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An *Ab Initio* Study on the Conformational and *Endo/exo* Preferences of Acrylates in Diels–Alder Reactions

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Abstract: The four transition structures (TS) of the reaction between butadiene and methyl acrylate have been studied at several *ab initio* levels considering both the non-catalyzed and the BF_3-catalyzed processes. Whereas in the non-catalyzed reaction the *s-cis* TS are more stable than the corresponding *s-trans* TS, and the *exo* approaches are preferred over the *endo*, both situations are reversed in the case of the catalyzed reaction, in which the *endo s-trans* is the most stable TS. The results obtained show that for the uncatalyzed reaction, the *endo/exo* selectivity mainly depends on the conformation of the dienophile in the TS, and therefore that the energy differences between the *s-cis* and *s-trans* TS also change from *endo* to *exo* approaches. The catalyst induces a strong preferential stabilization of the *endo s-trans* TS, which is in agreement with the experimental observations. © 1997 Elsevier Science Ltd.

α,β-Unsaturated carbonyl compounds are frequently used as dienophiles in Diels–Alder reactions. The behaviour of these compounds in such cycloadditions is heavily dependent on the *s-cis/s-trans* conformational equilibrium. Thus, whereas *s-cis* conformations are more reactive,[1,2] *s-trans* conformations lead to a greater *endo/exo* selectivity.[2–4] These differences have been detected in the reactions of cyclopentadiene and they have been explained on the basis of the steric interaction between the methylene group of the diene and the substituent of the dienophile double bond in the *exo* approach. Given that this interaction is stronger in the *s-trans* conformation, the *exo s-trans* transition state is particularly unstable, which leads to a higher *endo/exo* selectivity for the *s-trans* conformation.[4]

When chiral acrylates are used as dienophiles the asymmetric induction greatly depends on this conformational equilibrium.[4,5] Based on experimental studies, a number of models have been proposed to account for the diastereofacial selectivity observed. In these models, the transition state of lowest energy is assumed to have the most stable conformation of the dienophile.[5] However, because this assumption is not necessarily valid, some paradoxical situations appear. For instance, although experimental results indicate that the complex methacrolein–BF_3 preferentially adopts an *s-trans* conformation,[6] the results obtained in the reaction of this dienophile in the presence of some boron Lewis acids have been explained by models in which the reactions take place through the *s-cis*[7] or *s-trans*[8] conformation. Furthermore, both *endo* and *exo* approaches may lead to different asymmetric inductions because the different transition states are diastereomeric. Unfortunately, in most Diels–Alder reactions with chiral acrylates, the asymmetric induction is only determined for the major *endo* adducts, but these differences have also been demonstrated in the reactions of cyclopentadiene with (1*R*,2*S*,5*R*)-8-phenylmenthyl[9] and (1*R*,2*S*,5*R*)-menthyl-2-acetamido[10] acrylates. In both

cases the diastereofacial selectivity is higher in *exo* than in *endo* cycloadducts. This behaviour has been explained by steric reasons: the interaction of the methylene group of the cyclopentadiene with the chiral auxiliary increases the differentiation between both faces of the double bond in the *exo*, with regard to the *endo* approach. Therefore, it seems clear that the *s-cis/s-trans* conformational preferences influence the *endo/exo* and the diastereofacial selectivities of Diels–Alder reactions with cyclopentadiene, which has been explained by the steric interaction of the methylene group of the diene in the different transition states.[4,9,10] In view of this, we considered it interesting to assess whether the *s-cis/s-trans* equilibrium also influences these selectivities in the absence of such steric interactions, *i.e.*, in the reactions of acyclic dienes. To answer this question we studied the reaction between methyl acrylate and butadiene at several theoretical levels.

It is well known that the use of Lewis acids leads to significant changes in rate, regio-, *endo/exo*, and diastereofacial selectivities of Diels–Alder reactions in comparison with the uncatalyzed processes. In spite of the important role of the catalyst, theoretical studies dealing with Lewis acid-catalyzed reactions are rather scarce. The role of BH_3 as the Lewis acid has been considered[11] and, more recently, the role of BF_3 and $AlCl_3$ has been theoretically studied.[12] In all these reports, however, only the *s-cis* conformation of the dienophile has been studied. In view of the experimental importance of Lewis acids, and the lack of theoretical studies dealing with their influence on the *s-cis/s-trans* preferences, we have also considered the BF_3-catalyzed reaction of butadiene with methyl acrylate at the same levels of calculation.

RESULTS AND DISCUSSION

Total and relative energies of the structures studied at the RHF/6-31G*, RHF/6-311++G**//6-31G*, and B3LYP/6-311+G(2d,p)//6-31G* levels are gathered in Table 1.

Table 1. Total (in hartrees) and relative (in kcal mol^{-1}) energies of the reactants and the transition structures of the reaction between 1,3-butadiene and methyl acrylate, uncatalyzed and catalyzed by BF_3, calculated at several theory levels.

Structure	RHF/6-31G*// RHF/6-31G*		RHF/6-311++G**// RHF/6-31G*		B3LYP/6-311+G(2d,p)// RHF/6-31G*	
butadiene, *s-trans*	–154.919653		–154.962249		–156.044455	
methyl acrylate, *s-cis*	–304.680672	0.00	–304.765124	0.00	–306.569448	0.00
methyl acrylate, *s-trans*	–304.679773	0.56	–304.764425	0.44	–306.568407	0.65
methyl acrylate–BF_3, *s-cis*	–627.887629	1.77	–628.059948	1.98	–631.260826	1.71
methyl acrylate–BF_3, *s-trans*	–627.890442	0.00	–628.063104	0.00	–631.258104	0.00
TS *endo s-cis*	–459.534063	0.16	–459.655482	0.31	–462.577738	0.38
TS *endo s-trans*	–459.532078	1.41	–459.653568	1.51	–462.575710	1.65
TS *exo s-cis*	–459.534322	0.00	–459.655975	0.00	–462.578342	0.00
TS *exo s-trans*	–459.532143	1.36	–459.653901	1.30	–462.576053	1.44
TS *endo s-cis*–BF_3	–782.749754	2.84	–782.959815	2.51	–787.274886	2.23
TS *endo s-trans*–BF_3	–782.754290	0.00	–782.963810	0.00	–787.278442	0.00
TS *exo s-cis*–BF_3	–782.751645	1.66	–782.960503	2.07	–787.277135	0.82
TS *exo s-trans*–BF_3	–782.751519	1.74	–782.961505	1.45	–787.277118	0.83

With regard to the dienophile, a preference for the *s-cis* conformation, which is in agreement with the experimental data,[13] is found at all calculation levels. The coordination of a BF_3 molecule reverses this situation, the *s-trans* conformation becoming the most stable, again in agreement with previous theoretical results[14] and with experimental data for closely related compounds.[15]

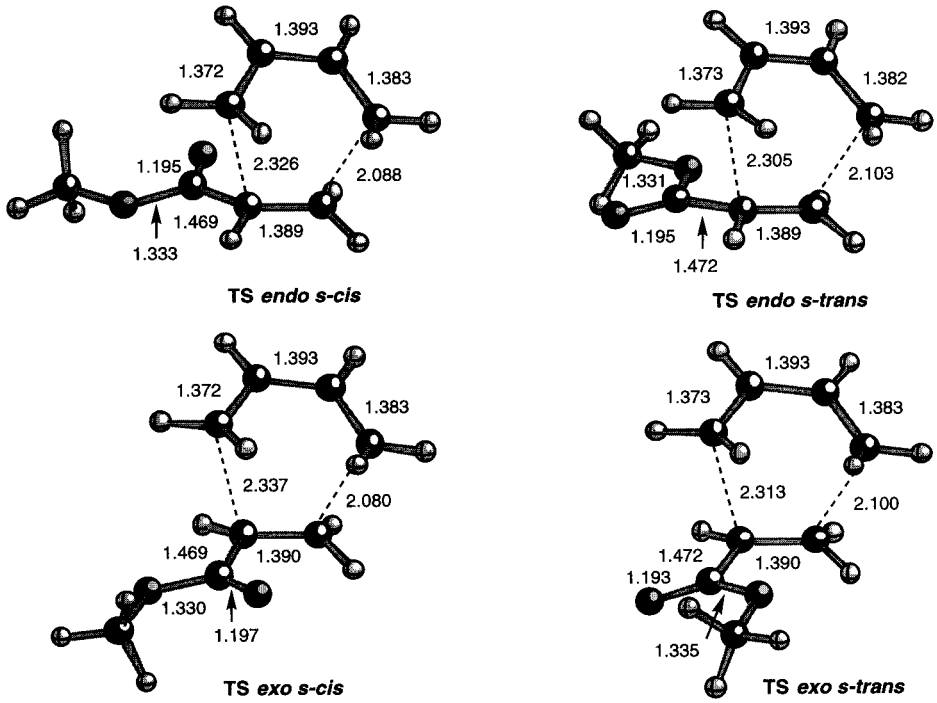

Figure 1. Transition structures of the reaction between 1,3-butadiene and methyl acrylate, calculated at the *ab initio* RHF/6-31G* level

Transition structures (TS), calculated at the RHF/6-31G* level, for the uncatalyzed reaction are shown in Figure 1, together with some relevant geometric parameters. The main geometric difference between the four TS lies in the relative orientation of the diene and dienophile moieties, given that the geometric parameters for each of these moieties are almost identical in all cases. As a consequence, the *s-cis* TS are slightly more asynchronous than their corresponding *s-trans* counterparts. The difference in synchronicity between *endo* and *exo* TS for a given conformation is much smaller. The same behaviour is also observed as far as the charge transfer from the diene to the dienophile is concerned. Thus, in the *s-cis* TS, the electron transfer takes place to a greater extent with regard to the corresponding *s-trans* TS (See the Computational Methods Section for details). However, the differences between both conformations are not dramatic (0.005 electron for the *endo* TS and 0.006 electron for the *exo* TS). Both the geometric and charge transfer arguments indicate that the *s-cis* TS are somewhat later than the corresponding *s-trans* TS in the reaction coordinate, which can help to explain the energetic results.

The energies of the TS of the uncatalyzed reaction show a clear preference for the *s-cis* conformers at all the theoretical levels used. Furthermore, the relative energies for the four TS are very similar in all cases, irrespective of the consideration of extended basis sets and correlation effects. Thermal corrections do not

change the relative stability of the TS, and the final $\Delta\Delta G^{\ddagger}$ values are very close to those of $\Delta\Delta E^{\ddagger}$ (Table 2). This result had also been described for the reactions of the same diene with other dienophiles[1] and of the same dienophile with cyclopentadiene.[4] However, the greater stability of the *s-cis* TS is not in agreement with the experimental results obtained in the uncatalyzed Diels–Alder reaction between butadiene and *(1R,2S,5R)*-menthyl acrylate.[16] The very low asymmetric induction obtained in this reaction indicates that the *s-cis* and *s-trans* TS are not very different in energy, but the major cycloadduct does indeed come from the attack of the diene on the less hindered face of the *s-trans* conformer. It is important to note that in these calculations the effect of the solvent has not been considered, and it has been described,[4] for the reaction of cyclopentadiene with methyl acrylate, that the *s-trans* TS are more stabilized by solvation than their corresponding *s-cis* counterparts.

Table 2. Zero point (ZPE) and thermal (T=298.15 K) energy corrections (in hartree) for the reactants and the transition structures of the reaction between 1,3-butadiene and methyl acrylate, uncatalyzed and catalyzed by BF_3, calculated at the RHF/6-31G* level. Calculated relative energies (in kcal mol^{-1}).

Structure	Internal Energy		Enthalpy		Free Energy	
	E+ZPE	ΔE	H	ΔH[a]	G	ΔG
butadiene, *s-trans*	–154.823670		–154.822725		–154.854498	
methyl acrylate, *s-cis*	–304.571100	0.00	–304.570156	0.00	–304.607467	0.00
methyl acrylate, *s-trans*	–304.570173	0.58	–304.569228	0.58	–304.606568	0.56
methyl acrylate–BF_3, *s-cis*	–627.758613	1.69	–627.757669	1.69	–627.806305	1.83
methyl acrylate–BF_3, *s-trans*	–627.761304	0.00	–627.760360	0.00	–627.809218	0.00
TS *endo s-cis*	–459.335662	0.12	–459.334718	0.12	–459.380847	0.42
TS *endo s-trans*	–459.333634	1.39	–459.332690	1.39	–459.378795	1.66
TS *exo s-cis*	–459.335850	0.00	–459.334906	0.00	–459.381285	0.00
TS *exo s-trans*	–459.333700	1.35	–459.332756	1.35	–459.379073	1.32
TS *endo s-cis*–BF_3	–782.536080	2.61	–782.535136	2.61	–782.591698	2.14
TS *endo s-trans*–BF_3	–782.540241	0.00	–782.539297	0.00	–782.595653	0.00
TS *exo s-cis*–BF_3	–782.537602	1.66	–782.536658	1.66	–782.593470	1.79
TS *exo s-trans*–BF_3	–782.537649	1.63	–782.536705	1.63	–782.593713	0.92

[a] ΔH and ΔE are necessarily identical, as both quantities differ by RT.

In order to test if solvent effects may also play a role in this case, single point calculations were carried out on the four TS, using a SCRF solvent model, namely that of Tomasi *et al.* at the RHF/6-31G* level of theory (see the Computational Methods section for details). As expected, the *s-trans* TS are preferentially solvated (calculated solvation free energies: –8.62 kcal mol^{-1} for the *endo* TS and –8.57 kcal mol^{-1} for the *exo* TS) with regard to their *s-cis* counterparts (–6.66 and –7.24 kcal mol^{-1}, respectively). As a consequence, the *endo s-trans* TS, which was the most unstable TS in the gas phase, becomes practically as stable as the *exo s-cis* TS. It is worth noting that it has previously been shown[4b] that reoptimization of the TS in the presence of the reaction field further stabilizes the *s-trans* TS in the case of the reaction between methyl acrylate and cyclopentadiene. On the basis of these results, it is expected that the *endo s-trans* TS would be the most stable in solution.

Both the single point RHF/6-311++G**//6-31G* and B3LYP/6-311+G(2d,p)//6-31G* calculations indicate a slight preference for the *exo* TS over the corresponding *endo* TS, which is also in contrast with the moderate

endo selectivity found experimentally in the uncatalyzed reaction between *(E)*-1,3-pentadiene and methyl acrylate.[17] Again, the solvent effect considerations lead to the conclusion that a slight *endo* preference is also to be expected in solution for the reaction studied.

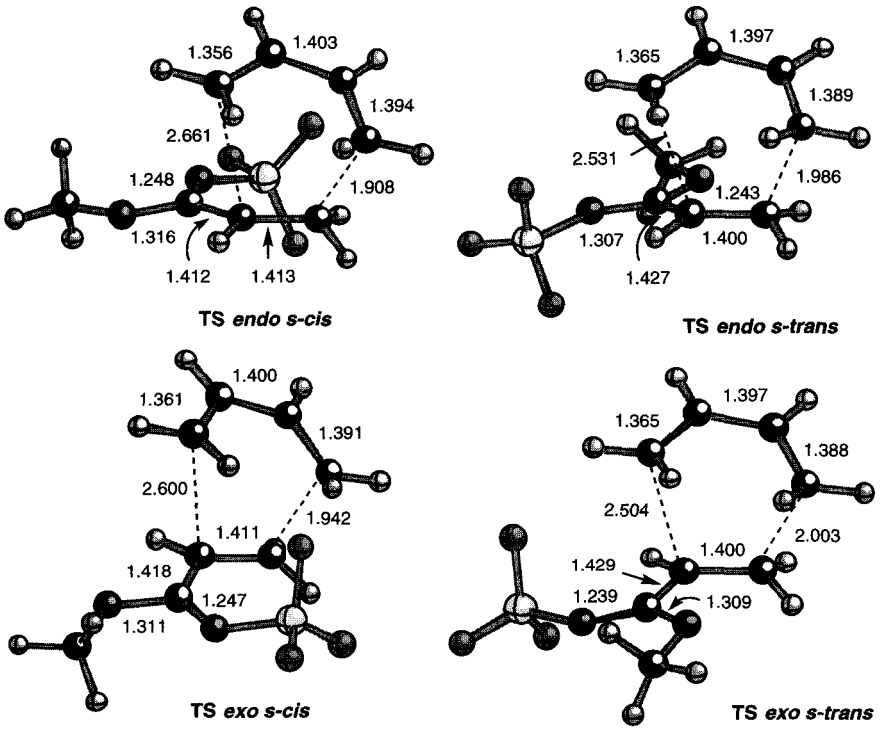

Figure 2. Transition structures of the reaction between 1,3-butadiene and methyl acrylate, catalyzed by BF_3, calculated at the *ab initio* RHF/6-31G* level

Transition structures (TS), calculated at the RHF/6-31G* level, for the BF_3-catalyzed reaction are shown in Figure 2, together with some relevant geometric parameters. In this case, the *s-cis* TS are also more asynchronous than their *s-trans* counterparts, but there is also a greater difference in the synchronicity between *endo* and *exo* TS, the latter being somewhat more synchronous. The study of the charge transfer between the diene and the dienophile moieties also shows the same picture. Thus, both *endo* and *exo s-cis* TS display a greater charge transfer (0.276 and 0.260 electron, respectively) than their *s-trans* counterparts (0.225 and 0.216 electron). It is worth noting that the Lewis acid has a strong influence on the global charge transfer, which is much more important than that calculated for the uncatalyzed process (0.090–0.100 electron). Also, all four TS of the BF_3-catalyzed reaction are much more asynchronous than their corresponding counterparts in the uncatalyzed process.

With regard to the calculated energies of the TS (Table 1), a significant increase in the *endo/exo* selectivity is caused by the use of BF_3, which is in agreement with the experimental results obtained in the BF_3-catalyzed reactions of methyl acrylate with *(E)*-1,3-pentadiene[17,18] and cyclopentadiene.[19] The decrease in the activation barriers also agrees with the experimental results.[20] The higher relative stability of the *s-trans* TS is in agreement

with the stereochemical course of the reaction between butadiene and *(1R,2S,5R)*-8-phenylmenthyl acrylate, catalyzed by $TiCl_4$, [21] with the major product coming from the approach of the diene on the less hindered face of the double bond of the dienophile in its *s-trans* conformation. As in the case of the uncatalyzed reaction, zero point energy and thermal corrections lead to minimal changes in the relative energies of the TS (Table 2), and do not change these conclusions.

The results obtained for the BF_3-catalyzed reaction shown that the *s-trans* preference is more important in the *endo* than in the *exo* approach, which indicates that the former should lead to a higher asymmetric induction. On the other hand, in the reaction of cyclopentadiene with chiral acrylates the higher asymmetric induction is obtained for the *exo* cycloadducts,[9,10] which has been explained mainly on the basis of steric interactions due to the methylene group of the diene. Therefore, given that these steric interactions are absent in the case of butadiene, we can conclude that the theoretical results described in this work confirm this hypothesis.

Finally, let us consider the different *endo/exo* selectivity associated with both conformations. As we have previously mentioned, the differences in *endo/exo* selectivity have been found in theoretical calculations using cyclopentadiene as the diene,[4] and they have been explained by steric interactions with the methylene group of the diene, which makes the *exo s-trans* TS particularly unstable. The calculations carried out with butadiene allow us to analyze this problem without the interference of the steric influence of this methylene group. In the absence of BF_3, the *exo* TS are slightly more stable, and both the *s-cis* and *s-trans* conformations show a similar *exo* preference. The calculations carried out with cyclopentadiene at a very similar theoretical level show a higher stability of the *endo* TS, and a higher *endo* preference for the *s-trans* conformation,[4a] which confirms the importance of the aforementioned steric interaction.

On the other hand, the use of BF_3 leads to an *endo* preference for the *s-trans* conformation, and to an *exo* preference for the *s-cis* conformation, and hence, the *endo/exo* selectivity is again higher for the *s-trans* conformations. This result shows how the different *endo/exo* selectivity for both conformations cannot only be due to steric interactions, but also to electronic reasons, in which the Lewis acid plays an important role.

To summarize, the results obtained in this work show that the *s-cis* and *s-trans* conformations of the methyl acrylate in the TS of its reaction with butadiene lead to a different *endo/exo* selectivity, or, in other words, that the *endo* and *exo* approaches also lead to different *s-cis/s-trans* preferences. The comparison of these calculations with those carried out for the reaction of methyl acrylate with cyclopentadiene[4a] show that both the Lewis acid and the steric interactions of the methylene group of the cyclopentadiene influence these selectivities.

COMPUTATIONAL METHODS

Ab initio theoretical calculations were carried out using the Gaussian 92 and Gaussian 94 programs.[21]

Butadiene was considered only in its most stable *s-trans* conformation.[22] All the geometrical optimizations, including transition structure searches, were carried out at the RHF/6-31G* level. The presence of a stationary point was confirmed in all cases by the correct number of negative eigenvalues of the Hessian matrix. In the case of the TS, the vibration associated with the imaginary frequency was checked to correspond with the reaction coordinate. For the RHF/6-31G* geometries, single point calculations were carried out using a more extended basis set (split valence triple zeta with polarization and diffuse functions added on all atoms, 6-311++G**). Also, electronic correlation effects were considered through single points calculations using the hybrid B3LYP functional,[23] together an extended basis set (split valence triple zeta with polarization functions added on all

atoms, and high angular momentum and diffuse functions added only on non-hydrogen atoms, 6-311+G(2d,p)). It is well-known that the standard Mulliken population analysis included in most of the quantum chemistry programs often leads to unrealistic charge distributions and so the natural charge distribution of the TS was performed by means of the NBO 3.1 program included in Gaussian 94.[24]

Solvent effects were considered by means of the Tomasi PCM model,[25] as implemented in the Gaussian 94 program, using the isodensity surface polarized continuum model (IPCM) with a dielectric constant of 8.93, corresponding to methylene chloride.

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