J. Org. Chem. **2000,** *65,* 8251−8259

The First Density Functional Study on the [4 + 2]-Cycloaddition Reactions of 1,2-Diaza-1,3-butadiene with Alkenes

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Received June 14, 2000

The hetero-Diels−Alder reactions of 1,2-diaza-1,3-butadiene with ethylene, methyl vinyl ether, and methyl acrylate have been investigated theoretically with the aid of density functional theory using the Becke3LYP/6-31G(d) computational level. In the reactions with substituted alkenes, the transition states are concerted but asynchronous; the shortest bond-forming distance involves the nonsubstituted carbon of the alkene. In agreement with the experimental results, the reaction with methyl vinyl ether proceeds with high *endo* stereoselectivity and with complete regioselectivity to form the 6-methoxy cycloadduct. The conformational study of the transition states shows a sharp *s-trans* preference. In contrast, the [4 + 2]-cycloaddition of 1,2-diaza-1,3-butadiene with methyl acrylate have been found to occur with low regio- and stereoselectivity but with a *s-cis* preference in the transition structures.

Introduction.

Since its invention, the hetero-Diels−Alder cycloaddition has been the favorite methodology for obtaining carbon−heteroatom bonds, especially to introduce nitrogen functionality.[1] The availability of simple and efficient hetero-dienes and dienophiles has been the driving force for the development of this powerful strategy. Azadienes in which the nitrogen atom is part of the conjugate system are also known to participate in cycloadditions. Experimentally, the use of azadienes in synthesis has been mainly limited to a few accessible and reactive intermediates. Thus, *N*-acyl-1-aza-1,3-butadienes, which can be generated in situ by pyrolysis of N-acylated *N*-allylhydroxylamines undergo intramolecular reactions to afford indolizidine and quinolizidine alkaloids.[2] α,β-Unsaturated hydrazones also react with electron-withdrawing dienophiles to give nitrogenated six-membered rings. The reactivity of the 1-azadiene is enhanced by an electron-donating substituent such as a dimethylamino group.[3] Likewise, 2-azadienes benefit from strong electron-donating groups which increase their reactivity toward deficient dienophiles.[4] Monoazadienes have been employed in elegant syntheses of naturally occurring substances such as gephyrotoxin,[5] epilupinine,[6] or cryptosporin,[7] to name a few. A plausible rationale to account for the reactivity and selectivity of these synthons has been provided by Houk and his associates, who have studied the reaction of 1,3-butadiene with ethylene at the B3LYP/6-31G(d) level of theory[8] and the reaction of 2-aza-1,3-butadiene with alkenes at HF/3-21G, HF/6-31G(d)//HF/3-21G, and MP2/6-31G(d)//HF/3-21G,[9] for comparative purposes. In addition, Lee and co-workers have studied a series of hetero-Diels−Alder reactions including that of 1-aza-1,3-butadiene with ethylene at the B3LYP/6-31G(d) and MP2/6-31G(d) levels of theory.[10] Moreover, semiempirical studies on more elaborated systems have also been reported.[11,12]

Like monoazadienes, 1,2-diaza-1,3-butadienes have also been exploited in synthetic chemistry for the construction of densely functionalized nitrogen heterocycles,[13] including diastereoselective versions as well.[14] Nevertheless, ab initio studies at a comparable level of

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10.1021/jo000907f CCC: $19.00

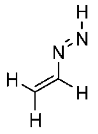
theory have not yet been reported. To elucidate the mechanistic details for these substances, we have performed density functional (DFT) calculations on the [4 + 2]-cycloaddition pathway. Electron tuning of reactivity was examined for three different alkenes: ethylene, methyl vinyl ether, and methyl acrylate. Results also enable a direct comparison with the patterns observed previously for monoazadienes.

Computational Methods

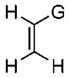
Calculations were performed using the GAUSSIAN94 series of programs.[15] The Becke3LYP hybrid functional, consisting of the nonlocal exchange functional of Becke's three-parameter set,[16] and the nonlocal correlation function of Lee, Yang, and Parr,[17] were used together with the 6-31G(d) basis set.[18] All geometries were fully optimized, and frequency analyses were performed to determine the nature of each stationary point. Moreover, the one negative eigenfrequency of the transition structures was animated using MOLDEN[19] to ensure that the optimized stationary point corresponds to the transition structure of the desired reaction. Delocalization energies due to the interactions among occupied and unoccupied bond orbitals were estimated with the natural bond orbital (NBO) basis.[20] Bond orders were calculated as the Wiberg indexes derived from the natural atomic orbital analysis.[21]

Results and Discussion

We have located the transition structures for the Diels−Alder reactions of 1,2-diaza-1,3-butadiene (**1**) with ethylene (**2**), methyl vinyl ether (**3**), and methyl acrylate (**4**). In the case of methyl vinyl ether and methyl acrylate, there are several issues of selectivity to be considered. There is an issue of regioselectivity in which the carbon bearing the electron-donating or electron-withdrawing group of the dienophile is attached to either the nitrogen atom (head-to-head) or to the carbon atom (head-to-tail) of the heterodiene. There is also one issue of stereoselectivity involving the orientation of the side group of the dienophile (*endo* or *exo*) with respect to the diene. In addition, the *s-cis* and *s-trans* conformations of the substituted alkene should also be evaluated. Overall this creates a set of eight possible transition structures from each dienophile.



1



2 G=H
3 G=OCH_3
4 G=$COOCH_3$

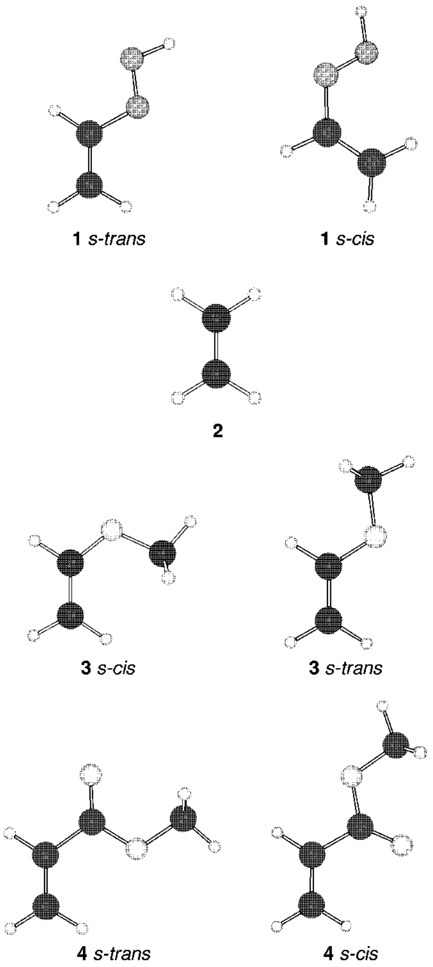


Figure 1. B3LYP/6-31G(d) optimized structures of the reactants.

The conformational features of the reaction partners are depicted in Figure 1. The most stable conformation of **1** is *s-trans* which is 4.3 kcal/mol lower in energy than the *s-cis* conformer in both the electronic and the zero-point corrected energies (Table 1). The *s-cis* conformation is not planar, the dihedral angle between the N═N and C═C double bonds being 37.2°. The structure with an angle of 0° has an electronic energy 0.8 kcal/mol higher than the minimum found with 37.2° while its zero-point corrected energy is 0.5 kcal/mol higher than that, and it corresponds to a transition structure as indicated by the presence of an imaginary frequency.

According to Houk,[22] the lowest energy conformation of methyl vinyl ether is the *s-cis* planar conformation. At the B3LYP/6-31G(d) level of theory, the *s-trans* conformation is higher in energy by 2.3 kcal/mol in terms of electronic energy and 1.6 kcal/mol in terms of zero-point corrected energy. In stark contrast the *s-trans* conformation is not planar, being 168.8° the dihedral angle between the C═C double bond and the O−C bond being 168.8°. The electronic and zero-point corrected energies of the structure having a dihedral angle of 180° differ less than 0.1 kcal/mol with respect to the minimum found with 168.8°. The reason for this *s-cis* preference has been attributed to the smaller dipole moment of the

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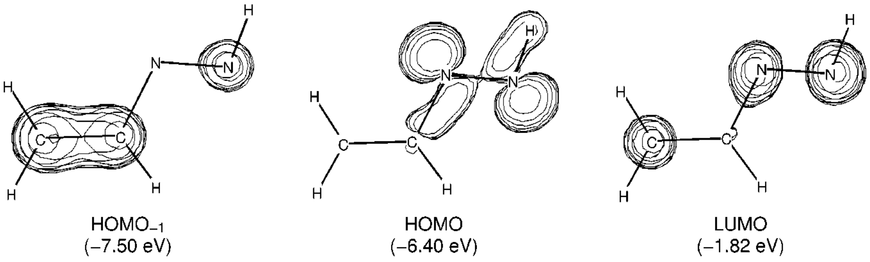
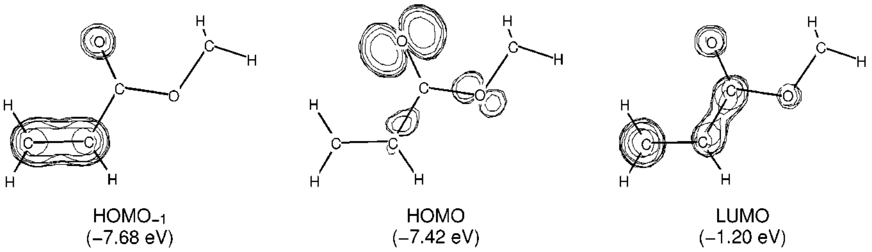
Table 1. B3LYP/6-31G(d) Electronic Energies (*E*), Zero-point Corrected Energies (E_0), Enthalpies (*H*), and Free Energies (*G*) in au Together with the Dipole Moment (Debye) for All the Reactants

		E	E_0	H[a]	G[a]	dipole moment
1	*s-cis*	−188.0346525	−187.972529	−187.967304	−187.998754	0.59
	s-trans	−188.0415698	−187.979305	−187.974092	−188.005385	0.92
2		−78.5874573	−78.536238	−78.532251	−78.558422	0.00
3	*s-cis*	−193.1140725	−193.028288	−193.022614	−193.054984	0.95
	s-trans	−193.1104106	−193.025789	−193.020407	−193.052283	1.75
4	*s-cis*	−306.4677513	−306.371921	−306.364359	−306.402303	1.50
	s-trans	−306.4666141	−306.370767	−306.363186	−306.401243	2.11

[a] Computed at 298.15 K.



1 *s-trans*



4 *s-cis*

Figure 2. Isopotential surfaces (cutoff value = 0.1) of the frontier molecular orbitals of the structures **1** (*s-trans*) and **4** (*s-cis*).

molecule in this conformation in which the lone-pair electrons of the oxygen avoid the π electrons of the double bond.

For methyl acrylate, there is also a small preference for the *s-cis* conformation of the carbonyl bond with respect to the carbon−carbon double bond. The calculation at the B3LYP/6-31G(d) level estimates the difference in energy between the *s-cis* and *s-trans* conformations in 0.7 kcal/mol in both electronic and zero-point corrected energies.

Frontier Molecular Orbital (FMO) Analysis. We have found that the highest occupied molecular orbital (HOMO) of the 1,2-diaza-1,3-butadiene is a nonbonding orbital in which the lone-pair electrons of the nitrogen atoms are involved (Figure 2).[19] Therefore, this orbital is not suitable to be involved in [4 + 2]-cycloaddition reactions. The nearest occupied orbital to the latter ($HOMO_{-1}$) is 1.10 eV lower in energy than the HOMO, and it has the right symmetry to react as a HOMO, having a nodal plane coincident with the plane of the dienic system. From now on this $HOMO_{-1}$ will be considered as the reacting HOMO of the 1,2-diaza-1,3-butadiene.

The reactions with ethylene and methyl vinyl ether are inverse electron-demand Diels−Alder cycloadditions, controlled by the LUMO of the heterodiene, as noted by the difference in energy between the $HOMO_{dienophile}-LUMO_{diene}$ and $HOMO_{diene}-LUMO_{dienophile}$ interactions for these two alkenes (Table 3).

The orbital distribution of methyl acrylate is similar to that found for 1,2-diaza-1,3-butadiene. Again, the HOMO is a nonbonding orbital in which the lone-pair electrons of the oxygen atoms are involved (Figure 2). Nevertheless the $HOMO_{-1}$ of the methyl acrylate is only 0.26 eV lower in energy than the HOMO, and it has also a nodal plane coincident with the plane of the molecule. Therefore, this $HOMO_{-1}$ will equally be considered as the HOMO of the methyl acrylate. With these two premises, an analysis of the differences in energy for the FMOs of the reactants, $HOMO_{dienophile}-LUMO_{diene}$ and $HOMO_{diene}-LUMO_{dienophile}$ allow us to conclude that none of them can be neglected albeit the first interaction is slightly lower.

The polarization of the LUMO in the heterodiene can be measured by the values of the atomic coefficients (Table 2), the one over N-1 being larger than the one over C-4. In addition, the HOMO of the diene has a smaller coefficient on N-1 than on C-4. Thus for this heterodiene, the FMO polarizations imply that N-1 is more electrophilic than C-4.

At this point, we can predict which of the two regioisomers is preferred in the cycloadditions of 1,2-diaza-1,3-butadiene with methyl vinyl ether and methyl acrylate. The HOMO of methyl vinyl ether is polarized to a significant extent, and the C-2 coefficient is larger than the C-1 coefficient. Accordingly, the predicted major regioisomers in this process are the 5-methoxy-1,4,5,6-tetrahydropyridazines, a result opposite to the regiochemistry observed experimentally.[23]

Table 2. Energies and Atomic Coefficients for the Frontier Molecular Orbitals of the Reactants at B3LYP/6-31G(d)

				c_1		c_2		c_3		c_4	
			E (eV)	2pz	3pz	2pz	3pz	2pz	3pz	2pz	3pz
1	*s-cis*	HOMO[a]	−7.47	−0.27	−0.19	−0.05	−0.04	+0.35	+0.25	+0.36	+0.25
		LUMO	−1.82	+0.36	+0.37	−0.34	−0.32	−0.14	−0.18	+0.26	+0.31
	s-trans	HOMO[a]	−7.50	−0.28	−0.21	−0.10	−0.07	+0.35	+0.23	+0.38	+0.28
		LUMO	−1.82	+0.43	+0.43	−0.37	−0.34	−0.16	−0.18	+0.32	+0.36
2		HOMO	−7.26	+0.40	+0.28	+0.40	+0.28				
		LUMO	+0.51	−0.42	−0.63	+0.42	+0.63				
3	*s-cis*	HOMO	−6.12	+0.27	+0.17	+0.40	+0.33	−0.37[b]	−0.29[b]		
		LUMO	+1.22	+0.48	+0.64	−0.61	−0.39	−0.22[b]	−0.24[b]		
	s-trans	HOMO	−5.94	+0.28	+0.18	+0.39	+0.31	−0.39[b]	−0.31[b]		
		LUMO	+1.05	+0.45	+0.62	−0.60	−0.38	−0.18[b]	−0.20[b]		
4	s-cis	HOMO[a]	−7.68	−0.04	−0.04	+0.38	+0.27	+0.37	+0.26	−0.27[c]	−0.19[c]
		LUMO	−1.20	−0.31	−0.24	−0.26	−0.36	+0.50	+0.38	+0.26[c]	+0.26[c]
	s-trans	HOMO[a]	−7.74	−0.03	−0.03	+0.38	+0.26	+0.38	+0.27	−0.20[c]	−0.14[c]
		LUMO	−1.23	−0.31	−0.24	−0.27	−0.35	+0.38	+0.49	+0.29[c]	+0.27[c]

[a] HOMO$_{-1}$ orbital. [b] c_3 = coefficient on the oxygen atom. [c] c_4 = coefficient on the oxygen atom of the carbonyl group.

Table 3. The Interfrontier MO Gaps for the Reactions of 1 with 2−4 (in eV)

	2	**3** *s-cis*	**4** *s-cis*
HOMO$_{\mathbf{1}}$[a]−LUMO$_{\mathrm{alkene}}$	8.01	8.72	6.30
HOMO$_{\mathrm{alkene}}$−LUMO$_{\mathbf{1}}$	5.44	4.30	5.86

[a] HOMO$_{-1}$ orbital.

In contrast, the HOMO of methyl acrylate is not polarized (Table 2), and no regiochemical preference should be expected but, as noted before, the interaction between HOMO$_{\mathrm{diene}}$ and LUMO$_{\mathrm{dienophile}}$ cannot be neglected in this case. On the other hand, it should be observed that the LUMO of methyl acrylate is quite polarized, the atomic coefficient over C-3 being larger than the one over C-2. Therefore, it is possible to predict only a slight preference for the formation of 6-methoxycarbonyl-1,4,5,6-tetrahydropyridazines as the major regioisomers based on the FMO assumptions. In this case, the experimental results agree with the FMO theory.[24]

Description of the Calculated Transition Structures. Although the mechanism of the hetero-Diels−Alder reaction is generally assumed to be a concerted, asynchronous cycloaddition, a stepwise, radical-mediated mechanism can also occur. In the present work, however, we have limited our investigation to the *restricted* B3LYP/6-31G(d) calculations of the *concerted pathway* without considering *unrestricted* B3LYP/6-31G(d) optimization of the open-shell pathway for the dirradical stepwise mechanism.

The transition structures **TS6**−**TS9** (Chart 1) correspond to the reaction of 1,2-diaza-1,3-butadiene with methyl vinyl ether. The transition structures that lead to the formation of 6-methoxy-1,4,5,6-tetrahydropyridazines are **TS6** and **TS7**, whereas **TS8** and **TS9** are those leading to the 5-substituted heterocycle. If we compare the energy barriers for the reaction in the most stable *s-trans* transition structures, it appears that both **TS6** and **TS7** are lower in energy than **TS8** and **TS9** by, at least, 2.15 kcal/mol. Therefore the favored regioisomers are the 6-substituted derivatives, a result contrary to the FMO prediction for this reaction. An immediate conclusion is that the FMO model cannot successfully represent the most nucleophilic and electrophilic ends of the heterodienic system under study. Experimentally, this system also undergoes nucleophilic additions at C-4,[13] a fact that reinforces the idea that this atom should be the most electrophilic one. Furthermore, this is supported by the direction of the dipole moment in the diene, which points toward the azo group in both conformations (Figure 3). Thus, the nucleophilic dienophile **3** should produce the 6-methoxy heterocycles preferentially with **TS6** and **TS7** having a lower energy barrier, which explains the result of the calculations for these transition states. Such a result fully agrees with the experiments which conclude that the [4 + 2]-cycloaddition reaction of 1,2-diaza-1,3-butadienes with ethyl vinyl ether takes place with complete regioselectivity yielding the 6-ethoxy-1,4,5,6-tetrahydropyridazines.[23]

For the cycloaddition reaction between 1,2-diaza-1,3-butadiene and methyl acrylate, the transition structures **TS10** and **TS11** correspond to the approaches that lead to 6-methoxycarbonyl-1,4,5,6-tetrahydropyridazines, while **TS12** and **TS13** afford the 5-substituted adduct. Comparing the transition structures in which the dienophile adopts the most stable *s-cis* conformation, we have found that all of the transition structures are within a narrow range of 1.41 kcal/mol, **TS11** being the one with the lowest energy barrier and **TS10** the one with the highest energy barrier, albeit both of them share the same regiochemistry. Accordingly, there is no regiochemical preference in this cycloaddition, a fact in agreement with the almost zero polarization found in the HOMO of the dienophile. Again, the theoretical result agrees with the experiment since the reaction proceeds with low regioselectivity, still favoring the 6-methoxycarbonyl heterocycle as the major product.[24]

Another important issue to be addressed in this study is the stereochemistry of these hetero-Diels−Alder reactions. We have compared the values of the energy barriers for the most stable conformations of the dienophile in the transition structures, *s-trans* for methyl vinyl ether and *s-cis* for methyl acrylate. The stereoselectivity of the cycloaddition is opposite in the two regioisomeric possibilities. The *exo* approach is favored in the transition structures that lead to the 6-substituted heterocycles. For the reaction with methyl vinyl ether, the *exo* orientation has an energy barrier that is 0.78 kcal/mol lower than the *endo* one, in good agreement with the stereoselectivity observed in the experiments.[23c] The *endo* transition

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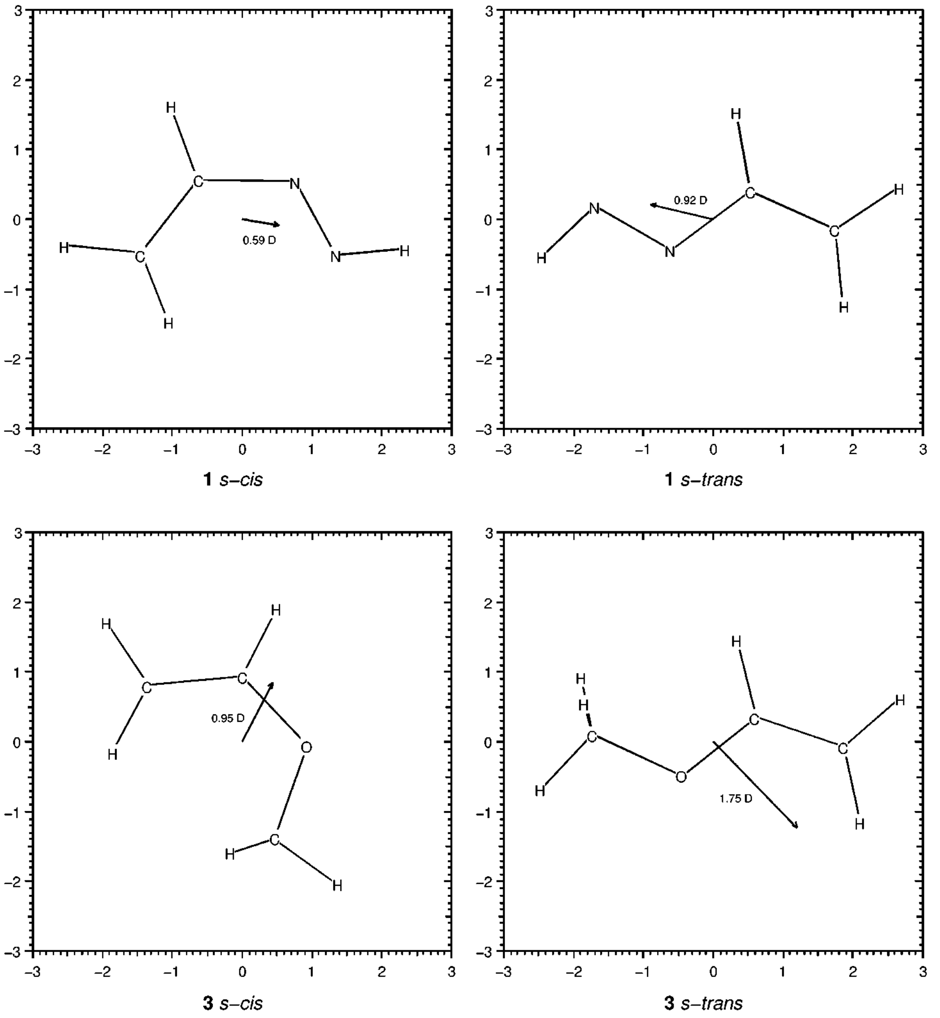


1 *s-cis* **1** *s-trans*

3 *s-cis* **3** *s-trans*

Figure 3. Vectorial representation of the dipole moments in Debyes of reactants **1** and **3** over the standard orientation of the molecules in Cartesian coordinates (Å).

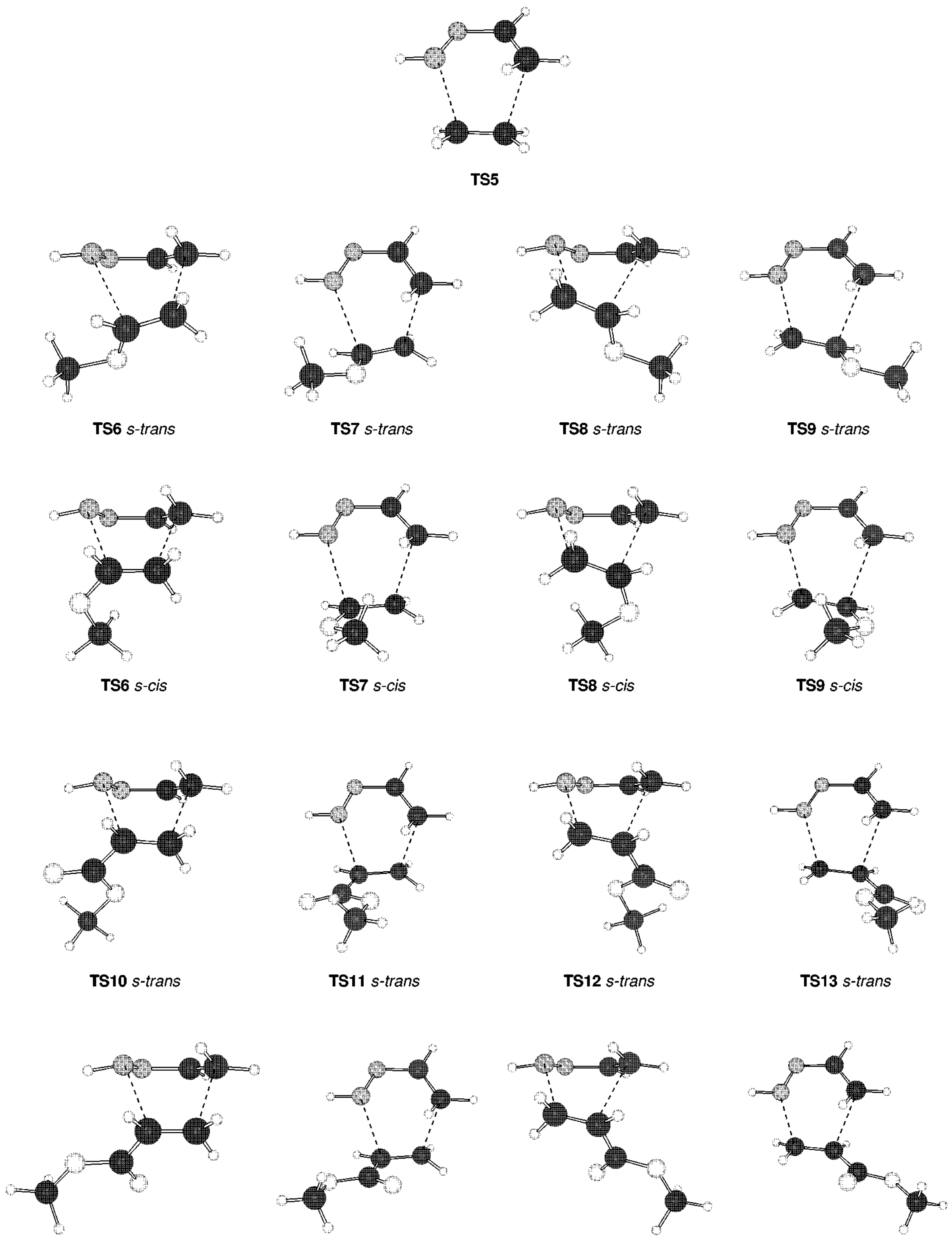
structure for the reaction with methyl acrylate presents an energy barrier of 1.41 kcal/mol higher than its *exo* counterpart. These results could be explained in terms of repulsive interactions between the lone-pair electrons at N-2 in the dienic system and the lone-pair electrons of the oxygen atom in the methyl vinyl ether fragment, or the π orbital of the carbonyl moiety in methyl acrylate.

Concerning the transition structures **TS8** and **TS9**, and **TS12** and **TS13**, the favored stereoisomers prefer the *endo* orientation (**TS8** and **TS12**) by 1.15 and 0.31 kcal/mol for the reactions with methyl vinyl ether and methyl acrylate, respectively. In the reaction with methyl acrylate, the slight *endo* preference could be rationalized on the basis of weak secondary orbital interactions between both reactants.

The third important aspect of this study is the conformation of the dienophile in the transition structures. In complete agreement with the results obtained by Houk et al[22] about the conformation of vinyl ethers in the transition structures of several cycloaddition reactions, we have also found a preference for the *s-trans* conformation of methyl vinyl ether in the transition structures of the [4 + 2]-cycloaddition reactions of 1,2-diaza-1,3-butadiene with such a dienophile. However, such a preference is anyway smaller than that found for the cycloadditions studied by Houk and co-workers. The calculation estimates that the *s-trans* transition structures (**TS6** and **TS7**) are 2.38 and 2.09 kcal/mol lower in energy than the *s-cis* ones in the *endo* and *exo* orientations, respectively. The differences in energy for the transition structures **TS8** and **TS9** are 1.88 and 0.99 kcal/mol respectively, with the *s-trans* transition structures having the lower energy anew. It has been argued that the *s-trans* preference is based on a smaller dipole moment of the molecule in this conformation with respect to the *s-cis*, which is true for **TS6** and **TS7** but not for **TS8** and **TS9** (Table 4).

To rationalize these results we have carried out a Second-Order Perturbation Theory (SOPT) analysis of the Fock Matrix in Natural Bond Orbital (NBO) Basis[20] which provides the delocalization energies owing to the interactions of the occupied natural bond orbitals of the molecule with the unoccupied ones. The total delocalization energy in a molecule has been computed as the sum of the energies of the individual interactions of the orbitals. Table 5 summarizes the results of the aforementioned analysis. There is an increment in the delocalization energy from the reactants to the transition states mostly due to the intermolecular interactions, but also there is an increment in the intramolecular interactions. In all the transition structures **TS6** and **TS7**, those with the methyl vinyl ether fragment in *s-trans* conformation show a larger increment in the delocalization energy with respect to those in a *s-cis* disposition, and

Chart 1



the same occurs in the transition structures **TS8** and **TS9**. Specially, if we pay attention to the change in the intramolecular delocalization of methyl vinyl ether from reactants to transition states, then there is a significant increment of about 5 kcal/mol for the *s-trans* conformation while for the *s-cis* conformer the delocalization decreases about 5 kcal/mol in the transition structures **TS6** and **TS7** and, in the cases of **TS8** and **TS9**, the delocalization always diminishes but less than 2 kcal/mol for the *s-trans* conformation and more than 12 kcal/mol for the *s-cis*.

In relation with the cycloaddition of **1** and methyl acrylate, there is likewise a preference for a conformation of the dienophile in the transition structures, but in this case, the preferred conformation in the transition structure is the same as that found in the starting material, i.e., the *s-cis* conformation. Because the energy difference between the conformations of methyl acrylate is smaller than between the conformers of methyl vinyl ether, the differences in energy in the transition structures are also smaller. These differences lie in the range of 0.6 to 1.2 kcal/mol for the transition structures **TS10**−**TS13**. Due

Table 4. B3LYP/6-31G(d) Electronic Energies (*E*), Zero-point Corrected Energies (E_0), Enthalpies (*H*), and Free Energies (*G*) in au Together with the Dipole Moment (Debye) for TS5-TS13

		E	E_0	H^a	G^a	dipole moment
TS5		−266.6029902	−266.485645	−266.478536	−266.515066	1.70
TS6	*s-cis*	−381.1236205	−380.972788	−380.963251	−381.006101	2.71
	s-trans	−381.1269053	−380.976574	−380.966830	−381.010292	2.53
TS7	*s-cis*	−381.1251632	−380.974500	−380.964934	−381.007855	2.83
	s-trans	−381.1280597	−380.977817	−380.968076	−381.011363	2.26
TS8	*s-cis*	−381.1212044	−380.970163	−380.960809	−381.003019	2.03
	s-trans	−381.1235975	−380.973160	−380.963604	−381.006388	3.08
TS9	*s-cis*	−381.1208431	−380.969892	−380.960497	−381.002917	2.27
	s-trans	−381.1216547	−380.971327	−380.961677	−381.004813	3.17
TS10	*s-cis*	−494.4843516	−494.323277	−494.311951	−494.359481	1.63
	s-trans	−494.4834124	−494.322278	−494.310925	−494.358556	3.04
TS11	*s-cis*	−494.4866635	−494.325528	−494.314220	−494.361654	1.23
	s-trans	−494.4848112	−494.323665	−494.312330	−494.359876	3.00
TS12	*s-cis*	−494.4855811	−494.324439	−494.313077	−494.360748	2.18
	s-trans	−494.4842041	−494.323109	−494.311709	−494.359524	1.45
TS13	*s-cis*	−494.4849931	−494.323912	−494.312485	−494.360436	1.81
	s-trans	−494.4836478	−494.322459	−494.311065	−494.358886	1.56

[a] Computed at 298.15 K.

Table 5. Energies in kcal/mol by Reactive Species of the Second-Order Perturbation Theory Analysis of the Fock Matrix in NBO Basis

		intermolecular	intramolecular		total	TS reactants
			dienophile	diene		
1	*s-cis*			116.86		
	s-trans			127.91		
3	*s-cis*		140.08		256.94[a]	
	s-trans		119.33		236.19[a]	
4	*s-cis*		191.76		308.62[a]	
	s-trans		188.35		305.21[a]	
TS6	*s-cis*	77.28	134.54	133.54	345.36	88.42
	s-trans	77.62	124.32	132.99	334.93	98.74
TS7	*s-cis*	74.60	134.38	133.40	342.28	85.44
	s-trans	70.69	124.19	134.60	329.48	93.29
TS8	*s-cis*	86.11	127.22	139.80	353.13	96.19
	s-trans	87.56	117.78	135.35	342.69	106.50
TS9	*s-cis*	93.60	126.48	139.83	359.91	102.97
	s-trans	88.92	117.68	136.99	343.59	107.40
TS10	*s-cis*	74.00	270.51	130.74	475.25	166.63
	s-trans	74.46	271.24	132.05	477.75	172.54
TS11	*s-cis*	74.47	268.17	133.35	475.99	167.37
	s-trans	74.96	267.52	132.60	475.08	169.87
TS12	*s-cis*	84.36	272.13	137.79	494.30	185.68
	s-trans	82.60	274.14	137.74	494.48	189.27
TS13	*s-cis*	81.18	274.70	135.68	491.54	182.92
	s-trans	80.44	273.48	135.78	489.70	184.49

[a] Sum with **1** *s-cis*.

Table 6. Activation Energies and Enthalpies in kcal/mol and Activation Entropies in eu for All the Transition Structures Related to Their Reactants in the Most Stable Conformation

		$\Delta E^{\ddagger}$	$\Delta E_0^{\ddagger}$	$\Delta H^{\ddagger a}$	$\Delta G^{\ddagger a}$	$\Delta S^{\ddagger a}$
TS5		+16.34	+18.76	+17.45	+30.59	−44.06
TS6	*s-cis*	+20.09	+21.84	+20.99	+34.05	−43.80
	s-trans	+18.03	+19.46	+18.75	+31.42	−42.52
TS7	*s-cis*	+19.13	+20.77	+19.94	+32.95	−43.65
	s-trans	+17.31	+18.68	+17.97	+30.75	−42.88
TS8	*s-cis*	+21.61	+23.49	+22.53	+35.99	−45.15
	s-trans	+20.11	+21.61	+20.77	+33.87	−43.94
TS9	*s-cis*	+21.84	+23.66	+22.72	+36.05	−44.71
	s-trans	+21.33	+22.76	+21.98	+34.86	−43.20
TS10	*s-cis*	+15.67	+17.54	+16.63	+30.25	−45.68
	s-trans	+16.26	+18.17	+17.27	+30.83	−45.47
TS11	*s-cis*	+14.22	+16.13	+15.21	+28.89	−45.89
	s-trans	+15.38	+17.29	+16.39	+30.00	−45.65
TS12	*s-cis*	+14.90	+16.81	+15.92	+29.46	−45.39
	s-trans	+15.76	+17.64	+16.78	+30.22	−45.08
TS13	*s-cis*	+15.27	+17.14	+16.29	+29.65	−44.80
	s-trans	+16.11	+18.05	+17.18	+30.62	−45.07

[a] Computed at 298.15 K.

to these short magnitudes, it is not easy to find a single factor accounting for this preference. As in the case of the reaction of **1** with **3**, the preferred conformation in the transition structures that lead to the 6-methoxycarbonyl derivative has the lowest dipole moment, although in the transition structures of the opposite regiochemistry it has the highest dipole moment. From the results of the SOPT analysis shown in Table 5, there is an important increment in the delocalization energy from reactants to transition states and not only for the intermolecular interaction which is similar to that in the reaction with **3**, but also for the intramolecular component. This larger increment comes from the dienophile fragment of the transition structures. In contrast with the reaction with methyl vinyl ether and in agreement with the differences in the energy barriers of the transition structures, the differences in the increments of the delocalization energy between the two conformations are lower with methyl acrylate (~2−5 kcal/mol with **4** and ~10−12 kcal/mol with **3**).

Energetics of the Transition Structures. The values in Hartrees of the electronic energies, zero-point corrected energies, enthalpies, and free energies for all the optimized structures are collected in Table 4. The activation values for these magnitudes together with the activation entropies for all the transition structures are collected in Table 6.

A comparative analysis of the values given in Table 6 provides us further information about what makes the alkene more reactive in the [4 + 2]-cycloaddition reactions with 1,2-diaza-1,3-butadiene. Thus, the most reactive alkene is methyl acrylate, whereas methyl vinyl ether is the least reactive one. Compared to the nonsubstituted alkene, ethylene, the formation of the most favored regioisomers in the reaction of the heterodiene with methyl vinyl ether, **TS6** and **TS7**, presents similar zero-point corrected energy barriers (0.70 kcal/mol higher and 0.08 kcal/mol lower, respectively), slightly higher activation enthalpies at 298.15 K (1.30 and 0.52 kcal/mol), along with similar activation free energies at 298.15 K (0.83 and 0.16 kcal/mol higher than with ethylene) due to a favorable entropic factor (activation entropies at 298.15 K are 1.54 and 1.18 cal·mol^{-1}·K^{-1} higher).

All the transition structures for the reaction of 1,2-diaza-1,3-butadiene with methyl acrylate (**TS10**−**TS13**)

Table 7. Atomic Distances (Å) and Bond Orders (Wiberg indexes) for the Two Forming Bonds in the TSs and Charge Transfer (au) in Terms of the Residual Charge of the Alkene Fragment in the Transition State

		d_{1-6}(Å)	bond order	d_{4-5}(Å)	bond order	$\theta_{3-4-5-6}$	charge transfer
TS5		2.222	0.311	2.304	0.306	−57.53	+0.076
TS6	*s-cis*	2.341	0.252	2.186	0.381	−50.97	+0.146
	s-trans	2.488	0.205	2.135	0.399	−31.89	+0.201
TS7	*s-cis*	2.310	0.247	2.220	0.360	−58.70	+0.150
	s-trans	2.434	0.212	2.190	0.363	−74.78	+0.171
TS8	*s-cis*	2.091	0.407	2.314	0.309	−69.98	+0.159
	s-trans	2.072	0.409	2.416	0.269	−71.97	+0.167
TS9	*s-cis*	2.075	0.415	2.331	0.303	−35.25	+0.161
	s-trans	2.062	0.412	2.420	0.270	−37.94	+0.160
TS10	*s-cis*	2.327	0.250	2.202	0.350	−52.54	+0.013
	s-trans	2.312	0.255	2.212	0.347	−55.59	+0.009
TS11	*s-cis*	2.303	0.258	2.209	0.346	−64.19	+0.013
	s-trans	2.292	0.262	2.217	0.343	−61.29	+0.011
TS12	*s-cis*	2.075	0.384	2.429	0.235	−58.48	−0.007
	s-trans	2.091	0.376	2.407	0.243	−58.08	−0.003
TS13	*s-cis*	2.086	0.376	2.436	0.236	−56.21	−0.007
	s-trans	2.100	0.371	2.415	0.243	−56.20	−0.003

are lower in energy than the corresponding ones with ethylene. The zero-point corrected energy barriers are lower by 1.22−2.63 kcal/mol, the activation enthalpies by 0.82−2.24 kcal/mol, and the activation free energies by 0.34−1.70 kcal/mol. For this reaction, the activation entropies are lower than in the case of ethylene.

Geometry of the Transition Structures. All the transition structures located in this study correspond to an asynchronous but concerted cycloaddition process except in the case of the reaction of **1** with ethylene whose transition structure suggests a concerted pathway with an almost complete synchronicity. Direct comparison of the two forming-bonds distances is not a correct criterion to estimate the synchronicity of the reaction because of the different nature of the two forming, nitrogen−carbon and carbon−carbon, bonds. Average values for these bond lengths can be found in the literature[25] and N−C(sp^3) bonds are shorter than C(sp^3)−C(sp^3) ones by about 0.06 Å. Together with the values of the bond distances, it is convenient to examine the values of the bond orders[26] (Table 7).

Thus, **TS5** presents a shorter distance for the N−C bond than for the C−C one by 0.082 Å, but the bond order, given as the Wiberg index[21] derived from the Natural Atomic Orbital (NAO) basis, is slightly larger by 0.005 for the N−C bond. This suggests that the transition structure is synchronous.

All the rest of the transition structures (**TS6**−**TS13**) are asynchronous having always shorter bond distances and higher bond orders for the bond in which the nonsubstituted carbon of the alkene is involved. The latter is the atom with the largest coefficient in the frontier molecular orbitals. In all cases the transition structures having the most favored conformation for the dienophile (*s-trans* with methyl vinyl ether and *s-cis* with methyl acrylate) are the most asynchronous ones.

For the reaction of 1,2-diaza-1,3-butadiene with methyl vinyl ether, the transition structures **TS6** and **TS7** which lead to the preferred regioisomers are more asynchronous than **TS8** and **TS9**, in terms of differences in bond orders and earlier transition states, longer bond lengths, and smaller bond orders. It is also to be noted that the most stable *exo* **TS7** is more synchronous than the *endo* **TS6**, while both stereoisomers present almost the same synchronicity for the other regioisomeric transition structures **TS8** and **TS9**.

In the case of methyl acrylate and contrary to the case of methyl vinyl ether, the most asynchronous transition structures are **TS12** and **TS13** yielding the 5-methoxycarbonyl regioisomers. The *exo* transition structures **TS11** and **TS13** are more synchronous than the *endo* **TS10** and **TS12** in both regioisomeric approaches.

The values of the dihedral angle $\theta_{3-4-5-6}$ are given in Table 7. This parameter reflects the deviation from the parallel approximation of the reactants in the transition states if we consider such an approximation when the C−C double bond of the dienophile is parallel to the line between the two ends of the dienic system (N1−C4). When this dihedral angle is close to the "virtual" angle C3−C4−N1 (50−60°), then the approximation is almost parallel. Taking into account the most stable conformation, *s-trans*, the reasons given before for explaining the stereochemistry can also provide a rationalization of the deviations observed in this parameter. In the reaction of **1** with **3**, to give the 6-derivative, the repulsion between the lone-pair electrons of oxygen and nitrogen either moves the oxygen atom further in the *exo* transition state ($\theta_{3-4-5-6} > 50-60°$) or it tends to avoid the overlap of the two atoms in the *endo* transition state ($\theta_{3-4-5-6} < 50-60°$). In the formation of the 5-derivative, a stabilizing interaction of the π^* orbital of the heterodiene with the lone-pair electrons of the oxygen atom is possible, and in the *endo* transition state, the oxygen atom is placed below the dienic system ($\theta_{3-4-5-6} < 50-60°$; this now means that the functional group in the alkene is moved toward a more *endo* position). For the reaction with methyl acrylate, there is almost no deviation: $55° < \theta_{3-4-5-6} < 61°$ in all of the transition structures considered.

The charge transfer in terms of the residual charge on the dienophile for all the optimized transition structures are shown in Table 7. The values collected are the charges computed by Natural Population Analysis. If we consider the charge transfer from the dienophile to the diene in the transition state, the reactions of 1,2-diaza-1,3-butadiene with ethylene and with methyl vinyl ether are inverse electron-demand [4 + 2]-cycloaddition reactions, as predicted by the FMO model. The more nucleophilic dienophile **3** exhibits a greater charge transfer in the transition states, being always larger in the more stable *s-trans* conformation than in the *s-cis*, with the sole exception of **TS9** which has almost the same charge transfer in both conformations. In the *s-trans* transition structures, the charge transfer is larger for the 6-methoxy regioisomers than for the 5-methoxy derivatives and for the *endo* stereoisomers than for the *exo* ones. The *s-cis* transition structures for this reaction exhibits just the opposite behavior in the charge transfer relationships among them.

The reaction of **1** with methyl acrylate is almost neutral due to the small charge transfer in the transition states, which has opposite signs for the two different regioisomers. This is also in agreement with the FMO model for this reaction as noted before in the fact that

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(25) (a) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1992; p 21. (b) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1−S19.

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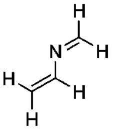
Table 8. B3LYP/6-31G(d) Zero-point Corrected Energy Barriers in kcal/mol for the Reaction of Azabutadienes with Ethylene Compared to the Reaction of 1,3-Butadiene and Ethylene

	$\Delta E_0^{\ddagger}$	reference
1,3-butadiene	+24.8	10
1-aza-1,3-butadiene	+25.1	12
2-aza-1,3-butadiene	+21.7	this work
1,2-diaza-1,3-butadiene	+18.8	this work

none of the two orbital interactions can be neglected. In this case, the charge transfers are so small that there is no practical distinction among the different conformations of the dienophile or the different stereoisomeric transition states.

Compared Reactivity of 1,3-Butadiene and 1-Aza-, 2-Aza-, and 1,2-Diaza-1,3-butadienes toward Ethylene. To compare the results from our study with the previous DFT studies,[8−10] we have reoptimized the structures of **14** and the transition state of its reaction with ethylene (**TS15**) at the B3LYP/6-31G(d) level of theory. The zero-point corrected energy barriers for the corresponding reactions are shown in Table 8. To sum up, the 1,2-diaza systems are the most reactive heterodienes in [4 + 2]-cycloaddition reactions toward ethylene. The effect of the insertion of nitrogen atoms in the 1,3-butadiene system is almost irrelevant if the nitrogen atom is located at position 1; it increases the reactivity at position 2 and a further and significant increment is observed with the 1,2-diaza derivative.



14

TS15

Conclusions

We have performed the first high level computational study of the [4 + 2]-cycloadditions of 1,2-diaza-1,3-butadiene with alkenes, ranging from the electron-releasing methyl vinyl ether to the electron-deficient methyl acrylate. The present study reveals that this heterodiene exhibits a greater reactivity than all-carbon and monoaza-1,3-butadienes. Likewise, this 1,2-diaza derivative shows an enhanced reactivity toward methyl acrylate with respect to methyl vinyl ether, although higher levels of regio- and stereocontrol are attained with the latter. Overall, these theoretical results fully agree with the experimental results. On the basis of the FMO theory as well as of the charge transfer from the alkene to the heterodiene in the transition structures, the Diels−Alder cycloadditions with ethylene and methyl vinyl ether can be regarded as inverse electron-demand processes, while a nearly electronically neutral cycloaddition occurs with methyl acrylate. In addition, it is hoped that these results with simple azadienes can also be extended to chiral derivatives in order to understand the factors controlling facial selection, thereby leading to the design of new dienes.

Acknowledgment. Financial support from the Dirección de Investigación Científica y Técnica (Project No. PB98-0997) and the Junta de Extremadura-Fondo Social Europeo (Projects IPR98-A064 and IPR99-C032) is gratefully acknowledged.

Supporting Information Available: Cartesian Coordinates of all the structures with their computed total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000907F