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Alternative Mechanistic Paths in the Hetero-Diels–Alder Reaction of α-Oxothiones: A Theoretical Study

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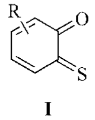
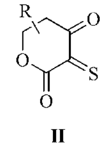
DFT calculations at the B3LYP/6-311+G(d,p) level for the C, H, and O atoms and at the 6-311+G(2df,p) level for the S atom were used to study the hetero-Diels–Alder reactions between several α-oxothiones and ethylene or methyl vinyl ether (MVE). All the transition states and the intermediates along the reaction pathways, as well as the reaction products, were located. The reactions with ethylene are all concerted though asynchronous whereas in the reactions with MVE the electron-releasing character of the methoxy substituent lowers the energy barriers and enhances the asynchronicity and the charge transfer process to such an extent that the reaction may become unconcerted and exhibit a two-step mechanism with a zwitterionic intermediate derived from nucleophilic attack of electron-rich MVE to the sulfur atom of the strongly electrophilically activated α-oxothiones. The reactions are also favored by the conjugation of the newly formed C=C bond. Moreover, the geometric features of the diene exert a nonnegligible role, as dienes that are planar or almost planar in their ground state show a lower energy barrier. Thus, both geometric and electronic features of the dienes as well as of the dienophiles play a significant role in the easiness of the reactions and in their mechanism.

Introduction

Hetero-Diels–Alder cycloadditions represent one of the most powerful tools in the synthetic chemistry.[1] A large variety of dienes and dienophiles have been used to perform such reactions. Among the dienes are α-oxothiones,[2–4] which are transient reactive species that are characterized by the presence of adjacent carbonyl and thiocarbonyl functionalities. They can be generated in situ under mild conditions and react with alkenes in inverse-electron-demand Diels–Alder reactions. Different kinds of α-oxothiones, such as *o*-thioquinones (**I**),[2] α-thiono-β-keto-δ-lactones (**II**),[3] and diacylthiones (**III**)[4] have been used to perform totally regio- and chemoselective as well as highly diastereoselective cycloaddition reactions that were particularly easy with electron-rich alkenes.


I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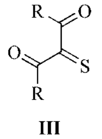
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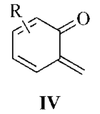
IV

A detailed computational study of the cycloaddition of *o*-thioquinones of general formula **I** with several substituted and/or cyclic 1,3-butadienes was reported.[5] Compounds **I** may behave as dienes giving cycloadditions that were shown to follow an asynchronous, but undoubtedly concerted mechanism; alternatively, they may behave as dienophiles, with the involvement of only the C=S bond, giving cycloadditions with a quite asynchronous or even unconcerted mechanism.

The strictly related *o*-quinone methides, compounds such as **IV**, were studied in their reaction as dienes with substituted alkenes.[6] Different molecular mechanisms were predicted depending on the nature of the substituent on the alkene. The concerted asynchronous mechanisms become, in the case of methyl vinyl ether (MVE) as the dienophile, highly asynchronous with a transition state having some zwitterionic character in consequence of the strong two center interaction between the more electrophilic site of **IV**, the methylene carbon atom, and the more nucleophilic site of MVE, the unsubstituted ethylene carbon.

In the last years, some of us have exploited the use of α-oxothiones **I**–**III** for synthetic purposes. Contrarily to **I**, no theoretical study exists for compounds with the general structures of **II** and **III**. In principle, they might follow different reaction paths as a consequence of their different electronic features. Thus, we performed an extensive computational study of the reactions of **1**–**3**, which represent the basis structures of these classes of heterodienes, with ethylene **7a** and with the electron-rich methyl vinyl ether

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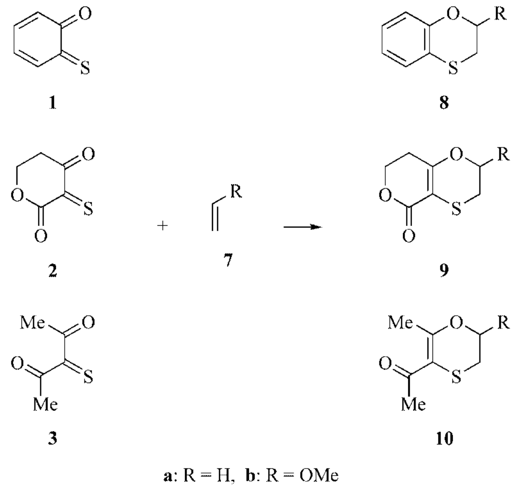
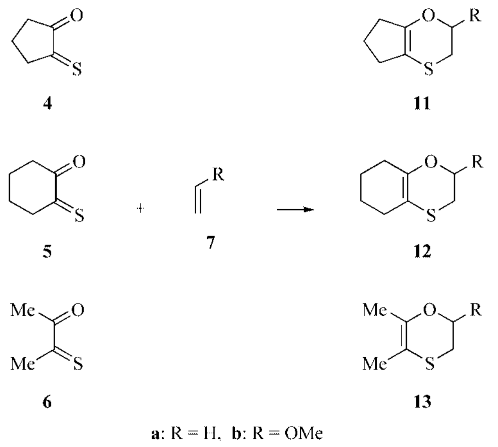
(**7b**; Scheme 1). Moreover, the reactions of three other dienes, **4**–**6**, with the same dienophiles were also studied for comparison to define the exact role of the geometric and electronic factors (Scheme 2) governing the reaction. This theoretical study was performed within the density functional approach through calculations at the B3LYP/6-311+G(2df,p) level for the S atom and at the 6-311+G(d,p) level for the other atoms. Moreover, single-point calculations in chloroform, using a solvent polarizable continuum model, were performed to take into account the solvent effects. The results are reported herein.



Scheme 1.



Scheme 2.

Results and Discussion

Cycloaddition of Dienes 1–3 with Ethylene (7a)

The reaction of dienes **1**–**3** with ethylene to yield cycloadducts **8**–**10** was investigated within the B3LYP[7] density functional approach. Some differences could be predicted for the three reactions. In fact, the incoming aromaticity of the transition state in the cycloadditions involving **1** as well as the aromatic nature of adduct **8** should favor the reaction; the effect should be less pronounced in the case of **2** and **3** in which the conjugation of the incoming C=C bond with the nonparticipating carbonyl group should produce a smaller benefit. Moreover, dienes **1**–**3** differ in their geometrical features; in fact, the system is completely planar in **1** with the carbonyl and thiocarbonyl groups correctly oriented for a good reaction; owing to the ring puckering, in **2** they should present a slight deviation from planarity whereas **3** might in principle largely deviate from planarity even showing a divergent orientation of the carbonyl and thiocarbonyl groups in its minimum energy conformation which could be geometrically not suitable for a cycloaddition reaction. The data on the optimized conformations of these dienes, reported in Table 1, support the above considerations. Compound **1** is completely planar, **2** has a value of the torsional angle $\tau_{(\mathrm{O=C-C=S})} = 33°$, but planarity can be easily attained. In fact, the difference in energy between the conformation in which $\tau_{(\mathrm{O=C-C=S})}$ is forced to 0° and that of the minimum energy conformation, $\Delta E(\tau_0 - \tau_{\mathrm{min}})$, is only 0.98 kcal/mol. On the contrary, **3** largely diverges from planarity [$\tau_{(\mathrm{O=C-C=S})} = 124°$] and 3.43 kcal/mol of energy are necessary to force the molecule to a *syn* planar arrangement of the reacting C=S and C=O bonds.

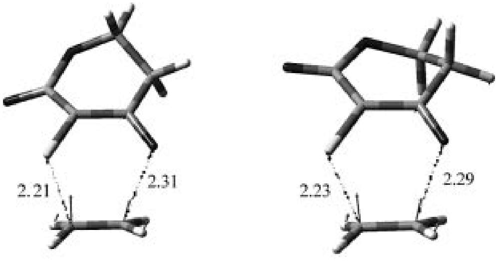
As far as the electronic effects are concerned, Table 1 also reports the energy of the HOMO and LUMO orbitals and the electrophilicity index ω.[8] The cycloadditions of **1**–**3** with ethylene are supposed to be inverse-electron-demand Diels–Alder reactions. This is confirmed by the data of the energy of the LUMO and HOMO orbitals of **1**–**3** compared with those of **7a** and by the high values of ω calculated for these dienes, in particular for **1** and **2**, which put them among the strongest electrophiles in the electrophilicity scale for common reagents involved in Diels–Alder reactions.[9] Indeed, the difference between $\mathrm{HOMO_{diene}}$ and $\mathrm{LUMO_{ethylene}}$ is greater than the difference between $\mathrm{HOMO_{ethylene}}$ and $\mathrm{LUMO_{diene}}$. In a comparison among the dienes, frontier orbital analysis and the electrophilicity in-

Table 1. Computed data of the minimum energy conformation of dienes **1**–**6** and of dienophiles **7**.

	$\tau_{(\mathrm{O=C-C=S})}$ [°]	$\Delta E(\tau_0 - \tau_{\mathrm{min}})$ [kcal/mol]	E_{LUMO} [eV]	E_{HOMO} [eV]	ω [eV]	μ [Debye]
1	0	0.00	–4.287	–6.663	6.31	4.81
2	33	0.98	–4.313	–7.128	5.81	4.48
3	124	3.43	–3.642	–6.819	4.31	1.84
4	3	0.01	–3.480	–6.411	4.17	4.41
5	55	2.85	–2.907	–6.356	3.11	4.60
6	180	5.82	–3.489	–6.566	4.11	0.61
7a			–0.294	–7.661	1.07	
7b			0.140	–6.545	0.82	

dex predict that **1** and **2** are almost equally reactive (E_{LUMO} = –4.287 and –4.313 eV, ω = 6.31 and 5.81 eV, respectively) whereas **3** (E_{LUMO} = –3.642 eV, ω = 4.31 eV) should give rise to a less easy reaction. Thus, both the geometrical and electronic analyses of dienes **1**–**3** agree in predicting the reaction of **1** and **2** easier than that of **3**.

Then, we located the transition states corresponding to the cycloadditions of **1**–**3** to ethylene and the results are summarized in Table 2. In the reactions of **1** and **3** only one reaction channel was studied as the two faces of the dienes are equivalent, so that only one TS was located in each case (TS-**8a** and TS-**10a**, respectively). Instead, in the case of **2** the lactone ring of the diene is puckered making its faces nonequivalent; thus, two reaction channels were investigated, TS-**9a** and TS-**9a′** (Figure 1), the former being preferred by 2–3 kcal/mol over the latter. Table 2 shows that in all these TSs both the C–S and C–O bonds are in formation but the processes are not completely synchronous. As a measure of asynchronicity the parameter $\Delta d_{\text{TS/P}}$, defined as the difference between the ratios of the forming bond lengths in the TS and the corresponding bond lengths in the product, was proposed.[5] Its value ranges from 0.31 to 0.39 suggesting that the reactions are clearly concerted though asynchronous. This conclusion was substantiated by IRC analyses performed starting from the located TSs which allowed to reach the reaction products in the forward direction and the cycloaddends in the reverse direction without evidence of any intermediate structure along the reaction paths. Moreover, it is worthy pointing out that low amounts of the charge transfer from ethylene to the dienes, calculated from the Mulliken charges of the atoms of the structures, were observed.



TS-9a TS-9a'

Figure 1. Transition states for the reaction of **2** with **7a**. Displacement vectors for TS imaginary frequencies are shown as grey arrows and the values of the forming bond lengths are reported in angstroms.

Though in terms of geometry all the TSs are quite similar, the three reactions are very different in their energetics which reflect the considerations made above on the nature

Table 2. Activation energies, enthalpies, free energies in vacuo, and activation energies in chloroform, dipole moment, charge transfer (*CT*), length of the forming C–O and C–S bonds, and degree of asynchronicity[a] of the reactions of **1**–**6** with **7a**,**b**.

	$\Delta E^{\ddagger}$ [kcal/mol]	$\Delta H^{\ddagger}$ [kcal/mol]	$\Delta G^{\ddagger}$ [kcal/mol]	$\Delta E^{\ddagger}_{\text{solv}}$ [kcal/mol]	μ [Debye]	*CT* [e]	C–O [Å]	C–S [Å]	$\Delta d_{\text{TS/P}}$[a]
Cycloadditions to ethylene									
TS-**8a**	6.54	7.23	19.87	8.33	2.44	0.126	2.335	2.412	0.31
TS-**9a**	8.71	9.59	22.04	8.58	4.38	0.183	2.315	2.213	0.39
TS-**9a′**	11.17	12.02	24.27	10.77	5.42	0.201	2.291	2.230	0.37
TS-**10a**	15.80	16.78	30.66	15.22	3.66	0.163	2.224	2.230	0.32
TS-**11a**	19.27	20.15	32.74	21.19	2.32	0.138	2.243	2.112	0.25
TS-**11a′**	21.24	22.14	34.37	23.15	2.32	0.148	2.234	2.102	0.25
TS-**12a**	19.97	20.68	33.12	21.79	2.52	0.120	2.134	2.266	0.26
TS-**12a′**	20.10	20.80	33.17	21.89	2.50	0.109	2.139	2.254	0.26
TS-**13a**	23.97	24.67	37.80	23.57	2.41	0.133	2.114	2.239	0.25
Cycloadditions to methyl vinyl ether									
TS1–**8bn**	–1.70	–1.09	12.08	–1.79	4.26	0.288	3.406	2.223	1.17
TS2–**8bn**	–1.89	–1.25	13.18	–3.46	5.43	0.393	3.146	2.008	1.10
TS-**8bx**	–1.17	–0.55	11.88	1.00	2.53	0.250	3.026	2.410	0.80
TS-**9bx**	–4.53	–3.40	10.30	–6.55	8.05	0.466	2.552	1.950	0.68
TS-**9bn**	–3.52	–2.48	11.64	–6.80	8.16	0.481	2.561	1.923	0.70
TS-**9b′x**	–2.23	–1.11	12.53	–5.01	9.21	0.494	2.556	1.940	0.69
TS-**9b′n**	–1.41	–0.38	13.65	–5.57	9.50	0.450	2.586	1.916	0.72
TS-**10bx**	4.88	5.92	20.39	3.16	6.43	0.349	2.618	2.080	0.67
TS-**10bn**	5.56	6.59	21.58	2.37	6.78	0.397	2.520	2.008	0.65
TS-**11bx**	12.60	13.36	26.63	14.58	3.34	0.293	2.375	2.130	0.48
TS-**11bn**	14.13	14.91	28.20	15.43	3.84	0.267	2.305	2.114	0.44
TS-**11b′x**	14.30	15.07	28.07	16.29	3.33	0.320	2.365	2.114	0.48
TS-**11b′n**	15.50	16.31	29.54	16.66	3.87	0.310	2.287	2.102	0.44
TS-**12bx**	13.29	13.90	27.11	15.45	3.81	0.266	2.399	2.143	0.50
TS-**12b′x**	13.47	14.05	27.16	15.69	3.24	0.267	2.412	2.162	0.50
TS-**12bn**	14.33	14.96	28.30	15.37	3.87	0.265	2.339	2.124	0.47
TS-**12b′n**	14.41	15.02	28.36	15.51	3.86	0.275	2.354	2.132	0.47
TS-**13bx**	17.45	17.99	31.58	17.41	3.40	0.292	2.355	2.131	0.48
TS-**13bn**	18.50	19.08	32.93	17.33	3.93	0.284	2.298	2.116	0.45

[a] $\Delta d_{\text{TS/P}} = |(\text{C–S})_{\text{TS}}/(\text{C–S})_{\text{p}} - (\text{C–O})_{\text{TS}}/(\text{C–O})_{\text{p}}|$.

of the dienes. The easiest reaction, in terms of energy, enthalpy, or free energy is that of diene **1** that, as already mentioned, takes advantage both from electronic and geometric factors. The reaction of **2** is less easy by about 2 kcal/mol whereas the reaction of **3** suffers from a very large penalty of 9–10 kcal/mol. The solvent (chloroform) has a marked negative effect on the activation energy of the reaction of **1** with ethylene as the corresponding barrier is increased by almost 2 kcal/mol (Table 2); instead, the energy barrier for the reactions of **2** and **3** is slightly lowered, in agreement with the greater dipole moment of the corresponding TSs and with the higher value of the charge transfer from ethylene to the diene.

Tables 2 and 3 show that the stability order of the TSs of the reaction of **1**–**3** with **7a** is maintained in cycloadducts **8a**–**10a** among which the energy differences are even enhanced (Table 3).

Table 3. Reaction energies, enthalpies, free energies in vacuo and reaction energies in chloroform of the reactions of **1**–**6** with **7a**,**b**.

	ΔE [kcal/mol]	ΔH [kcal/mol]	ΔG [kcal/mol]	ΔE_{solv} [kcal/mol]
8a	–45.15	–41.58	–27.31	–42.47
9a	–34.20	–30.37	–16.45	–33.53
10a	–24.40	–20.61	–5.49	–24.40
11a	–19.22	–15.42	–1.87	–16.24
12a	–21.53	–17.93	–4.21	–18.58
13a	–16.07	–12.46	1.68	–15.45
8b	–44.80	–41.83	–26.71	–41.74
9b	–33.90	–30.74	–16.11	–32.20
10b	–23.61	–20.48	–4.55	–23.13
11b	–18.77	–15.62	–1.38	–14.88
12b	–21.42	–18.48	–4.03	–17.64
13b	–15.47	–12.49	2.55	–14.47

Cycloaddition of Dienes 1–3 with Methyl Vinyl Ether (7b)

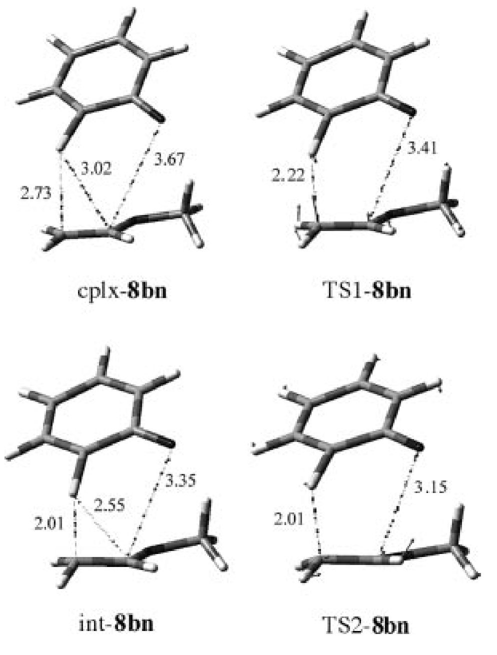
The reaction of dienes **1**–**3** with electron-rich alkene **7b** was then studied. In these cases, several reaction channels have to be considered as a consequence of the asymmetry of MVE along the plane containing the C=C bond. Preliminary investigations on the stability of the transition states in which MVE showed either the *syn* or the *anti* orientation indicated a marked preference for the latter orientation; thus, only the *anti* orientation of the methoxy group with respect to the C=C bond (a value of the torsional angle C2–C1–O–CH_3 about 180°) was considered. Similar *anti* arrangements were noted[10] in transition states of Diels–Alder and 1,3-dipolar cycloadditions of enol ethers which show a conformational switch from the *syn* conformation favored in the reactant to the *anti* favored in the transition structure. Moreover, the methoxy substituent of MVE can present the alternative *endo* or *exo* arrangements with respect to the diene; both these orientations were considered and are reported. At last, two regioisomeric adducts could be obtained from the approach of unsymmetrical dienes like **1**–**3** to unsymmetrical MVE. However, the reaction channels in which the more nucleophilic center of MVE, the C2 carbon, attacks the oxygen atom of **1**–**3** are remarkably disfavored over the channels in which it attacks the sulfur atom.[11] This is in agreement with the local electrophilicity index ω_k[12] calculated for the sulfur atom of **1**–**3** which indicates that it is the most electrophilic center of these molecules (Table 4). Thus, in the following discussion the disfavored regioisomeric channels were not considered.

Table 4. Values of the local electrophilicity index ω_k [eV] calculated for the atoms of the S=C–C=O system of **1**–**6**.

	S	C	C	O
1	2.10	0.85	0.55	0.86
2	2.58	1.51	0.46	0.52
3	1.69	1.49	0.20	0.22
4	1.51	1.11	0.56	0.54
5	1.24	1.04	0.28	0.22
6	1.50	1.15	0.54	0.55

Table 2 clearly shows a great heterogeneity of the TSs located for these reactions which in terms of $\Delta E^{\ddagger}$ as well as $\Delta G^{\ddagger}$ are easier than the corresponding reactions with **7a** by 8–15 kcal/mol. The reaction of **2** is the most favored, but also **1** reacts quite easily being disfavored over **2** by 2–3 kcal/mol. Compound **3** gives the least easy reaction. A comparison of the geometries of the TSs shows that the reactions with MVE are much more asynchronous than those with ethylene as the C–S bond is much more formed than the C–O bond. Also among the three dienes significant differences do exist as can be seen by an examination of the lengths of the forming bonds as well as of the displacement vectors for the negative frequency of each TS. Moreover, the high amounts of charge transfer suggest the involvement of zwitterionic intermediates.

In the reaction of **1** with MVE, two TSs were located along the *endo* reactive channel, TS1-**8bn** and TS2-**8bn** (Figure 2); the former corresponds to the formation of the C–S



cplx-**8bn** TS1-**8bn**
int-**8bn** TS2-**8bn**

Figure 2. Intermediates and transition states for the reaction of **1** with **7b**. Displacement vectors for TS imaginary frequencies are shown as grey arrows and distances are reported in angstroms.

bond, to which the larger vector is associated, whereas the C–O distance is still very high (>3 Å), the latter to the formation of the C–O bond. Instead, in the reactions of **2** and **3** with MVE only one TS was located, TS-**9bx** and TS-**10bx**, respectively (Figure 3); in these cases the C–S bond is almost completely formed. In particular in TS-**9bx**, and the longer displacement vector is associated with the formation of the C–O bond.

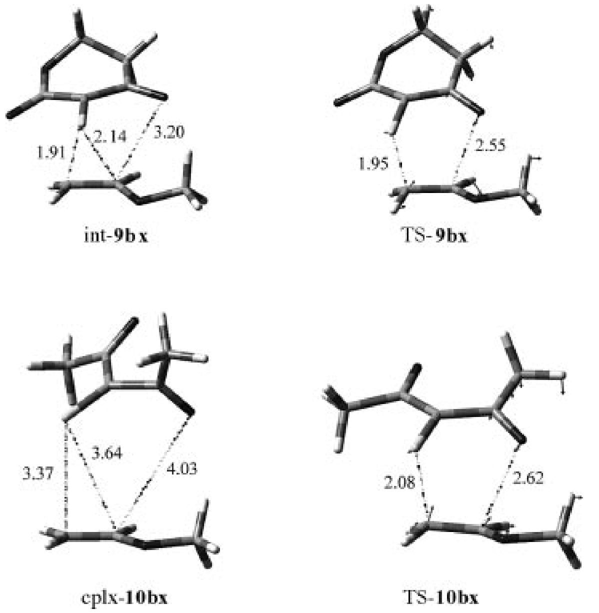


Figure 3. Intermediates and transition states for the reaction of **2** and **3** with **7b**. Displacement vectors for TS imaginary frequencies are shown as grey arrows and distances are reported in angstroms.

The differences in the geometry of the TSs suggest different reaction mechanisms which were investigated through IRC analyses starting from the TSs already located. Figure 4 pictures the energy profiles determined for the favorite reaction channel of each reaction starting from the *anti* conformation of **7b** which, as described above, is more reactive than the *syn* one though being less stable by 1.98 kcal/mol. The energy profiles show the presence of reaction intermediates/complexes and, in the case of the *endo* channel of **1**, of a second TS. Thus, this reaction of **1** with MVE clearly exhibits a two step mechanism with a sequential formation of the two new bonds. The two addends, **1** and **7b**, firstly pass through a bimolecular complex (cplx-**8bn**) with a nonbonding interaction between the sulfur atom of **1** and the double bond of MVE (the two C···S distances are 2.73 and 3.02 Å) and then through the transition state TS1-**8bn** to yield intermediate int-**8bn**. In this structure, the bond of the sulfur atom with the C2 carbon atom of MVE is completely formed, whereas the distance between the oxygen atom of **1** and C1 of MVE is still very high (>3 Å). This intermediate is stabilized by the gain of the complete aromaticity of the carbocyclic ring. At last, the product is obtained after passing through a very small energy barrier (TS2-**8bn**). The overall mechanism can be described as pictured in Scheme 3. The three-dimensional plots of all these intermediates and TSs are reported in Figure 2.[13]

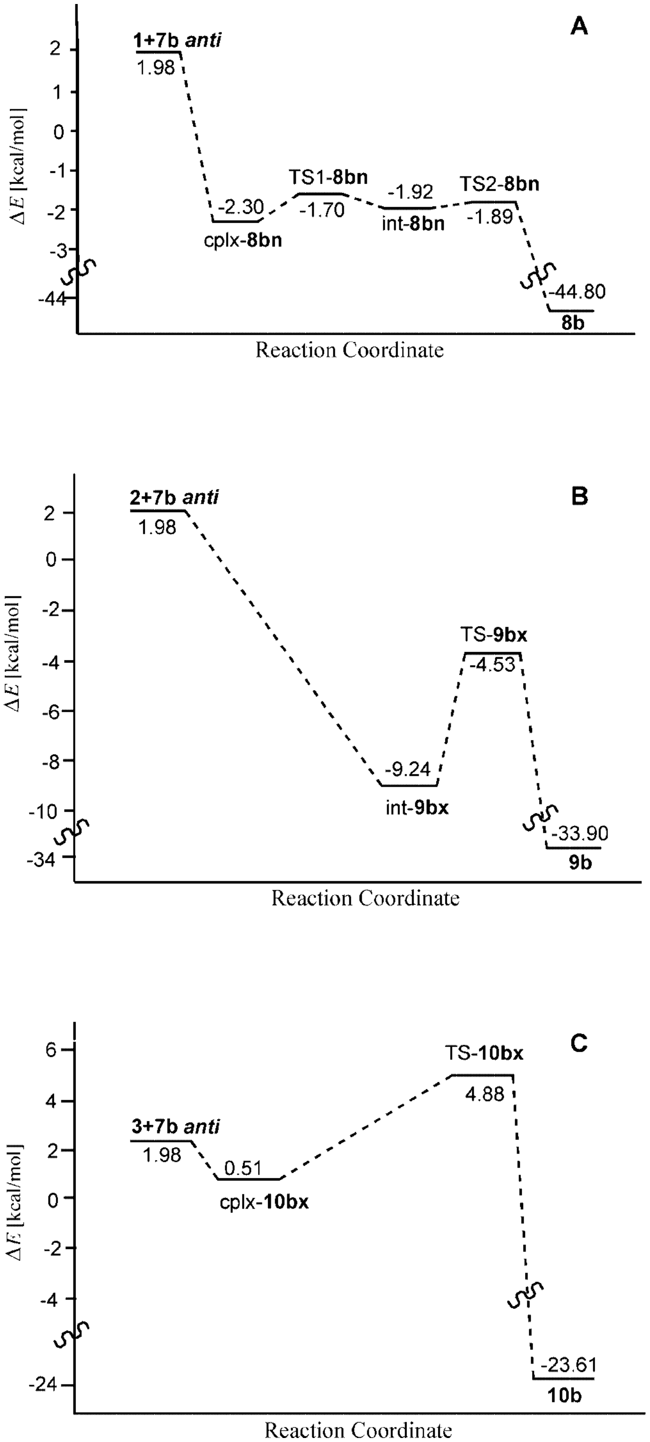
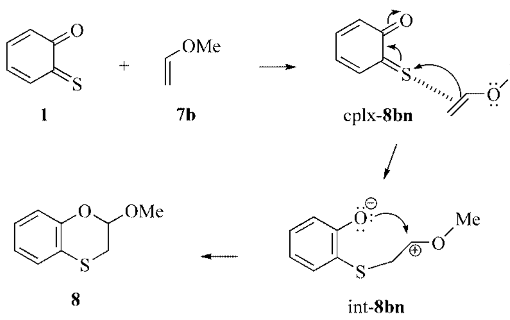


Figure 4. Energy profiles determined for the favorite channel of the reactions of **1**, **2**, and **3** with **7b**.

Also in this case, it was possible to calculate the charge transfer from MVE to the diene **1**. In initial complex cplx-**8bn** only 0.132 e resulted transferred; the value becomes 0.288, 0.381, and 0.393 e in TS1-**8bn**, int-**8bn**, and TS2-**8bn**, respectively, thus substantiating the reaction mechanism.



Scheme 3.

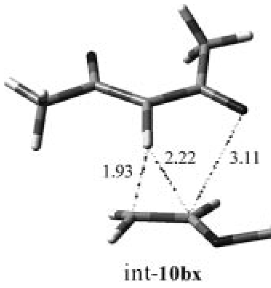
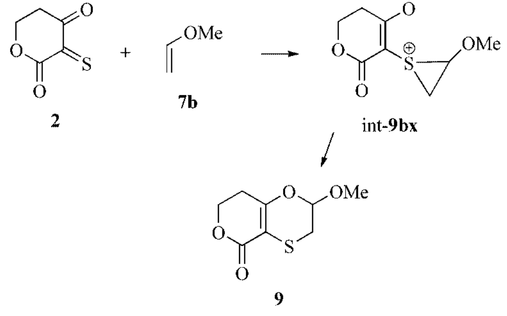


Figure 5. Intermediate for the reaction of **3** with **7b** obtained through an optimization in solvent.

For comparison, in the corresponding reaction of **1** with ethylene the charge transfer measured in TS-**8a** is only 0.126 e.

In the reaction of **2** with **7b** it was not possible to locate a reactant complex like cplx-**8bn** as intermediate structure int-**9bx** is formed directly from the reactants, without any TS leading to it (Figures 3 and 4). It presents a completely formed C2–S bond (1.91 Å) and a relative energy of –9.24 kcal/mol (compared to the value of –1.92 kcal/mol of int-**8bn**) in keeping with the higher delocalization of the negative charge in this zwitterionic intermediate. Moreover, int-**9bx** is characterized by an unusual C1–C2–S angle of only 78°, if compared with the C1–C2–S angle in int-**8bn** (95°). Furthermore, the distance C1–S results of only 2.14 Å indicating a quite strong interaction between these two atoms, whereas O and C1 are as far as 3.20 Å apart. This two-step mechanism can be described as pictured in Scheme 4 and is supported by the very large value of the charge transfer in int-**9bx** and TS-**9bx**, 0.438 and 0.466 e, respectively.



Scheme 4.

Diene **3** gives product **10** through the formation of complex cplx-**10bx** and then transition state TS-**10bx** (Figures 3 and 4). Actually, we were not able to locate any zwitterionic intermediate between cplx-**10bx** and TS-**10bx** through optimizations in vacuo. In this case the reaction can be considered concerted, though asynchronous and with a high zwitterionic character in the transition state as evidenced by the data in Table 2. Actually, contrary to the unsuccessful attempts in vacuo, when we tried to locate an intermediate preceding TS-**10bx** through an optimization in solvent, intermediate int-**10bx** was located; its structure (Figure 5) closely resembles that of int-**9bx**.

All the reactions of **1**–**3** with MVE have a polar character larger than those with ethylene, as a consequence of the more nucleophilic character of the former, and the solvent effect has significant incidence on the energies; in fact, the data in Table 2 show that all the channels, in particular the *endo*, are stabilized by the presence of the solvent.

Cycloaddition of Dienes 4–6 with Ethylene (7a) and Methyl Vinyl Ether (7b)

For comparison, we also studied dienes **4**, **5**, and **6**. The last one is a known compound[14] thermally obtainable through a retro-Diels–Alder reaction from **13a**. Dienes **4**–**6** do not take advantage from any electronic effect. Among them, **4** and **5** should exhibit a completely planar (**4**) or an almost planar (**5**) arrangement caused by the presence of the tri- and tetramethylene loop with the two double bonds correctly oriented for the reaction. On the contrary, compound **6** could deviate from planarity to an extent even larger than **3**.

Table 1 shows that, as expected, **4** is planar, **5** deviates from planarity by 55°, and **6** assumes a minimum energy conformation that makes it unfit to behave as a heterodiene as the two C=O and C=S bonds are in an antiperiplanar arrangement. Moreover, 2.85 and 5.82 kcal/mol of energy are necessary to force, respectively, **5** and **6** to planarity. As far as the electronic effects are concerned, the data in Table 1 show that the reactions of **4**–**6** with **7a** and **7b** should be even less easy than the corresponding reactions of **3**. As expected from the properties of the dienes, all the reactions resulted much more difficult as they present $\Delta E^{\ddagger}$ and $\Delta G^{\ddagger}$ values much higher than the corresponding reactions of **1**–**3** with both **7a** and **7b** (Table 2), confirming the importance of the electronic effects of conjugation present in **1**–**3**. Moreover, as expected from the analysis of the geometry of **4**–**6**, reactions of pentacyclic compound **4** are slightly easier than those of its hexacyclic analogue **5** whereas the highest barriers are encountered with **6**. All the reactions, in particular those with ethylene, are more synchronous than those of **1**–**3** and the TSs have much lower polar character. In fact, in the cases of **4** and **5**, the activation barriers in solvent are increased by 1–2 kcal/mol over the barriers in vacuo as a consequence of the larger stabilization of the reagents than the TSs.

Conclusions

DFT calculations at the B3LYP/6-311+G(d,p) level for the C, H, and O atoms and at the 6-311+G(2df,p) level for the S atom were used to study the hetero Diels–Alder reactions between several α-oxothiones and ethylene or methyl vinyl ether.

The reactions with ethylene are all concerted though asynchronous whereas in the reactions with MVE the electron-releasing character of the methoxy substituent enhances the asynchronicity and the charge transfer process. Similar effects were evidenced in the reaction of nitroethene with substituted ethenes[15] without intervention of any zwitterionic intermediate. In our cases, asyncronicity and charge transfer affect the reactions to such an extent that their mechanisms may become unconcerted with the formation of zwitterionic intermediates derived from a nucleophilic attack of electron-rich MVE to the sulfur atom of the strongly electrophilically activated α-oxothiones. In fact, in the reaction of **1** with MVE, zwitterionic structure int-**8bn** could be located, corresponding to a nucleophilic attack of MVE to **1**. In the reactions of **2** and **3** with MVE different zwitterionic structures were located, int-**9bx** and int-**10bx**; they can be described as episulfonium ion intermediates. Geometrical and electronic features of the dienes influence the easiness of the reactions as well as their mechanism. The reactions are favored by the conjugation of the newly formed C=C bond, which, in the reaction of **1**, completes the aromatic ring and, in the reactions of **2** and **3**, conjugates with the adjacent carbonyl group. In fact, reactions of dienes **4**–**6**, which do not take benefit from conjugation, have much higher energy barriers. Moreover, geometric factors exert a nonnegligible role, as clearly evidenced by the reaction of diene **6**, disfavored by >5 kcal/mol with respect to the corresponding reaction of **4** and **5** and also by a comparison between these two latter compounds which privileges the completely planar diene **4** over the twisted **5** by about 0.5 kcal/mol.

Computational Methods

All the calculations were carried out using the GAUSSIAN03 program package.[16] All the structures of reactants, transition states, intermediates, and products were optimized in the gas-phase at the B3LYP/6-311+G(2df,p) level for the S atom and 6-311+G(d,p) level for the other atoms to correctly describe the geometries and the electronic properties of compounds that contain a sulfur atom. The reaction pathways were confirmed by IRC analyses performed at the same level as above. The DFT stability of the wavefunction was checked with the STABLE option for all the stationary points to exclude competing preferred biradical pathways; no instabilities were observed. Vibrational frequencies were computed at the same level of theory to define the optimized structures as minima or transition states, which present an imaginary frequency corresponding to the forming bonds. Thermodynamics at 298.15 K allowed the enthalpies and the Gibbs free energies to be calculated. The solvent effects were considered by single-point calculations, at the same level as above, on the gas-phase optimized geometries, using a self-consistent reaction field (SCRF) method, based on the polarizable continuum model (PCM).[17] To investigate this aspect we selected chloroform, the solvent in which these reactions are usually carried out.[2–4] The global electrophilicity index ω was calculated from the chemical potential and the chemical hardness according to Parr et al.[8] The local electrophilicity power ω_k was calculated from ω and the regional Fukui function f^+_k determined as described by Contreras et al.[18]

Supporting Information (see footnote on the first page of this article): Energies in Hartrees, thermochemical corrections, and cartesian coordinates of all reported structures.

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[1] a) T. Ooi, K. Maruoka, "Hetero Diels–Alder and Related Reactions" in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, Germany, **1999**, vol. 3, pp. 1237–1254; b) F. Fringuelli, A. Taticchi, *The Diels–Alder Reaction: Selected Practical Methods*, John Wiley & Sons, Chichester, **2002**, pp. 66–73; c) F. Fringuelli, A. Taticchi, *Dienes in the Diels–Alder Reactions*, John Wiley & Sons, New York, **1990**, pp. 97–106; d) J. Gonzalez, J. A. Sordo, *Recent Res. Devel. Org. Chem.* **1997**, *1*, 239–257; e) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

[2] a) G. Capozzi, C. Falciani, S. Menichetti, C. Nativi, *J. Org. Chem.* **1997**, *62*, 2611–2615; b) G. Capozzi, C. Falciani, S. Menichetti, C. Nativi, B. Raffaelli, *Chem. Eur. J.* **1999**, *5*, 1748–1754; c) V. Nair, B. Mathew, K. V. Radhakrishnan, N. P. Rath, *Synlett* **2000**, *1*, 61–62; d) G. Capozzi, P. Lo Nostro, S. Menichetti, C. Nativi, P. Sarri, *Chem. Commun.* **2001**, 551–552; e) S. Menichetti, C. Viglianisi, *Tetrahedron* **2003**, *59*, 5523–5530; f) S. Menichetti, M. C. Aversa, F. Cimino, A. Contini, C. Viglianisi, A. Tomaino, *Org. Biomol. Chem.* **2005**, *3*, 3066–3072.

[3] A. Bartolozzi, G. Capozzi, S. Menichetti, C. Nativi, *Org. Lett.* **2000**, *2*, 251–253.

[4] G. Capozzi, A. Dios, R. W. Franck, A. Geer, C. Marzabadi, S. Menichetti, C. Nativi, M. Tamarez, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 777–779.

[5] A. Contini, S. Leone, S. Menichetti, C. Viglianisi, P. Trimarco, *J. Org. Chem.* **2006**, *71*, 5507–5514.

[6] H. Wang, Y. Wang, K. L. Han, X. J. Peng, *J. Org. Chem.* **2005**, *70*, 4910–4917.

[7] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.

[8] R. G. Parr, L. von Szentpály, S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 1922–1924.

[9] L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras, *Tetrahedron* **2002**, *58*, 4417–4423.

[10] J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 1064–1073.

[11] For example, in the regioisomeric reaction of **1** with **7b** (attack of S to C1 of MVE) the preferred channel shows $\Delta E^{\ddagger}$ = 7.92 kcal/mol and ΔE = –39.06 kcal/mol compared to –1.70 and –44.80 kcal/mol, respectively, in the reaction path to **8b**; moreover, the reaction is concerted and synchronous (the C1···S and the C2···O distances are 2.576 Å and 2.149 Å, respectively, and $\Delta d_{TS/P}$ is 0.11). Similarly, in the regioisomeric reaction of **2** with **7b** the preferred channel shows $\Delta E^{\ddagger}$ = 10.00 kcal/mol and ΔE = –26.41 kcal/mol compared to –4.53 and –33.90 kcal/mol, respectively, in the reaction path to **9b**. Also this reaction is concerted and synchronous (the C1···S and

the C2···O distances are 2.322 Å and 2.168 Å, respectively, and $\Delta d_{TS/P}$ is 0.26).

[12] L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras, *J. Phys. Chem. A* **2002**, *106*, 6871–6875.

[13] It is worthy to point out that the level of calculations influences the energy profile. As described, at the 6-311+G(2df,p) level for the S atom and at 6-311+G(d,p) for the other atoms, the reaction of **1** with **7b** is clearly unconcerted. Instead, at the 6-31G(d,p) level we were able to find only one TS corresponding to a highly asynchronous but still concerted mechanism (the C2···S and the C1···O distances are 2.354 and 2.871 Å, respectively, and $\Delta d_{TS/P}$ is 0.73).

[14] F. Bourdon, J. L. Ripoll, Y. Vellée, *Tetrahedron Lett.* **1990**, *31*, 6183–6184.

[15] L. R. Domingo, M. Arnó, J. Andrés, *J. Org. Chem.* **1999**, *64*, 5867–5875.

[16] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision B.04., Gaussian, Inc., Pittsburgh, PA, **2003**.

[17] a) E. Cances, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3042; b) M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett.* **1996**, *255*, 327–335; c) V. Barone, M. Cossi, J. Tomasi, *J. Comput. Chem.* **1998**, *19*, 404–417.

[18] a) R. Contreras, P. Fuentealba, M. Galván, P. Pérez, *Chem. Phys. Lett.* **1999**, *304*, 405–413; b) P. Fuentealba, P. Pérez, R. Contreras, *J. Chem. Phys.* **2000**, *113*, 2544–2551.

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