AM1 Study of a Substituent Transfer by means of a Diels–Alder and Retro-Diels–Alder Tandem Reaction

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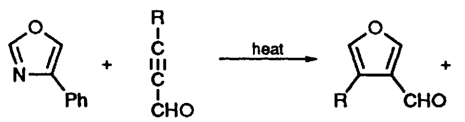
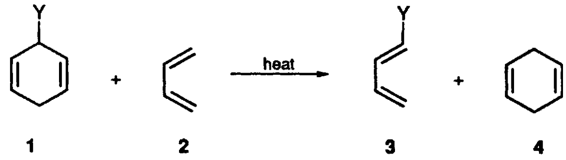
An AM1 study of two convergent Diels–Alder reactions shows that the formal transfer of a substituent from a dienophile to a diene through a Diels–Alder–retro-Diels–Alder tandem reaction is thermodynamically and kinetically feasible irrespective of the electron-donating or -withdrawing character of the substituent.

There are many examples of Diels–Alder and retro-Diels–Alder reactions in the chemical literature.[1,2] The retro reaction has been used mainly to break the same bonds as those formed in the initial Diels–Alder cycloaddition, for the purpose of regenerating previously protected double bonds.[3,4] Occasionally, the retro-Diels–Alder reaction has been used to cleave other bonds than those initially formed in the Diels–Alder reaction, in order to synthesize dienes and dienophiles which might otherwise be difficult to access,[5,6] *e.g.* Scheme 1.



Scheme 1

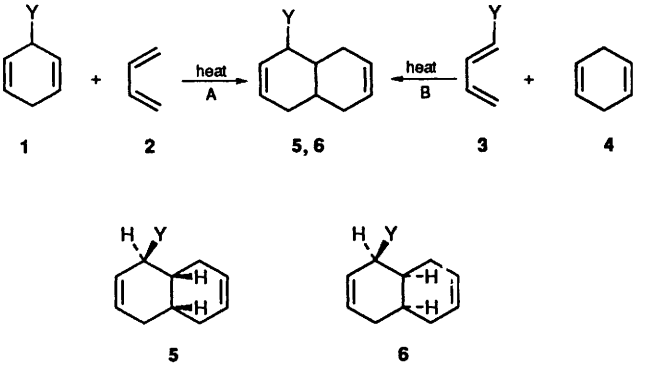
In connection with this more restrictive application, in an earlier study[7] we showed that the formal transfer of an alkoxy substituent from the dienophile to the diene using a Diels–Alder–retro-Diels–Alder tandem reaction is feasible [see Scheme 2 and consider Y = (*S*)-*sec*-butoxy].



Scheme 2

Using the same model reaction as that depicted in Scheme 2, the aim of the present work is to study the viability and possible variations of the formal transfer of substituents, with different σ_p Hammett values,[8] from the dienophile to the diene. The σ_p parameter reflects a commonly accepted ranking of the electron-donating/-withdrawing ability of these groups and it is considered as a quite suitable yardstick for comparison.[8]

In this paper we consider two convergent Diels–Alder reactions (as shown in Scheme 3) for each substituent. Thus, we have analysed the cycloreversion from adducts **5** and **6** to either **1** + **2** or **3** + **4** *via* reaction A or B (Scheme 3), respectively. The model used does not involve aromatic species, which might have a certain influence in the reaction course and thus prevent a proper understanding and analysis of the substituent transfer. Six Y substituents with values of σ_p ranging from −0.66 to 0.66 have been taken into account. In order to have a comparative reference, we have also studied the system in which Y = H, implying that reaction A equals reaction B.



	a	b	c	d	e	f	g
Y	CN	CO_2H	CHO	H	CH_3	OH	NH_2
σ_p	0.66	0.41	0.22	0	−0.17	−0.37	−0.66

Scheme 3

The structural features of the bicyclic adduct and the presence of substituent Y leads to four possible pathways (*endo*/*exo* combined with *syn*/*anti* attacks) for the cycloreversion of addults **5** and **6** through reaction A and two possible pathways (*endo*/*exo*) through reaction B if one considers only the formation of the *E*-isomer of diene **3**. All such pathways have been analysed and are discussed in the present paper. Furthermore, for the special case of Y = CN we have also investigated cycloreversion B that leads to the *Z*-isomer of the diene **3**.

Calculations

Enthalpy calculations were performed with the AM1[9] semiempirical MO method, as implemented in the AMPAC[10] program, which has provided reliable results for Diels–Alder cycloadditions[11] and retro-Diels–Alder cycloreversions.[12] Full geometry optimizations with no symmetry constraints have been carried out at the RHF level, using the Davidon–Fletcher–Powell[13] 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;[14] this number must equal one for any true transition state. We have also verified that the imaginary frequency exhibits the expected motion. Correlation energy has been neglected here for two reasons: first, because use of configuration interaction (CI) procedure with semiempirical methods implies that correlation effects are included actually twice, once *via* parameters and again during the CI procedure; and second, because it has been shown earlier that enthalpy barrier changes for the retro-Diels–Alder reaction in this model are negligible when correlation energy is included.[7]

Table 1 Calculated enthalpies of formation at 25 °C of reactants and adducts, along with orbital energies of the HOMO and LUMO of the reactants

		Orbital energy/eV	
	$\Delta_f H$/kcal mol^{-1}	HOMO	LUMO
Reactant[a]			
1a	51.4	−9.76	0.66
(*E*)-**3a**	59.0	−9.78	−0.53
(*Z*)-**3a**	60.6	−9.74	−0.49
1b	−70.1	−9.60	0.70
3b	−62.4	−9.93	−0.62
1c	−10.5	−9.40	0.74
3c	−2.5	−9.77	−0.53
1e	12.8	−9.19	1.21
3e	20.6	−9.08	0.48
1f	−23.6	−9.53	0.90
3f	−19.8	−8.86	0.42
1g	23.5	−9.94	1.02
3g	24.8	−8.23	0.66
2	30.7	−9.36	0.47
4	17.0	−9.12	1.19
Adduct[a]			
5a	41.2		
6a	42.9		
5b	−79.9		
6b	−78.2		
5c	−20.0		
6c	−18.8		
5d/**6d**	7.1		
5e	3.1		
6e	4.8		
5f	−35.6		
6f	−33.8		
5g	15.0		
6g	16.7		

[a] See Scheme 3.

Results and Discussion

Scheme 3 shows the reactions and the substituents considered for the study. The calculated enthalpies of formation of intervening reactants and adducts are summarized in Table 1, while the enthalpy of formation for the transition states of reactions A and B are collected in Table 2, which also contains the charge transfer from the diene to the dienophile in the transition state and the bond lengths corresponding to the two C–C breaking bonds. Further, from the values of Tables 1 and 2 we have calculated the enthalpy barriers for the Diels–Alder and retro-Diels–Alder reactions, which are gathered in Table 3. Since the Diels–Alder reactions take place from dienes **2** and **3** having the *cisoid* conformation, enthalpy barriers in Table 3 have been computed from this conformer, instead of computing them from the most stable *transoid* conformer. In any event, enthalpy differences between these two conformers is estimated to be as low as *ca.* 3 kcal mol^{-1}.[†,15]

In this discussion, one should bear in mind the fact that the activation enthalpies for the retro-Diels–Alder cycloreversions calculated by the AM1 method usually result in higher values (*ca.* 10 kcal mol^{-1})[12] than those found experimentally. Nevertheless, the relative trends among activation energies for different substituents are well reproduced, with the only reported exceptions being NO_2 and bromine.[12] Likewise, throughout this study it is considered that AM1 enthalpy differences between two transition states equal or above 3 kcal mol^{-1} are large enough to induce selectivity, as discussed recently by Casas *et al.*[16] in an earlier study of a Diels–Alder reaction. Those authors observed that two transition states separated by a calculated AM1 enthalpy difference of 2.9 kcal mol^{-1} result in an experimental selectivity of 95:5.

From the values of Table 1, one can see that from a thermodynamical point of view adducts **5** are favoured over **6** for all substituents, although the enthalpy difference is never larger than 1.6 kcal mol^{-1} and probably not enough to induce selectivity. Similarly, reactants **3** + **4** are also more stable than **1** + **2**, except for the trivial case Y = H. In the case of positive σ_p, the enthalpy difference between **3** + **4** with respect to **1** + **2** stays almost constant, having a value of *ca.* −6 kcal mol^{-1}. Interestingly, this difference increases when σ_p becomes more negative changing from −5.9 kcal mol^{-1} in the case of Y = CH_3 ($\sigma_p = -0.17$) to −12.4 kcal mol^{-1} for Y = NH_2 ($\sigma_p = -0.66$).

As compared to Y = H, substitution necessarily makes the transition states asynchronous. As one can see from Table 2, these asynchronous transition states have always one bond shorter and one bond longer than those corresponding to Y = H (2.13 Å). Because of the proximity of the substituent to the breaking bonds, asynchronicity (calculated as $r_2 - r_1$) is larger in reaction B than in reaction A (average asynchronicity values 0.18 *vs.* 0.00 Å for processes B and A, respectively). Interestingly, in the transition states for process B, the C–C breaking bond which is closest to the Y substituent is longer than that of the unsubstituted C in the diene, independently of the σ_p of the substituent. This seems to imply that the similar asynchronicity induced in the transition states corresponding to process B by substituents which have different σ_p but similar bulkiness, is caused by Pauli effects rather than by electrostatic interactions.

The direction in which the substituent Y is transferred depends ultimately on the bond breaking enthalpy of the C–C bonds next to either side of the adducts bridge. We can see from Table 3 that the enthalpy barriers for reaction A are very similar to those obtained for Y = H. This indicates that substituent effects on the cycloreversion reaction A are quite small, probably due to the larger distance from the substituent to the breaking bonds, as compared to process B. Moreover, activation enthalpies for cycloreversion B are different and smaller than those obtained when Y = H; they are also smaller than those corresponding to cycloreversion A. Clearly, substitution has a meaningful effect in cycloreversion B, leading in all cases to smaller enthalpy barriers.

Considering the Diels–Alder cycloadditions, the AM1 results in Table 3 predict the *exo* approach to be normally preferred over the *endo* approach although the differences are not significant. For the *endo* + *syn* attack leading to adduct **6** in process A, which is the most unfavoured attack, enthalpy differences are close to 3 kcal mol^{-1}. For cycloreversion A, the *exo* and *endo* approaches have a similar enthalpy barrier in the case of the *anti* attack, although for the *syn* attack the *exo* approach is clearly preferred over the *endo* one. We must note here that AM1 is well known[11c,d,12] to overfavour the *exo* approach over the *endo* approach, probably due to an overestimation of the core–core repulsion at intermediate distances.

In general, reaction A has zero or normal electronic demand[17] (electron transfer from the diene to the dienophile). It is also found that in reaction B substituents with positive σ_p induce inverse electronic demand with an almost constant charge transfer from the dienophile to the diene (see Table 2). This is not at all surprising, since it is well known that Diels–Alder reactions with inverse electron demand involve electron-poor diene or electron-rich dienophiles.[18] In process B, substituents with positive σ_p facilitate the orbital interaction between the HOMO of the dienophile and the LUMO of the diene. Furthermore, substituents with negative σ_p result in a normal charge transfer, which increases with the electron-donating character of the substituent. All in all, changing from Y = H to any substituent increases charge transfer and

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[†] 1 cal = 4.184 J.

Table 2 Enthalpies of formation, charge transfers from the diene to the dienophile and lengths of the two forming/breaking bonds for the transition states of the Diels–Alder–retro-Diels–Alder reactions computed with the AM1 method

Process A						Process B				
Approach	$\Delta_{\mathrm{f}}H$[a]	CT[b]	r_1[c]	r_2	Adduct obtained[d]	r_2	r_1[c]	CT[b]	$\Delta_{\mathrm{f}}H$[a]	Approach
exo,anti	114.7	0.03	2.11	2.14	**5a**	2.04	2.22	−0.07	109.5	*exo-E*
exo,syn	115.0	0.03	2.13	2.13	**6a**	2.04	2.23	−0.07	110.1	*endo-E*
endo,anti	114.9	0.05	2.13	2.12	**5a**	2.04	2.22	−0.06	113.3	*endo-Z*
endo,syn	117.7	0.05	2.16	2.10	**6a**	2.06	2.24	−0.07	114.5	*exo-Z*
exo,anti	−6.8	0.02	2.12	2.14	**5b**	2.05	2.21	−0.07	−13.8	*exo*
exo,syn	−6.8	0.04	2.13	2.12	**6b**	2.04	2.23	−0.09	−12.2	*endo*
endo,anti	−6.5	0.02	2.12	2.14	**5b**					
endo,syn	−4.1	0.05	2.14	2.12	**6b**					
exo,anti	52.4	0.02	2.11	2.14	**5c**	2.06	2.21	−0.07	47.2	*exo*
exo,syn	52.7	0.02	2.13	2.12	**6c**	2.04	2.23	−0.07	48.2	*endo*
endo,anti	52.6	0.02	2.12	2.14	**5c**					
endo,syn	55.4	0.03	2.14	2.12	**6c**					
exo	80.0	0.00	2.13	2.13	**5d/6d**					
endo	80.7	0.00	2.13	2.13	**5d/6d**					
exo,anti	75.6	0.00	2.11	2.14	**5e**	2.04	2.21	0.00	72.6	*exo*
exo,syn	76.7	0.01	2.13	2.12	**6e**	2.04	2.22	0.00	73.2	*endo*
endo,anti	76.2	0.00	2.12	2.14	**5e**					
endo,syn	79.4	0.01	2.13	2.12	**6e**					
exo,anti	39.0	0.00	2.11	2.14	**5f**	2.04	2.21	0.00	33.7	*exo*
exo,syn	38.4	0.01	2.13	2.12	**6f**	2.04	2.22	0.01	34.4	*endo*
endo,anti	39.1	0.00	2.12	2.14	**5f**					
endo,syn	41.4	0.05	2.13	2.12	**6f**					
exo,anti	89.3	−0.01	2.12	2.14	**5g**	2.04	2.22	0.02	76.9	*exo*
exo,syn	88.9	0.04	2.13	2.12	**6g**	2.04	2.23	0.01	77.7	*endo*
endo,anti	88.9	−0.01	2.13	2.13	**5g**					
endo,syn	92.2	0.04	2.13	2.11	**6g**					

[a] In kcal mol^{-1}. [b] Charge transfer (in a.u.) from the diene to the dienophile and for the Diels–Alder processes. Positive values mean a process with normal electronic demand. [c] r_1 (in Å) has been taken as the length of the forming/breaking C–C bond closest to the Y substituent. [d] See Scheme 3.

Table 3 Enthalpy barriers (kcal mol^{-1}) for the Diels–Alder and retro-Diels–Alder reactions

Process A				Process B		
Approach	$\Delta H^{\ddagger}_{\mathrm{DA}}$[a]	$\Delta H^{\ddagger}_{\mathrm{RDA}}$[b]	Adduct obtained[c]	$\Delta H^{\ddagger}_{\mathrm{RDA}}$[b]	$\Delta H^{\ddagger}_{\mathrm{DA}}$[a]	Approach
exo,anti	32.6	73.5	**5a**	68.3	33.5	*exo-E*
exo,syn	32.9	72.1	**6a**	67.2	34.1	*endo-E*
endo,anti	32.8	73.7	**5a**	72.1	35.7	*endo-Z*
endo,syn	35.6	74.8	**6a**	71.6	36.9	*exo-Z*
exo,anti	32.6	73.1	**5b**	66.1	31.6	*exo*
exo,syn	32.6	71.4	**6b**	66.0	33.2	*endo*
endo,anti	32.9	73.4	**5b**			
endo,syn	35.3	74.1	**6b**			
exo,anti	32.2	70.4	**5c**	67.2	32.7	*exo*
exo,syn	32.5	71.5	**6c**	67.0	33.7	*endo*
endo,anti	32.4	70.6	**5c**			
endo,syn	35.2	74.2	**6c**			
exo	32.3	72.9	**5d/6d**			
endo	33.0	73.6	**5d/6d**			
exo,anti	32.1	72.5	**5e**	69.5	35.0	*exo*
exo,syn	33.2	71.9	**6e**	68.4	35.6	*endo*
endo,anti	32.7	73.1	**5e**			
endo,syn	35.9	74.6	**6e**			
exo,anti	31.9	74.6	**5f**	69.3	36.5	*exo*
exo,syn	31.3	72.2	**6f**	68.2	37.2	*endo*
endo,anti	32.0	74.7	**5f**			
endo,syn	34.3	75.2	**6f**			
exo,anti	35.1	74.3	**5g**	61.9	35.1	*exo*
exo,syn	34.7	72.2	**6g**	61.0	35.9	*endo*
endo,anti	34.7	73.9	**5g**			
endo,syn	38.0	75.5	**6g**			

[a] Enthalpy barrier for the Diels–Alder reaction. [b] Enthalpy barrier for the retro-Diels–Alder reaction. [c] See Scheme 3.

polarization effects and as a consequence reduces the enthalpy barrier. This decrease is especially remarkable in the case of Y = NH_2 (11.9 kcal mol^{-1} measured with respect to Y = H). For the other substituents, the decrease in the enthalpy of activation turns out to be more moderate (4.5–6.9 kcal mol^{-1}), yet still meaningful.

The effect that the substituent might have on the diene portion of Diels–Alder reactions has been already studied by

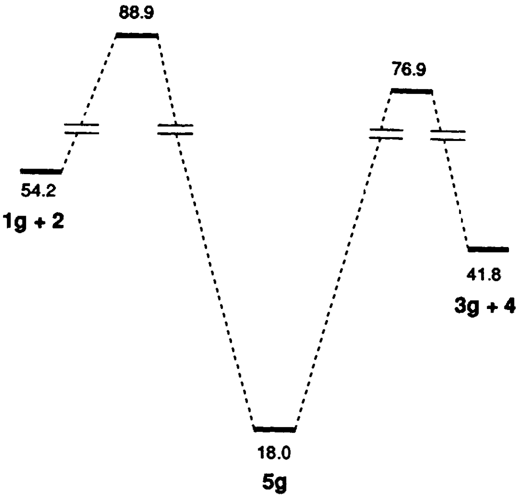

Fig. 1 Enthalpy profile (kcal mol^{-1}) for the tandem of Diels–Alder and retro-Diels–Alder reactions corresponding to adduct **5g**

Chung *et al.*[19] These authors found that the electron-donating groups increase the reaction rate of a retro-Diels–Alder process. The electron-withdrawing groups might increase or decrease the reaction rate, although their effect was always moderate. Our results for process B reinforce their conclusions. Further, the theoretical results obtained here for reaction B, showing a decrease in the enthalpy barrier for Y = CHO, CH_3, OH and NH_2, agree quite well with the experimental data reported in the chemical literature.[12,20] Unfortunately, we have not found similar experimental data for Y = CO_2H and CN, although from the results obtained it is expected that these two substituents exhibit a behaviour similar to that of CHO.

All enthalpy barriers gathered in Table 3 for cycloreversion B are calculated relative to the *E*-conformation of diene **3**. However, we have also computed for the case where Y = CN the enthalpy barriers corresponding to the *exo* and *endo* cycloreversions leading to the *Z*-isomer of diene **3a**. From the values of Table 3 and from the value of the enthalpy of formation of the *Z*-conformer of the diene **3a** in Table 1, the cycloreversion to diene (*Z*)-**3a** is, as expected, neither thermodynamically nor kinetically favoured. Because of the linear geometry of the CN substituent, we think that this result can also be extrapolated to the remainder of the substituents studied.

Fig. 1 shows the whole enthalpy profile for the cycloreversion reaction corresponding to adduct **5g** (Y = NH_2). Based on this enthalpy profile, the formal substituent transfer depicted in Scheme 2 seems feasible; this transfer would imply starting with **1** + **2**, so the corresponding adducts **5** and **6** would then later lead to **3** + **4** through a cycloreversion reaction.

Given that the enthalpy profile for all other substituents is similar to that shown in Fig. 1 (enthalpy differences for transition states of cycloreversions A and B are larger than 3 kcal mol^{-1} in all cases considered), the proposed formal substituent transfer is likely to take place for all cases. Finally, and because the difficulty of the cycloreversion depends on the substituent considered, the interconversion by change of oxidation state between substituents (nitro to amines, carbonyl to alcohol, *etc.*) may help to improve the proposed formal substituent transfer in the most unfavoured cases.

Conclusions

The results obtained using the AM1 methodology show that the studied substituents Y = CN, CO_2H, CHO, CH_3, OH and NH_2 can be formally transferred from cyclohexa-1,4-diene to buta-1,3-diene through a Diels–Alder–retro-Diels–Alder tandem reaction. It seems reasonable that such a substituent transfer may be extended to other cases of interest using this tandem reaction. Further theoretical studies together with experimental work on this process is being carried out in our laboratory and will be reported in the near future.

Note Added in Proof.—One of the referees suggested to us the values 0.42 and 0.45 for the σ_p Hammett parameters of CHO and COOH, respectively, as found in the following reference: C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165. These values do not modify the conclusions presented in this work.

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