A Quantum Chemical AM1 Study of a Diels–Alder and Retro-Diels–Alder Tandem Reaction

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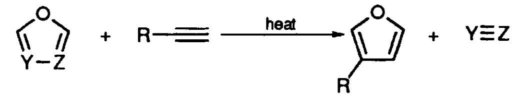
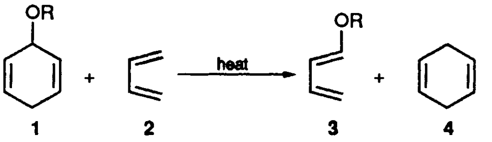
An AM1 study on a two convergent Diels–Alder reactions has shown that the formal transfer of an alkoxy substituent from a dienophile to a diene through a Diels–Alder/retro-Diels–Alder tandem reaction is feasible.

The Diels–Alder (DA)/retro-Diels–Alder (rDA) tandem reaction has been widely used in chemical synthesis.[1,2] The main use of the retro reaction has been to cleave the same bonds as those formed in the initial Diels–Alder cycloaddition, its purpose being to regenerate a double bonds protected previously.[3] Another use of this retro reaction involves breaking different bonds than those initially formed in the Diels–Alder reaction, which may result in the synthesis of dienes and dienophiles which are difficult to access[4,5] (see Scheme 1).



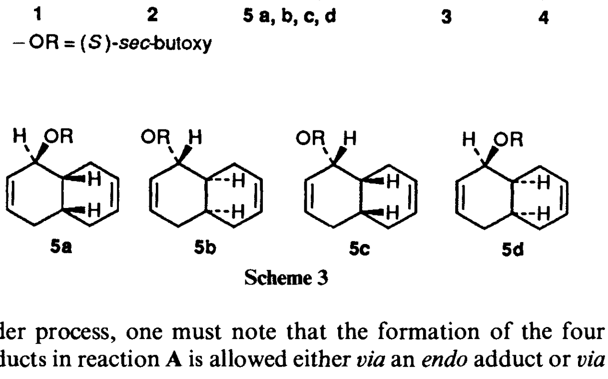
Scheme 1

Within this more restrictive application we have undertaken the study of the viability of a DA/rDA tandem reaction to carry out the formal transfer of an alkoxy substituent from the dienophile to the diene. This transfer would correspond to the interconversion of compounds **1** and **2** into **3** and **4** as shown in Scheme 2.



Scheme 2

The goal of this paper is to study the particular case of the two convergent Diels–Alder reactions depicted in Scheme 3. Given the characteristics of the decalin **5** and of the Diels–Alder process, one must note that the formation of the four adducts in reaction **A** is allowed either *via* an *endo* adduct or *via* an *exo* adduct. On the contrary, in reaction **B** the *endo* pathway allows the formation of adducts **5c** and **d**, whereas an *exo* pathway leads to adducts **5a** and **b**.



Scheme 3

Another purpose of the present work is to analyse the stereoselectivity in both Diels–Alder processes. For this reason, the (*S*)-*sec*-butoxy group has been chosen as the OR substituent.

Table 1 Calculated heat of formation of reactants and products at 25 °C. Orbital energies of the HOMO and LUMO of the reactants

	ΔH_f/kcal mol^{-1}		Orbital energy/eV	
Compound	RHF	CI	HOMO	LUMO
Reactant				
1	−32.2	−34.1	−9.37	1.01
2	30.7	27.1	−9.36	0.47
3	−28.2	−32.1	−8.68	0.58
4	17.0	14.7	−9.12	1.19
Adduct				
5a	−48.1	−51.8		
5b	−48.6	−52.2		
5c	−43.3	−47.6		
5d	−43.6	−47.8		

Method of Calculation.—The size of the systems studied prevents use of *ab initio* quantum mechanical methods. Therefore, we have employed the semiempirical method AM1[6] implemented in the AMPAC[7] program, which has proven to provide reliable results for Diels–Alder cycloadditions.[8]

Full geometry optimisations have been carried out at the RHF level, using the Davidon–Fletcher–Powell[9] conjugated-gradient technique. Transition states have been located by minimizing the root-mean-square gradient of the energy, and characterized through the correct number of negative eigenvalues of the energy second-derivative matrix;[10] this number must be one for any transition state.

We have recomputed energies at a 3 × 3 CI level using the RHF-optimised geometries, because non-dynamic correlation energies may be important in the evaluation of energies of transition states cycloaddition processes.

Results and Discussion

Table 1 gathers the results obtained for reactants and adducts, while the results for transition states of reactions **A** and **B** are collected in Table 2. Further, Table 3 gives the enthalpy barriers for the Diels–Alder and retro-Diels–Alder reactions for both **A** and **B** processes.

In order to discuss the results, throughout this paper it is considered that AM1 energy differences between two

Table 2 Lengths of the two forming bonds in the transition states and heats of formation of the different transition states for the Diels–Alder reactions computed with the AM1 method

Process A						Process B				
	ΔH_f/kcal mol^{-1}							ΔH_f/kcal mol^{-1}		
Approach	RHF	CI	r_1[a]/Å	r_2/Å	Adduct obtained	r_2/Å	r_1[a]/Å	RHF	CI	Approach
exo										*exo*
anti	29.0	25.1	2.12	2.13	**5a**	2.09	2.16	22.2	18.4	
anti	28.7	24.9	2.12	2.14	**5b**	2.05	2.20	21.8	17.6	
syn	28.2	24.3	2.13	2.12	**5c**	—	—	—	—	
syn	27.6	23.6	2.14	2.11	**5d**	—	—	—	—	
endo										*endo*
anti	29.5	25.7	2.13	2.13	**5a**	—	—	—	—	
anti	29.4	25.6	2.12	2.14	**5b**	—	—	—	—	
syn	31.3	27.5	2.13	2.13	**5c**	2.06	2.22	24.5	20.1	
syn	30.9	27.1	2.13	2.13	**5d**	2.04	2.23	22.7	18.1	

[a] r_1 has been taken as the length bond of the forming C–C bond nearest to the (*S*)-*sec*-butoxy substituent.

Table 3 Enthalpy barriers for the Diels–Alder and retro-Diels–Alder reactions. Energies are given in kcal mol^{-1}

Process A						Process B				
	$\Delta H^{\ddagger}_{DA}$/kcal mol^{-1}		$\Delta H^{\ddagger}_{RDA}$/kcal mol^{-1}			$\Delta H^{\ddagger}_{RDA}$/kcal mol^{-1}		$\Delta H^{\ddagger}_{DA}$/kcal mol^{-1}		
Approach	RHF	CI	RHF	CI	Adduct obtained	RHF	CI	RHF	CI	Approach
exo										*exo*
anti	30.5	32.1	77.1	76.9	**5a**	70.3	70.1	33.4	35.8	
anti	30.2	31.8	77.3	77.1	**5b**	70.4	69.8	33.0	35.0	
syn	29.8	31.2	73.4	71.9	**5c**	—	—	—	—	
syn	29.1	30.6	71.2	71.4	**5d**	—	—	—	—	
endo										*endo*
anti	31.0	32.6	77.6	77.5	**5a**	—	—	—	—	
anti	30.9	32.5	77.9	77.8	**5b**	—	—	—	—	
syn	32.8	34.5	74.7	75.1	**5c**	67.8	67.7	35.7	37.6	
syn	32.4	34.1	74.5	75.0	**5d**	66.3	66.0	33.9	35.6	

transition states larger than 3 kcal mol^{-1} are large enough to induce selectivity, as found recently by Casas *et al.*[11] in a former study of a Diels–Alder reaction. These authors found that for an AM1 enthalpy barrier difference of 1.5 kcal mol^{-1}, a 60:40 experimental proportion of adducts was obtained, whereas for a 2.9 kcal mol^{-1} difference, the experimental proportion was 95:5.

The more favoured adducts from a thermodynamic point of view are **5a** and **b**, which are more stable than **5c** and **d** by *ca.* 5 kcal mol^{-1}. We attribute this larger stability to steric effects rather than to a hypothetic interaction between the oxygen atom and one of the hydrogen atoms located at the C–C bridge ($d_{O\text{-}H}$ = 2.46 Å). As a matter of fact, energy partitioning (keyword ENPART in the AMPAC program) shows that the non-neighbouring repulsions (r > 1.9 Å) are larger for **5c** and **d** than for **5a** and **b** in part accounting for the energy differences observed.

The calculated orbital energies for each HOMO–LUMO pair of each reactant indicate that the favoured reaction **A** exhibits inverse electron demand. As first shown by Bachmann and Deno,[12] Diels–Alder reactions with inverse electron demand involve electron-poor dienes and electron-rich dienophiles.[13] This gives experimental support to the theoretical finding that whereas reaction **B** exhibits normal electron demand, reaction **A** has inverse electron demand, given that it involves a more electron-poor diene and a more electron-rich dienophile. In any event, it must be pointed out that the HOMO–LUMO energy differences found are quite small (0.202 eV for reaction **A** and 0.530 eV for reaction **B**). These small HOMO–LUMO energy differences between the diene and the dienophile explain the reduced charge transfer observed in the transition states (the maximum charge transfer is 0.05 a.u.).

In Fig. 1 we have drawn the three transition states giving rise to the obtention of adduct **5a**. The geometries of the transition states connecting reactants with adducts **5b**, **c** and **d** are quite similar. The distances r_1 and r_2 (see Table 2) of the two single bonds being formed in all studied reactions are remarkably constant (*ca.* 2.1–2.2 Å). These distances imply nearly synchronous transition states for process **A**. In reaction **B**, presence of the substituent in the diene induces some asynchronicity: the bond to the carbon bearing the substituent is lengthened, while the bond forming to the unsubstituted carbon atom is shortened. Nevertheless, the degree of asynchronicity [defined as $\alpha = (r_1 - r_2)/(r_1 + r_2)$[8c]] for the transition states in process **B** is never larger than 0.04, which indicates the synchronicity of the mechanism of this Diels–Alder reaction.

Inspection of vibrational normal modes shows that the main components of the transition vector of transition states for process **A** correspond essentially to the motion of the four carbons which intervene in the formation of the two new single bonds. In process **B** the transition vector corresponds mainly

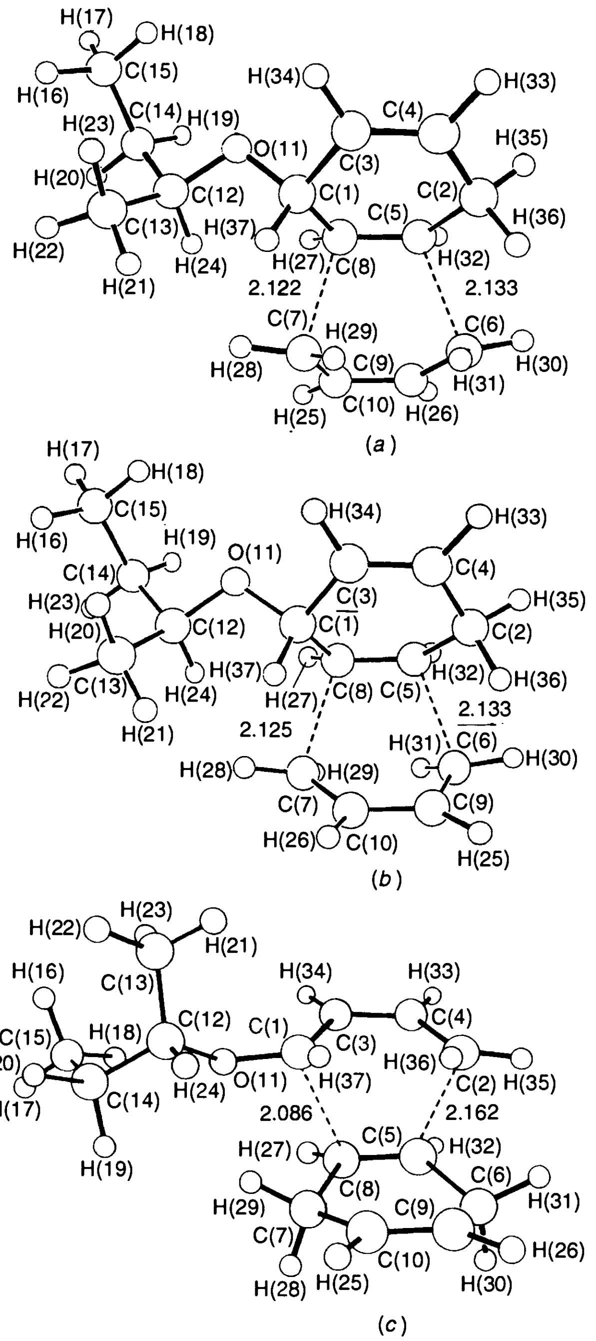


Fig. 1 Optimized geometries for the three transition states of the Diels–Alder reactions which give rise to the obtention of adduct **5a**: (*a*) exocyclic attack *via* reaction **A**; (*b*) endocyclic attack *via* reaction **A**; (*c*) exocyclic attack *via* reaction **B**

to the approach between the two unsubstituted carbons which form one of the new C–C single bonds.

The energy differences (< 3 kcal mol^{-1}) between the different transition states for reaction **B** are not significant (Table 2). For reaction **A**, however, the *endo* interaction from the *syn* face of the dienophile (see Fig. 2), leading to adducts **5c** and **d**, has an energy barrier somewhat higher (*ca.* 3.5 kcal mol^{-1}) than the *exo* interaction from the same face and on the same double bond. The origin of this difference may be found in steric effects since energy partitioning analysis gives larger non-neighbouring repulsions to *endo* than to *exo* transition states. Other energy differences between transition states are not meaningful.

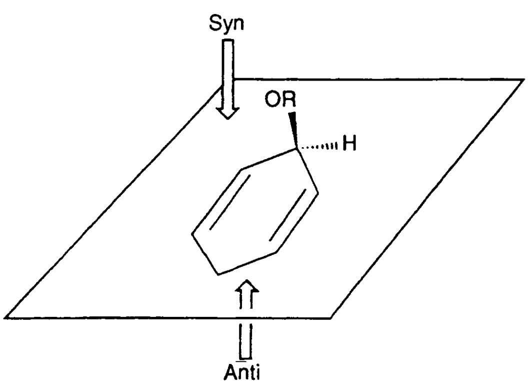


Fig. 2 *syn* and *anti* possible attacks for reaction **A**

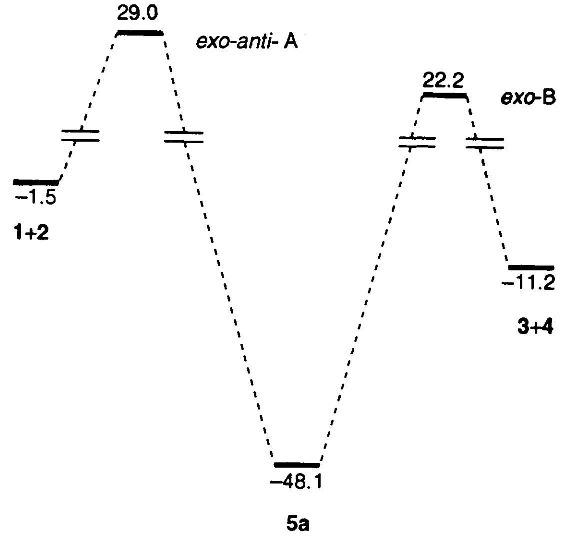


Fig. 3 Energy profile for the tandem of Diels–Alder and retro-Diels–Alder reactions corresponding to adduct **5a**

The reaction profile for the preparation of each of the four possible adducts either from process **A** or process **B** can be obtained by combining the data of Tables 1 and 2. The energy profile obtained in all four cases is very similar to the one shown in Fig. 3 for adduct **5a**.

From Fig. 3 and the data of Table 2, it can be seen that the Diels–Alder reaction has a smaller enthalpy barrier when coming from reactants **1** and **2** than from reactants **3** and **4** (*ca.* 3 kcal mol^{-1}). On these grounds we predict that reaction conditions for process **A** are less drastic than for process **B**.

Furthermore, from Fig. 3 and Table 3, it can be seen that once the adducts are obtained, the thermally allowed retro-Diels–Alder reaction will give rise to reactants **3** + **4**, rather than **1** + **2**, because the enthalpy barriers for the cyclorevertion of process **B** are *ca.* 7 kcal mol^{-1} smaller than for the cyclorevertion of process **A**.

From these AM1 results it can be concluded that it seems plausible to carry out the reaction of Scheme 2 by means of a cycloaddition/cyclorevertion tandem reaction.

Further, from the values of the retro-Diels–Alder reaction for process **B** given in Table 3, it can be seen that the adducts **5c** and **d** have a smaller enthalpy barrier than adducts **5a** and **b**. This difference leads us to conclude that **5c** and **d** will be the first adducts to be transformed into **3** + **4** by means of the cycloreversion reaction. If one is interested in **5a** and **b** adducts the retro-Diels–Alder reaction may be a solution to the lack of stereoselectivity observed in both **A** and **B** Diels–Alder processes.

As is well known,[8b–c] correlation effects are larger for the transition states than for stable molecules. In order to discuss these effects, correlation energy has been introduced by means of 3 × 3 CI calculations at the RHF geometries. From Table

3 it can be seen that in the studied reactions the enthalpy barriers obtained at the 3 × 3 CI level do not differ very much from the RHF barriers. As a general result, when correlation effects are taken into account, the enthalpy barriers of the Diels–Alder reactions increase by 1–2 kcal mol^{-1}, whereas the enthalpy barriers of the retro-Diels–Alder reactions keep almost constant.

Conclusions

According to the results obtained using the AM1 methodology, it seems reasonable to conclude that the (*S*)-2-butoxy substituent could be formally transferred from (*S*)-1-*sec*-butoxycyclohexa-2,5-diene to buta-1,3-diene using a Diels–Alder/retro-Diels–Alder tandem reaction.

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References

1 M. C. Lasne and J. L. Ripoll, *Synthesis*, 1985, 121.
2 J. L. Ripoll, A. Rouessac and F. Rouessac, *Tetrahedron*, 1978, **34**, 19.
3 M. Karpf, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 414.
4 D. Liotta, M. Saindane and W. Ott., *Tetrahedron Lett.*, 1983, **24**, 2473.
5 M. F. Ansell, M. P. L. Caton and P. C. North, *Tetrahedron Lett.*, 1981, **22**, 1727.
6 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
7 D. A. Liotard, E. F. Healy, J. M. Ruiz and M. J. S. Dewar, AMPAC-version 2.1. *Quantum Chemistry Program Exchange, Program 506, QCPE Bull.*, 1989, **9**, 123.
8 (*a*) W. T. Borden, R. J. Loncharich and K. N. Houk, *Ann. Rev. Phys. Chem.*, 1988, **39**, 213; (*b*) K. N. Houk, Y. Li and J. D. Evanseck, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 682; (*c*) V. Branchadell, J. Orti, R. M. Ortuño, A. Oliva, J. Font, J. Bertrán and J. J. Dannenberg, *J. Org. Chem.*, 1991, **56**, 2190; (*d*) V. Branchadell, M. Sodupe, R. M. Ortuño, A. Oliva, D. Gómez-Pardo, A. Guingant and J. d'Angelo, *J. Org. Chem.*, 1991, **56**, 4135.
9 (*a*) R. Fletcher and M. D. Powell, *Comput. J.*, 1963, **6**, 163; (*b*) W. C. Davidon, *Comput. J.*, 1968, **10**, 406.
10 J. W. McIver and A. Komornicki, *J. Am. Chem. Soc.*, 1972, **94**, 2625.
11 R. Casas, T. Parella, V. Branchadell, A. Oliva, R. M. Ortuño and A. Guingant, *Tetrahedron*, 1992, **48**, 2659.
12 W. E. Bachmann and N. C. Deno, *J. Am. Chem. Soc.*, 1949, **71**, 3062.
13 J. Sauer, *Bull. Soc. Chim. Belg.*, 1992, **101**, 521.

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