Quantum chemical AM1 study of dimerization by hetero-Diels–Alder reaction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-hexopyranoside-2-ulose

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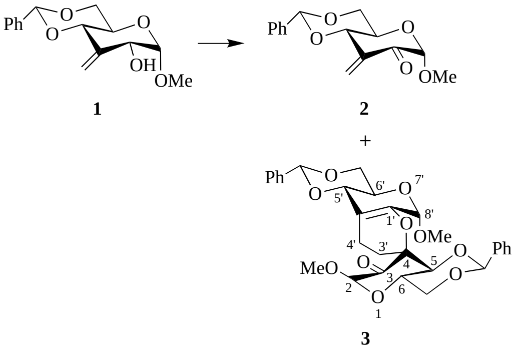
An unusual reaction, the dimerization by hetero-Diels–Alder reaction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methylene-α-D-hexapyranoside-2-ulose, has been studied by a detailed computational analysis using the AM1 method. A reaction mechanism is proposed based on the calculated results, and it is in good agreement with the experimental data. The theoretical calculations can explain the excellent regioselectivity of this dimerization and other phenomena observed during the experiments.

Recently, Czernecki *et al.* discovered an unusual dimerization reaction.[1] Surprisingly, oxidation of the allylic alcohol, methyl 4,6-*O*-benzylidene-3-dexoy-3-*C*-methylene-α-D-hexopyranoside-2-ulose[2] **1**, with pyridinium dichromate (PDC)[3] did not afford enone **2** in good yield, although equatorial allylic alcohols derived from carbohydrates were readily oxidized with this reagent.[4] A dimer **3** was determined to be the dominant product (Scheme 1).

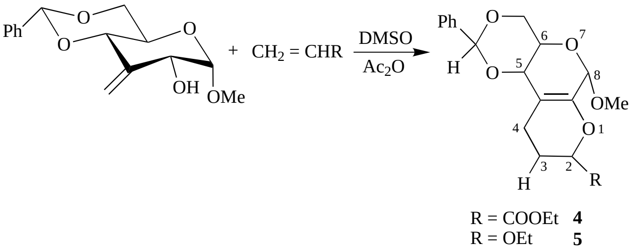


Scheme 1

Other oxidizing systems were evaluated, such as 4-methylmorpholine *N*-oxide in the presence of tetra-*n*-propylammonium perruthenate,[5] palladium acetate,[6] manganese dioxide[7] and dimethylsulfoxide–acetic anhydride (DMSO–Ac_2O).[8] The reaction was taken to completion only with the latter one, but the only product formed was compound **3** which was isolated in good yield (88%).[9]

Compound **3** could be the result of a [4+2] cyclization of enone **2** formed *in situ* behaving as a diene and dienophile. The regioselectivity of cycloaddition was confirmed.[9,10]

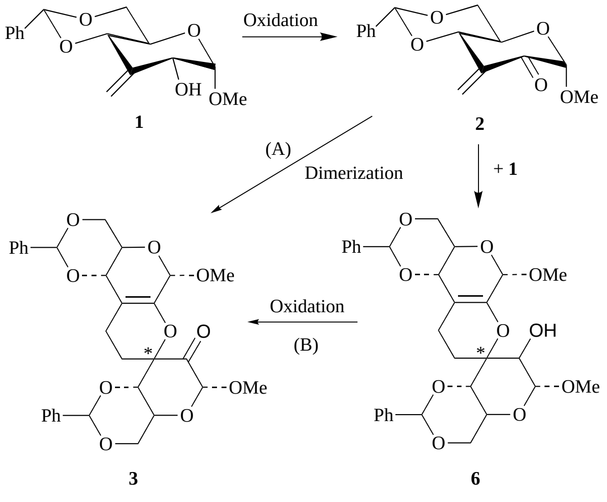
This facile dimerization is quite surprising because it is well known that hetero-Diels–Alder reactions with enones are rather difficult and that only moderate yields are obtained even under harsh conditions.[11] In the classical dimerization of enones, the enone behaves as an 'electron rich diene',[11] but an attempt to quench the formed enone **2** by adding an electron deficient double bond (acrylic acid ethyl ester) failed. The expected product **4** was not obtained. By contrast, when the oxidation was carried out in the presence of an electron rich double bond such as in ethyl vinyl ether, only 3.6% of dimer **3** was obtained. The cross-coupling product **5** was isolated (69%) and characterized, and the same regioselectivity was observed for this reaction as for the dimerization of enone **2** (Scheme 2).



Scheme 2

In order to understand this unusual dimerization mechanism, a systematic quantum chemistry study was carried out. This study allows us, from an energetic point of view, to verify the dimerization mechanism, to explain the ease of this reaction, to show the regioselectivity and to explain the quenching phenomena of the enone **2** formed by different reagents. This paper reports this study.

AM1 Analysis



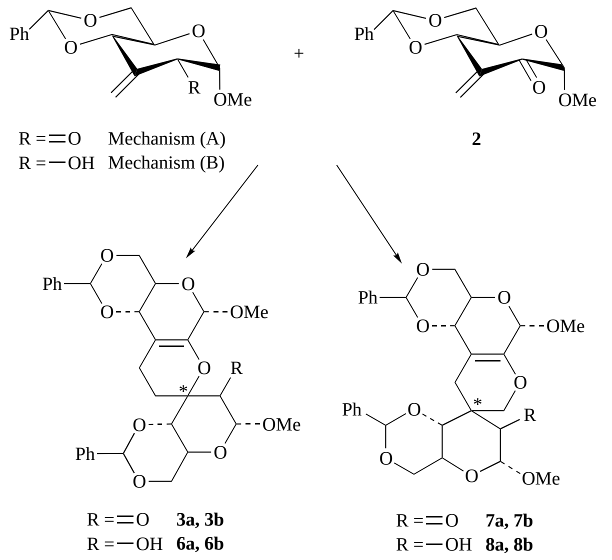
Scheme 3

Compound **3** could be obtained from **1** *via* two different possible mechanisms, illustrated in Scheme 3. The mechanism (B) involves a hetero-Diels–Alder reaction between allylic alcohol **1** and enone **2** to give adduct **6**, which is then oxidized to final product **3**. This mechanism is ruled out by experimental results, because a mixture obtained from the separation by chromatography on silica gel consists of only the compounds **2** and **3**. The mixture converts then almost entirely to **3**. This result favours another possible mechanism (A) of the formed enone **2**.

Some questions can be posed based upon experimental observations. (*i*) Why does the reaction proceed *via* mechanism (A) and not (B)? (*ii*) Why does the enone exhibit an exceptional reactivity in this reaction? (*iii*) What will be the configuration the final product **3**?

We attempt to answer these questions by a theoretical analysis using a semi-empirical approach.

The dimerization by a Diels–Alder reaction can be carried out *via* eight transition states, *endo* or *exo* combined with *syn* or *anti* isomerism, which give four possible adducts as shown in Scheme 4.



Scheme 4

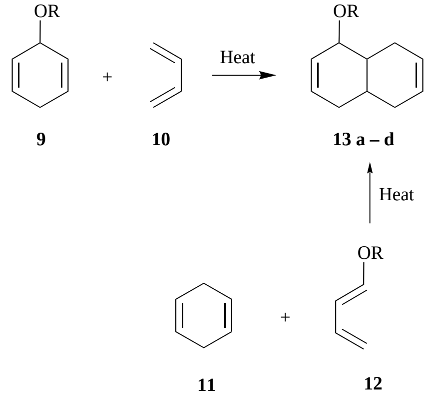
The presence of a chiral carbon atom (marked with symbol * in Scheme 4) after the Diels–Alder reaction would result in two different configuration products, **3a** and **3b**, **7a** and **7b** respectively for the mechanism (A). In mechanism (B) they are marked as **6a** and **6b**, **8a** and **8b**.

Method of calculation

The size of the studied molecules makes it impossible to use *ab initio* quantum mechanical methods. Therefore the semi-empirical method AM1,[12] which has given reliable results for Diels–Alder reactions,[13] has been used in our calculations. Full geometry optimizations were carried out at the RHF level, using the Broyden–Fletcher–Goldfarb–Shanno function minimizer (BFGS).[14] Transition states have been optimized by minimizing the root-mean-square gradient of the energy, and characterized through the correct number of negative eigenvalues of the energy second-derivatives matrix.[15]

Furthermore, because of the rather time-consuming computation for the transition states of the systems studied, we performed all calculations on four time- and memory-shared computers (two Silicon Graphics workstations, a Digital Alpha server and a CRAY-YMP) using the AM1 computation implemented in MOPAC7.[16]

In the following discussion, we use the results reported by Solà *et al.*[17] for comparison purposes. The system studied by Solà *et al.* using the AM1 method is shown in Scheme 5.



Scheme 5

Results and discussion

The calculated enthalpies for formation of reactants and products, and the orbital energies are gathered in Table 1.

A normal Diels–Alder reaction involves an electron-rich diene or analogue and an electron-poor dienophile, such as the

Table 1 Calculated enthalpies of formation of reactants and products. Orbital energies of the HOMO and LUMO of the reactants

	ΔH_f/kcal mol^{-1}		Orbital energy/eV	
Compound	RHF	$\Delta(\Delta H_f)^a$	HOMO	LUMO
1	−167.14		−9.62	0.34
2	−148.34		−9.69	−0.15
CH_2=CHCOOEt	−75.75		−11.03	0.06
CH_2=CHOEt	−31.94		−9.36	1.51
9	−32.20		−9.37	1.01
10	30.70		−9.36	0.47
11	17.00		9.12	1.19
12	−28.20		−8.68	0.58
6a	−338.39	−22.53		
6b	−328.79	−12.93		
8a	−340.52	−24.66		
8b	−288.43	27.43		
3a	−313.63	−16.19		
3b	−311.63	−15.14		
7a	−313.35	−16.67		
7b	−314.87	−18.19		
4	−249.34	−25.25		
5	−216.04	−35.76		

[a] $\Delta(\Delta H_f) = (\Delta H_f)_{\mathbf{product}} - \Sigma_i\{(\Delta H_f)_i\}_{\mathbf{reagents}}$. 1 cal = 4.184 J.

Table 2 Parameters for different transition states of dimerisation of enone **2**, computed with AM1 method

TS	$\Delta H^{\ddagger}$/kcal mol^{-1}	E_a/kcal mol^{-1}	r_1/Å	r_2/Å	α^a	Product
T1 (*endo–anti*)	−283.65	13.03	2.409	2.429	0.004	**3a**
T2 (*exo–syn*)	−264.46	32.22	2.604	2.404	0.040	**3b**
T3 (*endo–syn*)	−256.72	29.96	2.323	2.310	0.003	**7a**
T4 (*exo–anti*)	−262.56	34.12	2.626	2.481	0.028	**7b**
T5 (*exo–anti*)	−278.47	18.21	2.326	2.348	0.005	**3a**
T6 (*endo–syn*)	−219.71	76.97	2.612	2.477	0.026	**3b**
T7 (*exo–syn*)	−168.74	127.94	2.495	2.407	0.018	**7a**
T8 (*endo–anti*)	−165.75	130.93	2.615	2.357	0.052	**7b**

[a] α: degree of asynchronicity defined as $|r_2 - r_1|/(r_2 + r_1)$.

Table 3 Parameters for different transition states of hetero-Diels–Alder reaction between **1** and **2**, computed with the AM1 method

TS	$\Delta H^{\ddagger}$/kcal mol^{-1}	E_a/kcal mol^{-1}	r_1/Å	r_2/Å	*a*	Product
T1′ (*endo–anti*)	−297.65	18.00	2.440	2.436	0.001	**6a**
T2′ (*exo–syn*)	−276.86	38.79	2.425	2.351	0.016	**6b**
T3′ (*endo–syn*)	−239.88	75.77	2.498	2.394	0.021	**8a**
T4′ (*exo–anti*)	−277.24	38.41	2.569	2.458	0.022	**8b**
T5′ (*exo–anti*)	−283.88	31.77	2.409	2.375	0.007	**6a**
T6′ (*endo–syn*)	−161.14	154.51	2.600	2.375	0.045	**6b**
T7′ (*exo–syn*)	−109.48	206.17	2.443	2.389	0.011	**8a**
T8′ (*endo–anti*)	−182.98	132.67	2.601	2.459	0.028	**8b**

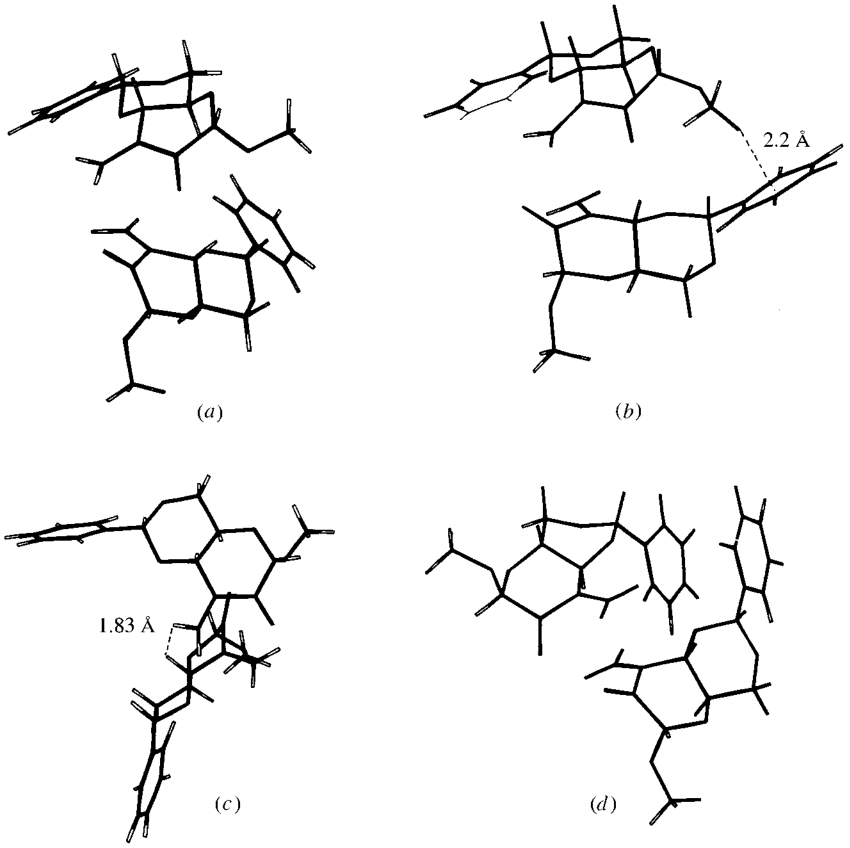


Fig. 1 Optimized geometries for four transition states of the dimerization. (*a*) Exocyclic attack on O-α position (**T1**); (*b*) endocyclic attack on O-α position (**T2**); (*c*) endocyclic attack on O-β position (**T3**); (*d*) exocyclic attack on O-β position (**T4**).

reaction between **11** and **12**. In the systems studied, the calculated orbital energies for each HOMO–LUMO pair of each reactant show that both the dimerization of **2** and the hetero-Diels–Alder reaction between **1** and **2** exhibit inverse electron demand. This means that if enone **2** behaves as a diene reagent in Diels–Alder cycloaddition, the reaction will be favoured when the dienophile is electron-rich.[18,19] The calculated results for two dienophiles, ethyl acrylate, CH_2=CHCOOEt, and ethyl vinyl ether (*O*-vinylethanol), CH_2=CHOEt, are also given in Table 1. The HOMO–LUMO pair for ethyl acrylate acid ethyl ester (−11.03 and 0.06 eV respectively) indicates that this dienophile is electron-poor. Its reaction with enone **2**, an electron-poor diene reagent, can be predicted as not being facile. In contrast, vinyl ethyl ether is a relatively electron-rich dienophile (HOMO: −9.36, LUMO: 1.51 eV) with respect to ethyl acrylate. Its reaction with enone **2** is possible. This deduction was verified by experiments. The vinyl ethyl ether was successfully used to quench the enone **2** to give **5**, as described above.

Analysing the heats of formation shows that the hetero-Diels–Alder reaction between allylic alcohol **1** and enone **2** (mechanism B) is more favoured thermodynamically compared with the dimerization (mechanism A). The greatest differences

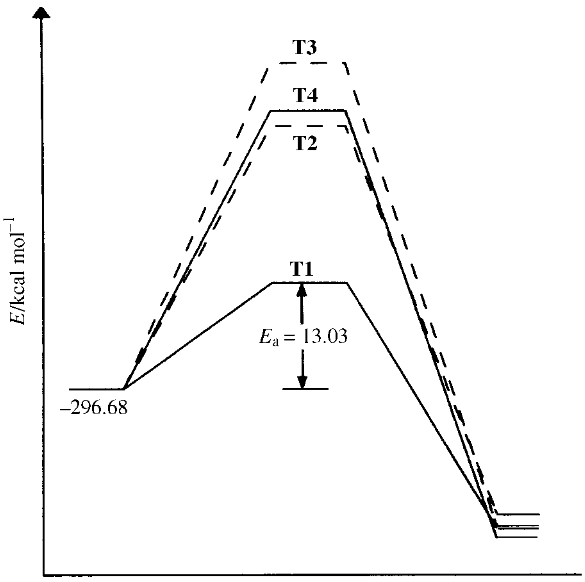


Fig. 2 Energy profile for the dimerization *via* four different transition states (*cf.* Fig. 1)

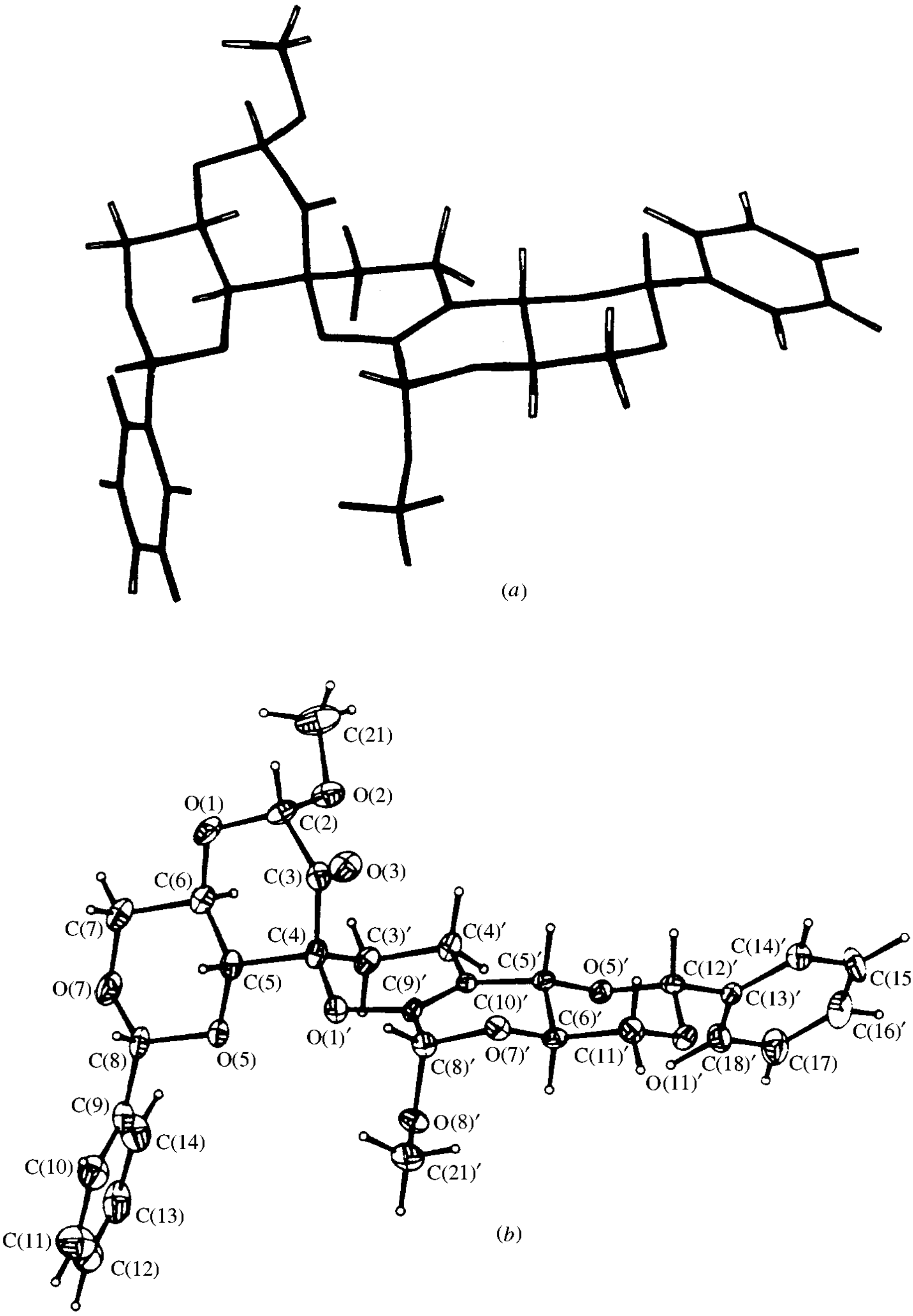


Fig. 3 Comparison between the structure of dimerization product *via* the transition state **T1**, calculated with AM1 (*a*), and that obtained from X-ray crystallographic data (*b*)

of enthalpy are found for the cycloaddition of **1** to **2**. They are -22.53 kcal mol^{-1} for **6a** and -24.66 kcal mol^{-1} for **8a**. It seems therefore that the reaction proceeds *via* mechanism (B) rather than (A). This point is contradictory to the experimental results.

Another observation can be made when we compare the enthalpies of formation for **3a**, **3b** and **7a** and **7b** in mechanism (A), for **6a**, **6b** and **8a** and **8b** in mechanism (B). In each case, the favourable addition occurs in position β relative to the carbonyl oxygen (denoted as O-β). As a consequence the adducts **7b** or **8a** would be obtained. Unfortunately, these observations from heats of formation were not confirmed by experimental data. The reaction seems to be kinetically controlled. We must therefore deal with the systems studied from a kinetic aspect by computing the transition states.

The computation of a transition state starts from a predefined geometry, manually constructed with a builder system. Generally, the Diels–Alder reaction needs a good synchronisation, and in the transition state the distance between the attacking atoms of the dienophile and that of diene is *ca.* 2.2 Å. The predefined geometries were constructed with these criteria, and the positions vary according to whether the reaction is *endo* or *exo* attacking, combined with *syn* and *anti*.

The results for transition states of reactions [*via* mechanism (A) and (B)] are collected in Tables 2 and 3, in which the different transition states are noted as **T1**–**T8** for dimerization mechanism (A) and as **T1**′–**T8**′ for mechanism (B). Comparing the activation energies (E_a), in both mechanisms, only one transition state (**T1** or **T1**′) is largely favoured energetically with respect to the others. This transition state in both mechanisms has the same geometric configuration, which gives the product **3a** or **6a** with the *S*-configuration. But when we compare the activation energies for **T1** and **T1**′, we note that for **T1**′, $E_a = 18.00$ kcal mol^{-1}, and for **T1** $E_a = 13.03$ kcal mol^{-1}. In the systems studied, the geometries and the sizes of two molecules allow us to consider the collision frequencies between the molecules involved in the reaction as identical for their transition states. We can deduce that, at room temperature, dimerization dominates (ratio of velocity constants $K/K' \approx 4000$). Mechanism (A) is most likely to occur. This result, contrasting with thermodynamic results, is in agreement with the experimental data. This theoretical analysis explains why the reaction proceeds *via* the dimerization mechanism, not *via* the hetero-Diels–Alder reaction between **1** and **2**.

Taking the work reported by Solà *et al.* (see Scheme 5) as reference, the most favourable process corresponds to an activation energy of 30.5 kcal mol^{-1}. but the dimerization studied in our systems needs only 13.03 kcal mol^{-1}. This weak activation energy may be the reason that the hetero-Diels–Alder reaction for this dimerization occurs unusually rapidly with a good yield, even at room temperature.

In Fig. 1, we show four transition states for the dimerization (**T1**–**T4**) from different perspectives, which were chosen to facilitate our discussion. The corresponding energy profiles are shown in Fig. 2. The distances r_1 and r_2 in Tables 2 and 3 refer to the two single bonds being formed. The parameter a, defined as $a = |r_1 - r_2|/(r_1 + r_2)$, represents the degree of asynchronicity.[13c] The greater the value of a, the less the transition state is synchronous. Because the Diels–Alder reaction needs a good synchronization, the a value is then an important index.

Fig. 1(*a*) shows the most stable transition state (**T1**, endocyclic attack), which corresponds to an O-α position addition for the adduct **3a** with configuration (*S*). The synchronicity of this transition state is also very high ($a = 0.004$, a very weak value). Fig. 1(*b*) represents an *exo* addition at O-α position. The a value shows a degree of synchronization much lower than in (*a*), because of the presence of an aromatic group which prevents the molecule rotating to approach the first enone with good synchronization. This steric effect was observed in other transition states. For instance, **T4** [see Fig. 1(*d*)] shows a strong steric effect between two aromatic groups, which results in an increased degree of asynchronicity. The synchronicity for **T3** seems to be very high ($a = 0.003$). But when we analyse Fig. 1(*c*), we find that the second enone approaches the first one from a crossed position. The distance between the two hydrogen atoms for the enones [*cf.* Fig. 1(*c*)] falls to 1.83 Å, which is far less than the sum of the van der Waals radii of the two hydrogen atoms ($R_H = 1.2$ Å). This steric effect prevents the second enone from approaching the first with the correct geometry, resulting in an increase in activation energy. This steric effect is probably also the principal effect responsible for the low stability of other transition states not illustrated in this paper.

In summary, the AM1 calculations suggest that the Diels–Alder reaction for enone **2** proceeds *via* transition state **T1** according to a dimerization mechanism (see Fig. 2). The unique adduct, the product of addition in the O-α position with an (*S*)-configuration, is due to the energy difference for transition states being larger than 3 kcal mol^{-1} and so ensuring selectivity.[20] This prediction of the (*S*) configuration product was verified by X-ray crystallography.[10] The structures obtained from crystallography and from AM1 calculation are given in Fig. 3. The calculated interatomic distances and bond angles are in good agreement with those from the crystallographic work. A detailed comparison is available as supplementary material (SUP 57279; 3 pp.) deposited with the British Library.†

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† For details see Instructions for Authors, *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, Issue 1, p. xviii.

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