors responsible for the diastereoselectivity in the IDA reaction of activated olefins are magnified by Lewis acid catalysis.[1-4] The transition structures for the uncatalyzed and the catalyzed Diels–Alder cycloadditions of butadiene and arolein are quite different. The lowest energy 3-21G s-cis endo transition structure of the BH_3-catalyzed Diels-Alder reaction of butadiene plus acrolein is shown in Figure 4.[48] The asynchronicity of the transition structure is large, but the calculations clearly indicate that the reaction is still concerted, even though the α bonding (atoms 1 and 3 in Figure 4) is primarily electrostatic.

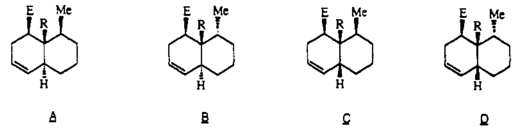
The asynchronicity makes the steric requirements quite different at either of the forming bonds; the extreme weakness of the α bond allows in fact a considerable flexibility for the favored s-cis endo transition structure. There is also a considerable twisting of the reactants about the stronger forming bond.

Table IV. Comparison of Experimental and Calculated Ratios of Stereoisomers on Lewis Acid Catalyzed IDA Reactions[a]

entry	triene	experimental trans/cis ratio ($\Delta G_{c\text{-}t}$,kcal/mol)	calculated trans/cis ratio ($\Delta E_{c\text{-}t}$,kcal/mol)	T (K)	reference
1	**21**	>99:1 (>2.70)	89:11 (1.24)	296	49
2	**22**	>99:1 (>1.78)	99.6:0.4 (2.14)	195	32
3	**23**	>99:1 (>1.78)	99:1 (1.78)	195	32
4	**24**	>99:1 (>2.70)	93:7 (1.52)	296	49
5	**27**	>99:1 (>1.78)	99.6:0.4 (2.14)	195	32
6	**28**	>99:1 (>1.78)	99.6:0.4 (2.14)	195	32
7	**29**	88:12 (1.17)	92:8 (1.44)	296	50
8	**42**	99:1 (2.13)	96:4 (1.51)	233	6n
9	**43**	>95:5 (>1.46)	98:2 (1.93)	250	6i[(b)]
10	**44**	>95:5 (>1.46)	99:1 (2.28)	250	6i[(b)]
11	**40**	90:10 (1.13; X=MOM)	88:12 (1.02)	258	6j[(c)]
12	**41**	96:4 (1.63; X=MOM)	90:10 (1.13)	254	6j[(c)]
	or	90:10 (1.13; X=TBDMS)			
13	**36**	99:1 (2.72)	89:11 (1.24)	298	39[(c)]
14	**37**	>99:1 (>2.72;X=OTBDMS)	87:13 (1.13; X=OMe)	298	39[(c)]
15	**30**	56:44 (0.14)	21:79 (-0.77)	296	49
16	**31**	68:32 (0.48)	14:86 (-1.16)	323	49
17	**33**	<8:92 (<-1.44)	15:85 (-1.02)	296	50

(a) Trienes structures are reported in Figure 5; see also footnote (a) in Table 1.

(b)

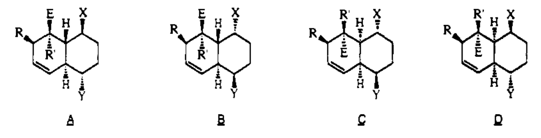


E = CHO

R=H (43) A:(B+C+D) (exp.) >95:5 A:B:C:D (calc.)= 97:1:2:0

R=Me (44) A:(B+C+D) (exp.) >95:5 A:B:C:D (calc.)= 99:0:1:0

(c)



E = COOMe
R=Me; R'=Y=H; X=OH (36)
A:B:C:D (exp.)= 45:55:1:0 A:B:C:D (calc.)= 78:11:7:4
R=Me; R'=Y=H; X=OTBDMS, OMe (37)
A:B:C:D (exp.)= 2:98:0:0 A:B:C:D (calc.)= 77:10:6:7

E = CHO

R=X=H; R'=Me; Y=OMOM, OMe (40)
A:B:C:D (exp.)= 41:49:7:3 A:B:C:D (calc.)= 84:4:12:0
R=R'=Me; X=H; Y=OMOM, OMe (41)
A:B:C:D (exp.)= 56:40:4:0 A:B:C:D (calc.)= 85:5:10:0
Y= OTBDMS (exp)= 15:75:0:10

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Table V. Comparison of Experimental and Calculated Ratios of Stereoisomers with the MM2 and MM3 Force Fields

		t/c ratio				
entry	triene[a]	exptl[b,c]	MM3[c]	MM2[b,c]	*T*, K	ref
1	1	30:70 (-1.03)	29:71(-1.10)	26:74 (-1.29)	613	18
2	**2**	48:52 (-0.10)	55:45 (0.26)	55:45 (0.26)	613	18
3	3	>95:5 (>2.53)	83:17 (1.38)	86:14 (1.53)	433	22
4	4	>95:5 (>2.71)	83:17 (1.45)	86:14 (1.66)	463	22
5	**21**	60:40 (0.34)	80:20 (1.15)	64:36 (0.49)	423	31
6	**25**	51:49 (0.03)	62:38 (0.41)	60:40 (0.34)	428	34
7	30	65:35 (0.56)	20:80 (-1.25)	17:83 (-1.41)	453	31
8	32	51:49 (0.03)	32:68 (-0.11)	50:50 (0.02)	428	34

(a) cf. Figures 3 and 5.

(b) cf. Tables 1 and 2.

(c) Experimental values are $\Delta G_{cis\text{-}trans}$ (kcal/mol); calculated values are $\Delta E_{cis\text{-}trans}$ (kcal/mol); see also footnote (a) in Table 1.

The MM2 force field was modified accordingly to these ab initio results. The reference values for bond lengths and angles were changed to the those of the 3-21G s-cis endo transition-state geometry. The stretching force constants were changed slightly (0.3 and 1.7 mdyn/Å for the external and internal bond, respectively); the stretch–bend force constants were set equal to zero as in the corresponding force field for the thermal reactions, and the cubic stretch term was reduced by the same amount as before. The results obtained from the ab initio studies confirmed the hypotheses originally made on the basis of the simple 3-21G butadiene plus ethylene transition structure:[16] any asynchronicity imposed on the system will be translated into a twist of the two reactants and an asymmetric degree of bond formation.

The dipole moments for the carbonyl C=O bond and for the C_4–C_6 bond of the diene were increased (μ = 4.0 and 1.5 D, respectively) to account for the charge attraction that is present between these two moieties. The high asynchronicity of the transition structure makes the reaction resemble an acid-catalyzed Michael-type addition to an electron-deficient alkene. For the sake of simplicity, the Lewis acid was not included in the force-field calculations. Another important feature of this transition structure involves the two hydrogens on the diene internal carbons that are not bent out-of-plane to the same extent as in the uncatalyzed processes (cf. Figures 3 and 4). The internal hydrogen, which is closer to the internal, shorter forming bond, shows the usual 15° bending toward the alkene; the corresponding torsional parameter given to ensure this bending was left unchanged (the dihedral angle H–C_6–C_4–C_2 is still about 90° and was given a V_2 = −7.5 kcal/mol). The other hydrogen, however, is closer to the weakly formed external bond; the reacting termini are nearly planar, and the characteristics at this terminus are definitely reactant-like. This latter hydrogen has a dihedral angle H–C_5–C_3–C_1 of 120°, not 90°: the torsional parameter was thus changed to V_3 = −7.5 kcal/mol.

Given the drastic assumptions, the agreement between the calculated and the experimental data is remarkable (Table IV). This is in part due to the high selectivity observed. The increase in selectivity from the uncatalyzed to the acid-catalyzed reaction performed on the same triene is also well reproduced (cf. the data for the thermal reaction of the corresponding trienes in Table II). There are problems with the general behavior of the (*Z*)-alkenes, as for the uncatalyzed processes. The nonatrienes IDA cycloadditions are trans-selective; the calculations, in accord with the previous results, favor the cis products (entries 10 and 11). The (*Z*)-decatrienes, on the other hand, exhibit the expected cis selectivity and the result obtained with our implemented force field is quite good (entry 12). Different substitutions at the reactants and the different nature of the Lewis acid can increase the importance of charge separation in the IDA transition structures; these effects are obviously not taken into account in this MM2 force-field model.

MM3 Force Field

During the completion of this work, details of the new MM3 force field were published, and the program became available.[14] The equations that describe the steric energy have been significantly modified in MM3. The MM3 results for unstrained molecules closely resemble those obtained with MM2, but marked improvements have been made in the case of strained molecules and aromatic systems. Moreover, the accuracy in the evaluation of the vibrational frequencies has been improved, and these can now be calculated with the MM3 program.

Another feature of the MM3 program was of interest to us: a quartic term was included in the equation that describes the bond stretching. Consequently, the energy goes to plus infinity rather than minus infinity for major elongations of the bond length. In our cases, even with a good starting geometry, the combination of this artificial well in the stretching potential and of the stretch–bend interaction caused the transition structures to fly apart when the stretching force constants for the two forming bonds were set to values lower than 1 mdyn/Å. In order to obtain reproducible results, we were forced to delete the stretch–bend term in the MM2 force field. The cubic stretch term was also reduced but not completely eliminated; a small anharmonicity was still allowed in this way. In the MM3 force field, this problem has been eliminated.

The data in Table V were obtained using the MM3 force field augmented with our parameters for the IDA reaction. The performance of the MM3 force field is parallel to that of the related MM2 for the unactivated hydrocarbon cases. However, when heteroatoms are present in the transition structure, the results obtained with this new force field are less satisfactory but qualitatively analogous to the MM2 ones. The (*Z*)-nonatrienes are still incorrectly predicted to be strongly cis-selective (entry 7), while for the other compounds a reasonable qualitative agreement with the experimental data is found (entries 5, 6, and 8). It must be kept is mind that the MM3 force field is not completed yet, and significant differences can arise from the use of implemented parameters. Moreover, the IDA parameters we developed were based quantitatively on the MM2 force field and will have to be slightly modified for their inclusion in MM3.

Conclusions

The new parameters for the IDA reactions we have developed allow a qualitative, and in some cases quantitative, evaluation of the stereoselectivities of intramolecular Diels–Alder cycloadditions on (*E*)-alkenes. For a wide range of reactants, a force-field method is now available for the study and prediction of intramolecular Diels–Alder reactions.

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Registry No. 1, 96308-44-0; **2**, 97745-95-4; **3**, 68262-77-1; **4**, 68262-78-2; **5**, 141063-20-9; 6, 87463-24-9; **7**, 141063-21-0; **8**, 141063-22-1; **9**, 141063-23-2; **10**, 97745-96-5; **11**, 109307-86-0; **12**, 141063-24-3; **13**, 141063-25-4; **14**, 141063-26-5; **15**, 141063-27-6; **16**, 141063-28-7; **17**, 141063-29-8; **18**, 141063-30-1; **19**, 141063-31-2; **20**, 141063-32-3; **21**, 2409-89-4; **22**, 113115-69-8; **23**, 113115-68-7; **24**, 74930-38-4; **25**, 78669-19-9; **26**, 141088-14-4; **27**, 113115-81-4; **28**, 113115-80-3; **29**, 83486-81-1; **30**, 74930-37-3; **31**, 74930-39-5; **32**, 78669-22-4; **33**, 83486-82-2; **34**, 71516-83-1; **35**, 71516-85-3; **36**, 141088-15-5; **37**, 141063-33-4; **38**, 141063-34-5; **39**, 78669-01-9; **40**, 141063-35-6; **41**, 141063-36-7; **45**, 112069-37-1; **46**, 108186-40-9; **47**, 141063-37-8; **48**, 141063-38-9; **49**, 141063-39-0; **50**, 57404-95-2; **51**, 107723-99-9; 1,7,9-decatrien-3-one, 106992-45-4.

Supplementary Material Available: Complete list of MM2 parameters and the RHF/3-21G-optimized transition structures for the IDA reaction of 1,7,9-decatrien-3-one (22 pages). Ordering information is given on any current masthead page.