Hetero-Diels–Alder Reaction Transition Structures: Reactivity, Stereoselectivity, Catalysis, Solvent Effects, and the exo-Lone-Pair Effect

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Transition structures for the Diels–Alder reactions of butadiene with formaldehyde, thioformaldehyde, formaldimine, *N*-methylformaldimine, diazene, nitrosyl hydride, singlet oxygen, BH$_3$-coordinated formaldehyde and formaldimine, and protonated formaldimine have been located with ab initio molecular orbital calculations using the 3-21G basis set. Activation energies have been evaluated with MP2/6-31G* calculations on these geometries. Formaldehyde and the imines are predicted to be comparable in reactivity to ethylene, whereas the other dienophiles are predicted to be more reactive. Transition structures with the nitrogen lone pair(s) in the endo position are less stable than the corresponding transition structures with exo lone pairs. Formaldimine, *cis*-diazene, and nitrosyl hydride are predicted to favor the transition structures with the imino hydrogens endo by 4.9, 11.6, and 8.1 kcal/mol, respectively. The exo-lone-pair preference of formaldimine is 4.1 kcal/mol at high levels of theory (up to MP4SDTQ/6-31G*//6-31G*). These preferences result from electrostatic repulsions between the heteroatom lone pairs and the butadiene π electrons when the lone pairs are endo. The partial C–O and C–N bonds in the uncatalyzed Diels–Alder transition structures are shorter than the forming C–C bonds, while the partial C–S bond is significantly longer. These relationships reflect the normal single bond lengths in the products. Protonation and BH$_3$ coordination, used to model strong and weak Lewis acid catalysis, respectively, cause lower activation energies and less symmetrical transition structures. BH$_3$ has a preference for the exo position in the transition structures. The effect of BH$_3$ coordination on the activation energy is more pronounced for the aldehyde than the imine. The influence of solvent on the transition structure is assessed with a solvent cavity model.

Introduction

The hetero-Diels–Alder reaction is a powerful tool for the synthesis of heterocyclic compounds.[1-10] For example, Lewis acid-catalyzed reactions of carbonyl compounds with dienes are important methods for synthesizing carbohydrates and other natural products.[9] These reactions are generally assumed to be concerted, asynchronous cycloadditions, although a stepwise zwitterionic mechanism is also a possibility for polar dienophiles or for catalyzed processes. There are only a few mechanistic[11] and theoretical[12] studies of hetero Diels–Alder reactions, although all-carbon Diels–Alder reactions have been studied extensively.[13-19] We

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have begun a general theoretical study of Diels–Alder reactions with heteroatom-containing dienophiles; here we report our results on the reactions of butadiene with formaldehyde, thioformaldehyde, formaldimine, *N*-methylformaldimine, diazene, nitrosyl hydride, singlet oxygen, BH$_3$-coordinated formaldehyde and formaldimine, and protonated formaldimine.[20] These studies are carried out at relatively low theoretical levels, but at levels known to give a good account of stereoselectivity and relative reactivity for other Diels–Alder reactions.[19c] On the basis of the geometries and relative energies of the transition structures, the origins of reactivity differences and stereochemical preferences for these dienophiles will be discussed.

Methods

Geometry optimizations were carried out at the restricted Hartree–Fock level using the GAUSSIAN 86, 88, 90, and 92 programs.[21] For each reaction, the reactants, transition structures, and products were fully optimized with the 3-21G basis set, including a set of d orbitals for the sulfur atom of thioformaldehyde (3-21G*). Each transition structure gave only one imaginary harmonic vibrational frequency, corresponding to the motion forming the new C–C and C–X bonds for concerted transition structures. The activation energies were estimated from MP2/6-31G* calculations on the 3-21G or 3-21G* optimized geometries. For the reactions of BH$_3$-coordinated

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Table I. Calculated Energies (au) of Reactants, Transition Structures and Products for the Reactions of Butadiene with Heterodienophiles

compound	3-21G	3-21G ZPE[a]	6-31G*// 3-21G	MP2/6-31G*// 3-21G
trans-butadiene	−154.05946	0.09205	−154.91961	−155.42069
H$_2$CO	−113.22182	0.02898	−113.86529	−114.16680
H$_2$CS	−434.44646[b]	0.02682	−436.50644	−436.75436
H$_2$CNH	−93.49422	0.04283	−94.02740	−94.31270
H$_2$CNCH$_3$	−132.31232	0.07331	−133.06070	−133.47671
cis-HNNH	−109.34240	0.02945	−109.98350	−110.30094
trans-HNNH	−109.35477	0.03009	−109.99337	−110.31318
HNO	−129.03829	0.01487	−129.78275	−130.12357
^{1}O$_2$, RHF	−148.68718	0.00365	−149.52242	−149.89893
^{1}O$_2$, UHF[c]	−148.73864	0.00367	−149.57920	−149.93090
H$_2$CO·BH$_3$	−139.48641	0.06366	−140.26673	−140.65581
H$_2$CNH·BH$_3$	−119.78667	0.07864	−120.45477	−120.83220
H$_2$CNH$_2$$^+$	−93.86284	0.05818	−94.38306	−94.65869
TS 1	−267.22949	0.12646	−268.71155	−269.55422
product 1	−267.33576	0.13158	−268.82511	−269.63810
TS 2	−588.47550[a]	0.12368	−591.38390	−592.16897
product 2	−588.57126[a]	0.12818	−591.49048	−592.25263
TS 3	−247.49570	0.13961	−248.87036	−249.70138
TS 4	−247.50404	0.14000	−248.87721	−249.70920
product 3,4				
eq H	−247.61287	0.14482	−248.99675	−249.79624
ax H	−247.61428	0.14490	−248.99710	−249.79710
TS 5	−286.30777	0.16906	−287.89690	−288.86262
TS 6	−286.31377	0.16954	−287.90225	−288.86920
product 5, 6				
eq CH$_3$	−286.42851	0.17475	−288.02787	−288.96063
ax CH$_3$	−286.42768	0.17500	−288.02437	−288.95829
TS 7	−263.33852	0.12626	−264.81387	−265.69365
TS 8	−263.35859	0.12696	−264.83210	−265.71206
TS 9	−263.36724	0.12766	−264.84080	−265.71958
product 7, 8, 9				
dieq H	−263.47029	0.13256	−264.94539	−265.77922
eq/ax H	−263.47592	0.13235	−264.95154	−265.78399
diax H	−263.47603	0.13188	−264.95061	−265.78186
TS 10	−283.05421	0.11273	−284.63004	−285.52852
TS 11	−283.06622	0.11304	−284.64283	−285.54146
product 10, 11				
eq H	−283.18227	0.11879	−284.75715	−285.60714
ax H	−283.17774	0.11845	−284.75473	−285.60461
TS 12	−302.73155	0.09873	−304.39958	−305.32737
product 12	−302.87669	0.10474	−304.54646	−305.41706
TS 13	−293.51468	0.16051	−295.13945	−296.06234
TS 14	−293.51128	0.16032	−295.13494	−296.05830
product 13, 14				
eq BH$_3$	−293.61544	0.16604	−295.23317	−296.13719
ax BH$_3$	−293.61479	0.16603	−295.23161	−296.13581
TS 15	−273.79737	0.17530	−275.30881	−276.23270
TS 16	−273.79041	0.17500	−275.30277	−276.22691
product 15, 16				
eq BH$_3$	−273.91269	0.18118	−275.43084	−276.32753
ax BH$_3$	−273.90783	0.18143	−275.42649	−276.32419
TS 17	−247.92442	0.15321	−249.29714	−250.09456
intermediate 18	−247.97366	0.15796	−249.34412	−250.13754
product 17, 18	−248.00807	0.16123	−249.37923	−250.17453

[a] Zero-point vibrational energy. [b] 3-21G* basis set used. [c] $S^2 = 1.0$ before spin projection.

formaldehyde, BH$_3$-coordinated formaldimine, and protonated formaldimine, the role of acyclic intermediates was also explored with gas phase and solvent reaction field calculations, since closed-shell intermediates might compare in energy with the concerted transition structures.

Results and Discussion

A concerted, but not necessarily synchronous, reaction mechanism was presumed. For a prototypical Diels–Alder reaction of butadiene with ethylene, semiempirical, RHF, MP2, and MCSCF calculations all predict concerted transition structures with remarkably similar geometries.[15-18] However, thermochemical estimates[22] and

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Table II. Calculated Energies (kcal/mol) of the Transition Structures with Respect to Reactants for the Reactions of Butadiene with Heterodienophiles

TS	dienophile	activation energy				ΔE_{rxn}, 3-21G
		3-21G	3-21G, corr[a]	6-31G*[b]	MP2/6-31G*[b]	
	H_2CCH_2[c]	35.9	38.3	43.0	17.6	-43.1
1	H_2CO	32.5 (-3.4)	35.9	46.0 (+3.0)	20.9 (+3.3)	-34.2
2	H_2CS	19.1 (-16.8)	22.1	26.4 (-16.6)	3.8 (-13.8)	-41.0
3	H_2CNH exo	36.4 (+0.5)	39.4	48.1 (+5.1)	20.1 (+2.5)	-38.0
4	H_2CNH endo	31.1 (-4.8)	34.4	43.8 (+0.8)	15.2 (-2.4)	
5	H_2CNCH_3 exo	40.2 (+4.3)	42.5	52.3 (+9.3)	21.8 (+4.2)	-35.6
6	H_2CNCH_3 endo	36.4 (+0.5)	39.0	49.0 (+6.0)	17.7 (+0.1)	
7	cis-HNNH exo	39.9 (+4.0)	42.7	56.0 (+13.0)	17.6 (0.0)	-38.8
8	cis-HNNH endo	27.4 (-8.5)	30.6	44.6 (+1.6)	6.0 (-11.6)	
9	trans-HNNH	29.5 (-6.4)	33.0	45.3 (+2.3)	9.0 (-8.6)	
10	HNO exo	27.3 (-8.6)	31.0	45.4 (+2.4)	9.9 (-7.7)	-53.0
11	HNO endo	19.8 (-16.1)	23.6	37.4 (-5.6)	1.8 (-15.8)	
12	$^1O_2$	9.5 (-26.4)	11.4	26.6 (-16.4)	-4.9 (-22.5)	-81.6
13	H_2COBH_3 exo	19.6 (-16.3)	22.6	29.4 (-13.6)	8.9 (-8.7)	-43.7
14	H_2COBH_3 endo	21.7 (-14.2)	24.6	32.3 (-10.7)	11.6 (-6.0)	
15	H_2CNHBH_3 exo	30.6 (-5.3)	33.5	41.1 (-1.9)	12.7 (-4.9)	-41.8
16	H_2CNHBH_3 endo	35.0 (-0.9)	37.7	44.9 (+1.9)	16.3 (-1.3)	
17	$H_2CNH_2^+$	-1.3 (-37.2)	0.5	3.5 (-39.5)	-9.5 (-27.1)	-53.8
18[d]	$H_2CNH_2^+$ (int)	-32.2	-27.4	-26.0	-36.5	

[a] Corrected for zero-point vibrational energy. [b] Single-point calculations done on 3-21G(*) geometries. [c] Reference 12. [d] Minimum, not saddle point.

MCSCF calculations[18] indicate that diradical intermediates are only a few kcal/mol higher in energy than the concerted transition state. The forming CC bond lengths for the concerted structures at different levels of theory range from 2.20 to 2.28 Å, with much smaller variations in other bond lengths and angles.

Although RHF/3-21G calculations give reasonable transition structure geometries as compared to MP2/6-31G* and MCSCF calculations, much higher levels of calculation are required to obtain accurate activation energies. For the Diels–Alder reaction, the MP2 correlation energy correction overestimates the effect of electron correlation in the transition structure and lowers the activation energy too much. At the MP2/6-31G* level,[16c] $\Delta E^{\ddagger}$ is 6.8–9.9 kcal/mol less than experimental activation energies of 24.4–27.5 kcal/mol for the reaction of butadiene with ethylene;[23] MP4SDTQ/6-31G* energy calculations[16b] give an activation energy (25.4 kcal/mol) which is within the range of experimental values. Nevertheless, MP2/6-31G* relative energies should give a reasonable estimate of the effect of substituents, since the magnitude of the correlation energy is largely dependent on the number of electrons involved in bonding changes.[24]

A comparison of the RHF/3-21G, 6-31G*, and MP2/6-31G* optimized transition structures for the Diels–Alder reaction of butadiene with acrolein shows more variation of the geometry with the level of theory than is seen for the reaction of butadiene with ethylene.[19a,b] At the MP2 level, the transition structure is significantly more asynchronous than the RHF structures, with a 0.2-Å lengthening of the C–C forming bond at the substituted terminus. The activation energies show the same trend with basis set and correlation energy correction as in the reaction of butadiene with ethylene. The relative activation energies

predicted by RHF and MP2 calculations for the reactions of butadiene with acrolein and of butadiene with ethylene agree well with experimental values.[25]

In the work described here, 17 transition structures were located for the 10 dienophiles, since some of the reactions have both endo and exo transition states. Concerted transition structures were found for all of the reactions, except that of protonated formaldimine. The borane-coordinated and protonated transition structures were also treated with Onsager solvent reaction field theory.[26] Calculated energies of the reactants, transition structures, and products are given in Table I. Predicted activation energies with respect to reactants are given in Table II. Geometrical parameters are summarized in Table III, and transition structures are shown in Figures 1–12. Scheme VI shows the atomic numbering used in the discussion and in Table III. In Table IV, calculated endo preferences are given for all dienophiles which can give both exo and endo stereochemical possibilities.

1. Transition Structures for Reactions of Formaldehyde and Thioformaldehyde with Butadiene. Figure 1 shows the transition structures for the reactions of formaldehyde and thioformaldehyde with butadiene. The forming carbon–carbon single bond lengths (C_2–C_3) in the two structures are 2.133 and 2.155 Å, respectively. These are similar to the forming bond lengths in the synchronous transition structure of ethylene with butadiene, which are 2.210 Å at the 3-21G level.[16a] The forming S_1–C_6 bond length in 2 is 2.588 Å, which is longer than the C_2–C_3 bond by 0.433 Å. The forming O_1–C_6 bond in 1 is 1.998 Å, which is 0.135 Å shorter than the C_2–C_3 bond. This is an interesting result, because it would be expected based on frontier molecular orbital theory that the O–C bond should be less fully formed than the C–C bond.[27] That is, since the formaldehyde carbon has a larger LUMO coefficient than the oxygen, the bond to carbon should be more fully formed than the bond to oxygen. A MINDO/3 calculation predicted longer C–O than C–C bonds in the

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Table III.   Selected Geometrical Parameters and Dipole Moments (in debye) from the 3-21G Transition Structures 1-17 and 13S-17S.   (Bond lengths and distances are in Å, angles are in degrees)
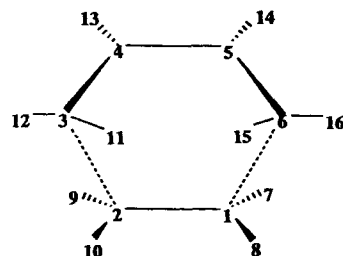
|	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	13S	14S	15S	16S	17S
1-2	1.276	1.661	1.312	1.308	1.305	1.302	1.323	1.309	1.301	1.299	1.289	1.305	1.314	1.311	1.335	1.334	1.354	1.328	1.318	1.340	1.340	1.360
1-6	1.998	2.588	1.982	1.930	1.952	1.901	2.143	1.913	2.178	2.122	1.981	2.173	2.422	2.406	2.257	2.267	3.058	2.753	2.767	2.310	2.319	2.986
2-3	2.133	2.155	2.266	2.356	2.296	2.394	2.014	2.242	2.010	2.042	2.189	2.173	1.907	1.924	2.037	2.056	1.919	1.844	1.891	2.002	2.025	1.893
6-5	1.370	1.358	1.380	1.385	1.384	1.388	1.370	1.384	1.364	1.366	1.374	1.350	1.351	1.349	1.363	1.359	1.338	1.342	1.338	1.360	1.356	1.340
3-4	1.377	1.369	1.373	1.365	1.373	1.365	1.375	1.364	1.376	1.364	1.354	1.350	1.391	1.390	1.380	1.379	1.385	1.397	1.387	1.383	1.381	1.389
5-4	1.393	1.403	1.394	1.398	1.395	1.398	1.389	1.399	1.399	1.398	1.406	1.416	1.402	1.402	1.395	1.394	1.426	1.415	1.420	1.396	1.395	1.421
9-12	2.757	2.645	3.000	2.825	3.050	2.861	–	2.659	2.723	–	–	–	2.725	2.539	2.676	2.675	2.647	2.708	2.554	2.662	2.657	2.633
9-4	2.783	2.623	2.626	3.082	2.554	3.181	–	2.847	2.508	–	–	–	2.623	2.801	2.767	2.779	2.640	2.591	2.742	2.743	2.764	2.649
10-12	2.649	2.534	2.769	3.042	2.832	3.120	2.731	–	–	–	–	–	2.430	2.526	2.537	2.557	2.374	2.352	2.412	2.503	2.521	2.372
10-11	2.307	2.334	2.496	2.219	2.565	2.172	2.134	–	–	–	–	–	2.400	2.294	2.314	2.338	2.448	2.467	2.341	2.329	2.337	2.441
2-1-6	115.5	98.9	112.3	112.0	111.1	111.2	107.8	111.5	109.0	109.2	110.2	111.4	109.2	110.6	109.5	109.0	99.8	103.3	107.1	108.1	108.0	100.7
1-2-3	108.1	111.0	105.5	108.0	104.4	105.7	111.6	108.1	111.6	113.4	111.0	111.4	108.7	110.0	110.0	111.1	112.6	111.2	111.2	110.1	111.7	112.4
1-6-5	102.8	97.8	107.8	100.0	109.2	102.0	96.0	99.0	100.9	99.7	96.2	95.0	95.5	93.1	99.4	98.3	83.1	92.7	91.3	98.9	97.7	85.1
2-3-4	97.7	102.0	93.4	98.7	91.7	97.8	105.2	98.5	97.6	113.4	98.4	95.0	99.4	101.7	100.2	100.0	99.4	101.4	102.6	100.7	110.0	110.3
6-5-4	119.6	122.8	120.3	120.4	119.9	120.3	122.1	120.6	122.0	122.4	122.5	123.0	121.1	121.0	120.4	120.4	123.4	122.2	122.1	120.4	120.5	123.1
3-4-5	122.9	123.3	124.0	123.7	124.1	124.1	120.6	122.3	121.9	121.3	121.9	123.0	124.6	124.0	122.3	122.6	126.3	126.1	125.3	122.3	122.7	126.1
6-1-7N	–	–	–	99.4	–	108.9	–	99.5	–	–	98.8	–	–	99.2	87.6	99.0	79.1	–	97.1	86.1	99.3	81.5
6-1-8X	–	–	101.9	–	107.5	–	85.9	–	93.0	90.1	–	–	99.8	–	97.8	90.9	98.5	101.7	–	98.6	90.6	100.2
3-2-9N	95.8	95.3	92.8	90.2	91.2	90.2	–	87.1	97.1	–	–	–	103.0	100.1	98.2	97.3	102.8	n104.5	102.2	99.0	98.3	103.3
3-2-10X	89.2	88.1	89.3	88.7	90.6	87.7	96.3	–	–	–	–	–	93.8	93.3	90.9	90.7	92.9	95.3	93.1	91.5	90.4	93.8
6-1-2-3	-9.0	-5.6	-27.8	20.4	-33.5	28.8	21.2	22.4	-21.3	-11.8	21.9	0.0	-24.1	-0.9	-11.8	-5.0	18.1	-27.9	-10.7	-13.5	-6.6	-18.0
6-5-4-3	0.8	-2.5	-0.6	4.7	-1.5	7.8	0.4	3.3	-2.0	-1.7	0.9	0.0	-3.8	2.6	-1.7	0.1	-6.4	-1.6	4.5	-2.1	-0.3	-4.9
4-5-6-16	163.8	170.5	167.9	171.3	168.6	170.8	170.6	171.9	168.0	169.4	172.6	169.7	165.6	164.6	166.8	165.0	177.1	172.9	171.9	166.9	165.7	175.5
4-5-6-15	-37.2	-24.1	-42.5	-37.7	-43.7	-40.3	-33.7	-35.2	-34.2	-34.2	-30.5	-22.1	-20.5	-19.5	-28.6	-30.7	-5.3	-8.2	-7.1	-26.9	-29.1	-6.8
5-4-3-12	-173.8	-177.2	-174.0	-172.6	-173.8	-172.4	-167.4	-169.7	-170.7	-166.7	-166.4	-169.7	179.5	178.3	-175.7	-175.6	170.7	173.0	171.9	-176.8	-176.6	171.0
5-4-3-11	34.7	28.1	30.2	30.1	29.8	30.4	41.0	29.0	34.3	31.9	26.8	22.1	33.8	34.8	34.0	35.0	25.1	31.5	30.6	34.7	35.2	27.1
C4 o.o.p.	13.3	11.4	12.2	10.9	12.2	17.5	15.7	11.8	14.1	15.4	13.1	11.4	11.8	10.9	12.5	13.1	6.9	8.0	6.9	12.0	12.3	7.5
C5 o.o.p.	17.0	11.1	15.8	15.6	15.4	10.3	14.1	14.0	13.8	13.8	12.4	11.4	10.9	14.0	12.4	15.5	1.4	5.2	7.2	11.5	14.3	2.9
3-2-1-7N	–	–	–	-92.0	–	-96.6	–	-89.2	–	–	-85.3	–	–	-114.1	-108.9	-118.1	-101.3	–	-119.9	-108.1	-119.9	-104.5
3-2-1-8X	–	–	86.5	–	90.1	–	113.9	–	78.3	84.4	–	–	89.4	–	100.1	95.6	88.1	84.2	–	99.0	92.9	90.7
6-1-2-9N	99.3	103.8	73.9	121.4	65.8	129.2	–	116.7	84.2	–	–	–	91.3	113.3	100.5	105.0	100.0	89.4	106.5	100.0	105.0	100.4
6-1-2-10X	-108.7	-105.7	-127.1	-77.0	-133.4	-67.3	-85.3	–	–	–	–	–	-128.7	-105.6	-113.1	-108.3	-123.2	-135.2	-115.2	-115.8	-109.9	-124.0
μ (6-31G*)	1.74	3.18	1.43	0.98	1.57	1.31	2.78	2.27	1.02	2.54	2.52	2.65	7.82	7.37	6.73	6.57	1.21	9.62	8.94	7.64	7.34	2.36
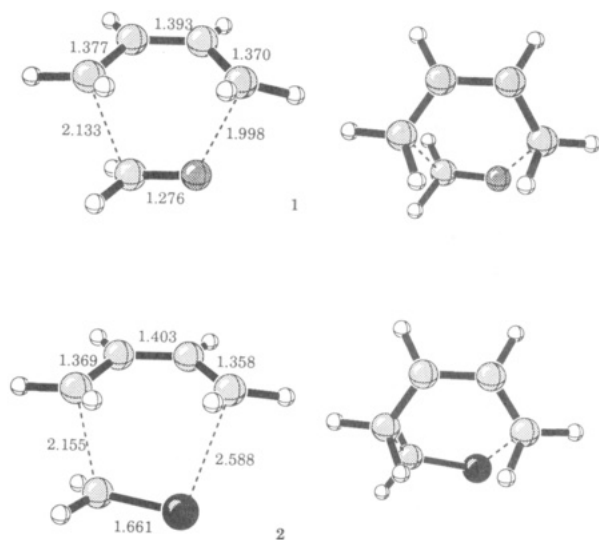
Figure 1. Transition structures for the reactions of butadiene with formaldehyde and thioformaldehyde.

transition structures for the reaction of butadiene with formaldehyde and of acrolein with ethylene.[12a] Our results seem to reflect the differences in the product single bond lengths; a C–O single bond is about 0.1 Å shorter than a C–C bond, while a C–S bond is 0.3 Å longer. The two bonds have formed to about the same extent in both of these hetero-Diels–Alder reactions, judging by the bond lengths and degree of pyramidalization in the butadiene component. We conclude that these reactions are concerted and nearly synchronous.

As in other Diels–Alder transition structures,[16,19] the C_4 and C_5 atoms are pyramidalized in the transition structures, although they are not involved in bond formation and are not pyramidalized in either the reactants or products. The out-of-plane angles, given in Table III, range from 11° to 17°. The pyramidalization occurs in such a way that the p orbitals on C_4 and C_5 are aligned to maximize orbital overlap with the forming bonds.

The butadiene moiety in the transition structures is twisted with respect to the dienophile. This phenomenon has also been found in the transition structures of the reaction of butadiene with vinyl alcohol[28] and in intramolecular Diels–Alder reactions.[29] The twisting motion corresponds to the lowest energy real vibrational mode in the parent Diels–Alder reaction of butadiene with ethylene.[16a] The amount of twisting in 1 and 2 is small, and the potential surface for twisting is relatively flat. For example, constraint of the C_6–O_1–C_2–C_3 dihedral angle to 0° raises the energy by only 0.2 kcal/mol. We believe the twisting is caused by electrostatic repulsion between the butadiene π system and the O and S endo lone pairs. More dramatic examples of this type of repulsion are shown later.

The calculated activation energy for the reaction of butadiene with formaldehyde, 20.9 kcal/mol at the MP2/6-31G* level, is much higher than that for the reaction of thioformaldehyde, 3.8 kcal/mol. The reaction of butadiene with ethylene falls between the two, with a calculated activation energy of 17.6 kcal/mol at the MP2/6-31G* level.[16a] FMO theory predicts that the incorporation of an electronegative atom into the dienophile will decrease

its LUMO energy and lower the activation energy of a Diels–Alder reaction.[27] Rate accelerations have been calculated for other pericyclic reactions upon oxo substitution: the Claisen[30] vs the Cope rearrangement[31] and the hetero-ene vs the ene reaction,[32] for example. However, the calculations predict that formaldehyde is less reactive than ethylene by 3.3 kcal/mol at the MP2/6-31G* level. In the reaction of formaldehyde and other heterodienophiles with butadiene, several other factors raise the activation energy. As noted above, the oxygen endo lone pair interacts with the π system at C_4 and C_5 of butadiene, causing repulsion. Twisting of the formaldehyde moiety with respect to the butadiene increases the O_1–C_5 distance, reducing this interaction. Another factor is the influence of reaction exothermicity on the activation energy, since the reaction of butadiene with formaldehyde is less exothermic than the reaction with butadiene. The 3-21G calculated energies of reaction are –43.1 and –34.2 kcal/mol for the reactions of butadiene with ethylene and formaldehyde, respectively.

Formaldehyde has been found to react with many substituted butadienes, although it fails to react with 1,3-butadiene and other simple 1,3-dienes.[33] The retro-Diels–Alder reaction of dihydro-2,3-α-pyran has been observed at 600 °C.[34] There are a few examples of aldehydes and ketones with electron-withdrawing groups undergoing uncatalyzed Diels–Alder reactions.[3,35]

The predicted activation energy for the reaction of butadiene with thioformaldehyde is significantly lower than the reaction with formaldehyde, in accord with experimental observations that thioaldehydes and activated thioketones rapidly undergo hetero-Diels–Alder reactions at or below room temperature.[2,36] The activation energy is calculated to be only 3.8 kcal/mol at the MP2/6-31G* level, which seems much too low. Nevertheless, it is reasonable that this reaction has a very low activation energy. The weakness of the C=S π bond contributes to its reactivity. In addition, the π* orbital energies of thioaldehydes are much lower than those of aldehydes, as suggested by experiments and calculations performed by Vedejs et al.[2a] The repulsive lone pair–butadiene interaction is not as important in the thioformaldehyde transition structure 2 as it is in 1 since the forming C–S bond is much longer (2.59 Å); the thioformaldehyde is only slightly twisted with respect to the butadiene in the transition structure. The long S_1–C_2 bond length probably also contributes to its low activation energy compared with formaldehyde. Butadiene must be strained to achieve simultaneous overlap at the two ends of a dienophile. The strain is larger in carbonyls, which have short C=O bonds and smaller in thiocarbonyls, which have long C=S bonds.

For heterodienophiles with substituents at the carbon terminus, endo products are generally favored. Recent experiments and theoretical models suggest that for alkyl substituents, the endo selectivity is caused mainly by steric effects. For example, Vedejs et al. reported that the reactions of cyclopentadiene with a series of thioaldehydes

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Table IV. Calculated Endo Preferences (kcal/mol). Negative Numbers Indicated That Exo is Favored

dienophile	3-21G	3-21G, corr	6-31G*	MP2/6-31G*
$H_2C=NH$	5.3	5.0	4.3	4.9
$H_2C=NCH_3$	3.8	3.5	3.3	4.1
cis-HN=NH	12.5	12.1	11.4	11.6
HN=O	7.5	7.4	8.0	8.1
$H_2C=OBH_3$	-2.1	-2.1	-2.9	-2.7
$H_2C=OBH_3$, SCRF[b]	-0.9	-0.5	-1.6	-2.3
$H_2C=NHBH_3$	-4.4	-4.2	-3.8	-3.6
$H_2C=NHBH_3$, SCRF[b]	-3.8	-3.6	-3.3	-3.5
$H_2C=CHCH_3$[a]	0.1	0.1	0.1	0.4

[a] Included in this table as an indication of the endo preference due to steric effects alone. [b] Dielectric constant = 9.08.

give predominantly endo products.[2b] The ratio of endo to exo increases as the size of the substituent increases from methyl to *tert*-butyl. They proposed that the exo transition state is destabilized by the interaction of the methylene group of cyclopentadiene with the substituent.

The endo position of these transition structures with butadiene, which appears at first glance to be more crowded, may actually be less sterically crowded than the exo position, judging from a close inspection of **1** and **2**. In these structures, butadiene is not exactly perpendicular to the plane of the C=X π bond. That is, the X_1–C_6–C_5 and C_2–C_3–C_4 angles are about 100 °C. As shown in Table III, the distances between the endo hydrogen, H_9, and C_4 and H_{12} of butadiene are 2.76 and 2.78 Å, respectively, in structure **1**. The distances between the exo hydrogen, H_{10}, and H_{12} and H_{11} are 2.65 and 2.31 Å, respectively; consequently, H_{10} is in the more crowded position. The same situation is found in structure **2**, where the H_9–C_4, H_9–H_{12}, H_{10}–H_{12}, and H_{10}–H_{11} interatomic distances are 2.62, 2.65, 2.53, and 2.33 Å, respectively. The short H_{10}–H_{11} distance is particularly important and may explain the endo preference for substituents on aldehydes and thioaldehydes. Furthermore, for the reaction of butadiene with propene, the transition structure with methyl endo is slightly favored over exo (by 0.4 kcal/mol) at the MP2/6-31G* level (Table IV).

2. Transition Structures for the Reaction of Butadiene with Formaldimine. Two diastereomeric transition structures were found for the reaction of formaldimine with butadiene, with the imino hydrogen exo in **3** and endo in **4** (see Figure 2). The endo transition structure is predicted to have a lower activation energy than the reaction of butadiene with ethylene, while the exo transition structure is predicted to have a higher activation energy. As in the case of formaldehyde, there are no experimental results for simple imines reacting with unactivated dienes; Lewis acids, or the presence of electron-withdrawing groups on the dienophile, are required to afford reaction. *N*-alkylimines would be expected to be less reactive than formaldimine, due to steric hindrance and electron donation, while *N*-acyl and *N*-sulfonyl groups increase the reactivity of imines appreciably.[6,7]

Several aspects of these transition structures are intriguing. (1) The forming N_1–C_6 bond is shorter than the forming C_2–C_3 bond, by 0.28 and 0.43 Å in transition structures **3** and **4**, respectively. Since a normal C–N bond is shorter than a C–C bond by less than 0.1 Å, there must be more bonding between N_1 and C_6 in the transition structures than between C_2 and C_3. This is also suggested by a longer C_5–C_6 bond length, as compared to C_3–C_4. (2) The N_1–C_6 bond is longer in **3** than in **4** by 0.05 Å, while the C_2–C_3 bond in **3** is shorter than that of **4** by 0.09 Å. (3) There is significant twisting between butadiene and
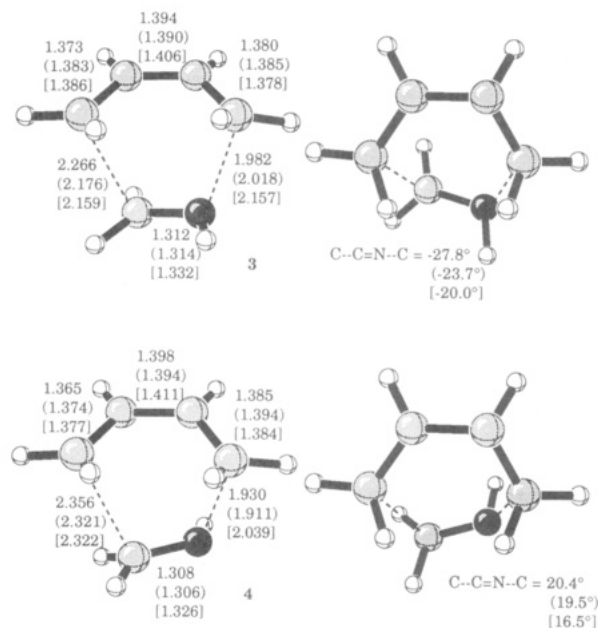

Figure 2. Transition structures for the reaction of butadiene with formaldimine. Calculations were RHF/3-21G (RHF/6-31G*) [MP2/6-31G*].

formaldimine in both structures. The C_6–N_1–C_2–C_3 dihedral angle is $-28°$ in **3** and $20°$ in **4**. Moreover, the formaldimine twists in opposite directions in **3** and **4**. (4) Structure **4** is calculated to be more stable than **3** by 4.3–5.3 kcal/mol, depending on the level of calculation (see Table IV). The magnitude of this endo preference is considerably larger than the endo preference for all-carbon Diels–Alder reactions.[37]

As in the case of formaldehyde, FMO theory would suggest that the C–C partial bond should be more fully formed than the C–N bond, since the larger LUMO coefficient is on the carbon of the imine. However, the C–N bond is substantially shorter. In addition, the direction of electron donation in the transition state is from the imine to the diene. Apparently, dienophile HOMO/diene LUMO interactions are important in these transition structures. The HOMO of formaldimine has a larger coefficient at N than at C.

The other interesting features appear to be caused by nitrogen lone pair interactions with the butadiene π system. In structure **3**, the nitrogen lone pair is in the endo position, where it can interact with π orbitals at C_4 and C_5 of butadiene. There is evidence for the repulsive interaction of a nitrogen lone pair with a π bond in 7-azanorbornene and several of its derivatives.[38] Experiments indicate that there is a preference for the syn conformation, with the N lone pair anti to the double bond. This is attributed to electronic repulsion in the anti configuration, which has a destabilizing 4π homo-antiaromatic interaction between the lone pair and the alkene π orbitals. The exo transition structure **3** is also disfavored sterically; the H_8–H_{15} distance in **3** is only 2.18 Å. In structure **3**, the formaldimine twists so that the lone pair is farther away

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Scheme I
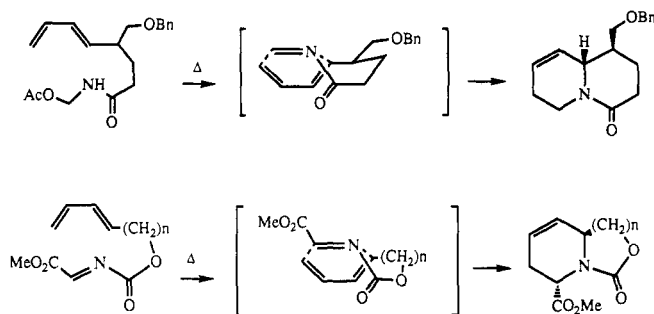
from C_5; conversely, the formaldimine twists so that H_7 is closer to C_5 in 4. This is probably due to an attractive electrostatic attraction between π electrons at C_4 and C_5 of butadiene and the imino hydrogen. Constraining the $C_6-N_1-C_2-C_3$ dihedral angle to 0° raises the energy by 2.6 kcal/mol in 3 and 1.7 kcal/mol in 4, much greater than the effect on 1, which is expected since the amount of twisting is larger in 3 and 4.

In cases where the imine is constrained to the cis form by incorporation in a ring, experiments have shown clearly that reactions such as eq 1 give only one product, which

(1)
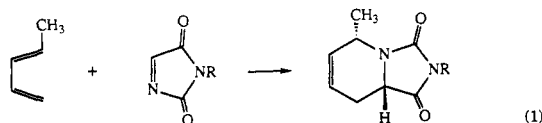
is derived from the endo transition structure.[7e,39] This, however, does not prove that there is a special endo preference for the *N*-acyl group because reactions of all carbon analogs also give predominantly endo products, attributed to electrostatic effects and secondary orbital interactions.[37]

The strongest evidence for the endo preference is from intramolecular Diels–Alder reactions with *N*-acylimines as shown in Scheme I.[7,40] Weinreb et al. observed that these thermal reactions give only one product which is derived from the transition structures shown, with the *N*-acyl group endo.[7] For the corresponding all carbon reactions, mixtures of *cis-* and *trans*-fused products are obtained.[41]

To test the effect of basis set and correlation corrections on hetero-Diels–Alder reaction transition structures and relative energies, we selected structures 3 and 4 on which to perform further calculations. Tables V and VI show the absolute and relative energies, respectively. Structures 3 and 4 were reoptimized at the RHF/6-31G* and MP2/6-31G* levels. Energy calculations were carried out on the MP2/6-31G* transition structures with third- and fourth-order Moller–Plesset perburation theory. In Figure 2, the bond lengths for the RHF/3-21G structures are

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(40) Sauer, J.; Schroder, B. *Chem. Ber.* 1967, 100, 678. Nomoto, T.; Takayama, H. *Heterocycles* 1985, 23, 2913. Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* 1980, 102, 5265. Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* 1972, 11, 1031.

(41) Roush, W. R.; Coe, J. W. *Tetrahedron Lett.* 1987, 28, 931. Coe, J. W.; Roush, W. R. *J. Org. Chem.* 1989, 54, 915. Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* 1979, 101, 3992. Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* 1981, 103, 6696. Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* 1981, 3929. Boekman, R. K.; Demko, D. M. *J. Org. Chem.* 1982, 47, 1789. Gras, J. L.; Bertrand, M. *Tetrahedron Lett.* 1979, 4549. Hirama, M.; Uei, M. *J. Am. Chem. Soc.* 1982, 104, 4251.

shown first, followed by the RHF/6-31G* bond lengths in parentheses and MP2/6-31G* bond lengths in square brackets. At higher levels of theory, the geometries shift toward more synchronous transition structures, in contrast to the reaction of acrolein with butadiene.[19a,b] The exo lone-pair preference is 4.1 kcal/mol at the highest level of our calculations and is almost independent of basis set and correlation energy corrections. The activation energies for 3 and 4 show the same large variations with level of theory as has been found for the reaction of butadiene with ethylene.[16b] This gives us reason to believe that the structures and stereochemical preferences predicted to the MP2/6-31G*//3-21G level reported here will not change significantly with higher level calculations.

Transition Structures of *N*-Methylformaldimine with Butadiene. The exo (5) and endo (6) transition structures for the reactions of *N*-methylformaldimine with butadiene were located in order to examine the effect of lone pair–π repulsion while reducing the influence of the attractive NH–π interaction. These are shown in Figure 3. The endo transition structure is still favored, but the difference is reduced to 4.1 kcal/mol. Thus, the exo lone-pair effect accounts for a large portion of the endo preference of formaldimine itself. Structure 5 is slightly less synchronous than the exo formaldimine structure 3. The twisting is –34° in 5 and 29° in 6. The methyl substituent is predicted to raise the activation energy as compared to formaldimine by 1.7 kcal/mol for the exo transition structure and by 2.5 kcal/mol for the endo case. Since carbonyl substituents stabilize the endo Diels–Alder transition state,[37] the endo preference for *N*-acyl groups is probably larger than that of *N*-alkyl groups.

3. Transition Structures of the Reaction of Diazene with Butadiene. Diazene (diimide) can exist in cis and trans forms, the latter being more stable by about 7.7 kcal/mol according to our calculations. Three transition structures were calculated for the reactions of *cis-* and *trans*-diazene with butadiene, the former either endo or exo. As shown in Figure 4, two transition structures involve *cis*-diazene, with the imino hydrogens exo in 7 and endo in 8. Transition structure 9 (Figure 5) involves *trans*-diazene and is quite unsymmetrical. The two forming bond lengths in 9 are different by 0.17 Å. The forming bond near the exo hydrogen is longer than the endo terminus. The repulsive interaction of an endo lone pair with the diene π electrons is reflected in these forming bond lengths, as well as by a –21° twisting of the dienophile with respect to butadiene. The average forming bond lengths in these transition structures are similar, with shorter forming bonds than in all-carbon Diels–Alder transition structures. Although 7 and 8 contain symmetrical reactants, the transition structures are asymmetrical. In 7, the diazene component twists so that the N terminus which is nearer to the π electrons of butadiene has a longer forming bond length, lessening repulsion. For structure 8, the N terminus which is closer to C_4 and C_5 has a shorter forming bond, increasing the electrostatic attraction. The energies of the C_s symmetrical exo and endo structures are 0.2 and 1.4 kcal above unsymmetrical structures 7 and 8, respectively.

Azodicarbonyl compounds are among the most reactive dienophiles and have been used extensively in organic synthesis. The high reactivity of the N=N bond as compared to the C=C bond is due to the low LUMO energy of the former. Our calculated activation energies for 7, 8, and 9 are 17.6, 6.0, and 9.0 kcal/mol, respectively, at the

Table V. Calculated Energies (au) for 3 and 4 Optimized at Higher Levels of Theory

structure	6-31G*	6-31G*ZPE	MP2/6-31G*	MP3/6-31G* [a]	MP4SDTQ/6-31G* [a]
trans-butadiene	−154.91347	0.09122	−155.43608	−155.45020	−155.47893
formaldimine	−94.02864	0.04328	−94.32308	−94.32983	−94.34552
TS 3	−248.87092	0.13949	−249.73288	−249.73648	−249.79027
TS 4	−248.87754	0.13971	−249.73946	−249.74313	−249.79662

[a] Energies given for geometries optimized at the MP2/6-31G* level.
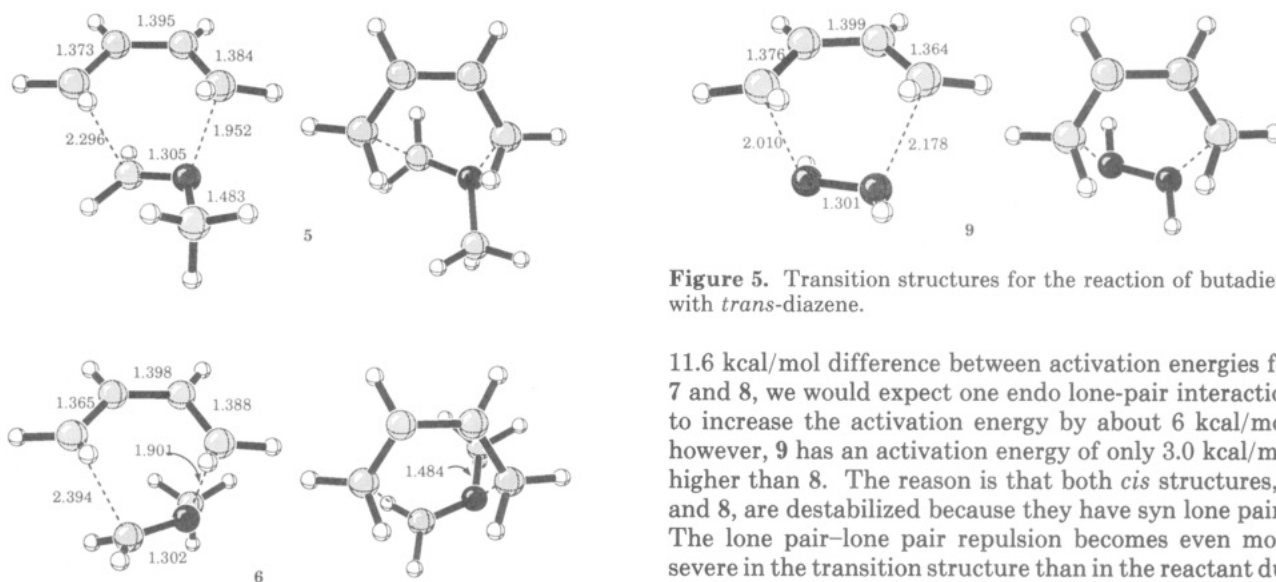
Figure 3. Transition structures for the reaction of butadiene with *N*-methylformaldimine.
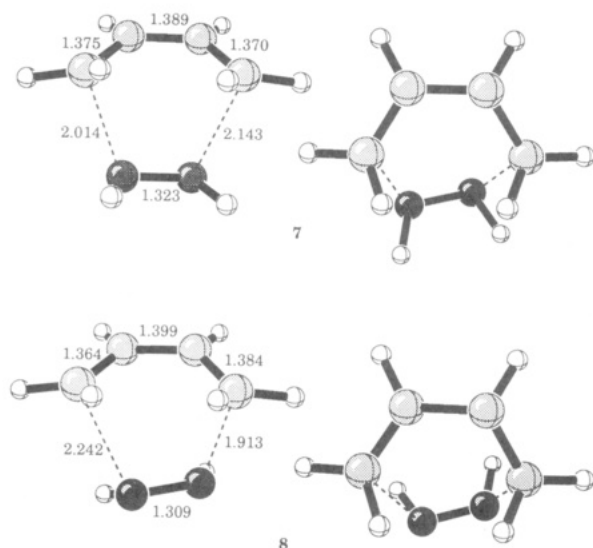
Figure 4. Transition structures for the reaction of butadiene with *cis*-diazene.

Table VI. Activation Energies for 3 and 4 at Higher Levels of Theory. Numbers in Parentheses are Corrected for Zero-Point Vibrational Energies at the HF/6-31G* Level

structure	6-31G*	MP2/6-31G*	MP3/6-31G*	MP4/6-31G*
TS 3	44.5 (47.6)	16.5 (19.6)	27.3 (30.4)	21.6 (24.7)
TS 4	40.4 (43.7)	12.4 (15.7)	23.2 (26.5)	17.5 (20.8)

MP2/6-31G* level. The calculations indicate that when the diazene is *cis*, it strongly prefers the endo transition structure. This is the result of electrostatic repulsion between the endo lone pairs and the π system of butadiene in structure **7**, and attraction between the imino hydrogens and the π electrons of butadiene in **8**. There is one endo and one exo lone pair in structure **9**. On the basis of the
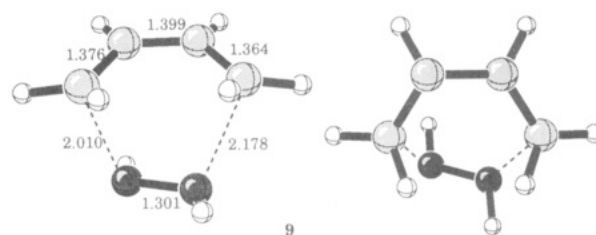
Figure 5. Transition structures for the reaction of butadiene with *trans*-diazene.

11.6 kcal/mol difference between activation energies for **7** and **8**, we would expect one endo lone-pair interaction to increase the activation energy by about 6 kcal/mol; however, **9** has an activation energy of only 3.0 kcal/mol higher than **8**. The reason is that both *cis* structures, **7** and **8**, are destabilized because they have syn lone pairs. The lone pair–lone pair repulsion becomes even more severe in the transition structure than in the reactant due to the change in hybridization of the two nitrogen atoms. Recently, Coxon and McDonald reported similar results with PM3 calculations.[12d]

The reactions of azo compounds with dienes usually proceed with retention of diene stereochemistry.[42] These experimental findings and our calculations support a concerted mechanism.[43] Recently, Jensen and Foote reported that the Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with (*Z*,*Z*)-2,4-hexadiene leads predominantly to the trans product, which implies this reaction occurs by a stepwise mechanism.[11a] Because of severe steric interactions, this diene cannot achieve the *s-cis* conformation required for a concerted mechanism, so a stepwise mechanism becomes favored. They propose an aziridinium imide intermediate which opens to a zwitterion and then closes to form Diels–Alder-type products. Similar results were found using alkoxy-substituted butadienes.[11h]

Cyclic azo compounds which are constrained to have *cis* stereochemistry are much more reactive than their acyclic counterparts.[43] Although the endo transition structure for cyclic azo compounds is strongly preferred, no stereoselectivity is observed, because the nitrogen centers undergo rapid inversion. However, placing a bulky chiral group on the azo compound may in principle lead to a highly enantioselective reaction due to the large endo preference. Paquette and Doehner reported very low (0–9%) asymmetric induction in the reactions of chiral triazolinediones such as **A** and **B** with racemic 2,4-*p*-menthadiene, **C**, and α-phellandrene, **D** (see Scheme II).[44] The low stereoselectivity of these reactions may be due to the presence of several reactive conformations about the N–C bond attached to the chiral center which lead to different facial selectivities.

(42) Fahr, E.; Lind, H. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 372.
(43) (a) Daniels, R.; Roseman, K. A. *Tetrahedron Lett.* **1966**, 1335. (b) Konovalov, A. I.; Breus, I. P.; Shosagin, I. A.; Kiselev, V. D. *J. Org. Chem. USSR (Engl. Trans.)* **1979**, *15*, 315.
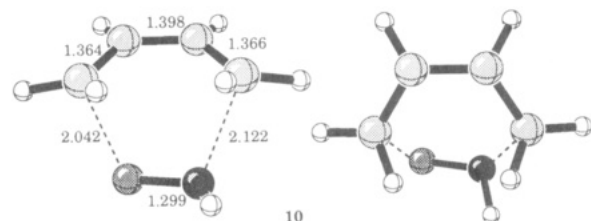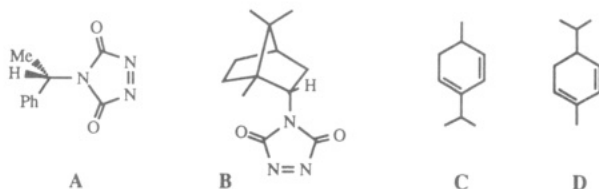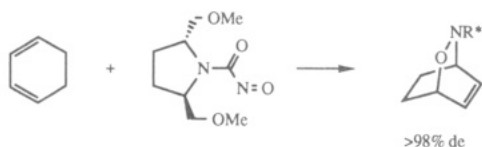(44) Paquette, L. A.; Doehner, R. F. *J. Org. Chem.* **1980**, *45*, 5105.

Figure 6. Transition structures for the reaction of butadiene with nitrosyl hydride.

Figure 7. Transition structure for the reaction of butadiene with singlet oxygen.

Scheme II

A   B   C   D

Scheme III

>98% de

Scheme IV

E   F

4. Transition Structures of Nitrosyl Hydride with Butadiene.

The endo and exo transition structures of butadiene with nitrosyl hydride, the simplest nitroso compound, are shown in Figure 6. The calculated structures are nearly synchronous. The forming N_2–C_3 and O_1–C_6 bond lengths are 2.122 and 2.042 Å in the exo structure 10, and 1.981 and 2.189 Å in the endo transition structure 11. The average forming bond lengths are slightly shorter than those in all-carbon Diels–Alder transition structures. These reactions have calculated activation energies of only 9.9 and 1.8 kcal/mol with respect to reactants. Although the calculated activation energies at the MP2/6-31G* level are underestimated, they do reflect the high reactivity of nitroso compounds as dienophiles, a fact which has been exploited for the synthesis of amino alcohols.[45,46] This reactivity can be attributed to an extremely low LUMO energy and weak π bond. Nitrosyl hydride has been generated by the retro-Diels–Alder reaction of the 9,10-dimethylanthracene ad-
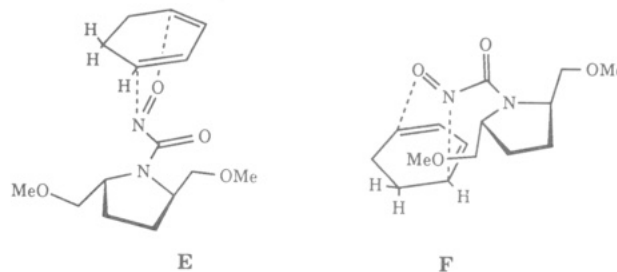
duct and trapped with cyclohexadiene or 2-*tert*-butyl-butadiene.[45c]

The endo transition structure is calculated to be 8.1 kcal/mol more stable than the exo structure. We believe that this is caused by electrostatic interactions, as indicated by a 0.14 Å lengthening of the N_2–C_3 forming bond in 10 vs 11 and a twisting of the C_6–N_1–O_2–C_3 dihedral, which is 21.9° in 11. The C_6–N_1–O_2–C_3 dihedral is much smaller in 10 (–11.8°). This large endo preference is similar to the preference for 9 vs 7 (8.6 kcal/mol). In both cases, the structure with one endo lone pair is far more stable than the structure with two endo lone pairs, and the twisting of the dienophile with respect to butadiene seems to magnify this difference.

The large calculated endo preference could be useful in designing reagents for diastereoselective Diels–Alder reactions. For example, it has been reported that some chiral α-chloronitroso compounds undergo Diels–Alder reactions with very high diastereoselectivities.[45d–h] Highly diastereoselective reactions of chiral carbamoylnitroso compounds of the type shown in Scheme III have also been reported recently.[46] The sense of selectivity can be explained if endo attack occurs from the least-hindered face of the nitroso compound (E in Scheme IV), assuming that the reactive conformation is the *s-cis*-acylnitroso geometry shown. The endo transition structure F places the methoxymethyl group too close to the diene. These chiral nitroso compounds are similar to the chiral diazo compounds A and B, which exhibit very low stereoselectivity. One factor that has been shown to be important for stereoselection is the C_2-symmetric pyrrolidine ring containing two chiral centers.[46c] This arrangement in effect locks the conformation of the chiral groups, as long as the preference for the *s-cis*-acylnitroso conformation is high. Modest stereoselectivity is observed for compounds with only one chiral center on the pyrrolidine ring.[47]

5. Transition Structure of Singlet Oxygen with Butadiene.

The transition structure for the concerted, synchronous hetero-Diels–Alder reaction of butadiene with singlet oxygen, 12, shown in Figure 7, was calculated for comparison with other heterodienophiles. A concerted

(45) (a) Defoin, A.; Pires, J.; Streith, J. *Synlett* 1990, 111. (b) Werbitzky, O.; Klier, K.; Felber, H. *Liebigs Ann. Chem.* 1990, 267. (c) Ensley, H. E.; Mahadevan, S. *Tetrahedron Lett.* 1989, 3255. (d) Felber, H.; Kresze, G.; Braun, H.; Vasella, A. *Tetrahedron Lett.* 1984, 5381. (e) Sabuni, M.; Kresze, G.; Braun, H. *Tetrahedron Lett.* 1984, 5377. (f) Aebischer, B.; Vasella, A.; Weber, H.-P. *Helv. Chim. Acta* 1982, 65, 621. (g) Nitsch, H.; Kresze, G. *Angew. Chem. Int. Ed. Engl.* 1976, 15, 760. (h) Felber, H.; Kresze, G.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* 1986, 69, 1137.

(46) (a) Gouverneur, V.; Ghosez, L. *Tetrahedron: Asymmetry* 1990, 1, 363. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* 1991, 32, 5349. (c) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* 1991, 74, 103.

(47) (a) Brouillard-Poichet, A.; Defoin, A.; Streith, J. *Tetrahedron Lett.* 1989, 7061. (b) Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* 1992, 75, 109.

mechanism is often assumed for singlet oxygen addition to dienophiles, although the mechanistic evidence is inconclusive.[11b,48] Solvent effects on the activation energies of singlet oxygen 1,4-additions seem to indicate a polar transition state. For example, the gas phase activation energy for the reaction of singlet oxygen with cyclopentadiene is 4 kcal/mol, while in methanol it is lowered to 0.25 kcal/mol.[49] In addition, loss of stereochemistry has been observed in the reactions of singlet oxygen with (Z,Z)- and (E,Z)-2,4-hexadiene.[11b] However, complete retention of the diene configuration has been observed in several cases, and the reaction proceeds 100 times faster for (E,E)-hexadiene, which can easily achieve the s-cis conformation, than for (E,Z)-hexadiene.[11b] This is consistent with a concerted mechanism which is slightly favored over a stepwise mechanism. Jensen and Foote estimate that the barrier to achieve the s-cis conformation of (E,Z)-hexadiene is 6 kcal/mol according to MM2 calculations. Thus, the difference in activation energies between the concerted Diels–Alder reaction and the stepwise ionic process for hexadienes with $^1O_2$ in CD_2Cl_2 is less than 6 kcal/mol. For the reaction of PTAD with 2,4-hexadienes, the energy difference between the concerted and ionic mechanisms is greater, with the stepwise reaction favored only for (Z,Z)-hexadiene, which has an MM2 barrier of 11 kcal/mol to achieving the cis conformation.[11a]

The concerted butadiene-singlet oxygen reaction has a barrier of only 9.5 kcal/mol at the 3-21G level. The barrier disappears with MP2/6-31G* single point calculations, and the energy of **12** is predicted to be 4.9 kcal/mol lower than reactants. This is much lower than the activation energies of the other heterodienophiles studied, and reflects the extremely weak π bond of this dienophile. Since MP2 calculations give activation energies which are too low for Diels–Alder reactions, these results do not imply an activationless reaction. The reaction is predicted to be much more exothermic than those of the other dienophiles ($\Delta E_{rxn} = -81.6$ kcal/mol). Activation energies for reactions of singlet oxygen have been measured experimentally for several dienes and are near zero.[49] In fact, RHF calculations are not adequate in describing the electronic structure of singlet oxygen. The UMP2/6-31G*//3-21G energy of singlet oxygen is 20 kcal/mol lower than the corresponding RMP2 energy (see Table I). We are presently investigating this reaction with MCSCF calculations. Previous MINDO/3 calculations predicted a stepwise mechanism, with the transition structure leading to perepoxide favored over concerted endoperoxide formation by 10 kcal/mol.[50]

6. Transition Structures of BH₃-Coordinated Formaldehyde with Butadiene. Coordination of BH_3 with the formaldehyde oxygen, a model for Lewis acid catalysis, has a pronounced effect on the geometry of the transition structure. Two transition structures were located (Figure 8), with borane coordinated in the exo position in **13** and in the endo position in **14**. Structure **13** is much less symmetrical than 1; the forming O_1–C_6 bond i **13** is 0.42 Å longer than in 1, while the forming C_2–C_3 bond is 0.23 Å shorter. This transition structure has a significant amount of zwitterionic character, with partial positive charge on the diene (0.37) and negative charge on the
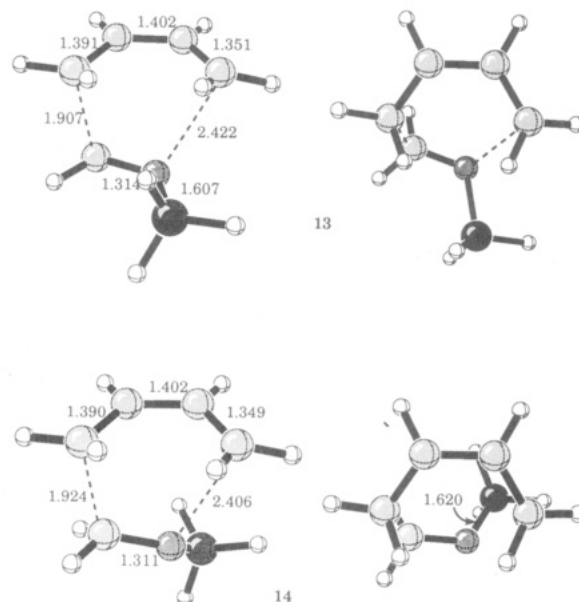

Figure 8. Transition structures for the reaction of butadiene with BH_3-coordinated formaldehyde.

formaldehyde oxygen (−0.65) and BH_3 (−0.28). The effect of coordination is larger than the effect of a covalently bonded substituent such as CHO or CN, but is similar to the effect of BH_3 coordination on the transition structure for the Diels–Alder reaction of butadiene with acrolein.[19d] For example, placing a formyl or cyano group on the dienophile (ethylene or acetylene) causes one of the forming bonds to elongate by 0.1–0.2 Å and the other bond to shorten by 0.1–0.2 Å in transition structures of Diels–Alder reactions.[19c,51] The coordination of BH_3 to the transition structure of butadiene with acrolein, however, causes significant asymmetrical distortion; the forming bond attached to the coordinated carbonyl lengthens by 0.61 Å, while the other forming bond is shortened by 0.16 Å.[19d] The BH_3 group makes the carbonyl a superior acceptor of negative charge, and the O–B bond in **13** is 0.12 Å shorter than that of the BH_3–formaldehyde complex, indicating tighter complexation in the transition state.

Structure **14** shows the geometry of the transition structure with BH_3 in the endo position. This structure is quite similar to **13**, but is disfavored by 2.7 kcal/mol at the MP2/6-31G* level. The interaction of the oxygen lone pair with butadiene is not as destabilizing as the BH_3 interaction. The oxygen lone pair should contract upon coordination of the oxygen with Lewis acids. In the two transition structures, the coordinated borane carriers a significant amount of negative charge. When BH_3 is exo, the lone pair–butadiene repulsion is mitigated by the long O_1–C_6 forming bond length. Structure **13** shows a pronounced twist (−24°) of the formaldehyde with respect to the butadiene, while the twist in **14** is only −1°. This is an unusually small degree of dienophile twisting for this series of transition structures. It seems that in this case twisting cannot alleviate the steric or electrostatic repulsions present in the endo transition structure. The O–B bond in **14** is 0.013 Å longer than that of **13**.
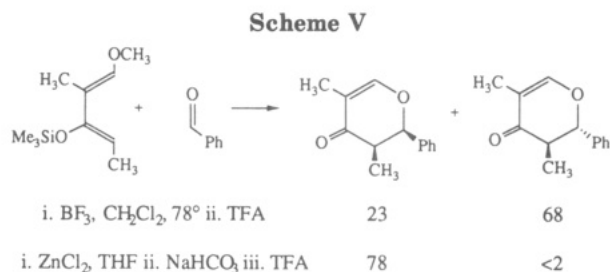
There are a few mechanistic studies of Lewis acid-catalyzed hetero-Diels–Alder reactions with carbonyl dienophiles. Danishefsky et al. conclude that the BF_3-catalyzed reactions of 1-methoxy-3-(trimethylsiloxy)-1,3-

(48) (a) Bloodworth, A. J.; Eggelte, H. J. In *Singlet Oxygen*; Frimer, A. A., Ed.; Vol. II, Part 1; CRC Press: Boca Raton, FL, 1985, Vol. II, Part 1, Chapt. 4, pp 93–203. (b) Clennan, E. L.; Nagraba, K. *J. Org. Chem.* **1987**, *52*, 294.

(49) Ashford, R. D.; Ogryzlo, E. A. *Can. J. Chem.* **1974**, *52*, 3544.

(50) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 2338.

(51) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N., unpublished results.

Scheme V

i. BF$_3$, CH$_2$Cl$_2$, 78° ii. TFA	23	68
i. ZnCl$_2$, THF ii. NaHCO$_3$ iii. TFA	78	<2

butadiene with aldehydes occur via a stepwise mechanism, whereas the reaction is concerted when zinc chloride or lanthanides are used as Lewis acids.[9a] The evidence of a change in mechanism is that the stereoselectivities of the reactions reverse when BF$_3$ is used as the catalyst, giving predominantly the *trans* isomer resulting from exo addition at carbon of the dienophile (see Scheme V). Acyclic products are formed as well.

We have explored the possibility of an ionic intermediate starting from structure **13**. The optimization of this structure to a minimum led to the cyclic product. The energy of a zwitterionic structure with all C–C bonds anti was destabilized with respect to the cyclic product by about 100 kcal/mol at the 3-21G level. Obviously, the extended zwitterionic intermediate is highly disfavored in the gas phase. In a polar solution, a zwitterion would be stabilized, and the stepwise reaction may become the dominant mechanism in some cases. Danishefsky concluded that when a stronger Lewis acid is used, the stepwise mechanism becomes more important.[9a]

Upon coordination of BH$_3$, the activation energy for the reaction of butadiene with formaldehyde drops considerably. This agrees with experimental results, since Lewis acid catalysis is in general necessary to afford reactions of carbonyl dienophiles.[9c] At the highest level of our calculations, the activation energy is 8.9 kcal/mol, which is 12.0 kcal/mol lower than reaction 1. This is comparable to other calculations on the catalytic effect of BH$_3$. For example, BH$_3$ coordination on acrolein decreases the activation energy of its reaction with butadiene by 7.0 kcal/mol at the MP2/6-31G* level.[19b] The activation energy of the ene reaction of formaldehyde with propene is decreased by 15.4 kcal/mol at the 3-21G level upon coordination of BH$_3$ to formaldehyde.[52]

Experimentally, Lewis acid catalysis affects the stereoselectivity of aldehyde Diels–Alder reactions. The uncatalyzed reactions of aldehydes usually show endo selectivity for the carbonyl substituent.[3] Danishefsky has proposed that the Lewis acid is trans to the carbonyl substituent in catalyzed reactions and that the modest endo selectivity observed in most cases suggests that the solvated Lewis acid prefers the exo position, because of its size.[9a] Our calculations indicate that the exo position is favored, due to greater electrostatic repulsion between the borane and the butadiene fragment in the endo transition structure **14**.

Solvent Effects. Since transition structures **13** and **14** possess large dipole moments (7.82 and 7.37 D, respectively; see Table III), the geometries in the gas phase may be quite different from those in solution. To estimate the effect of solvation on these structures, the Onsager reaction field model as incorporated in Gaussian 92 was used.[21d,26,53] In this model, the solute is placed in a spherical cavity surrounded by a continuous dielectric medium. The dipole of the solute induces a dipole in the
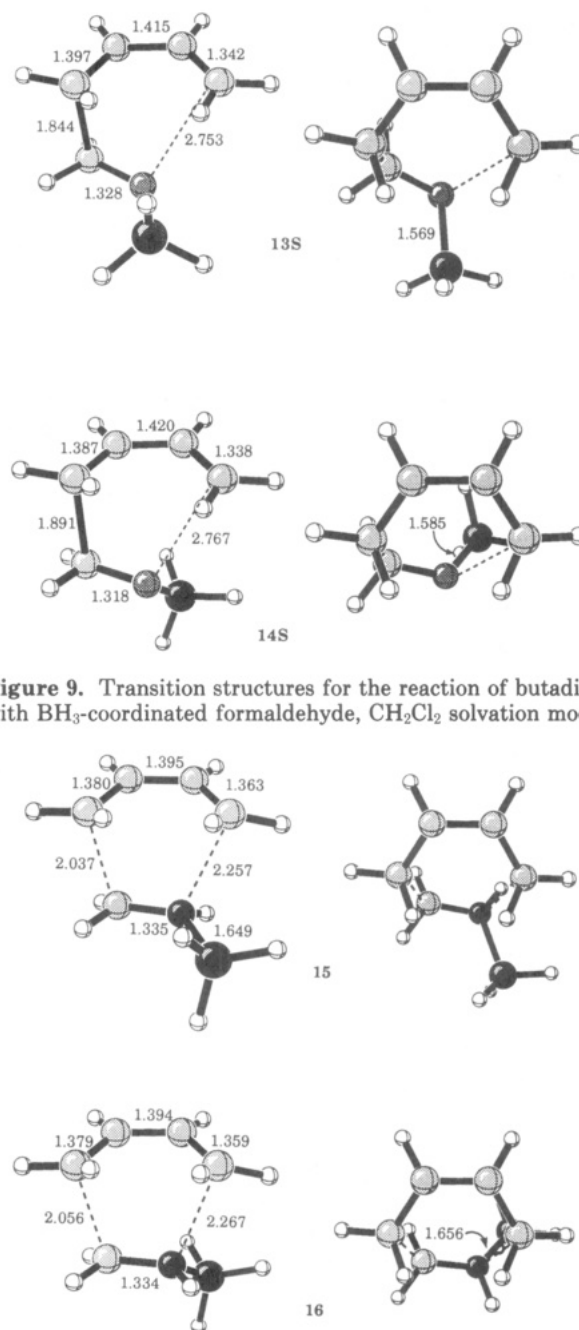

Figure 9. Transition structures for the reaction of butadiene with BH$_3$-coordinated formaldehyde, CH$_2$Cl$_2$ solvation model.

Figure 10. Transition structures for the reaction of butadiene with BH$_3$-coordinated formaldimine.

medium, which leads to a stabilizing solute/solvent electrostatic interaction. This method has been successfully used to investigate solvent effects on conformational and tautomeric equilibria.[53]

A dielectric constant of 9.08 was used to simulate methylene chloride, a typical solvent for Lewis acid-catalyzed Diels–Alder reactions. The diameter of the spherical cavity was calculated by adding the largest interatomic distance of the structure to the van der Waals radii of the two atoms involved. The solvated transition structures **13S** and **14S** in Figure 9 are more asynchronous than the gas-phase structures **13** and **14**. The vibrational mode corresponding to the single imaginary frequency has a much larger component along the C$_2$–C$_3$ bond than the

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(52) Birney, D.; Houk, K. N., unpublished result.

(53) (a) Wong, M. W.; Wiberg, K. B. *J. Chem. Phys.* **1991**, *95*, 8991. (b) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (c) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 523.

Table VII. Calculated Energies (au) of Reactants of Transition Structures for the Reactions of Butadiene with BH₃-Coordinated Formaldehyde, BH₃-Coordinated Formaldimine, and Formaldiminium Ion Including SCRF Solvation Model

compound	dielectric (solvent)	3-21G	3-21G ZPE	3-21G	MP2/6-31G*//3-21G
H_2COBH_3	9.08 (CH_2Cl_2)	−139.49765	0.06373	−140.27431	−140.66447
H_2CNHBH_3	9.08	−119.79955	0.07866	−120.46540	−120.84325
$H_2CNH_2^+$	78.0 (H_2O)	−93.86284	0.05802	−94.38313	−94.65888
TS 13S	9.08	−293.52493	0.15969	−295.15076	−296.06689
TS 14S	9.08	−293.52354	0.15904	−295.14824	−296.06309
TS 15S	9.08	−273.80435	0.17503	−275.31540	−276.23901
TS 16S	9.08	−273.79832	0.17470	−275.31019	−276.23352
TS 17S	78.0	−247.92492	0.15315	−249.29807	−250.09565

Table VIII. Calculated Energies (kcal/mol) of the Transition Structures with Respect to Reactants for the Reactions of Butadiene with BH₃-Coordinated Formaldehyde, BH₃-Coordinated Formaldimine, and Formaldiminium Ion Including SCRF Solvation Model

TS	3-21G	3-21G, corr[a]	6-31G*[b]	MP2/6-31G*[b]
13S	20.2	22.6	27.1	11.5
14S	21.1	23.1	28.7	13.8
15S	34.3	37.0	43.7	15.6
16S	38.1	40.6	47.0	19.1
17S	−1.6	0.3	2.9	−10.1

[a] Corrected for zero-point vibrational energy. [b] Single-point calculations done on 3-21G geometries.

C_1–C_6 bond in both **13S** and **14S**. The C_2–C_3 bond length is shorter in the solvated transition structures by 0.063 and 0.033 Å in **13S** and **14S**, respectively. The O_1–C_6 bond lengthens by 0.331–0.361 Å, making the transition structures essentially stepwise in nature.

MP2/6-31G* single-point energy calculations were performed including solvation. The energies of solvated structures are given in Table VII, and Table VIII gives the activation energies of solvated reactions. The activation energy for the endo transition structure **14S** of BH₃-coordinated formaldehyde with butadiene is lowered by solvation with RHF calculations, but the correlated activation energy is 2.2 kcal/mol higher in solvent. For the exo structure, only the 6-31G* activation energy is lowered, and the 3-21G and MP2/6-31G* energies are increased. The MP2/6-31G* activation energy of **13S** is 2.6 kcal/mol higher in methylene chloride than in the gas phase. This means that the reactant borane–formaldehyde complex is stabilized more than the transition structures in the dielectric field.

In spite of the apparent shift of the BH₃-coordinated transition structures from a concerted, asynchronous mechanism toward a stepwise mechanism, the predicted energy difference between the endo and exo structures does not change drastically. The exo preference of BH₃ in these solvated transition structures is 2.3 kcal/mol, which is nearly the same as the gas phase preference. However, if the energy of these structures is close to the energy of acyclic transition structures, then the overall stereochemistry of the reaction could change. Therefore, we attempted to locate a stepwise transition structure in the presence of the solvent reaction field. Starting from a structure with butadiene in the s-cis conformation and the C=O bond anti to the diene C=C bond, no transition structure or zwitterionic intermediate could be located. As the forming C–C bond was shortened in increments from 2.4 to 1.5 Å, the energy increased steeply.

7. Transition Structures of BH₃-Coordinated Formaldimine with Butadiene. Pfrengle and Kunz reported that the reactions of chiral imines with reactive dienes in the presence of $ZnCl_2$ occurred via a tandem Mannich–Michael reaction mechanism, as evidenced by the formation of acyclic products in addition to cyclic Diels–Alder products.[5a,b] However, a recent study on the reactions of Lewis acid-coordinated N-substituted phenylimines with reactive dienes found no intermediates, and the authors postulated a concerted, easily reversible Diels–Alder reaction.[11d] The stereochemistry of the major product corresponded to exo addition for the substituent at carbon, and it was assumed that the imine substituent was endo, with the Lewis acid occupying the exo position in the transition structure.

We wished to compare the effects of Lewis acid catalysis (modeled again by BH₃) on imino versus carbonyl hetero-Diels–Alder reactions. Two transition structures were found with the BH₃ group exo in **15** and endo in **16** (see Figure 10). The N_1–C_6 forming bond is longer than the C_2–C_3 forming bond by 0.22 and 0.21 Å in **15** and **16**, respectively. The activation energies of **15** are lower than **4** by only 0.9, 2.7, and 2.5 kcal/mol at the 3-21G, 6-31G*, and MP2/6-31G* levels, respectively. BH₃ coordination does not have a large effect on the endo/exo preference of formaldimine. The transition structure with BH₃ exo and the imino hydrogen endo is favored by 3.6 kcal/mol at the MP2/6-31G* level (Table IV), smaller than the endo preferences of uncatalyzed imine reactions.

To determine the magnitude of the endo preference due to steric effects, we investigated the structurally similar reaction of butadiene with propene, in which electrostatic effects should be small. Endo and exo transition structures for the Diels–Alder reaction of butadiene with propene were located at the 3-21G level, followed by MP2/6-31G* energy calculations on the 3-21G transition structures. The endo transition structure of propene is favored by 0.4 kcal/mol at the MP2/6-31G* level, suggesting that the steric effects for CH_3 (which is only slightly smaller than BH₃) are minimal and favor endo transition structures. In light of these results, the exo preferences of BH₃-coordinated formaldehyde and formaldimine must be due to electrostatic interactions of the imino hydrogen and borane moieties with the π electrons of butadiene.

Why does BH₃ coordination have such a small effect on the activation energy for the reaction of formaldimine with butadiene, compared to its effect on the formaldehyde transition structure? To answer this, we examined the energies and structures of uncomplexed and BH₃-complexed reactants and transition states in detail. Geometries were optimized using the 3-21G basis set, 6-31G* Mulliken charges were compared for these geometries, and the energies were calculated at the MP2/6-31G* level. BH₃-coordinated formaldehyde is 15.5 kcal/mol more stable than isolated BH₃ and formaldehyde at the MP2/6-31G* level, while the coordination energy of formaldimine with BH₃ is −34.7 kcal/mol. The B–N bond (1.654 Å) is 0.070 Å shorter than the B–O bond. These differences are expected, since the nitrogen lone pair is more basic than the oxygen lone pair, and nitrogen is less electronegative than oxygen. In the transition structures, however, the B–O bond shortens appreciably from 1.724 to 1.607 Å in
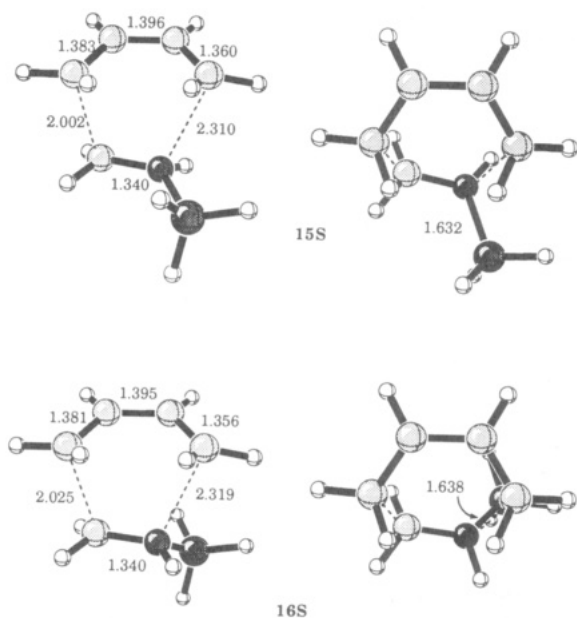
Figure 11. Transition structures for the reaction of butadiene with BH₃-coordinated formaldimine, CH_2Cl_2 solvation model.

13, while the B–N bond length remains almost unchanged. In the BH₃-formaldehyde complex, the BH₃ moiety has a negative charge of 0.19 electron. The negative charges on BH₃ in structures 13 and 14 are 0.27. Apparently, in the formaldehyde case, BH₃ is stabilizing a transition structure with a high degree of polar character. The formaldimine transition structure has less charge transfer, because nitrogen is a poorer acceptor of negative charge than oxygen. The negative charge on BH₃ is almost the same in transition structures 13–16, but in 13 and 14 more positive charge resides on the butadiene portion. There is no direct experimental comparison of the effect of Lewis acid catalysis on hetero-Diels–Alder reactions of comparable aldehydes and imines, since the reactivity of imines is governed by the nature of the N substituent.

Transition structures 15 and 16 were reoptimized in the presence of a dielectric field, in the same manner as in the previous section. Structures 15S and 16S, shown in Figure 11, are less synchronous than their gas-phase counterparts, but the difference is quite small compared to the BH₃–formaldehyde results. Aside from the forming bond lengths, the changes in the transition structure geometries upon solvation are quite small. Vibrational frequency calculations demonstrate that the imaginary mode has large components along both forming bonds, corresponding to a synchronous reaction. The solvated activation energies are raised by 2.8–2.9 kcal/mol at the highest level of our calculations. The MP2/6-31G* energy difference between 15S and 16S is 3.5 kcal/mol, as compared to 3.6 for the gas-phase structures. The dipole moments of 15 and 16 are 6.73 and 6.57 D, smaller than 13 and 14, but much larger than the uncatalyzed transition structures 1–12. Thus it is probably safe to assume that solvation will have a modest effect on the structures, activation energies, and especially the stereochemical preferences of 1–12.

8. Transition Structures and Extended Intermediates for the Reaction of Protonated Formaldimine with Butadiene. Iminium salts are frequently used in hetero-Diels–Alder reactions, because they are far more reactive than neutral imines.[4] Lewis acid catalysis is usually effective in promoting imino Diels–Alder reactions of activated imines with electron-withdrawing substitu-
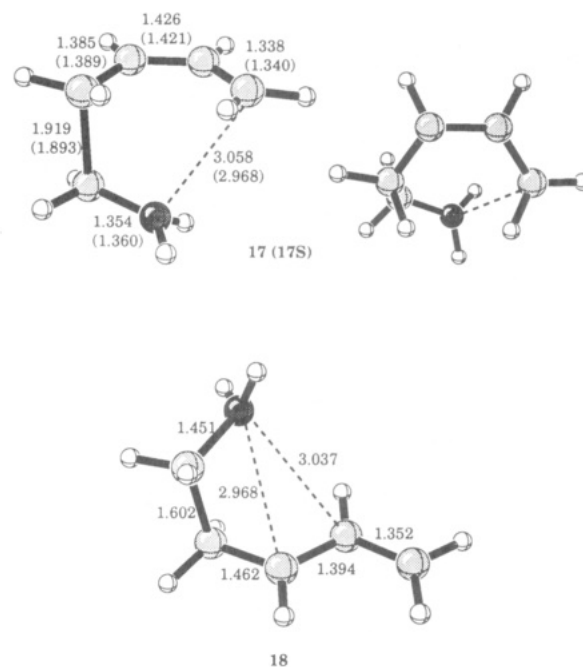

Figure 12. Transition structure and an acyclic intermediate for the reaction of butadiene with formaldiminium ion. Bond lengths for H_2O solvation model are shown in parentheses.

ents, while alkyl-substituted imines generally require acid conditions to react. We have performed calculations on the reaction of butadiene with protonated formaldimine as a model for acid-catalyzed reactions, comparing concerted with stepwise pathways. At the 3-21G level, an asynchronous Diels–Alder-like transition structure, 17, is found (FIgure 12). The asynchronous transition structure has C_2–C_3 and N_1–C_6 forming bond lengths of 1.919 and 3.058 Å, respectively. The N_1–C_6 bond is essentially not formed, judging from the planar geometry about C_5 and C_6 of the butadiene moiety. The single imaginary frequency, according to a 3-21G vibrational frequency calculation, corresponds to closure of the C_2–C_3 forming bond only, preserving the near-planarity of the C_5 and C_6 centers.

Several possible intermediate structures with the carbon and nitrogen termini far apart were also located. In each case, the structure resembles an allylic cation, with a C_2–C_3 bond approximately parallel to the π system. The C_2–C_3 bonds are lengthened (1.602 to 1.773 Å), evidence of hyperconjugation with the allylic system. The most stable intermediate 18, shown in Figure 12, is 32.2 kcal/mol lower in energy than the isolated reactants, and the transition structure is 1.3 kcal/mol lower than reactants at the 3-21G level. At the highest level of our calculations, the activation energy for the reaction of formaldiminium ion with butadiene is −9.5 kcal/mol and the energy of 18 is 36.5 kcal/mol lower than reactants. Our gas-phase calculations overestimate the stabilities of 17 and 18 with respect to the reactants because of the delocalization of charge. In solution, the activation energy should increase. Similar results have been obtained for gas-phase anionic S_N2 calculations,[54] where the complexes and transition structures are stabilized due to their delocalized character.

Transition structure 17 was reoptimized in a solvent reaction field with a dielectric constant of 78, to model Grieco's aqueous studies of protonated imines. Surpris-

(54) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 154, and references therein.

ingly, the solvated transition structure is almost identical to the unsolvated reaction in terms of energy and geometry, although the dielectric constant used in this calculation is much larger than that used for the BH_3-coordinated structures. The reason for this behavior is quite clear from Table III: the dipole of 17 is only 1.21 D and that of protonated formaldimine itself is only 0.5 D. The bond lengths of the solvated transition structure 17S are shown in parentheses beneath the gas-phase bond lengths in Figure 12.

Grieco and co-workers have studied a number of aqueous hetero–Diels–Alder reactions of iminium ions generated in situ from the Mannich reactions of amine hydrochlorides with aldehydes and found that even unactivated N-alkyl-substituted imines are reactive dienophiles when protonated.[4a–c] The major product corresponds to endo addition with respect to the substituent on carbon with imines derived from NH_4Cl. However, when the iminium species possesses both C- and N-substituents, exo products are usually favored.

Krow et al. studied the stereoselectivity of hetero–Diels–Alder reactions with a series of acyclic imino dienophiles under conditions in which the protonated imines were formed.[55] They have established that an N-substituent generally has a larger preference for the endo position than the same substituent at the C-terminus. The dienophile was assumed to be in the (E)-configuration, and the major product corresponded to exo addition at the imino carbon.

Summary

According to our calculations, the reactions of butadiene with formaldehyde, thioformaldehyde, formaldimine, N-methylformaldimine, cis- and trans-diazene, and nitrosyl hydride are concerted and nearly synchronous. Forming C–O and C–N bonds are generally shorter than forming C–C bonds, while the forming C–S bond is longer, reflecting the differences in single bond lengths of the products. The calculated activation energies for the above reactions are underestimated at the MP2/6-31G* level, but the relative activation energies seem to reflect accurately the relative reactivities of these dienophiles. Dienophile reactivities are largely dependent on the strength of the π bond and the LUMO energy.

Stereoselectivities are determined by interactions of the dienophile with the occupied orbitals of butadiene in the transition structure. Closed shell repulsion is responsible for the large activation energies for reactions such as the addition of three acetylenes to form benzene.[56] Coxon et al. recently found that the activation barrier for the reaction of acetylene with butadiene is also influenced by the destabilizing interaction of the nonreacting acetylene π electrons with butadiene filled orbitals.[57] Here, we have shown that lone-pair orbitals on dienophiles can exert a large destabilizing influence on the filled orbitals of butadiene. We have discovered that these dienophile lone-pair, diene π-electron interactions can have a very large influence on stereoselectives.

There is a strong tendency for the nitrogen lone pair to occupy the exo position in the imino transition structures. The stereochemical preferences are not strongly dependent on the level of calculation, as is shown for the formaldimine transition structures. The repulsive interaction of the lone pair with the π electrons of butadiene is mainly responsible for this preference. These conclusions are in agreement with experimental evidence that N-substituents have a larger endo preference than C-substituents on the dienophile. There is also a noticeable twisting of the dienophiles with respect to the diene in transition structures 1–11 and 13–16, unlike most all-carbon Diels–Alder transition structures. This results from electrostatic interactions of C_4 and C_5 of butadiene with endo lone pairs, BH_3, and imino hydrogens.

Coordination of BH_3 on formaldehyde not only makes it much more reactive, but also increases asynchronicity and charge separation in the transition structure to the extent that a stepwise mechanism may be favored in solution. BH_3 coordination of formaldimine also lowers the activation energy and increases the degree of asynchronicity in the transition structure, but the effect is weaker than in the case of formaldehyde as dienophile. Formaldiminium ion, which serves as a model for strong Lewis acid catalysis, causes a shift to a stepwise mechanism in the gas phase. A dielectric model of solvation was compared with gas-phase ab initio results for the reactions of butadiene with BH_3-coordinated formaldehyde, BH_3-coordinated formaldimine, and protonated formaldimine. For the latter two dienophiles, little change was seen upon inclusion of solvent. The BH_3-coordinated formaldehyde transition structures, which have the largest dipole moments, shifted from a concerted, asynchronous mechanism to essentially stepwise bond formation in solution.

In transition structures with BH_3 coordinated to formaldehyde or formaldimine, the exo transition structure is favored due to repulsive interactions of the negatively charged BH_3 group with the π electrons of butadiene. The influence of steric effects on the exo preference for BH_3 is small, since the structurally similar endo transition structure for the reaction of propene with butadiene is favored by a small amount. The exo preference of BH_3 does not change significantly upon solvation, according to our calculations.

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