DOI: 10.1002/ejoc.200701082

Diels–Alder Reactions of Symmetrically 1,4-Disubstituted Dienes: Theoretical Study on the Influence of the Configuration of the Double Bonds on the Regio- and Endoselectivity

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Keywords: Cycloaddition / Diels–Alder reaction / Regioselectivity / Density functional calculations

It was experimentally shown in Diels-Alder reactions that symmetrically 1,4-disubstituted dienes exhibit high regio- and endoselectivity induced by the (*E*,*Z*) configuration of the double bonds. In order to understand the origin of this selectivity, the transition states associated with the reaction between a series of such dienes (R = OMe, CH_3, NH_2, F, CN) on substituted ethylene (R′ = CO_2Me, CN, F, OMe) were determined by DFT calculations. If the regioselectivity confirmed by a single-point MP2 calculation is predicted to be good in most cases, its direction remains difficult to predict; the R′ group of the dienophile can orient itself toward either the (*Z*) or the (*E*) side of the diene. Neither primary nor secondary frontier orbital interactions appear to be able to rationalize these results. They are more likely explained by a delicate balance between steric and electrostatic interactions. This hypothesis is further supported by the calculated reactivity of the (*E*,*E*) and (*Z*,*Z*) corresponding dienes. In any case, a standard DFT calculation, confirmed by a single-point MP2 step, is likely to provide a reliable guideline for a synthesis strategy that allows the control of up to four stereogenic centres in a single reaction step.

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Introduction

The [4+2] cycloaddition reaction is one of the most straightforward ways to assemble six-membered rings through a perfectly atom-economical process. Rapid and controlled introduction of varied functionalities in the newly created structure explains why this reaction is also very convergent. When it comes to the control of the stereochemical characteristics, the Diels–Alder cycloaddition is regarded as a prototypal member of the orbital-controlled class of reactions.[1] To take full advantage of the symmetry conservation rules, the general equation predicts that 1,4-disubstituted dienes are the best synthons. Indeed, two allylic substituents result from the ring closing, which are, under thermal conditions, *syn* if the configuration of the diene is (*E*,*E*) or (*Z*,*Z*) or *anti* when (*E*,*Z*) or (*Z*,*E*) dienes are employed. Overall, up to four stereogenic centres can be controlled during this single step, which should be compared to the maximum of three centres when the far more popular 1,3-disubstituted dienes are used in the reaction (Figure 1).

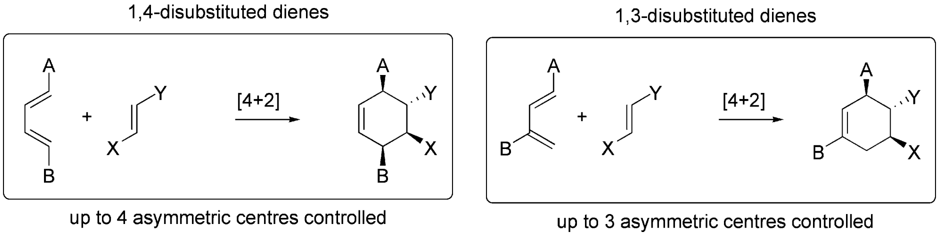

Figure 1. 1,4- and 1,3-Disubstituted dienes in Diels–Alder cycloadditions.

However, 1,4-disubstituted dienes suffer from major drawbacks. If A and B are of opposite electron-demand nature (one is electron withdrawing and the other electron donating), the so-called "push–pull" diene and its reactivity was shown to be generally weakened.[2] If A and B are of similar nature (both electron-withdrawing or -donating groups), the contradictory influence of the substituents on the polarization of the double bonds is expected to also

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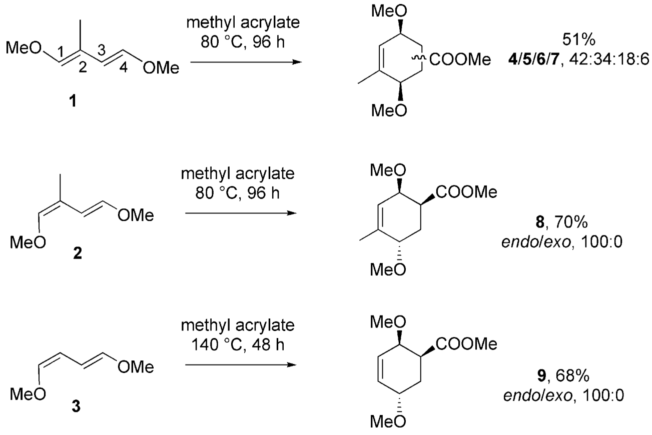
attenuate the reactivity and regioselectivity imposed by the diene. This phenomenon affects both the reactivity and regioselectivity. In contrast, the possibly synergetic effect of A and B in 1,3-disubstituted dienes enhances their performances. These facts associated with the difficulties often encountered during the stereocontrolled synthesis of 1,4-disubstituted dienes[3] explain why these reagents are rarely employed in organic chemistry.[4]

The configurations of the double bonds have an obvious influence on the reactivity, and the *s-cis* conformation required for the diene to approach the transition state will be easily adopted by (*E*,*E*) species but hardly reached by the (*Z*,*Z*) species; the (*E*,*Z*) dienes lie somewhere in between. In contrast, cycloadditions involving (*E*,*Z*) dienes exhibit remarkable regio-[5] and endoselectivities as illustrated in Scheme 1.[6] Whereas the thermal reaction of dimethoxy diene (*E*,*E*)-**1** provides the four possible isomeric adducts **4**–**7** in unattractive ratios, its (*Z*,*E*) analogue **2** affords a single, fully controlled, cyclohexene **8**. Comparison to the results obtained with 1,4-dimethoxybuta-1,3-diene (**3**) indicates that the effect of the allylic methyl group in the 2-position is limited.



Scheme 1. Influence of the configurations of the double bonds on the selectivities of the Diels–Alder cycloaddition.

These results suggested that the relative configuration of the double bonds in dienes such as **3** exerts a direct influence on the interactions between the diene and the dienophile at the transition states (TS), which controls the stereochemical outcome of the reaction. The origins of this phenomenon were seemingly unclear, and we decided to determine the transition states (TS) of Diels–Alder reactions for a panel of (*E*,*Z*) dienes bearing two identical R groups in the 1- and 4-positions. Ethylene monosubstituted by one R′ group was retained as a model dienophile. For each couple of reactants we considered four possible TS structures (Figure 2). They correspond to the two regioisomers [denoted "*trans*" (*t*) and "*cis*" (*c*) when the carbon atom bearing the R′ group connects to the carbon atom of the diene bearing the R group in the *E* and *Z* position, respectively]; the *endo* (*n*) and *exo* (*x*) situations were then considered for each regioisomer.

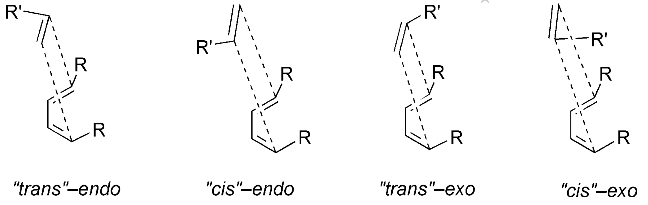


Figure 2. Four possible transition states for the [4+2] cycloaddition between an (*E*,*Z*) 1,4-disbstituted diene and a monosubstituted ethylene.

Computational Details

Calculations were performed by using the B3LYP density functional with the 6-311++G** basis set. The geometry of the transition states was checked by vibrational analysis and the energies were ZPE corrected. Because long-range interactions are poorly described by DFT, which thus tends to underestimate the *endo*/*exo* selectivity, we performed MP2 single-point calculations by using the B3LYP/6-311++G** geometry, ZPE corrected from B3LYP/6-311++G** frequencies. For qualitative discussions involving MO coefficients, we refer to AM1 results. Atomic charges were computed by using NBO analysis at the B3LYP/6-31G** level. The GAUSSIAN 03 series of program was used throughout this work.[7]

Results and Discussion

Addition of Methyl Acrylate (10) and Acrylonitrile (11) to (*E*,*Z*) 1,4-Dimethoxybuta-1,3-diene (3)

The addition of methyl acrylate (**10**) to (*E*,*Z*)-**3** was first considered because experimental results are available, although its study is made quite difficult by the number of possible combinations of reactant conformations in the TS. As a matter of fact, four possible conformations **3a**–**d** of dimethoxybutadiene are to be considered (Figure 3, top), with the **10a** and **10b** *s-cis* and *s-trans* main conformations of methyl acrylate (the two other conformations resulting from C–O methyl rotation were not included, as they are 8.28 and 11.10 kcal mol^{-1} higher in energy, respectively).

The five lowest TSs yield the "*trans*" regioisomer. Their relative energies are reported in Figure 4, and they result, by order of increasing energy, from the reaction of **3b** + **10a** (*endo*), **3b** + **10a** (*exo*), **3b** + **10b** (*endo*), **3b** + **10b** (*exo*), and **3a** + **10a** (*exo*). The lowest "*cis*" TS lies at 2.64 kcal mol^{-1}. By assuming a Boltzmann population of these five TSs, the major products should be the "*trans*"–*endo* (ca 70%) and "*trans*"–*exo* (ca. 30%); the "*cis*" regioisomer accounts for less than 2% of the products. These results are in qualitative agreement with experimental results giving only the "*trans*"–*endo* isomer. At the MP2 level (in parentheses in Figure 4), the lowest *tx* TS is shifted 1.65 kcal mol^{-1} higher, and the *endo*/*exo* ratio raises to more than 90%, which is within the uncertainty of the experimental measure.[6]

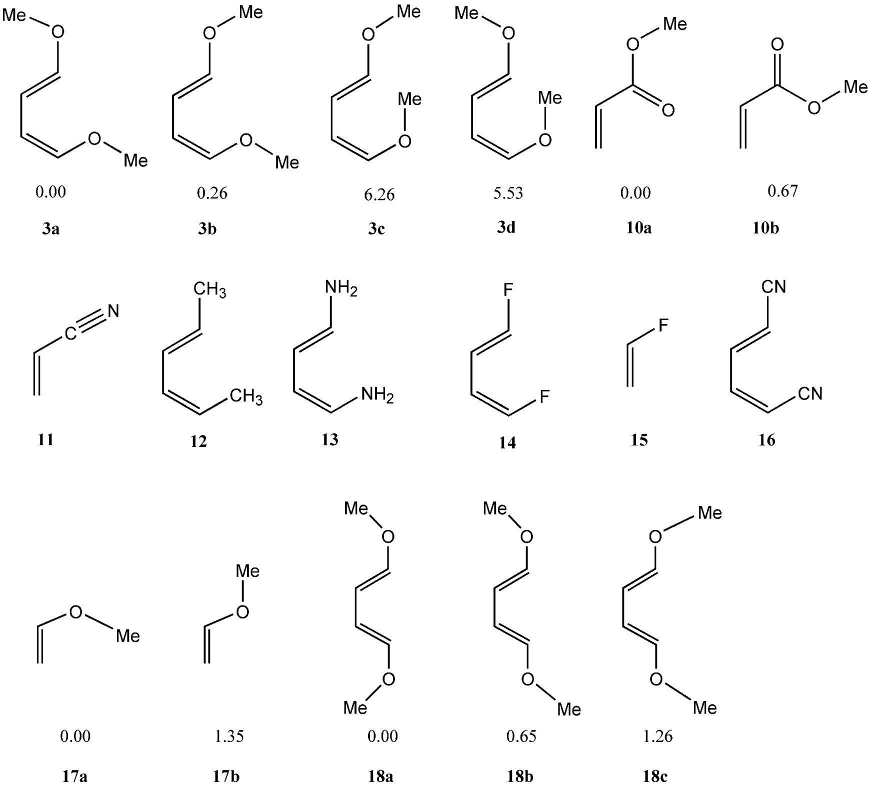


Figure 3. Structures and conformers of model dienes and dienophiles (relative energies in kcal mol^{-1}).

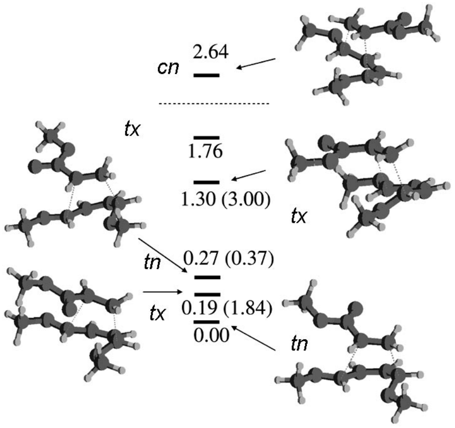


Figure 4. Selected TSs of the reaction of (*E*,*Z*)-**3** and methyl acrylate (**10**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

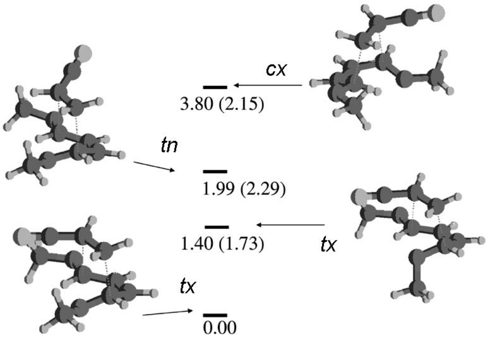


Figure 5. Selected TSs of the reaction of (*E*,*Z*)-**3** with acrylonitrile (**11**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

Modelling the reaction of acrylonitrile (**11**) with diene **3** is simplified by the rigidity of the dienophile. Here again, the lowest TSs correspond to the "*trans*" isomer (Figure 5). The lowest "*cis*" isomer lies at 3.80 kcal mol^{-1} at the B3LYP level, and even though it is strongly stabilized at the MP2 level it should represent no more than 2% of the products. In contrast to methyl acrylate, a strong predominance (ca. 95% and even more after MP2) of the *exo* adduct is predicted. The lowest *exo* TS involves conformer **3b** of the diene; the second TS is obtained when starting from **3c**, but after optimization; the O–Me bond borne by the (*Z*) double bond is oriented almost perpendicular to the dienic system.

Because these rather complex situations are not favourable to a qualitative discussion of the driving forces acting on the regio- and stereoselectivity, calculations were performed on a family of model dienes and dienophiles selected to (i) circumvent the problems generated by the manifold conformations of the reactants and (ii) offer a panel of various electron-demand situations.

Addition of Acrylonitrile (11) to (*E*,*Z*)-1,4-Dimethylbuta-1,3-diene 12

The cycloaddition of (*E*,*Z*)-**12** with styrene and substituted styrene has already been described.[8] Unfortunately, the nature of the substrates did not enable the determination of the stereoselectivity. A (*E*,*Z*)-1,4-dimethylbutadienic species was found to undergo regio- and stereoselective cycloadditions.[9] Nevertheless, the diene moiety was grafted on a dissymmetrical substrate so that the regioselectivity cannot be attributed only to the (*E*,*Z*) configuration.

At the B3LYP level, a strong predominance (ca. 80%) of the "*trans*"–*exo* isomer is expected, which rises to ca. 90% at the MP2 level (Figure 6). Note that at this level the major secondary product becomes the *cn* one.

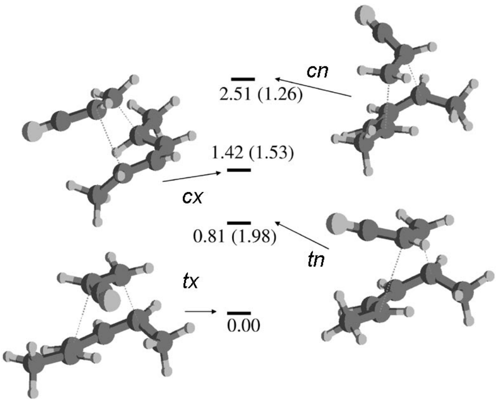


Figure 6. Transition states of the reaction of (*E*,*Z*) 1,4-dimethylbutadiene **12** with acrylonitrile **11**. The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single point calculations.

Addition of Acrylonitrile (11) to (*E*,*Z*)-1,4-Diaminobuta-1,3-diene (13)

Though the predicted instability of primary dieneamines prohibits its experimental study, such compounds have been used in previous theoretical studies[10] as a model of a highly electron-rich diene, with less bulky substituents than, for example, OMe.

The results obtained with this model system are particularly clear cut. According to these data, the major product should be the "*trans*"–*endo*, the TS of which lies 2.64 kcal mol^{-1} below the "*cis*"–*exo* TS and 2.79 kcal mol^{-1} below that of the "*trans*"–*exo* TSs (Figure 7). Therefore, a fully stereocontrolled cycloadduct would be expected in this case.

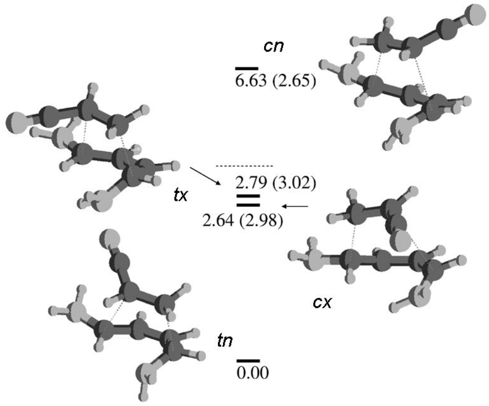


Figure 7. Transition states of the reaction of (*E*,*Z*)-**13** with acrylonitrile (**11**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

Addition of Acrylonitrile (11) and Fluoroethylene (15) to (*E*,*Z*)-1,4-Difluorobuta-1,3-diene (14)

A first model study dealt with the addition of acrylonitrile (**11**) to difluorobutadiene **14**. At the B3LYP level, no significant difference was found between the three "*trans*"–*endo*, "*trans*"–*exo*, and "*cis*"–*endo* TSs, a situation expected to yield strongly competitive reaction, whereas the "*cis*"–*exo* TS should have a negligible participation (Figure 8). However, MP2 calculations result in a strong destabilization of the *tx* and *tn* stereoisomers with respect to that of the *cn* isomer, which should represent, according to the perturbation computation, more than 80% of the products.

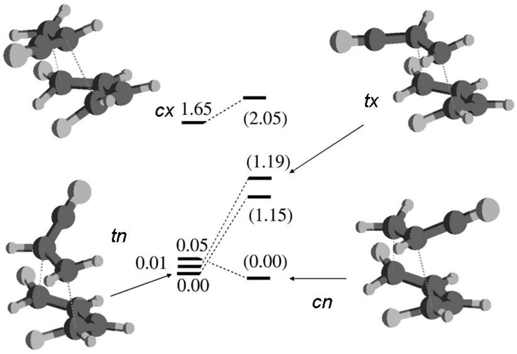


Figure 8. Transition states of the reaction between (*E*,*Z*)-**14** with acrylonitrile (**11**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

In contrast, the reaction of fluoroethylene (**15**) and difluorobutadiene **14** yields almost selectively the "*cis*"–*endo* TS, and the other three lie more than 2 kcal mol^{-1} above this TS (Figure 9) with remarkable agreement in both calculation methods.

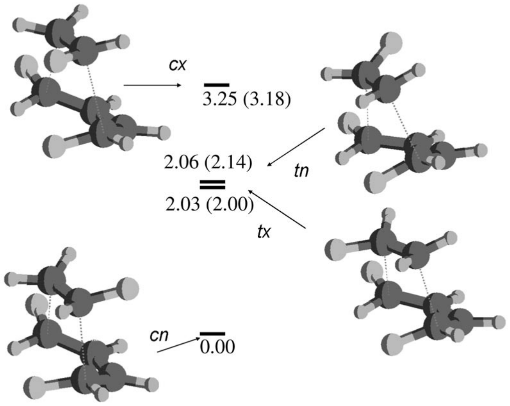


Figure 9. Transition states of the reaction between (*E*,*Z*)-**14** with fluoroethylene (**15**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

Because of the ambiguous character of fluorine, which as a substituent acts both as a strong π donor and σ attractor, the nature of the electron demand is not obvious in these cases. The orbital examination indicates that the reaction between acrylonitrile and difluorobutadiene follows normal electron demand. In the reaction between fluoroethylene and difluorobutadiene, the two HOMO–LUMO gaps are almost equal and relatively large, which results in a high activation barrier of ca. 31 kcal mol^{-1}, as displayed in Table 3. Note that all three isomers of 1,4-difluorobutadiene have been characterized experimentally,[11] but to the best of our knowledge, no cycloaddition of the (*E*,*Z*) isomer has been carried out.

Addition of Acrylonitrile (11), Fluoroethylene (15), and Methyl Vinyl Ether (17) to (*E*,*Z*)-1,4-Dicyanobuta-1,3-diene (16)

The next step involved the strongly electron-deficient model diene **16** and three prototypic dienophiles: acrylonitrile (electron-poor), fluoroethylene (borderline), and methyl vinyl ether (electron-rich). The first two couples of reactants give very similar selectivity (Figures 10 and 11): the "*cis*"–*endo* product is strongly favoured over, in decreasing order, the "*trans*"–*endo*, "*trans*"–*exo*, and "*cis*"–*exo* products.

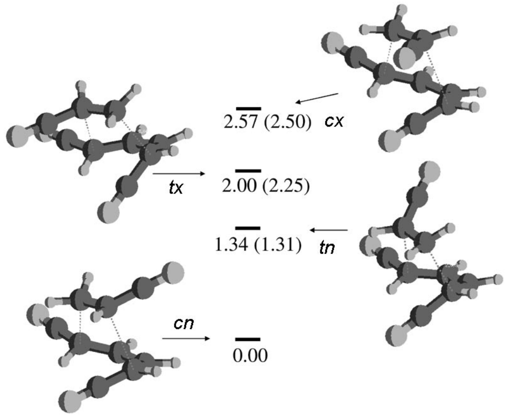


Figure 10. Transition states of the reaction of (*E*,*Z*)-**16** with acrylonitrile (**11**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

With methyl vinyl ether (**17**; Figure 12), the difference between the TS energy levels decreases sharply. The reaction is thus expected, at this level of calculation, to yield a mixture of the "*cis*"–*endo* (ca. 50%), "*trans*"–*endo* (ca. 20%), "*cis*"–*exo* (ca. 20%), and "*trans*"–*exo* (ca. 10%) isomers. At the MP2 level, a 3:1 mixture of *cn* and *tn* is expected with negligible amounts of the other products.

Again, the nature of the electron demand calls for a brief comment. The reaction between dicyanobutadiene and methyl vinyl ether is characteristic of an inverse-demand situation. According to HOMO–LUMO interactions, the other two cases are weakly inverse demand, which results in high energy barriers (ca. 27 kcal mol^{-1}, cf. Table 3). Note that the isomers of 1,4-dicyanobutadiene were obtained experimentally, but, to the best of our knowledge, they have not been used in Diels–Alder reactions.[12]

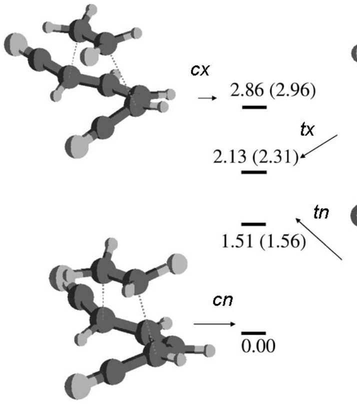


Figure 11. Transition states of the reactions between (*E*,*Z*)-**16** and fluoroethylene (**15**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

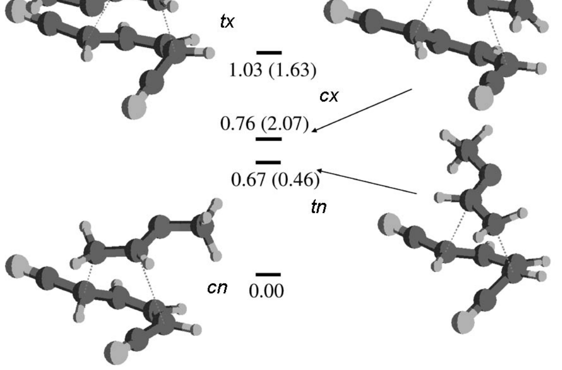


Figure 12. Transition states of the reaction between (*E*,*Z*)-**16** and methyl vinyl ether (**17**). The relative energies are in kcal mol^{-1}. Values in parentheses refer to MP2 single-point calculations.

The most salient of these results are gathered in Table 1, which highlights their dramatic dependency on the nature of the reactants.

It is worthy to note that MP2 calculations in most cases increase the selectivity predicted at the B3LYP level for the major product, though they can also modify the relative amounts of minor or very minor products. It has been established that if MP2 results satisfactorily reproduces the general trends of Diels–Alder reactions they tend to give irrelevant absolute values of their activation energies.[13]

The regioselectivity and *endo*/*exo* selectivity in Diels–Alder reactions are usually rationalized by considering that the reaction, according to the FMO method, is controlled by the prominent frontier orbital interaction, namely the diene HOMO with the dienophile LUMO in the "normal-electron-demand" reaction, and the diene LUMO with the dienophile HOMO in the "inverse-electron-demand" situation.[14] In borderline cases, both HOMO–LUMO interactions should be taken into account. These interactions are

Table 1. Major products P in Diels–Alder reactions of (*E*,*Z*) R-homodisubstituted dienes with $R'CH=CH_2$ dienophiles: *c* "*cis*", *t* "*trans*" (see Figure 2), *n endo*, *x exo*. Only the isomer(s) corresponding to more than ca. 20% of products are included.

R	OMe **3**	OMe **3**	CH_3 **12**	NH_2 **13**	F **14**	F **14**	CN **16**	CN **16**	CN **16**
R′	CO_2Me **10**	CN **11**	CN **11**	CN **11**	CN **11**	F **15**	CN **11**	F **15**	OMe **17**
P(DFT)	*tn tx*	*tx*	*tx tn*	*tn*	*tx tn cn*	*cn*	*cn*	*cn*	*cn tn cx*
P(MP2)	*tn*	*tx*	*tx*	*tn*	*cn*	*cn*	*cn*	*cn*	*cn tn*

considered as "primary" when they take place between the centres to be bonded or as "secondary" when they arise (in general) between the HOMO of the diene and an unsaturated conjugating substituent of the dienophile.[15] Moreover, it has been stated that other secondary orbital interactions can occur between terminal σ MOs of the diene and π MOs of the dienophile.[16] In addition, electrostatic effects may be considered, either again "primary", between the centres to be bonded, or "secondary" between the substituents of diene and dienophile moieties, as evidenced by Houk et al.[17] More specific electrostatic interactions, in the form of hydrogen bonds, have been also characterized.[18] Moreover, it has been established that the formation of prereactive van der Waals complexes are likely to play a role in the endoselectivity.[19] Obvious steric hindrance effects are superimposed to all these electronic parameters.[20]

In an attempt to rationalize these results, we will first examine the orbital interactions. The primary interaction appears to be unable to explain the "*cis*"/"*trans*" regioselectivity. As a matter of fact, the MO coefficients borne by the terminal carbon atoms of the dienes considered here are very similar to one another. At the AM1 level, their absolute values differ typically by less than 0.01. Their difference is enhanced for the HOMO of dimethoxybutadiene in its **3a** conformation [0.47 (*Z*) vs. 0.44 (*E*)], but in conformation **3b**, which is involved in the lower TSs of its reaction with methyl acrylate or acrylonitrile, the HOMO has nearly equal coefficients up to the third digit [0.4623 (*Z*) vs. 0.4615 (*E*)]. In only the case of dimethylbutadiene **12**, a significant difference appears in the coefficients of the HOMO [0.50 (*Z*) vs. 0.42 (*E*)], which agree with the "*trans*" regioselectivity of its reaction with acrylonitrile (**11**); as a matter of fact, the dienophile **11** has a larger LUMO coefficient on the terminal carbon atom.

In a previous paper dealing with the cycloaddition of dimethoxybutadiene **3** with methyl acrylate (**10**), it was suggested that a steric hindrance at the *Z* side could induce a rotation of the corresponding OMe group and result in its deconjugation, which thus enhances the dissymmetry of the dienic system.[6] This hypothesis is invalidated by the structures of the TSs (Figures 4 and 5), which show that this system remains roughly planar, except in the case of the *tx* TS in Figure 5, which is not the lowest in energy. Moreover, such a phenomenon evidently could not be put forward in the cases of "rigid" dienes **14** and **16**.

The influence of secondary MO interactions on the *endo–exo* selectivity has been put forward a long time ago;[21] their importance has been questioned,[22,23] and very recently evidenced again.[24] They have been studied in great detail, mostly when the dienophile is a diene or diene-shaped molecule such as acrylate, and the interactions between each couple of diene–dienophile centres has been quantitatively compared.[25] The situation encountered here is rather different, as we have to take into account the substituents of the diene. Those participate to the π system of the diene, and thus influence both the regio- and the *endo*/*exo* selectivity.

This is exemplified (Figure 13) in the cases of the reactions of dienes having substituents containing lone pairs of electrons (R = OMe, NH_2 and F) with (i) a conjugated (R′ = CN) dienophile and (ii) a nonconjugated (R′ = F) one.

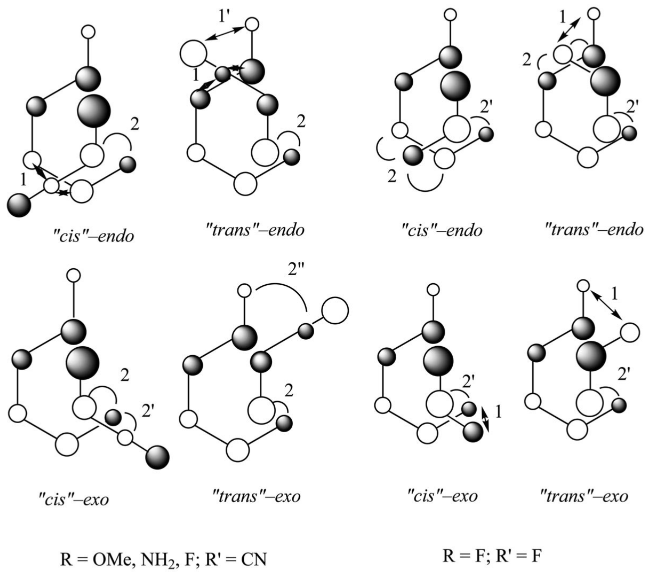


Figure 13. Secondary interactions between the HOMO of an (*E*,*Z*) R-disubstituted diene with the LUMO of a dienophile R′–$CH=CH_2$. Left: R = lone-pair substituent (OMe, NH_2, F); R′ = CN; right: R = R′ = F; double arrows represent stabilizing interactions; curved lines represent destabilizing interactions.

With acrylonitrile, Figure 13 (left) suggests: (i) The two regioisomeric *endo* approaches should be favoured, according to the stabilizing interaction indicated by the double arrows labelled 1 and 1′. (ii) Another interaction, labelled 2 should decrease the overlap at the *Z* side and thus has, this time, a destabilizing character. This interaction is minimized when the smaller coefficient of the dienophile approaches this *Z* double bond of the diene, which should favour the "*cis*" regioisomers. (iii) An additional destabilizing interaction 2′ is found in *cx* and to a lesser extent (2′′)

in *tx* isomers. The "*cis*"–*endo* isomer should be finally expected, which is in disagreement with the results displayed in Table 1.

For nonconjugated dienophiles such as fluoroethylene (Figure 13, right part), the same HOMO–LUMO interaction seems to stabilize the "*cis*"–*exo* TS by interaction 1. However, this structure is found at the highest energy in the reaction between **14** and **15** (Figure 9). On the contrary, the "*cis*"–*endo* arrangement, which is the most stable, should be disfavoured by the interactions 2 and 2′.

Evidently, the qualitative examination of FMO interactions is unable to rationalize unambiguously the regio- and stereoselectivity of these systems. As far as they are the prominent ones (which is not self evident), a quantitative analysis of these interactions should be necessary to reach a predictive level, which is beyond the scope of this study.

Another possible way of understanding these results was suggested in a study by Inagaki and Ikeda about secondary interactions between the π MOs of ethylene and terminal σ MOs of a diene monosubstituted either in the (*E*) or (*Z*) position.[16] These authors concluded that this interaction is controlled by the couple formed by the π* of the dienophile and the σ (*Z*) of the diene (Figure 14). Thus, if the diene bears an R substituent that is more electronegative than H this interaction should be amplified when H is in the (*Z*) position because the energy gap separating the π* from the σ_{CH} would become smaller than that between π* and σ_{CR}. At first glance, these results could be extrapolated to explain the regioselectivity of the reaction of a dissymmetric dienophile on an (*E*,*Z*) disubstituted diene: one can guess that the larger lobe of the dienophile will orientate towards the C–H bond in the "inner" position to maximize this stabilizing interaction. We conclude that with R′ = CN or CO_2Me, the "*cis*" regioisomer should be always obtained; with R′ = OMe, the polarity of the π* MO is opposite to that of the preceding ones and thus the "*trans*" isomer would be expected, which is in complete disagreement with the calculation results. Note that for R′ = F, the coefficients of the π* MO are nearly equal.

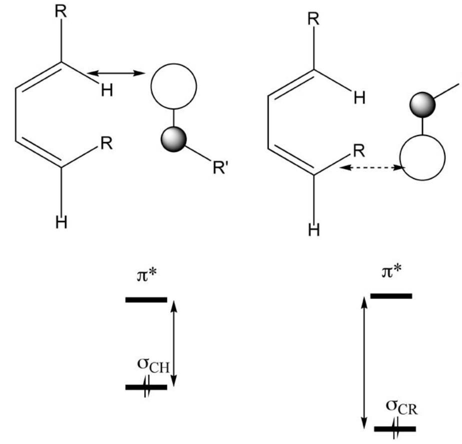


Figure 14. MO interactions between π* of dienophile (R′ = CN, CO_2Me) and terminal σ MOs of dienes.

Let us now examine the primary electrostatic interactions that possibly play important roles in regiocontrol.[26] The NBO charges of the terminal carbon atoms of the reactants are given in Table 2. The dissymmetry of the dienes is noticeable. For several couples of reactants (**16** + **15**, **16** + **11**, **14** + **15**, **16** + **17**) the regioselectivity is in agreement with these charge interactions. Nevertheless, the similitude between the charges borne by the two carbon atoms of the olefin of methyl acrylate and acrylonitrile forbids establishment of a general explanation for these interactions.

Finally, it appears that this selectivity does not result from a unique type of parameter, but from a delicate balance where steric hindrance and various electrostatic interactions seem to play the leading roles. In the TS, the steric repulsion exerted by the diene should decrease along the sequence "*cis*"–*endo* > "*cis*"–*exo* > "*trans*"–*endo* ≈ "*trans*"–*exo*. With the relatively bulky OMe, CH_3 (and to a lesser extent, NH_2) groups, this interaction thus favours the "*trans*" isomers. Electrostatic interactions of substituents seem also to play a role: in the reaction of dimethoxybutadiene **3** with acrylonitrile (**11**) (Figure 6), we remark that according to Houk,[17] the lowest TSs should minimize the interaction between the oxygen lone pair and the CN group. This criterion is not met in the "*cis*" approach, in which the MeO–N distance is shorter (3.47 Å) than that in the two lowest TSs (4.30 and 4.25 Å). In the case of diaminobutadiene **13**, we remark (Figure 7) that a hydrogen NH–NC bond shows up in the two lowest TSs, *tn* and *cx*, the role of which has already been pointed out by using SO_2 as a dienophile.[18] With compact substituents (F, CN), the corresponding reactions appear to be controlled to a large extent by electrostatic interactions between substituents. The energy of the four TSs of the **14** + **15** reaction (Figure 9) increases as the distance of the two closest F atoms decreases: 3.69 (*cn*), 3.37 (*tx*), 3.11 (*tn*), and 2.64 Å (*cx*). The situation is very similar in the reactions of dicyanobutadiene (**16**) with, on the one hand, acrylonitrile (**11**) where the shorter N–N distance decreases from 5.74 Å in (*cn*) to 3.67 Å in (*cx*) (Figure 10), and on the other hand, with fluoroethylene (**15**) (Figure 11) where the shorter F–N distance decreases from

Table 2. NBO/B3LYP/6-31G** atomic charges on terminal carbon atoms of (*E*,*Z*) homodisubstituted dienes and R′ substituted dienophiles. The conformation of methyl acrylate and methyl vinyl ether is either *s-trans* or *s-cis* (in parentheses).

R(diene)	C1(*E*)	C4(*Z*)	R′(dienophile)	C1(R′)	C2
OMe (**3a**)	0.15	0.11	CO_2Me (**10**)	–0.34 (–0.35)	–0.36 (–0.35)
NH_2 (**13**)	–0.04	–0.02	CN (**11**)	–0.35	–0.34
F (**14**)	0.26	0.23	F (**15**)	0.23	–0.55
CN (**16**)	–0.29	–0.32	OMe (**17**)	0.12 (0.13)	–0.54 (–0.59)
CH_3 (12)	–0.20	–0.20			

Table 3. Activation energy (kcal mol^{-1}) for the lowest TS and relative energies of the other TSs above the lowest one for the (*E*,*Z*), (*E*,*E*), and (*Z*,*Z*) configurations of 1,4 homodisubstituted dienes (B3LYP-6-311++G**). The TSs with (*Z*,*Z*) dimethoxybutadienes and (*Z*,*Z*) diaminobutadiene could not be located.

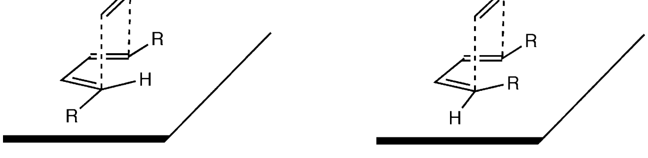
R	R′	(*E*,*E*)		(*E*,*Z*)					(*Z*,*Z*)	
		(*t*)*n*	(*t*)*x*	Reaction	*tn*	*tx*	*cn*	*cx*	(*c*)*n*	(*c*)*x*
OMe	CO_2Me	1.13	20.83[b,c]	**3** + **10**	23.84[a,b]	0.19	2.64	3.65	–	–
OMe	CN	2.22	20.38[c]	**3** + **11**	2.00	22.70[a]	3.88	3.80	–	–
CH_3	CN	0.75	21.67	**12** + **11**	0.81	25.69	2.51	1.42	2.45	34.65
NH_2	CN	0.09	18.02	**13** + **11**	21.55	2.79	6.63	2.64	–	–
F	CN	1.15	21.71	**14** + **11**	24.93	0.01	0.05	1.65	30.69	2.02
F	F	0.60	24.99	**14** + **15**	2.06	2.03	31.09	3.25	33.76	3.29
CN	CN	0.89	25.79	**16** + **11**	1.34	2.00	27.54	2.57	34.75	3.52
CN	F	0.39	25.88	**16** + **15**	1.51	2.13	27.38	2.86	34.80	3.43
CN	OMe	0.05	21.84	**16** + **17**	0.67	1.03	23.71	0.76	29.25	1.46

[a] Calculated from the lowest *s-cis* conformation **3a**. [b] Calculated from the *s-cis* conformation **10a**. [c] Calculated from the lowest (*E*,*E*) conformation **18a**.

4.72 Å (*cn*) to 3.14 Å (*cx*). The quasidegeneracy at the B3LYP level of the three lowest TSs (*tn*, *tx*, and *cn*) of the **14** + **11** (Figure 8) reaction remains somewhat puzzling. Nevertheless, MP2 calculations favour the *cn* TS having the longer distance F–N (4.76 Å). Because of its weak predicted selectivity, the reaction of dicyanobutadiene (**16**) with methyl vinyl ether (**17**) is difficult to discuss. It results probably from a compromise between the steric hindrance of the OMe group and the electrostatic repulsion between the oxygen and nitrogen atoms.

Let us now compare the activation energies of the reactions involving (*E*,*Z*) dienes to those of the corresponding (*E*,*E*) and (*Z*,*Z*) ones (Table 3). Although the "*cis*"/"*trans*" notion defined at the beginning becomes meaningless in these cases, the (*t*) and (*s*) notation is conserved in Table 3 for the sake of comparison to the (*E*,*Z*) series. The results are consistent with the preceding trends and give further insights on the complexity of the interactions between the R and R′ substituents.

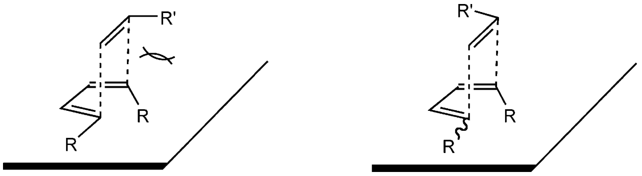
As expected, the absolute values of the activation energies follow the sequence (*E*,*E*) < (*E*,*Z*) << (*Z*,*Z*) for each couple of reactants. For the reactions of "rigid" dienes (**12**, **13**, **14**, **16**), the *endo*/*exo* preferences are relatively weak in the "*trans*" approaches: Table 3 shows that the *tn* and *tx* TS energies are generally similar in the (*E*,*Z*) series, whereas that of the (*t*)*n* TS resembles that of the (*t*)*x* TS in the (*E*,*E*) series. As a matter of fact, the distances between R (borne by the *E* double bond) and R′ are not very different in the two diastereoisomeric TSs (Figure 15), but surprisingly, the preference *tn*/*tx* is generally inverted from one series to another: the *tn* TS is preferred in the (*E*,*Z*) series, whereas the (*t*)*x* TS is preferred in the (*E*,*E*) series. It can only arise from differences in long-range interactions that arise during or even before the TS between R′ and the substituent R at the other end of the diene moiety, which is borne by a (*Z*) double bond in the (*E*,*Z*) dienes and by an (n) double bond in the (*E*,*E*) dienes (Figure 15). In contrast, the (*Z*,*Z*) TSs and most of the "*cis*" (*E*,*Z*) ones exhibit a marked preference for the *endo* stereoisomer (typically by 2–3 kcal mol^{-1}). This indicates control by the strong destabilizing interaction between the R group borne by the (*Z*) double bond and the nearby R′ group in the "*cis*"–*exo* position (Figure 16).



(*E*,*E*) diene: the *exo* approach is preferred

(*E*,*Z*) diene: the *endo* approach is preferred

Figure 15. Influence of the configurations of the double bonds on the *endo*/*exo* preference during the "*trans*" approaches.



(*E*,*Z*) or (*Z*,*Z*) dienes: the *exo* approach (left) undergoes steric/electrostatic umpairments. These disapear in the *endo* situation (right).

Figure 16. Possible origin for the *endo* preference during the "*cis*" approaches.

Conclusions

The study of the origin of the regio- and stereoselectivity of the Diels–Alder addition of (*E*,*Z*) homodisubstituted dienes offers a wide range of results depending on the nature of the substituents. Though the differences in the activation energies of the competing reactions are relatively weak, they should trigger a clearly marked regio/endoselectivity in most cases.

The MO analyses appear unable to account qualitatively for these results, which are likely to be controlled by a combination of parameters, among which steric hindrance and electrostatic interaction are the most important, especially between the reactant substituents, but the balance between them cannot be easily predicted. Nevertheless, a standard DFT calculation, with the confirmation of a single-point MP2 step, is likely to provide a reliable guideline for a synthesis strategy. Understanding these phenomena remain of major interest, as these dienes open an interesting way to control four stereogenic centres in a single reaction step.

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Received: November 15, 2007