On the origin of the *endo/exo* selectivity in Diels–Alder reactions

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The *endo/exo* selectivity in Diels–Alder reactions is analyzed in terms of the pre-reactive van der Waals complexes located on the potential energy surface.

The Diels–Alder reaction has been the subject of a wide variety of both experimental and theoretical studies.[1] Of particular relevance from the mechanistic viewpoint is the explanation of the observed *endo/exo* selectivity. As established from the very beginning, there is usually a preference for the *endo* adducts (*endo* Alder rule[2]). Such an *endo* preference has been ascribed to quite different factors.[3] On the other hand, the first documented example of regiospecifity of Diels–Alder reactions being primarily controlled by the dispersion (attractive van der Waals) interactions has been recently reported by Cioslowski *et al.*[4] Additional work in this direction was announced by Gillies *et al.*[5b]

The above explanations have in common that they all focus on the transition structures. The impressive advances in the last two decades leading to the development of rather sophisticated spectroscopic techniques, including Raman, microwave and infrared spectrocopies,[5c] have made it possible to gain a deeper insight into the nature of van der Waals interactions, and it has been recently recognized[5b] that the formation of van der Waals systems in the very early (pre-reactive) stages of certain cycloaddition reactions can exert a significant influence upon the stereochemical outcome. Gillies *et al.* concluded[5b] that it is possible to relate the geometry of van der Waals intermediates to the geometry of the transition structure and the product of certain cycloaddition reactions. Recent findings using inter-molecular perturbation theory[6] seem to provide further support to this point. Here, theoretical evidence is presented showing the important role that pre-reactive van der Waals complexes, present in the potential energy surface, might play in determining the stereochemical outcome of Diels–Alder reactions. The prototype reaction between cyclopentadiene and maleic anhydride has been investigated.

The geometries of the significant structures located at the MP2/6-31G* level on the potential energy surface of the Diels–Alder reaction between cyclopentadiene and maleic anhydride: three van der Waals intermediates (**vdW1** and **vdW2**, leading to the *endo* and *exo* transition structures, respectively, and **vdW3**, showing a T-shaped structure intermediate between **vdW1** and **vdW2**), two van der Waals transition structures connecting **vdW1** and **vdW3** (**vdW1 → 3**) and **vdW2** and **vdW3** (**vdW2 → 3**), and two transition structures leading to the *endo* (**TS1**) and *exo* (**TS2**) products (**P1** and **P2**), are not presented because of space limitations but are available upon request. All these structures were characterized by computing the Hessian matrix (at the HF level) and checking the sign of the corresponding eigenvalues. Table 1 collects the energy results, which include single-point calculations at the MP4SDQ/6-31G* level and an estimate of the solvent effects. In cycloaddition reactions between ethylene and ozone, occurring both in the gas phase and in condensed media, a van der Waals (pre-reactive) intermediate was experimentally detected in the gas phase[5] (where rather sophisticated spectroscopic techniques are available). It is difficult to make *a priori* predictions about the role played by different solvents on the stabilization/destabiliza-

tion[7a] (a detailed discussion on this point for a reaction involving a *zwitterionic* intermediate can be found elsewhere[7b]) of these van der Waals intermediates (exploratory calculations using a model where the solvent is represented by a dielectric continuum characterized by its static dielectric permittivity[7c] ε_0, suggest that the energy changes introduced by the solvent are not too drastic, see Table 1, but there is experimental evidence for the important role played by van der Waals interactions in Diels–Alder reactions in solution.[4]

In Fig. 1 a simplified scheme of the potential energy surface is presented. Examination of this figure suggests that the van der Waals structures might play a decisive role in determining the stereochemical outcome of Diels–Alder reactions. Indeed, the *endo/exo* ratio is related to the barrier $\Delta\Delta E^{\neq}(\text{vdW}) = [E(\text{TS2}) - E(\text{vdW2})] - [E(\text{TS1}) - E(\text{vdW1})]$. If the van der Waals structures were not present in the potential energy surface the *endo/exo* ratio should be computed as $\Delta\Delta E^{\neq}(\text{R}) = [E(\text{TS2}) - E(\text{R})] - [E(\text{TS1}) - E(\text{R})]$ (R = reactants). In the present case (at the MP4SDQ/6-31G*//MP2/6-31G* level of theory), $\Delta\Delta E^{\neq}(\text{R}) = 2.1$ kcal mol^{-1} (97.1% *endo* at 298 K) and $\Delta\Delta E^{\neq}(\text{vdW}) = 2.6$ kcal mol^{-1} (98.8% *endo* at 298 K); the greater stability of **vdW2** leading to the *exo* transition structure **TS2** enhances the *endo* preference. The experimental *endo* preference is[8] 2.5 kcal mol^{-1} (98.5% *endo* at 298 K). It is important to remark that, while $\Delta\Delta E^{\neq}(\text{R})$ is affected by the basis set superposition error (BSSE)[9] [consideration of the BSSE by means of the *counterpoise* procedure,[9] including fragment relaxation terms,[10] gives $\Delta\Delta E^{\neq}(\text{R}) = 2.0$ kcal mol^{-1} (96.5% *endo* at 298 K), moving away from the experimental

Table 1 Relative Energies (including zero point energy correction from HF/6-31G* frequencies) of van der Waals intermediates, transition structures and products with respect to reactants for the [4 + 2] cycloaddition reaction between cyclopentadiene and maleic anhydride. Geometries were optimized at the MP2/6-31G* theory level (single-point SCRF = self-consistent-reaction field calculations to estimate electrostatic solvent effects). Relative energies of the Diels–Alder transition structures with respect to the corresponding van der Waals intermediates are shown in parentheses

	Relative energy/kcal mol^{-1}		
	MP2/6-31G*	MP2/6-31G* (SCRF^a ε_0 = 2.24^b)	MP4SDQ/6-31G*
vdW1 *endo*	−7.4	−7.0	−3.8
TS **vdW1 → 3**	−3.2	−2.9	−2.1
vdW3	−4.2	−3.8	−3.2
TS **vdW2 → 3**	−4.1	−3.7	−3.1
vdW2 *exo*	−6.6	−5.9	−4.3
[4 + 2] **TS1** *endo*	−0.4 (7.0)	−0.8 (6.2)	14.1 (17.9)
[4 + 2] **TS2** *exo*	1.9 (8.5)	1.8 (7.7)	16.2 (20.5)
[4 + 2] *endo* Adduct **P1**	−34.1	−33.8	−29.0
[4 + 2] *exo* Adduct **P2**	−34.5	−34.0	−29.6

^{a} See ref. 7(*d*) for an excellent example of how the estimate of barriers in solution by means of single-point SCRF calculations are approximate but useful indicators of energetic trends. ^{b} A relative permittivity of 2.24 was used to simulate benzene, which has been used as solvent in this reaction (see ref. 8).
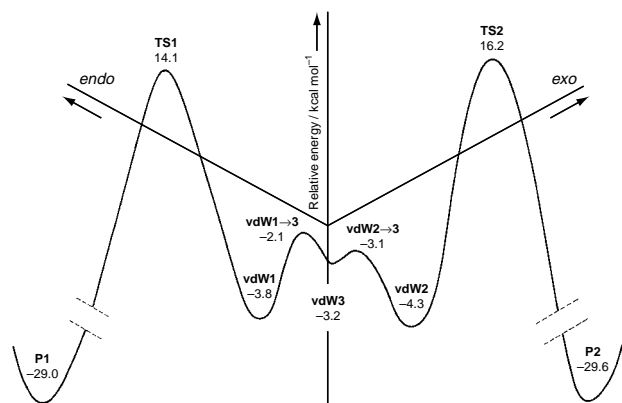
Fig. 1 Simplified scheme of the potential energy surface corresponding to the Diels–Alder reaction between cyclopentadiene and maleic anhydride

value], $\Delta\Delta E^{\neq}(\mathbf{vdW})$ is BSSE free.[11]. It is important to stress at this point that the above results are consistent with the so-called Curtin–Hammett principle,[12] which states that when the barriers involving the **vdW** systems in Fig. 1 are much lower than the reaction barriers **TS1** and **TS2**, then the (endo/exo) product ratio depends only upon the difference in energy of the transition structures **TS1** and **TS2**. In the present case, the Curtin–Hammett principle should apply (see Fig. 1) and the endo/exo ratio could be estimated from $\Delta\Delta E^{\neq}(\mathbf{R})$, in agreement with the above results [i.e. $\Delta\Delta E^{\neq}(\mathbf{vdW}) \approx \Delta\Delta E^{\neq}(\mathbf{R})$].

Although the difference between $\Delta\Delta E^{\neq}(\mathbf{R})$ and $\Delta\Delta E^{\neq}(\mathbf{vdW})$ is not (quantitatively) drastic in the present case, it must be stressed that a detailed inspection of the potential energy surface shows that consideration of the van der Waals structures is strictly needed to avoid serious topological inconsistencies in the computed potential energy surface. Indeed, at the MP2/6-31G* level, where optimizations were carried out, the **TS1** and **TS2** structures (without taking into account the zero-point energy correction) are energetically lower than reactants and higher than products (the energies relative to reactants are -2.3 and -0.1 kcal mol^{-1} for **TS1** and **TS2**, respectively). Therefore, if the van der Waals intermediates were not considered, **TS1** and **TS2** would not be maximums along the reaction paths and, consequently, they could not be real transition structures (saddle points separating two energy minima) in clear contradiction with the information provided by the Hessian matrix (see above). Of course, consideration of the van der Waals structures reported in this work indicates that **TS1** and **TS2** are saddle points connecting two minima (i.e. transition structures): **vdW1** and **P1**, and **vdW2** and **P2**, respectively (the energies of **TS1** relative to **vdW1**, and of **TS2** relative to **vdW2**, without considering the zero-point energy correction, are both positive: $+7.4$ and $+9.1$ kcal mol^{-1}, respectively).

Finally, we would like to make a short comment on the nature of the interaction in the van der Waals intermediates and transition structures. The application of a configurational analysis on the corresponding wave functions[13] shows that for **TS1** and **TS2** the most significant contributions, apart from the zero configuration AB (A = cyclopentadiene, B = maleic anhydride) come from the HOMO(cyclopentadiene) $\rightarrow$ LUMO(maleic anhydride) ($w \approx 0.35$)† A$^+$B$^-$ and HOMO-(maleic anhydride) $\rightarrow$ LUMO(cyclopentadiene) ($w \approx 0.15$) A$^-$B$^+$ (back donation[14]) monotransferred configurations. The same kind of interactions, with smaller weights ($w \approx 0.10$, A$^+$B$^-$, and $w \approx 0.02$, A$^-$B$^+$) are already present in the van der

Waals intermediates **vdW1** and **vdW2**. Therefore, in agreement with previous suggestions,[5] the present calculations show that the (pre-reactive) van der Waals intermediates are located at the entrance of the cycloaddition reaction (endo/exo) channels, thus being precursors to the actual Diels–Alder products.

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