

## Substituent Effects in the Hetero-Diels–Alder Reaction of Thiocarbonyl Compounds with Butadiene

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Structural, kinetic, and thermodynamic parameters for the Diels–Alder reactions of butadiene with different thiocarbonyl compounds have been computed with the 6-31G(d) basis set using Hartree–Fock (HF), post HF (MP2), and a density functional (DF) methods. In the last case, a recent hybrid approach (B3LYP) has been selected, which incorporates gradient corrections and some HF exchange. The general trends provided by the three methods are similar, but some test computations by the more refined MP4 approach indicate that only the B3LYP approach provides reliable absolute values for the activation barriers. Our results show that reactivity is enhanced for electron-deficient thioaldehydes and reduced in electron-rich thioaldehydes. The reactivity order should be driven by the strength of the  $\pi$  C=S bond which is broken during the reaction. Since the singlet–triplet gap  $\Delta E_{ST}$  in the dienophile is closely related to this quantity, it is a very good reactivity index. This is particularly significant since  $\Delta E_{ST}$  values obtained at the B3LYP level are both reliable and inexpensive. From a more practical point of view, both complete computations and  $\Delta E_{ST}$  gaps suggest that substitution of aminic hydrogens in thioamides by acceptor groups provides effective reagents even in the absence of Lewis acid catalysts.

### 1. Introduction

The mechanism of the Diels–Alder (DA) reaction has attracted interest and stimulated debate since its discovery.<sup>1–3</sup> Both experimental data and quantum-mechanical calculations indicate that the reaction occurs through a concerted mechanism, although, in some cases, stepwise mechanisms involving diradical intermediates are only slightly less favorable.<sup>4–6</sup> Furthermore the effect of different substrates and substituents has been analyzed in some detail for regular<sup>6–8</sup> and hetero-Diels–Alder reactions involving nitrogen<sup>9–12</sup> and oxygen<sup>9,13,14</sup> containing dienes and dienophiles. Reactions between alcadienes and thiocarbonyl dienophiles have recently

attracted considerable experimental interest, but are still poorly characterized by a theoretical point of view.<sup>8a,14,15</sup> As a matter of fact some of the 6-membered heterocycles obtained in this way<sup>9,16</sup> are useful intermediates for the synthesis of various other compounds, including 5-<sup>17</sup> and 3-<sup>18</sup>membered carbocycles as well as thiaanalogs of natural products.<sup>19</sup> Thioketones,<sup>20</sup> thiophosgene,<sup>21</sup> thioesters,<sup>22</sup> and thioacetates<sup>23</sup> have been used as dienophiles. However, better yields were generally obtained with electron-poor derivatives, such as hexafluoropropanethione,<sup>24</sup> diethyl trifluoroethanedithioate,<sup>24</sup> and cyano-substituted<sup>25</sup> compounds. The recent development of convenient methods to generate thioaldehydes *in situ* has allowed the study of the cycloaddition of these reactive thiocarbonyl compounds with dienes.<sup>26</sup> It has been found that electron-deficient thioaldehydes such as thioformyl cyanide and thioacetates are excellent dienophiles.<sup>14</sup> The only theoretical analysis of substituent effects on the

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reactivity of thiocarbonyl dienophiles relies on a perturbative analysis based on frontier molecular orbitals (FMO).<sup>14</sup> As a consequence, a first aim of the present paper is to perform a more systematic and accurate study of this problem through the localization of transition states for some model thiocarbonyls (H<sub>3</sub>CCHS, H<sub>2</sub>NCHS, NCCHS) to butadiene.

From another point of view, even though *N,N*-dimethylthioformamide has been reported to undergo reverse electron demand Diels–Alder reaction with tetrazines,<sup>27</sup> thioamides generally make poor dienophiles.<sup>28</sup> However, we have recently described the [4 + 2] cycloaddition of certain *N*-acylthioformamides with alcaadienes in the presence of a Lewis acid catalyst.<sup>29</sup> The resulting nitrogen-substituted 2*H*-dihydrothiopyrans are expected to be convenient precursors for various nitrogen heterocycles and sugar analogues. However, the synthetic scope of this method, especially the choice of the substituent on the alcaadiene, remains limited by the need to use 1 equiv of a strong Lewis acid such as TiCl<sub>4</sub> at temperatures ranging between –20 and 20 °C. Having in mind the use of elaborated dienes, we are looking for thioformamides which would undergo [4π + 2π] cycloadditions at room temperature or below and without the need of using Lewis acids. Therefore, our second purpose in this paper is to present a systematic theoretical protocol toward the selection of the right thioformamides. Together with its intrinsic interest, this protocol should be readily generalizable to other significant synthetic problems. To this end we need to select and validate a reliable quantum-chemical approach, which is also routinely applicable to relatively large systems. Methods rooted on the density functional (DFT) theory are particularly attractive in this connection since they are able to recover a significant part of the correlation energy with essentially the same resources as Hartree–Fock (HF) computations.<sup>30</sup> Particularly good results have been recently obtained for a number of physicochemical properties by the so-called self-consistent hybrid (SCH) or adiabatic connection (AC) models,<sup>31–34</sup> which include some HF exchange to capture the characteristics of systems with low electron–electron coupling, poorly described by current density functionals.<sup>35</sup> Preliminary applications of a particular variant of these approaches (usually referred to as B3LYP) to prototype Diels–Alder reactions gave very encouraging results.<sup>15</sup> Here we will systematically compare B3LYP results to HF ones and to those obtained by the cheapest conventional method including some correlation energy, namely the second-order Moller–Plesset perturbative approach (MP2).<sup>36</sup>

A third aim of this study is to apply recent energy partitioning techniques to the analysis of general trends

in the kinetic and thermodynamic parameters obtained from complete computations. Effective independent particle methods (like all the DF variants based on the Kohn–Sham (KS) approach including SCH methods) are particularly attractive in this connection, since they allow the straightforward extension of techniques developed for the HF methods to models including correlation energy.

## 2. Computational Details

All the electronic computations have been performed with the help of the GAUSSIAN/94 package<sup>37</sup> using the standard 6-31G(d) basis set.<sup>38</sup> Starting from HF wave functions, correlation energy has been computed perturbatively up to the second order by the MP2 approach.<sup>36</sup> On the other hand the expression used for the exchange–correlation energy ( $E_{XC}$ ) in SCH models is rooted into the adiabatic connection formula,<sup>39</sup> and can be represented as<sup>35</sup>

$$E_{XC} = E_{XC}^{LSD} + a_{HF}(E_X^{HF} - E_X^{LSD}) + a_x \Delta E_x + a_c \Delta E_c \quad (1)$$

where  $E_{XC}^{LSD}$  is the exchange–correlation energy of a homogeneous electron gas,<sup>40,41</sup>  $E_X^{HF}$  is the Hartree–Fock exchange, and the  $\Delta E$ s are gradient corrections to exchange and correlation. We have used the so-called B3LYP variant which employs the Becke gradient correction to exchange,<sup>42</sup> the Lee–Yang–Parr correlation functional,<sup>43</sup> the approximation

$$\Delta E_c = E_c^{LYP} - E_c^{LSD} \quad (2)$$

and the semiempirical coefficients  $a_{HF} = 0.2$ ,  $a_x = 0.72$ , and  $a_c = 0.81$ .<sup>35</sup>

On the basis of previous experience and of some tests with large grids, the standard fine grid in Gaussian 94 has been selected for all DF calculations. This grid was produced from a basic grid having 75 radial shells and 302 angular points per radial shell for each atom and by reducing the number of angular points for different ranges of radial shells, leaving about 7000 points per atom while retaining an accuracy similar to the original (75,302) grid.

A concerted, but not necessarily synchronous, reaction mechanism was presumed in any case.

Next minima and transition structures (TS) have been located by quasi-Newton methods at the HF, MP2, and B3LYP levels. HF and B3LYP harmonic frequencies have also been computed using analytical second derivatives. Furthermore the whole intrinsic reaction coordinate (IRC) has been computed in some cases in order to confirm that endo transition states always lead to axial

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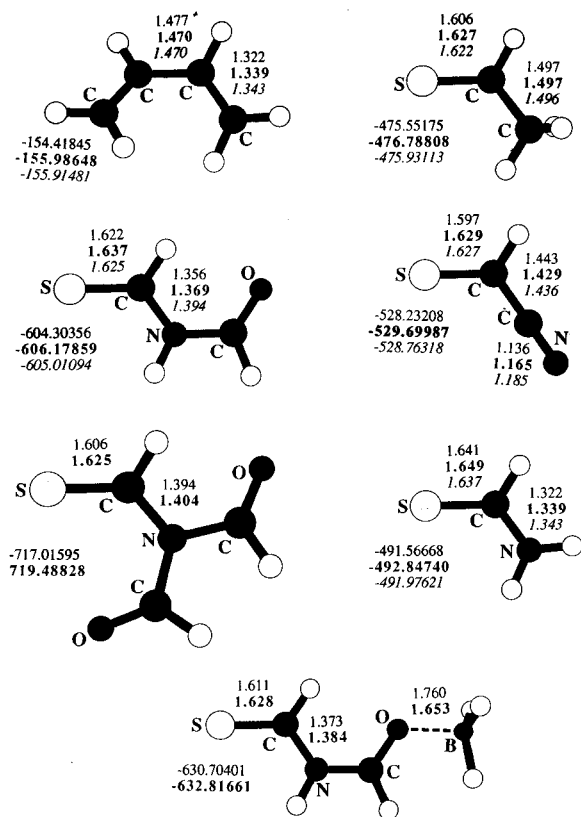
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**Figure 1.** Electronic energies (au) and principal bond lengths (Å) of the thiocarbonyls considered in the present study.

cycloadducts, whereas exo transition states leads to equatorial cycloadducts.

The trends of activation energies have been investigated by different tools, including the standard frontier molecular orbital (FMO) perturbative approach,<sup>44,45</sup> the state correlation diagrams (SCD),<sup>46,47</sup> and the natural population analysis (NPA),<sup>48</sup> based on the natural bond orbital (NBO)<sup>49</sup> approach.

### 3. Results and Discussion

**a. Qualitative Trends.** Let us start by discussing substituent effects on the geometry and electronic structure of the thiocarbonyl group with special reference to thioformamide and its derivatives.

The total energies and main geometrical parameters of all the XCHS compounds considered in the present study are shown in Figure 1. Taking as a reference thioformaldehyde ( $\epsilon_{\text{HOMO}} = -11.4$  eV and  $\epsilon_{\text{LUMO}} = 1.54$  eV at the HF/6-31G(d) level) the  $\pi$ -acceptor CN substituent stabilizes both the HOMO ( $\epsilon = -11.75$  eV) and, to a larger extent, the LUMO ( $\epsilon = -0.10$  eV), whereas the electron-donating  $\text{NH}_2$  group has just the opposite effect ( $\epsilon_{\text{HOMO}} = -9.18$  eV,  $\epsilon_{\text{LUMO}} = 3.13$  eV). In any case,

addition of thiocarbonyls to butadiene is LUMO–dienophile-controlled with normal electron demand.

Our computations indicate that thioformamide ( $\text{X} = \text{H}_2\text{N}$ ) has a planar equilibrium structure. This is at variance from vinylamine whose planar structure corresponds to the transition state for inversion of the  $\text{NH}_2$  moiety according to both experimental<sup>50</sup> and quantum-mechanical<sup>51</sup> studies. The lengthening of the  $\text{C}=\text{S}$  bond with respect to thioformaldehyde [1.597 Å (HF), 1.618 Å (B3LYP), 1.614 Å (MP2)] and the shortening of the  $\text{C}-\text{N}$  bond with respect to vinylamine [1.393 Å (HF), 1.400 Å (MP2)]<sup>51a</sup> suggest the presence of a strong stabilizing interaction between the nitrogen lone pair ( $n_{\text{N}}$ ) and the antibonding  $\pi$  orbital of the CS moiety ( $\pi_{\text{CS}}^*$ ), which could stabilize the planar structure. The  $n_{\text{N}} \rightarrow \pi_{\text{CS}}^*$  interaction has a double effect on the reactivity of thioformamide as a dienophile: (i) the  $\text{C}=\text{S}$  bond becomes more electron rich and hence less reactive; (ii) this stabilizing effect is no longer operative in the cycloaddition product with the consequent reduction of the exothermicity of the reaction.

On these grounds we think that reduction of the  $n_{\text{N}} \rightarrow \pi_{\text{CS}}^*$  interaction would lead to better dienophiles. This can be achieved by replacing the H atoms in the amino group by  $\pi$ -acceptor substituents. In this study we have replaced one or both the H atoms by formyl (CHO) groups, and we have also considered the complex of the monosubstituted compound with a model Lewis acid ( $\text{BH}_3$ , see Figure 1). The cycloaddition of this last compound with butadiene represents our standard, since it is now known that in the presence of Lewis acids, thioformamides become quite effective dienophiles in hetero-Diels–Alder reactions.<sup>29</sup>

The delocalization energy ( $\Delta E_{n \rightarrow \pi^*}$ ) issuing from the  $n_{\text{N}} \rightarrow \pi_{\text{CS}}^*$  interaction can be computed with the help of the NBO analysis.<sup>49</sup> All the quantum-mechanical methods indicate a strong interaction between the  $n_{\text{N}}$  and  $\pi_{\text{CS}}^*$  orbitals in thioformamide ( $\Delta E_{n \rightarrow \pi^*} = 67.9$  and  $-82.0$  kcal/mol by HF and B3LYP methods, respectively) and a regular reduction of this interaction upon successive replacement of the hydrogen atoms by formyl groups (in kcal/mol,  $\Delta E_{n \rightarrow \pi^*} = -41.3$  (HF),  $-47.9$  (B3LYP) for  $(\text{OHC})\text{HN}-\text{CHS}$ ;  $-37.9$  (HF),  $-31.1$  (B3LYP) for  $(\text{OHC})_2\text{N}-\text{CHS}$ ). Inspection of Figure 1 shows a parallel lengthening of the  $\text{C}=\text{S}$  and shortening of the  $\text{CN}$  bond. Note that complexation of  $(\text{OHC})\text{HNCHS}$  by  $\text{BH}_3$  is less effective in reducing this interaction than substitution of the second aminic hydrogen by a formyl group. If this analysis is correct we should expect a lower exothermicity for the cycloaddition of the  $\text{BH}_3$  complex than for the diformyl compound.

State correlation diagrams recently proposed by Shaik *et al.*<sup>46</sup> provide a very effective tool in the study of reactivity. The correlation diagram for the cycloaddition reaction is shown in Figure 2.<sup>47b</sup> For a given diene, the height of the activation barrier is essentially determined by the singlet–triplet energy gap ( $\Delta E_{\text{ST}}$ ) of the dienophile. Our CIS and B3LYP computations performed with the 6-31+G(d,p) basis set (see Table 1) indicate that  $\Delta E_{\text{ST}}$  is lower in NCCHS than in thioformaldehyde (2.57 and 1.78 eV at the CIS and B3LYP levels, respectively) and that the highest value is obtained for thioformamide. Furthermore,  $\Delta E_{\text{ST}}$  is very similar for  $\text{H}_3\text{CCHS}$ ,  $(\text{OCH})_2\text{NCHS}$ ,

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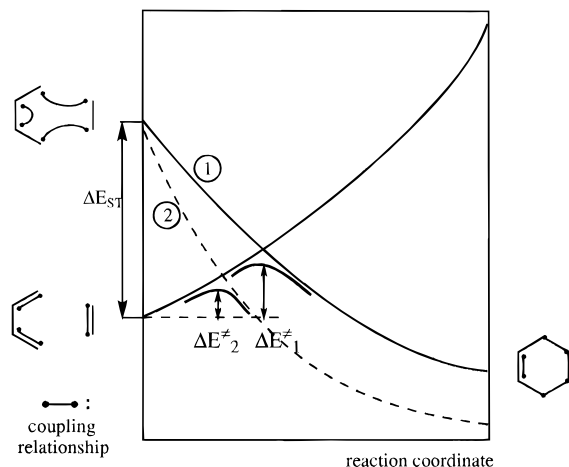
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**Table 1. Principal Geometrical Parameters (Å), Pauling Bond Orders, Electronic and Zero Point Energy Differences with Respect to Reactants (kcal/mol) for Transition-State Structures and Products in the Cycloadditions of Substituted Thiocarbonyls XCHS to Butadiene Gauche<sup>a</sup>**

	X = H <sub>3</sub> C endo (axial)						X = H <sub>3</sub> C exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.684	1.825	1.685	1.849	1.661	1.824	1.682	1.823	1.682	1.846	1.663	1.820
3-5	1.380	1.509	1.380	1.510	1.372	1.505	1.378	1.528	1.378	1.532	1.373	1.504
4-6	1.364	1.505	1.372	1.505	1.373	1.501	1.365	1.508	1.376	1.508	1.377	1.502
5-6	1.401	1.320	1.416	1.336	1.421	1.342	1.400	1.320	1.414	1.336	1.419	1.341
<b>1-3</b>	2.106	1.532	2.259	1.537	2.349	1.528	2.131	1.506	2.300	1.505	2.399	1.524
<b>2-4</b>	2.606	1.816	2.625	1.837	2.539	1.815	2.577	1.815	2.551	1.836	2.463	1.815
1-7	1.514	1.530	1.513	1.533	1.509	1.526	1.518	1.526	1.514	1.529	1.508	1.523
$\phi$	-11.0		-9.7		-7.2		-0.6		6.7		10.6	
np1-3	0.148		0.090		0.065		0.125		0.071		0.054	
np2-4	0.072		0.072		0.090		0.079		0.092		0.115	
$\Delta E$	28.8	-36.4	9.4	-36.1	4.6	-46.3	29.9	-37.7	9.8	-37.4	4.7	-47.0
	X = NC endo (axial)						X = NC exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.666	1.820	1.682	1.850	1.666	1.824	1.664	1.824	1.679	1.854	1.663	1.827
3-5	1.375	1.508	1.375	1.508	1.370	1.503	1.372	1.507	1.373	1.508	1.367	1.503
4-6	1.369	1.505	1.382	1.504	1.380	1.501	1.375	1.506	1.393	1.505	1.377	1.501
5-6	1.400	1.319	1.414	1.336	1.424	1.342	1.398	1.320	1.413	1.336	1.425	1.342
<b>1-3</b>	2.214	1.535	2.429	1.542	2.469	1.531	2.281	1.533	2.534	1.540	2.551	1.531
<b>2-4</b>	2.510	1.816	2.431	1.836	2.495	1.815	2.427	1.815	2.319	1.836	2.437	1.815
1-7	1.449	1.475	1.431	1.467	1.435	1.466	1.446	1.470	1.426	1.462	1.432	1.462
$\phi$	-4.7		1.7		1.0		2.9		15.3		13.8	
np1-3	0.104		0.052		0.044		0.083		0.036		0.033	
np2-4	0.099		0.138		0.104		0.130		0.200		0.126	
$\Delta E$	20.1	-45.0	1.6	-41.6	-3.3	-51.3	20.6	-44.4	0.9	-41.0	-3.6	-49.5
	X = H <sub>2</sub> N endo (axial)						X = H <sub>2</sub> N exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.704	1.818	1.715	1.845	1.679	1.818	1.699	1.822	1.704	1.852	1.673	1.821
3-5	1.386	1.508	1.393	1.508	1.383	1.503	1.386	1.509	1.391	1.509	1.381	1.504
4-6	1.370	1.504	1.391	1.503	1.391	1.499	1.375	1.507	1.395	1.506	1.394	1.503
5-6	1.394	1.381	1.400	1.335	1.406	1.340	1.392	1.320	1.400	1.336	1.407	1.342
<b>1-3</b>	2.061	1.529	2.192	1.534	2.244	1.525	2.088	1.523	2.230	1.526	2.320	1.519
<b>2-4</b>	2.549	1.816	2.411	1.838	2.378	1.816	2.492	1.815	2.359	1.836	2.280	1.816
1-7	1.399	1.451	1.387	1.461	1.398	1.461	1.404	1.447	1.399	1.456	1.408	1.457
$\phi$	-15.5		-18.6		-18.5		4.7		14.8		20.1	
np1-3	0.170		0.112		0.091		0.152		0.096		0.069	
np2-4	0.087		0.148		0.154		0.105		0.175		0.213	
$\Delta E$	43.4	-18.5	22.7	-16.7	17.4	-29.0	44.8	-18.0	23.2	-16.4	16.7	-27.8
$\Delta ZPE^b$	1.8	5.1	1.7	4.6			1.8	4.9	1.7	4.5		

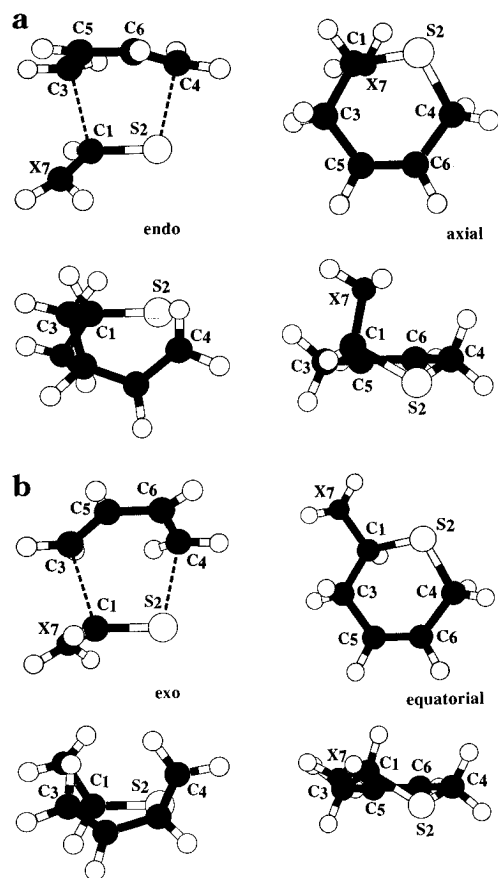
<sup>a</sup> See Figure 3 for the atom numbering and main text for further details. <sup>b</sup> The ZPEs (in kcal/mol) of butadiene and H<sub>2</sub>N-CHS are 57.4 (HF), 53.5 (B3LYP), and 29.8 (HF), 27.5 (B3LYP), respectively.

**Figure 2.** Schematic SCD diagram for Diels-Alder reactions.

and BH<sub>3</sub>-(OHC)HNCHS. As a consequence, if this model is reliable, these compounds should have a similar reactivity with respect to butadiene.

The Diels-Alder reaction essentially replaces a C=S  $\pi$  bond by a CS and a CC  $\sigma$  bond. If the strength of the  $\sigma$  bonds is nearly the same in a series of related compounds, the kinetics and thermodynamics are determined by the strength of the  $\pi$  bonds which are broken. Since  $\Delta E_{ST}$  provides a measure of the strength of the CS  $\pi$  bond in the dienophile, the simplest version of the SCD model has a significant previsionsal power. This behavior is not shared by the FMO model since the LUMO energy in the dienophile is not directly related to the  $\pi$ -bond strength. The complete computations of the following sections will allow an unbiased judgement of the respective merits of these qualitative models.

**b. Cycloaddition of Model Thiocarbonyls XCHS to Butadiene (X = H<sub>3</sub>C, H<sub>2</sub>N, NC).** The main geometrical parameters for TS's and products characterizing the cycloadditions of typical thiocarbonyls with butadiene are shown in Table 1. Since the reactions are not perfectly synchronous, diradical structures could in principle be involved. This has been ruled out by testing the wave functions of all TS's for UHF instability.



**Figure 3.** Schematic drawing of transition states and cyclo-products issuing from different attacks of thioformamide to butadiene: (a) endo transition state and corresponding axial product; and (b) exo transition state and corresponding equatorial product.

As a general trend the transition structures have a “pseudo-boat” conformation, whereas the products prefer a “pseudo-chair” structure (see Figure 3).

Since substituents have been introduced only on  $C_1$ , we expect significant effects especially on the  $C_1$ – $C_3$  bond length. All the computational methods indicate a lengthening of this distance in the order  $NC > H_3C > H_2N$  with a parallel decrease of Pauling bond order  $n_p$ .<sup>52</sup> This result is in agreement with experimental evidences,<sup>26b</sup> indicating a more advanced  $C_1$ – $C_3$  bonding in the TS when X is an electron-donor substituent. However it is quite surprising that according to our computations, a significant shortening of the  $C_4$ – $S_2$  distance accompanies the lengthening of the  $C_1$ – $C_3$  distance. Furthermore the lowest deformation of the XCHS dienophile is obtained for  $X = NC$  and the largest deformation for  $X = H_2N$ . So, for instance, the lengthening of the  $C_1$ – $S_2$  bond at the TS is 0.053, 0.058, and 0.066 Å for  $X = NC$ ,  $H_3C$ , and  $H_2N$ , respectively. This trend is in agreement with the computed deformation energies (vide infra).

Another point of interest is the difference between the exo and endo transition structures for a given substituent. The essential difference concerns the relative orientation of the two fragments, which can be quantified by the value of the dihedral angle  $\phi \equiv C_1S_2C_4C_3$  (see Figure 3). The endo TS's are characterized by a very small and negative value of  $\phi$ , whereas exo TS's are characterized by larger positive values of  $\phi$ . Note that in the former case more negative values of  $\phi$  correspond

to larger distances between the X substituent and the  $HC_3H$  moiety of butadiene, whereas in the latter case the same effect is obtained by increasing the positive value of  $\phi$ . The largest value of  $\Delta\phi = \phi(\text{exo}) - \phi(\text{endo})$  is obtained when  $X = NH_2$ , that is for the TS characterized by the shortest  $C_1$ – $C_3$  distance. This result suggests that “steric constraints” can be particularly significant for  $X = H_2N$ . Furthermore B3LYP and MP2 computations lead to values of  $\Delta\phi$  significantly larger than those provided by HF computations. It is also noteworthy that the formation of one of the  $\sigma$  bonds ( $C_1$ – $C_3$ ) is less advanced in the exo TS's, whereas the opposite is true for the  $C_4$ – $S_2$  bond.

Activation ( $\Delta E^\ddagger$ ) and reaction ( $\Delta E_r$ ) energies are given in Table 1. Concerning reaction energies  $\Delta E_r$ , HF and B3LYP computations provide comparable results, whereas MP2 computations lead to higher exothermicities. This trend might be related to the underestimation of activation energies by the MP2 approach. In particular negative values of  $\Delta E^\ddagger$  are obtained for  $X = NC$  (see Table 1). As a matter of fact we have been able to characterize for both endo and exo additions stable intermediates characterized by  $C_1$ – $C_3$  and  $C_2$ – $S_4$  distances of 2.971 and 3.013 Å (endo) or 3.001 and 2.961 Å (exo) which are more stable than the reactants by 4.9 (endo) and 5.0 (exo) kcal/mol.

More reliable results could be obtained by MP4 computations at MP2 geometries, but the computational times of this procedure become prohibitive for the largest substituents considered in the next section. The results obtained for  $X = H_3C$  (11.3 kcal/mol for the exo addition) and  $X = H_2N$  (21.5 kcal/mol again for the exo addition) are in fair quantitative agreement with B3LYP results and, what is even more important, confirm the trends obtained by all the other quantum-mechanical approaches. Furthermore B3LYP geometries lead to MP4 activation energies (e.g. 21.7 kcal/mol for the exo addition with  $X = H_2N$ ) essentially indistinguishable from those obtained using MP2 geometries. The reported structures correspond to true first-order saddle points (computation of harmonic frequencies give one and only one imaginary frequency). One of the objectives of the present study is the establishment of a reactivity scale for hetero-Diels–Alder reactions involving substituted thiocarbonyls. In this connection it is reassuring that the three quantum-mechanical methods provide the same order ( $NC > H > H_3C > H_2N$ ), which is, furthermore, in agreement with the available experimental data. Note that the variations are quite limited for H,  $H_3C$ , and NC, whereas a very large increase of the activation energy is obtained for thioformamide.

Concerning the stereoselectivity of the reaction, the indications provided by the different methods are more ambiguous. Regardless of the substituent X, an endo attack is favored at the HF level. The difference between endo and exo TS's is much lower at the B3LYP and MP2 levels. We have already pointed out that a different orientation between the interacting fragments is obtained for endo and exo TS's, the origin of this difference being probably related to the steric repulsion between the X substituent and the  $HC_3H$  moiety of butadiene. Taking also into account that the difference  $\Delta E_{\text{endo}}^\ddagger - \Delta E_{\text{exo}}^\ddagger$  decreases or becomes even negative increasing the  $C_1$ – $C_3$  distance at the TS, one can suggest that the steric repulsion is more important in the endo approach. In any case, the only general conclusion issuing from our results is that hetero Diels–Alder reactions of thiocarbonyls with

(52) Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542.

**Table 2. Principal Geometrical Parameters (Å), Pauling Bond Orders, Electronic and Zero Point Energy Differences with Respect to Reactants (kcal/mol) for Transition-State Structures and Products in the Cycloadditions of Substituted Thioamides XCHS to Butadiene Gauche<sup>a</sup>**

	X = (OHC)HN endo (axial)						X = (OHC)HN exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.691	1.831	1.693	1.867	1.665	1.837	1.691	1.830	1.695	1.860	1.666	1.830
3-5	1.384	1.511	1.387	1.512	1.379	1.506	1.385	1.508	1.387	1.508	1.378	1.504
4-6	1.367	1.506	1.381	1.505	1.380	1.502	1.373	1.505	1.387	1.503	1.388	1.501
5-6	1.397	1.321	1.408	1.337	1.413	1.343	1.393	1.320	1.405	1.335	1.411	1.341
<b>1-3</b>	2.068	1.528	2.197	1.533	2.281	1.524	2.109	1.525	2.232	1.530	2.340	1.521
<b>2-4</b>	2.589	1.816	2.522	1.836	2.460	1.815	2.515	1.816	2.446	1.838	2.343	1.817
1-7	1.406	1.440	1.407	1.443	1.407	1.443	1.402	1.439	1.406	1.444	1.406	1.441
$\phi$	-13.6		-12.3				3.5		8.7			
np1-3	0.165		0.109		0.080		0.143		0.096		0.065	
np2-4	0.076		0.102		0.116		0.097		0.131		0.173	
$\Delta E$	34.1	-25.2	13.6	-24.6	7.3	-36.0	38.8	-26.4	16.6	-25.6	10.3	-36.1
$\Delta ZPE$	2.0	4.7	1.8	4.2			1.6	4.7	1.5	4.3		

	X = (OHC) <sub>2</sub> N endo (axial)						X = (OHC) <sub>2</sub> N exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.679	1.816	1.675	1.835			1.667	1.826	1.667	1.855		
3-5	1.381	1.506	1.381	1.506			1.377	1.509	1.376	1.509		
4-6	1.359	1.500	1.372	1.499			1.368	1.507	1.381	1.506		
5-6	1.403	1.316	1.415	1.333			1.401	1.320	1.415	1.336		
<b>1-3</b>	2.081	1.543	2.252	1.548			2.167	1.525	2.366	1.529		
<b>2-4</b>	2.658	1.816	2.597	1.840			2.549	1.816	2.488	1.837		
1-7	1.439	1.473	1.441	1.483			1.442	1.463	1.443	1.467		
$\phi$	-8.6		-8.8				7.8		12.0			
np1-3	0.167		0.096				0.118		0.087			
np2-4	0.060		0.080				0.061		0.114			
$\Delta E$	28.7	-36.4	9.0	-35.3			27.7	-38.2	6.9	-36.6		
$\Delta ZPE$	2.3	5.5	2.0	4.9			2.3	5.4	2.1	4.9		

	X = H <sub>3</sub> B-(OHC)HN endo (axial)						X = H <sub>3</sub> B-(OHC)HN exo (equatorial)					
	HF		B3LYP		MP2		HF		B3LYP		MP2	
	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.	TS	prod.
1-2	1.681	1.822	1.682	1.852			1.680	1.824	1.683	1.853		
3-5	1.383	1.510	1.385	1.511			1.383	1.508	1.384	1.508		
4-6	1.364	1.506	1.379	1.505			1.369	1.504	1.384	1.503		
5-6	1.400	1.321	1.410	1.337			1.396	1.319	1.408	1.335		
<b>1-3</b>	2.083	1.527	2.239	1.533			2.115	1.525	2.264	1.530		
<b>2-4</b>	2.631	1.817	2.545	1.839			2.565	1.817	2.472	1.838		
1-7	1.421	1.452	1.421	1.457			1.417	1.450	1.419	1.455		
$\phi$	-12.6		-11.4				2.8		8.5			
np1-3	0.157		0.095				0.140		0.095			
np2-4	0.066		0.086				0.082		0.121			
$\Delta E$	29.2	-31.4	9.0	-30.3			33.8	-32.0	12.0	-30.7		
$\Delta ZPE^b$	2.3	5.1	1.9	4.3			1.9	5.2	1.5	4.5		

<sup>a</sup> See Figure 3 for the atom numbering and main text for further details. <sup>b</sup> ZPEs of reactants, in kcal/mol: 39.1 (HF), 36.9 (B3LYP) for (OHC)HN-CHS; 43.2 (HF), 39.5 (B3LYP) for (OHC)<sub>2</sub>N-CHS and 57.8 (HF), 54.4 (B3LYP) for H<sub>3</sub>B-(OHC)HN-CHS.

unsubstituted dienes should proceed with small or even vanishing stereoselectivities. These results cannot be directly compared to experimental evidences (preference for an endo attack for whatever substituent X)<sup>14</sup> since the experimental determination of stereoselective effects requires the use of substituted dienes.

A last noteworthy point is that for a given substituent, there is no relationship between the relative stabilities of axial and equatorial cycloadducts and the relative stabilities of endo and exo TS's. So considering, for instance, the B3LYP results X = H<sub>2</sub>N stabilizes the axial cycloadduct and the endo TS; X = H<sub>3</sub>C stabilizes the equatorial cycloadducts and the endo TS and X = NC stabilizes the axial cycloadduct and the exo TS.

**c. Thioformamides XCHS + Butadiene (X = (OHC)HN, (OHC)<sub>2</sub>N, and H<sub>3</sub>B-(OHC)HN).** The principal geometric parameters for the TS's and cycloaddition products are collected in Table 2. Note that only the first member of the series (X = (OHC)HN) has been studied also at the MP2 level. As is well evidenced by the regular

lengthening of C<sub>1</sub>-C<sub>3</sub> and C<sub>2</sub>-S<sub>4</sub> distances, progressive substitution of aminic hydrogen atoms by formyl groups leads to progressively looser TS's. This tendency is observed both at the HF and B3LYP levels, and also the MP2 results for the first member of the series indicate the same trend. The analysis of the other geometrical parameters shows that the H/CHO substitution leads to comparatively negligible intrafragment deformations. The values of the  $\phi$  dihedral angles (Table 2) point out again the different relative orientations of diene and dienophile in the endo and exo TS's.

The computations also show that complexation of the formyl group by BH<sub>3</sub> leads to an increase of the C<sub>1</sub>-C<sub>3</sub> and C<sub>4</sub>-S<sub>2</sub> distances (earlier TS) for the endo addition. This effect is exactly the same as that issuing from replacement of an aminic hydrogen by a formyl group. Less clear-cut effects are obtained at the HF and B3LYP levels for the complexation by BH<sub>3</sub> of the endo TS. For instance, only the C<sub>4</sub>-S<sub>2</sub> distance is modified at the B3LYP level. In any case the effects induced by BH<sub>3</sub> are

**Table 3. Kinetic and Thermodynamic Quantities at 298 K (in kcal/mol, Except Entropies in cal/mol K) for Addition of Different Thioamides to Butadiene According to Different Methods Using the 6-31G(d) Basis Set**

parameters	substituent	HF		B3LYP	
		endo (ax)	exo (eq)	endo (ax)	exo (eq)
$\Delta E^\ddagger + \Delta ZPE$		45.0	46.4	24.4	24.9
$\Delta H^\ddagger$		45.2	46.6	24.6	25.1
$\Delta S^\ddagger$		-46.9	-45.8	-46.1	-46.1
$\Delta G^\ddagger$		58.7	60.0	38.3	38.8
$\Delta E_r^\ddagger + \Delta ZPE$	H <sub>2</sub> N	-13.4	-13.1	-12.1	-12.9
$\Delta H_r^\ddagger$		-15.0	-14.6	-13.0	-12.8
$\Delta S_r^\ddagger$		-49.3	-49.8	-49.3	-49.6
$\Delta G_r^\ddagger$		-0.3	0.2	1.7	2.0
$\Delta E^\ddagger + \Delta ZPE$		35.9	40.2	15.4	18.1
$\Delta H^\ddagger$		36.1	40.4	15.7	18.5
$\Delta S^\ddagger$		-46.8	-45.9	-46.1	-45.1
$\Delta G^\ddagger$		49.8	54.1	29.4	31.9
$\Delta E_r^\ddagger + \Delta ZPE$	(OHC)HN	-20.5	-20.4	-21.7	-21.3
$\Delta H_r^\ddagger$		-21.8	-22.9	-21.0	-21.9
$\Delta S_r^\ddagger$		-47.6	-48.4	-47.0	-47.3
$\Delta G_r^\ddagger$		-7.6	-8.5	-7.0	-7.8
$\Delta E^\ddagger + \Delta ZPE$		30.8	29.7	11.0	9.0
$\Delta H^\ddagger$		31.0	30.0	11.4	9.2
$\Delta S^\ddagger$		-48.9	-49.9	-47.8	-48.6
$\Delta G^\ddagger$		45.4	44.6	25.6	23.7
$\Delta E_r^\ddagger + \Delta ZPE$	(OHC) <sub>2</sub> N	-30.9	-33.1	-30.4	-31.7
$\Delta H_r^\ddagger$		-32.4	-34.3	-31.2	-32.4
$\Delta S_r^\ddagger$		-51.6	-51.4	-50.3	-50.1
$\Delta G_r^\ddagger$		-17.0	-19.0	-16.2	-17.5
$\Delta E^\ddagger + \Delta ZPE$		31.2	35.6	10.9	13.5
$\Delta H^\ddagger$		31.5	35.7	11.3	14.0
$\Delta S^\ddagger$		-47.6	-46.8	-46.0	-44.7
$\Delta G^\ddagger$		45.4	49.5	25.0	27.3
$\Delta E_r^\ddagger + \Delta ZPE$	H <sub>3</sub> B-(CHO)HN	-26.3	-26.8	-26.0	-26.2
$\Delta H_r^\ddagger$		-27.7	-28.2	-26.5	-27.6
$\Delta S_r^\ddagger$		-48.3	-49.3	-46.5	-46.5
$\Delta G_r^\ddagger$		-13.3	-13.5	-12.6	-13.7

much less dramatic than those computed for the analogous interaction with acrolein.<sup>53</sup>

Thermodynamic and kinetic characteristics of hetero-Diels–Alder reactions involving substituted thioformamides are collected in Table 3. When X = (OHC)HN the relative values of the activation energies with respect to thioformamide obtained at the MP2 level (-10.1 and -6.4 kcal/mol for the endo and exo additions, respectively) are comparable to those obtained at the HF (-9.3 and -6.6 kcal/mol) and B3LYP (-9.1 and -6.6 kcal/mol) levels. The same behavior is found for the reaction energies, whose variations (in kcal/mol) with respect to thioformamide are -6.0 (endo) and -8.3 (exo) at the MP2 level, -7.9 (endo) and -9.2 (exo) at the B3LYP level and -6.7 (endo) and -8.4 (exo) at the HF level.

In general terms nonpotential energy effects (ZPE, etc.) do not modify the trend provided by the bare electronic energies concerning both activation and reaction energies. It is, anyway, gratifying that the results obtained by scaling HF harmonic frequencies are very similar to those provided by unscaled B3LYP frequencies. This extends to transition states the very good performances of the B3LYP approach previously reported for energy minima.<sup>54–56</sup> The only noteworthy general trend is some compensation between energetic and entropic contributions in determining substituent effects on reaction rates. For instance the most negative  $\Delta S^\ddagger$  corresponds to the

smallest activation energy (X = N(CHO)<sub>2</sub>-exo). In any case entropy variations are very small, so that the trend of reaction rates is determined by energetic effects.

The quantitative study of reactivity confirms our preliminary analysis. We observe, indeed, a significant diminution of  $\Delta E^\ddagger$  when both the aminic hydrogens are replaced by formyl groups. Reaction energies are related to the  $n_N \rightarrow \pi^*$  interaction energies in the dienophiles: the strongest interaction energy (X = H<sub>2</sub>N) is associated to the least exothermic reaction, whereas the weakest interaction energy (X = (OHC)<sub>2</sub>N) corresponds to the most exothermic reaction. It is, in particular, confirmed that (OHC)<sub>2</sub>NCHS is more reactive toward butadiene than our reference system H<sub>3</sub>B-(OHC)HNCHS. We can, therefore, conclude that, unless solvent effects strongly modify matters, thioformamides substituted by  $\pi$ -acceptor groups can effectively react with dienes in the absence of Lewis acids.

Substituted thioformamides give more stereospecific reactions than the substituted thiocarbonyls considered in the preceding section. The TS's issuing from an endo attack of systems with X = (OHC)HN and H<sub>3</sub>B-(OHC)HNCHS (hereafter referred to as **endo1** and **endo2**, respectively) are more stable than the corresponding exo TS's (in the following **exo1** and **exo2**) by ~4.5 kcal/mol at the HF level and by ~3.0 at the B3LYP level. On the other hand the TS issuing from the exo attack when X = (OHC)<sub>2</sub>N (**exo3**) is more stable than the corresponding TS governing endo attack (**endo3**) by ~2.1 kcal/mol at the HF level and by ~2.8 kcal/mol at the B3LYP level. This regioselectivity might be of electrostatic origin taking into account the significant charges born by the hydrogen atoms in the HC<sub>3</sub>H moiety (~0.2 |e<sup>-</sup>|) and the oxygen atom of the formyl moiety (~-0.6 |e<sup>-</sup>|). As a matter of fact the distance between one of the hydrogen atoms in the HC<sub>3</sub>H moiety and the formyl oxygen atom is 2.701 (HF) or 2.691 Å (B3LYP) in **endo1** and 2.677 (HF) or 2.675 Å (B3LYP) for **endo2**, whereas none of these distances is below 3.96 Å in **exo1** and **exo2**. On the other hand both these distances are relatively short in **exo3** (2.380 and 2.516 Å at the HF level or 2.516 and 2.356 Å at the B3LYP level), whereas they are above 3.000 Å in **endo3**. Note that the above H–O distances in **endo1**, **endo2**, and **exo3** are in the range of those reported for typical CH–O hydrogen bonded systems.<sup>57</sup> It is, therefore, reasonable to conclude that these three TS's benefit from some sort of extrastabilization.

Let us now discuss the origin of the above trends with the help of the data reported in Table 4.

For all the transition structures, a natural population analysis shows a net charge transfer (CT)  $\Delta q$  from the diene (D) to the dienophile (d).  $\Delta q$  is always significant and points out the electron acceptor character of all the dienophiles. In particular the lowest charge is transferred in the TS issuing from attack of H<sub>2</sub>NCHS and the largest charge when the dienophile is NCCHS. It is also noteworthy that the presence of BH<sub>3</sub> increases the charge transfer from the diene toward the dienophile. Finally, for a given substituent, a lower charge is transferred in the exo transition state.

NBO interactions of the CT type are associated with the off-diagonal elements of the Hamiltonian matrix that couple the donor ( $\sigma$ ,  $\pi$ , or  $n$ ) orbitals of one fragment (D or d) with the acceptor orbitals ( $\sigma^*$ ,  $\pi^*$ ) of its partner. CT ( $H_D \rightarrow L_d$ ) is obtained by deleting the matrix elements between the two localized  $\pi_{CC}$  NBO's of D and the  $\pi^*_{CX}$

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**Table 4. Energetic Parameters Characterizing Transition Structures for the Diels–Alder Reaction of Model Thiocarbonyls X–CHS with Butadiene (See Text for Details)**

	X = H <sub>3</sub> C						X = NC						X = H <sub>2</sub> N					
	HF		B3LYP		HF		B3LYP		HF		B3LYP		HF		B3LYP			
	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo		
$\Delta q$ (NPA)	0.182	0.175	0.134	0.122	0.252	0.236	0.211	0.182	0.169	0.147	0.057	0.058	0.188	0.209	0.151	0.132	0.209	
CT (H <sub>b</sub> → L <sub>d</sub> )	-56.0	-52.8	-51.3	-51.4	-48.1	-47.9	-48.3	-47.6	-61.5	-52.3	-54.6	-53.0	0.209	-60.9	-50.7	-47.5	-60.9	
CT (H <sub>d</sub> → L <sub>b</sub> )	-24.6	-24.9	-24.1	-23.6	-21.3	-21.5	-20.2	-20.6	-29.2	-26.0	-26.3	-29.1	-26.3	-26.3	-31.6	-34.9	-26.3	
CT (D → d*)	-93.5	-90.7	-78.7	-80.1	-89.6	-88.9	-86.5	-87.8	-100.9	-98.0	-79.5	-85.1	-83.8	-102.1	-96.9	-79.8	-102.1	
CT (d → D*)	-40.1	-39.2	-39.1	-39.7	-35.0	-37.2	-31.7	-36.3	-46.0	-48.5	-47.4	-51.9	-41.7	-42.6	-44.6	-38.2	-42.6	
E <sub>CT</sub>	-119.0	-115.9	-104.9	-106.2	-111.6	-112.4	-105.6	-108.8	-128.5	-127.9	-110.7	-121.1	-98.6	-128.3	-124.4	-104.2	-128.3	
E <sub>def</sub> (D)	18.0	18.6	10.2	10.9	17.0	17.9	10.4	10.9	21.8	23.6	17.9	18.6	14.0	19.6	13.6	15.8	19.6	
E <sub>def</sub> (d)	12.2	12.0	6.8	6.2	8.4	7.5	3.7	2.7	19.8	18.9	11.6	11.3	12.0	15.9	9.3	15.9	16.1	
	X = (OHC)HN						X = (OHC) <sub>2</sub> N						X = H <sub>3</sub> B–(OHC)HN					
	HF		B3LYP		HF		B3LYP		HF		B3LYP		HF		B3LYP		HF	
	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo	exo
$\Delta q$ (NPA)	0.209	0.173	0.151	0.132	0.253	0.209	0.186	0.162	0.252	0.235	0.208	0.188	0.252	0.235	0.208	0.188	0.252	0.235
CT (H <sub>b</sub> → L <sub>d</sub> )	-60.9	-52.5	-50.7	-47.5	-61.7	-48.8	-46.4	-45.5	-60.8	-54.2	-52.0	-51.2	-60.8	-54.2	-52.0	-51.2	-60.8	-54.2
CT (H <sub>d</sub> → L <sub>b</sub> )	-26.3	-30.1	-31.6	-34.9	-21.7	-22.7	-22.2	-20.9	-23.0	-26.0	-26.3	-29.1	-23.0	-26.0	-26.3	-29.1	-23.0	-26.0
CT (D → d*)	-102.1	-96.9	-82.0	-79.8	-101.0	-88.5	-80.7	-95.4	-100.8	-96.8	-83.8	-82.6	-100.8	-96.8	-83.8	-82.6	-100.8	-96.8
CT (d → D*)	-42.6	-44.6	-38.2	-37.0	-38.6	-42.4	-39.9	-50.9	-38.7	-39.6	-41.3	-41.7	-38.7	-39.6	-41.3	-41.7	-38.7	-39.6
E <sub>CT</sub>	-128.3	-124.4	-104.2	-103.1	-125.9	-117.3	-109.3	-118.5	-125.0	-121.6	-100.3	-98.6	-125.0	-121.6	-100.3	-98.6	-125.0	-121.6
E <sub>def</sub> (D)	19.6	22.8	13.6	15.8	17.3	17.9	10.5	10.2	17.8	20.7	14.0	14.0	17.8	20.7	14.0	14.0	17.8	20.7
E <sub>def</sub> (d)	16.1	15.9	9.3	9.1	15.4	13.2	8.4	7.5	15.8	15.9	8.6	8.3	15.8	15.9	8.6	8.3	15.8	15.9

NBO of d, whereas CT (H<sub>d</sub> → L<sub>b</sub>) is obtained by deleting the matrix elements between the  $\pi_{CX}$  NBO of d and the two localized  $\pi^*_{CC}$  NBO's of D. Next CT (D → d\*) is obtained by deleting all the interactions between occupied NBO's of the diene and empty orbitals of the dienophile, whereas CT (d → D\*) corresponds to the opposite deletion.<sup>58</sup> The overall  $E_{CT}$  is obtained when both kinds of interactions between the two partners are deleted. The procedure is not self-consistent, but as long as the particular interactions deleted in the Hamiltonian matrix are not strongly coupled with other interactions, the resulting error in the energy is negligible.<sup>49</sup> The results of this kind of analysis are also collected in Table 4. From a methodological point of view, the CT stabilization energy and the amount of charge transferred are always larger at the HF than at the B3LYP level. However both methods predict the same general trends. As expected, donation of  $\pi$ -electron density from the diene to the dienophile is more important than the corresponding back-donation. These trends are consistent with the variations of  $\Delta q$ . In our opinion the variation of  $\Delta q$  with substituents can be essentially attributed to the variation of the relative weight of the D → d\* and d → D\* contributions. So the lowest  $\Delta q$  (X = H<sub>2</sub>N) is associated to the smallest ratio CT (D → d\*)/CT (d → D\*), whereas this ratio sensibly increases for X = (OHC)<sub>2</sub>N. Also the reduction of  $\Delta q$  computed for the exo TS's seems to have the same origin: for X = (OHC)<sub>2</sub>N where  $\Delta q(\text{endo}) - \Delta q(\text{exo})$  is significant at the HF level the corresponding ratios are 2.616 (endo) and 2.087 (exo), whereas for X = H<sub>2</sub>N, where  $\Delta q(\text{exo}) \approx \Delta q(\text{endo})$  at the B3LYP level, the ratios are 1.677 and 1.640, respectively. However this relationship must be taken with some care since the sum of D → d\* and d → D\* contributions is more negative than  $E_{CT}$ .

It is also noteworthy that  $\pi$  interactions represent in all cases 65–70% of the whole CT stabilization. This nearly constant contribution legitimizes in a sense the FMO analysis. However, there is no correlation between the CT stabilization energy and the activation energies, the magnitude of  $E_{CT}$  being apparently related to the intermolecular distance between the two partners in the TS. In this sense tight transition states (e.g. X = H<sub>2</sub>N) are characterized by larger CT contributions than loose TS's (e.g. X = NC).

A comprehensive analysis of the factors affecting reactivity orders cannot neglect deformation energies, namely the energies required to distort the partners from their equilibrium structures to the geometries assumed in the TS. The results of Table 4 show that the B3LYP approach provides, in agreement with other correlated methods,<sup>15</sup> deformation energies much lower than HF values. This finding is in agreement with the earlier character of the TS structures obtained by quantum mechanical methods including correlation energy. In any case, the general trends provided by all methods are very similar. In particular the largest deformation energy of butadiene corresponds to the tighter TS and to the less exothermic reaction (X = H<sub>2</sub>N).

The deformation energy of the diene thus appears as a good index of the earliness of the transition structures. In this context, the variations in the deformation energies of dienophiles are of more difficult interpretation since they contain also terms issuing from the different intrin-

(58) Second-order perturbation analysis of the Fock matrix in the NBO basis indicates a delocalization interaction between  $\pi^*_{CS}$  (which is partially filled) of the dienophile and  $\pi^*_{CC}$  of diene; this interaction is not taken into account in the  $\Delta E(d \rightarrow D^*)$  contribution.



sis deformability for different substituents X. In any case, the data of Table 4 show that the deformation energies of the diene and the dienophile in the different TS's have a parallel trend. Another noteworthy observation is that for a given substituent the deformation energies of the diene are larger for an exo attack, whereas the deformation energies of the dienophiles show an opposite behavior. These trends are in agreement with the less advanced formation of the C<sub>1</sub>–C<sub>3</sub> bond in transition structures issuing from exo attacks than in those obtained upon endo attack (see previous sections). It is, in fact, reasonable that a less completely formed bond entails lower deformations in the environments of the atoms directly involved. Thus the environment of the C<sub>1</sub> atom of the dienophile is less deformed in exo TS's. In the case of butadiene the lower deformation around C<sub>3</sub> is overcompensated by a larger deformation around C<sub>4</sub>, issuing from the more advanced formation of the C<sub>4</sub>–S<sub>2</sub> bond in exo transition structures than in endo ones.

**d. Reactivity Scale.** As already mentioned, one of the objectives of the present study is the establishment of a reactivity scale allowing the *a priori* prediction of the effectivity of substituted thioformamides as dienophiles in hetero-Diels–Alder reactions with respect to other known dienophiles.

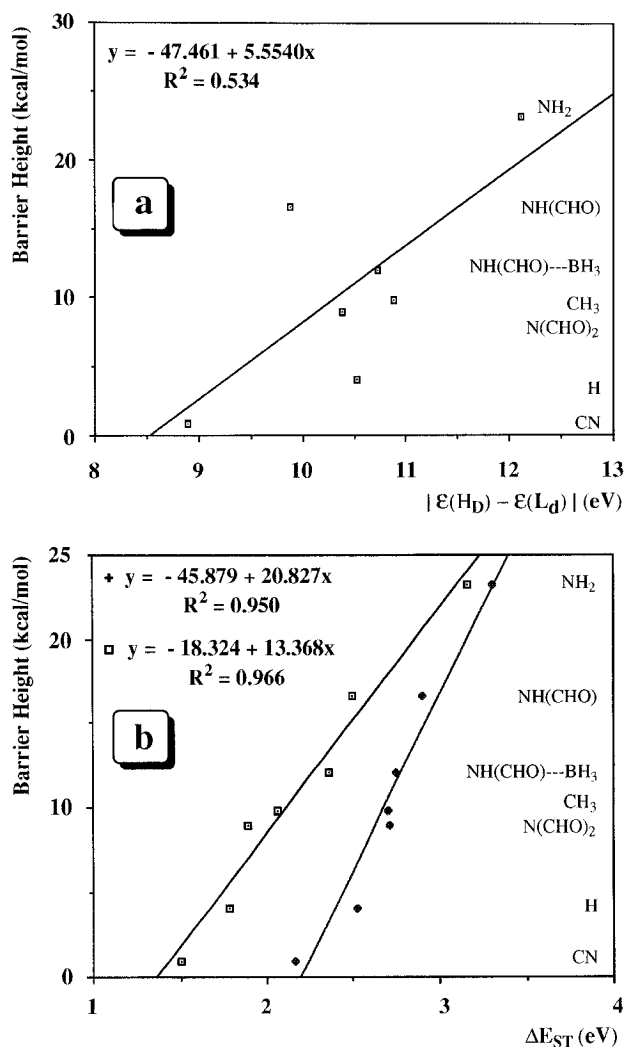
The results of our computations indicate that appropriately substituted thioamides can react with dienes without the addition of any Lewis acid. It remains to investigate if the models discussed in the first section of this paper have any previsions ability in this connection. Figure 4 shows the activation barriers computed at the B3LYP level<sup>59</sup> as a function of the HF energy difference between frontier orbitals ( $\pi$ -HOMO of diene and  $\pi^*$ -LUMO of the dienophile) or as a function of the singlet–triplet energy gap in the dienophile. The first series of data gives a very bad correlation ( $R^2 = 0.534$ ), whereas the correlation between activation energies and singlet–triplet gaps is very stringent ( $R^2 = 0.950$  at the CIS/6-31+G(d,p) level and  $0.966$  at the B3LYP/6-31+G(d,p) level). These results indicate that the FMO models is ill adapted to semiquantitative studies of substituent effects in the reactivity of thiocarbonyls. On the other hand, the SCD approach, even in its simplest form, is quite successful. This model is even more attractive taking into account that the CIS-6-31+G(d,p) and, especially, B3LYP/6-31+G(d,p) methods provide qualitatively correct singlet–triplet gaps in reasonable computer times. We have mentioned at the beginning of this paper the role played by the enthalpic factor (measured by  $\Delta E_r$ ) in determining the activation barrier. For most systems  $\Delta E_{ST}$  and  $\Delta E_r$  show the same trend and this is probably the reason why we compute large variations in the activation barriers.

#### 4. Concluding Remarks

We have performed systematic computations for prototypical hetero-Diels–Alder reactions of substituted thiocarbonyls with butadiene.

From a methodological point of view, the B3LYP approach seems particularly adequate for this type of problems since it couples a speed comparable to that of the Hartree–Fock model to a reliability at least of the

(59) We have chosen the activation barriers corresponding to an exo approach for X = CH<sub>3</sub>, NH<sub>2</sub>, and CN; for the substituted thioamides we have chosen the transition states for which there is no "extrastabilization", i.e. exo for X = NHCHO and NHCHO...BH<sub>3</sub> and endo for X = N(CHO)<sub>2</sub>.



**Figure 4.** Correlation between energy barriers of hetero Diels–Alder reactions of thiocarbonyls with butadiene computed at the B3LYP/6-31G(d) level and (a) HOMO–LUMO energy gaps computed at the HF/6-31G(d) level; (b) singlet–triplet energy gaps computed at the CIS/6-31+G(d,p) (filled squares) and B3LYP/6-31+G(d,p) (open squares) levels.

same level as that of the MP2 approach. A further advantage of the B3LYP approach is the ease of interpretation of the results in terms of different energy partitioning schemes, whose extension to post-HF wave functions is not straightforward. In the specific case of hetero-Diels–Alder reactions involving thiocarbonyls, substituent effects play a significant role in modifying the reactivity of the dienophile. In particular our computations indicate that, in the absence of particularly strong solvent effects, substitution of amidic hydrogens in thioamides by  $\pi$ -acceptor groups provides effective reagents avoiding the need to employ Lewis acids. As mentioned in the Introduction, the synthetic implications of this finding could be quite interesting. What is even more significant is that the results of complete computations are in remarkable agreement with the predictions of models (SCD, NBO) based on the electronic characteristics of the reactants. If this trend is confirmed for other classes of reactant, SCD and NBO approaches could represent, when coupled to some consideration of enthalpic factors, relatively simple general purpose tools for the rationale planning of specific reactions.