

Importance of Electronic and Nuclear Polarization Energy on Diastereofacial Selectivity of Diels–Alder Reactions in Aqueous Solution

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Ab initio calculations at the 6-31G** level using a self-consistent reaction field continuum model show that electronic and nuclear polarization effects in solution are crucial to explain the stereoselectivity of asymmetric Diels–Alder reactions.

Theoretical studies of medium effects on chemical reactions can be carried out with a variety of solvent models.¹ Two main approximations are usually made. On one hand, the solvent may be assumed to be in equilibrium with the reagents at every stage of the chemical process. This hypothesis is reasonable for processes that do not involve large electronic charge reorganization, like most Diels–Alder cycloaddition reactions, but it can be unrealistic otherwise. Non-equilibrium solvent effects are known to be significant in S_N2 reactions, for instance, and have been studied by many authors.² On the other hand, the geometry of the transition state (TS) is often assumed to be either independent of the medium or constrained to change following the displacement vector that defines the gas-phase reaction coordinate ρ_g .³ In the latter case, the magnitude of the displacement is obtained by inspecting the curve $E_g(\rho_g) + \Delta G_{\text{solv}}(\rho_g)$. Here, $E_g(\rho_g)$ is the gas-phase potential energy and $\Delta G_{\text{solv}}(\rho_g)$ is the solvation free energy for a given configuration on the gas-phase reaction path. Depending on the solvent model, ΔG_{solv} includes, or not, the solute electronic polarization due to the solvent potential. However, even when electronic polarization is taken into account, this approach has two important shortcomings. It neglects the part of the solvation energy due to geometrical relaxation and it fails to predict solvent-induced reaction mechanism changes. Our aim in this paper is to show that this hypothesis has to be abandoned in order to correctly describe some fundamental aspects of Diels–Alder reactions.

Interest in solvent effects on Diels–Alder reactions has increased since the first experimental studies in aqueous solvents.⁴ A number of theoretical studies have been reported,⁵ and some experimental findings have been successfully interpreted. However, a number of controversial points remain. We shall be concerned here with solvent effects on diastereofacial selectivities. Experimentally,^{5a,c} the major product of the reaction of cyclopentadiene with (–)-menthyl acrylate in solution is the *endo* (1*R*,2*R*,4*R*) bicyclo[2.2.1]hept-5-en-2-carboxylate of (–)-menthol. This experimental result requires that the reaction takes place preferentially through the *Si* face of the dienophile, which is the least shielded in the *s-trans* conformation. Nevertheless, computations^{5c} on model reactions in the gas phase predicted the *endo s-cis* transition state (TS) to have a lower energy than the corresponding *endo s-trans* TS, so that the major product would be the corresponding (1*S*,2*S*,4*S*) cycloadduct. In water solution, the same cycloadduct was predicted to be the major product^{5c} although the electrostatic solvent effect substantially stabilizes the *endo s-trans* vs. the *endo s-cis* TS. Those calculations were carried out at the MP2/6-31G**//RHF/3-21G level,[†] and disagreement with experimental data may be due mainly to the use of an approximate geometry.

In this study, we present more accurate results which demonstrate the importance of geometrical factors in the solvation process. We have optimized the transition states (*endo s-cis* and *endo s-trans*) for the reaction of cyclopentadiene with methyl acrylate, which is the simplest model allowing discussion of diastereofacial selectivity in asymmetric Diels–Alder reactions of chiral acrylates. The *exo* transition states are not considered since their energy is substantially greater than the

endo ones in solution.[‡] The solute–solvent interactions are taken into account through the use of an electrostatic continuum model⁶ using the same approximations as in previous work.^{5c} This model allows us to estimate nuclear relaxation effects in solution. The solvent is assumed to be pure water (dielectric constant $\epsilon = 78.4$). Calculations have been carried out at the *ab initio* RHF/6-31G** level.⁶ The correlation energy is not computed since it has been shown that it has only a small effect on the relative energies of the transition states.^{5c}

In Fig. 1, the structure of the *endo s-trans* TS is given together with the transition vector (imaginary-frequency normal mode eigenvector) in the gas phase. In this Figure, we have also schematically represented the displacement vector deduced from the forces exerted by the solvent when the vacuum TS structure is placed into solution. The computed C–C distances for the bonds being formed, in a vacuum and in solution, are gathered in Table 1. Clearly, the solvent effect is to increase the asynchronicity of the TS, especially in the case of the *s-trans* structure.

The calculations show that this solvent effect cannot be predicted if the displacement vector is constrained to lie along the gas-phase reaction coordinate. Indeed, the reaction co-

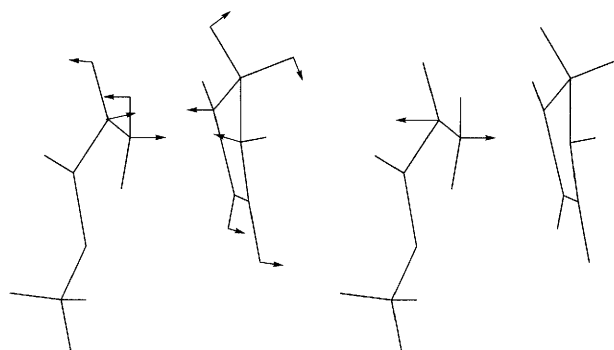


Fig. 1 Gas-phase transition state structure (*endo s-trans*) for the reaction of cyclopentadiene with methyl acrylate computed at the RHF/6-31G** level. Left: transition vector in the gas phase. Right: schematic representation of the C–C bond displacement vectors due to the solvent effect.

Table 1 Computed C–C distances (R_1 and R_2) in Å for the bonds being formed in the transition states of the reaction studied, at the RHF/6-31G** level; R_2 is the length for the bond adjacent to the carbomethoxy group

	Vacuum	Solution ($\epsilon = 78.4$)	δ_{sv}
<i>endo s-cis</i>			
R_1	2.068	2.050	–0.018
R_2	2.328	2.351	+0.023
$R_2 - R_1$	0.260	0.301	0.041
<i>endo s-trans</i>			
R_1	2.088	2.033	–0.055
R_2	2.295	2.374	+0.079
$R_2 - R_1$	0.207	0.341	0.134

ordinate is a nearly symmetric mode whereas the solvent perturbation of the TS geometry is essentially antisymmetric with respect to the C–C forming bonds. The increase in asynchronicity in solution may be explained by two main factors: (i) the polarity of the TS is enhanced by increasing asynchronicity, as is the electrostatic solvation energy, and (ii) the reaction field increases with the polarity of the solute and favours charge transfer from the diene to the dienophile. Since the charge transfer increases with increasing asynchronicity, these factors are cooperative and lead to a substantial modification of the vacuum TS structure. Our calculations show that in water, the effect is very large for the *s-trans* TS and much smaller for the *s-cis* TS in the reaction studied. It is important to point out that a correct description of the polarization can be fundamental to obtain accurate TS geometries. In particular, the use of a basis set with polarization orbitals is crucial. In fact, it may also be essential to allow multiconfigurational effects in the SCF step, and it should be interesting to explore that in further work.

In Table 2, we give the total, solvation and relative energies for the transition states. In the gas phase, the *s-cis* TS is still predicted to be the most stable. However, in water solution the *s-trans* TS is the preferred one, which is in agreement with experimental data concerning the diastereoisomeric excess for the reaction of cyclopentadiene with (–)-menthyl acrylate (see above). Although a direct comparison with experimental data is not possible, the order of magnitude of the energy difference ($-0.45 \text{ kcal mol}^{-1}$, $\text{cal} \approx 4.184 \text{ J}$) seems to be reasonable. § As shown in Table 2, the electrostatic and the polarization solvation energies favour the *s-trans* form, especially the former, although in order to predict the correct relative stability in solution one cannot neglect the latter.

In summary, these results show for the first time that in the reaction of cyclopentadiene with methyl acrylate in polar media, the *s-trans* form of the *endo* TS is the most stable. This agrees with the experimental d.e. in asymmetric synthesis with chiral acrylates, and those results could not be explained by previous theoretical work. In fact, in going from the gas phase to aqueous solution, a change in the preferred conformation of the TS is predicted. This is due not only to electrostatic

Table 2 RHF/6-31G** activation free energy difference and solvation free energies for the transition states *endo s-cis* and *endo s-trans* of the Diels–Alder reaction between cyclopentadiene and methyl acrylate (values in kcal mol^{-1}). Total energies in the gas phase are $-497.4362954 \text{ a.u.}$ (*endo s-cis*) and $-497.4340114 \text{ a.u.}$ (*endo s-trans*). Zero-point energy and thermal contributions are assumed to be similar for both conformations

	Free energy of activation: $\Delta G_{s\text{-}trans}^{\ddagger} - \Delta G_{s\text{-}cis}^{\ddagger}$		
	Gas phase	Solution	
	+1.43	–0.45	
Free energy of solvation			
	<i>endo s-trans</i>	<i>endo s-cis</i>	δ
Electrostatic ^a	–4.88	–3.56	–1.32
Electronic + Nuclear Polarization ^b	–1.29	–0.72	–0.57
Total ^c	–6.17	–4.28	–1.89

^a This is the solvation energy computed using the optimized geometry and the wavefunction of the gas phase. ^b This is the difference between the total and the electrostatic energy. ^c This is the solvation energy computed using the optimized geometry and wavefunction in solution.

interactions but also to polarization effects, and TS geometry relaxation, by substantially increasing the reaction asynchronicity, plays a key role.

Financial support from a joint project (Acción Integrada HF93-164 and Acciones Intégréas-Programme PICASSO, No. 93139) is acknowledged.

Received, 22nd March 1995; Com. 5/01826I

Footnotes

† The 3-21G basis set is given in: J. S. Binkley, J. A. Pople and W. J. Hehre, *J. Am. Chem. Soc.*, 1980, **102**, 939. The 6-31G basis set is given in: W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*, 1972, **56**, 2257. The usual ** notation holds for polarization functions on hydrogen and first-row atoms (see: P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213). For second-order Möller–Plesset energy expressions, see, for example: A. Szabo and N. S. Ostlund, in *Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory*, Macmillan, New York, 1986, ch. 6. The computational level notation B//A means that the molecular energy is computed at level B for the optimized geometry at level A.

‡ In the reaction of methyl acrylate with cyclopentadiene, carried out in water, only 7% of the *exo* cycloadduct is obtained.

§ The catalysed reaction, which is assumed to take place through the *s-trans* forms, leads to a d.e. from 47 to 54% at 30 °C.⁷ A 13.7% d.e. is obtained in the non-catalysed reaction carried out in MeOH–H₂O (6:4) at the same temperature (see ref. 5c). These values allow an estimation of $\Delta\Delta G^{\ddagger}$ between the *s-trans* and the *s-cis* TS of 0.3–0.6 kcal mol^{-1} , the former being the most stable in this solvent.

References

- For recent reviews, see: R. M. Whitnell and K. R. Wilson, *Rev. Comput. Chem.*, 1993, vol. IV, ch. 3; C. J. Cramer and D. G. Truhlar, *Rev. Comput. Chem.*, in press; J. Gao, *Rev. Comput. Chem.*, in press.
- See for example: J. P. Bergsma, B. J. Gertnet, K. R. Wilson and J. T. Hynes, *J. Chem. Phys.*, 1987, **86**, 1356; B. J. Gertnet, J. P. Bergsma, K. R. Wilson, S. Lec and J. T. Hynes, *J. Chem. Phys.*, 1987, **86**, 1377; B. J. Gertnet, K. R. Wilson and J. T. Hynes, *J. Chem. Phys.*, 1989, **90**, 3537; S. C. Tucker and D. G. Truhlar, *J. Am. Chem. Soc.*, 1990, **112**, 3347; M. Aguilar, R. Bianco, S. Miertus, M. Persico and J. Tomasi, *Chem. Phys.*, 1993, **174**, 397; D. G. Truhlar, G. K. Schenter and B. C. Garrett, *J. Chem. Phys.*, 1993, **98**, 5756.
- J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 7430; M. Solá, A. Lledós, M. Durán, J. Bertrán and J. L. M. Abboud, *J. Am. Chem. Soc.*, 1991, **113**, 2873; W. L. Jorgensen, J. F. Blake, D. Lim and D. L. Severance, *J. Chem. Soc., Faraday Trans.*, 1994, **90**, 1727.
- D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816; R. Breslow, U. Maitra and D. C. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901; P. A. Grieco, P. Garner and Z. He, *Tetrahedron Lett.*, 1983, **24**, 1897; P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, 1983, **48**, 3137; R. Breslow and U. Maitra, *Tetrahedron Lett.*, 1984, **25**, 1239.
- (a) T. Karcher, W. Sickling, J. Sauer and R. Sustmann, *Tetrahedron Lett.*, 1992, **33**, 8027; (b) C. Cativiela, J. I. García, J. A. Mayoral, A. J. Royo, L. Salvatella, X. Assfeld and M. F. Ruiz-López, *J. Phys. Org. Chem.*, 1992, **5**, 230; (c) M. F. Ruiz-López, X. Assfeld, J. I. García, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, 1993, **115**, 8780; (d) J. F. Blake, L. Lim and W. L. Jorgensen, *J. Org. Chem.*, 1994, **59**, 803; (e) C. Cativiela, V. Dillet, J. I. García, J. A. Mayoral, M. F. Ruiz-Lopez and L. Salvatella, *Theochem.*, 1995, **331**, 37.
- R. Rinaldi, M. F. Ruiz-López and J. L. Rivail, *J. Chem. Phys.*, 1983, **78**, 834; J. L. Rivail, D. Rinaldi and M. F. Ruiz-López, in *Theoretical and Computational models for Organic Chemistry*, ed. S. J. Formosinho, I. G. Csizmadia and L. Arnaut, Kluwer Academic Publishers, Dordrecht, NATO ASI Ser. C, 1991, **339**, 79.
- W. Oppolzer, M. Kurth, D. Reichlin and F. Moffatt, *Tetrahedron Lett.*, 1981, **22**, 2545.