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EXPERIMENTAL AND THEORETICAL STUDY OF THE INFLUENCE OF THE SOLVENT ON ASYMMETRIC DIELS–ALDER REACTIONS

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Rate, *endo/exo* and diastereofacial selectivities of the Diels–Alder reaction between cyclopentadiene and (−)-menthyl acrylate were measured in a series of organic solvents and organic–aqueous mixtures. Regression analyses show that a model with the α empirical solvent parameter accounts for most of the changes in rates and diastereofacial selectivities, whereas in the case of the *endo/exo* selectivity, inclusion of the π^* and δ parameters is needed. Theoretical calculations carried out on the model reaction between methyl acrylate and cyclopentadiene using dielectric continuum and supermolecule models do not clearly show the effect of the different solvation mechanisms on rate. However, they agree with the above-mentioned influence of α and π^* on the *endo/exo* and diastereofacial selectivities

INTRODUCTION

Interest in the role of the solvent in Diels–Alder reactions has increased over the last few years because of the noticeable improvement in these reactions achieved by the use of aqueous solvents.[1] While several authors[2,3] have shown that log *k* of intermolecular Diels–Alder reactions is linearly correlated with values of solvophobic power (*Sp*),[4] Desimoni and co-workers[5] have used Gutmann's *AN* parameter.[6] The influence of the solvent on *endo/exo* selectivity has been explained on the basis of polarity parameters,[7] solvophobic parameters[8] or both.[3] Recently, Blokzijl *et al.*[9] discussed the rate enhancements for Diels–Alder reactions in media with a high water content in terms of enforced hydrophobic interaction between diene and dienophile.

Leconte *et al.*[10] studied the reduction of α,β-didehydroamino acids in various media, showing a relationship between the enantioselectivity and the solvophobic parameter *Sp*. Although Lubineau and co-workers[11] studied the use of glyco-organic substrates in aqueous Diels–Alder reactions, to the best of our knowledge there are no studies of the influence of the solvent on asymmetric Diels–Alder reactions.

The Diels–Alder reaction of (−)-menthyl acrylate with cyclopentadiene has become a benchmark for asymmetric induction in cycloaddition reactions. Several workers[12] have reported that this reaction gives 8% diastereomeric excess (*de*) for the *endo* cycloadducts when run neat or in a series of solvents. The diastereofacial and *endo/exo* selectivities increase when Lewis acids are used.[12,13] Corey *et al.*[14] recently found that the *de* of this reaction can be further increased by the use of an optically active catalyst.

In this paper we report an experimental and theoretical study of the influence of the solvent on rate, *endo/exo* selectivity and *de* of the Diels–Alder reaction between cyclopentadiene (**1**) and (−)-menthyl acrylate (**2**) (Scheme 1).

RESULTS AND DISCUSSION

Experimental results and statistical analyses

As we tried to cover a broad range of solvent characteristics, the solvents were selected according to their

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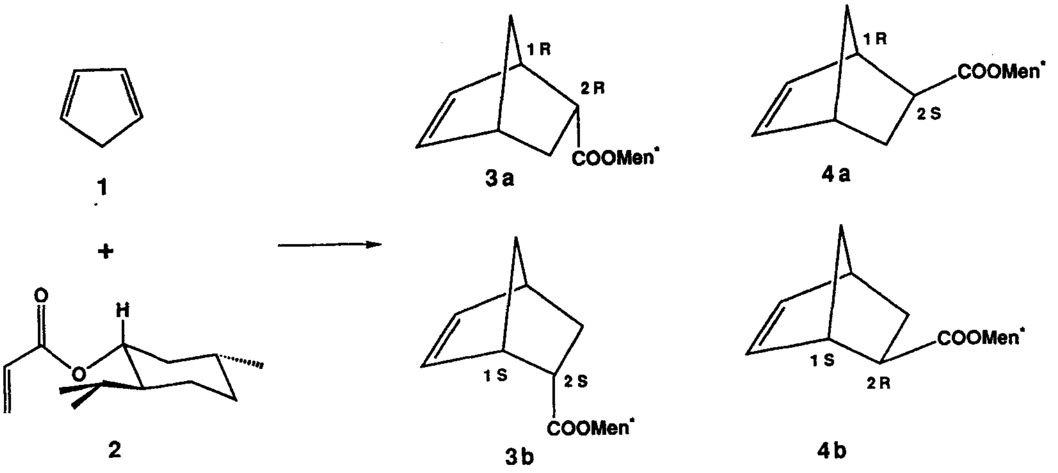


Scheme 1

Sp values[4] and normalized $E_T(30)(E_T^N)$ values.[15] The reason for choosing these two solvent parameters is twofold. First, they have already proved to be of use in explaining results of rate and *endo*/*exo* selectivity in Diels–Alder reactions.[2,3,8] Second, there are to date few empirical solvent parameters which have been determined for a comprehensive set of organic solvents and binary aqueous mixtures. Further, they account for most solvation mechanisms, namely solvophobic or cavity effects, polar effects and hydrogen-bonding (HBD) effects.[15]

The reactions were monitored by gas chromatography. The flame ionization detector was calibrated by repeated injection of mixtures of (−)-menthyl acrylate and cycloadducts at different relative concentrations. Compounds **3a** and **3b** were assigned by comparison of the gas chromatograms obtained in the reactions studied with those obtained in several reactions of cyclopentadiene and (−)-methyl acrylate using Lewis acids as catalysts, the diastereoselectivites and absolute configurations were described in previous papers.[13]

Table 1 shows the twenty solvents and solvent mixtures finally chosen together with their corresponding *Sp* and E_T^N values and the results obtained in the

Table 1. Experimental results for the reaction between (−)-menthyl acrylate and cyclopentadiene in several organic solvents and organic–aqueous mixtures

Code	Solvent	E_T^N	*Sp*	π^*	δ	α	β	Log *k*	[3/4]	Log [3/4]	[**3a**/**3b**]	*de* (%)	Log [**3a**/**3b**]
a	Dichloromethane	0·309	0·0000	0·820	0·5	0·300	0·000	−4·473	3·662 ± 0·058	0·564	1·175 ± 0·014	8·1	0·070
b	*n*-Hexane	0·009	0·0091	−0·080	0·0	0·000	0·000	−4·645	2·379 ± 0·081	0·394	1·182 ± 0·019	8·3	0·081
c	Ethyl acetate	0·228	0·0635	0·550	0·0	0·450	0·000	−4·578	3·196 ± 0·058	0·505	1·158 ± 0·014	7·3	0·064
d	Acetonitrile	0·460	0·2167	0·750	0·0	0·190	0·310	−4·408	4·347 ± 0·040	0·638	1·204 ± 0·016	9·3	0·081
e	Benzene	0·111	0·0000	0·590	1·0	0·000	0·100	−4·443	2·715 ± 0·017	0·434	1·156 ± 0·004	7·2	0·063
f	Toluene	0·099	0·0000	0·540	1·0	0·000	0·110	−4·539	2·734 ± 0·049	0·437	1·210 ± 0·010	9·5	0·083
g	Chlorobenzene	0·188	0·0000	0·710	1·0	0·000	0·070	−4·456	3·009 ± 0·009	0·478	1·213 ± 0·005	9·6	0·084
h	Benzonitrile	0·333	0·0810	0·900	1·0	0·000	0·410	−4·411	3·981 ± 0·015	0·600	1·284 ± 0·006	12·4	0·109
i	Nitrobenzene	0·324	0·0650	1·010	1·0	0·000	0·390	−4·296	3·821 ± 0·049	0·582	1·316 ± 0·019	13·7	0·119
j	Acetone	0·355	0·1267	0·710	0·0	0·080	0·480	−4·545	3·581 ± 0·106	0·554	1·199 ± 0·011	9·1	0·079
k	Acetone (80%)	0·664	0·2390	–	–	–	–	−4·000	5·055 ± 0·062	0·704	1·255 ± 0·021	11·3	0·099
l	Dioxane	0·164	0·0794	0·550	0·0	0·000	0·370	−4·470	3·109 ± 0·055	0·493	1·155 ± 0·015	7·2	0·063
m	Dioxane (60%)	0·667	0·3900	–	–	–	–	−3·512	6·046 ± 0·159	0·781	1·276 ± 0·014	12·1	0·106
n	Dioxane (50%)	0·707	0·5210	–	–	–	–	–	7·057 ± 0·247	0·849	1·308 ± 0·027	13·3	0·117
o	Propan-2-ol	0·546	0·1000	0·480	0·0	0·760	0·950	−4·094	4·607 ± 0·106	0·663	1·241 ± 0·023	10·8	0·094
p	Methanol	0·765	0·2000	0·600	0·0	0·930	0·620	−4·073	5·363 ± 0·112	0·730	1·195 ± 0·024	8·9	0·084
q	Methanol (70%)	0·818	0·4460	0·910	0·0	0·910	0·530	–	7·786 ± 0·247	0·891	1·295 ± 0·025	12·9	0·112
r	Methanol (60%)	0·836	0·5310	0·980	0·0	0·870	0·500	–	9·191 ± 0·533	0·963	1·316 ± 0·026	13·7	0·119
s	Trifluoroethanol	0·898	0·3250	0·730	0·0	1·510	0·000	−3·697	6·574 ± 0·053	0·818	1·460 ± 0·003	18·7	0·164
t	Hexafluoroisopropanol	1·068	0·2800	0·650	0·0	1·960	0·000	−3·707	7·106 ± 0·109	0·852	1·717 ± 0·012	26·4	0·235

Diels–Alder reaction between cyclopentadiene (**1**) and (–)-menthyl acrylate (**2**). Log *k* values for reaction media **n**, **q** and **r** could not be determined because of the low solubility of the reagents, which makes the use of very dilute solutions necessary. Water and binary aqueous mixtures with higher water contents were also considered, but the even lower solubility of the reagents prevented their use as reaction media. As can be seen from the results in Table 1, the reaction medium significantly influences the reaction rate and the *endo*/*exo* and diastereofacial selectivities. In fact, the results obtained for *de* in the case of hexafluoroisopropanol (**t**) are close to those obtained using a conventional Lewis acid catalyst (such as $AlCl_3$).

In order to analyse the influence of these solvent parameters on the reaction rate, *endo*/*exo* selectivity and diastereoselectivity, we tested linear regression models of log *k*, log [**3**/**4**] and log [**3a**/**3b**] with *Sp* and E_T^N. The results obtained are given in Table 2.

The regression models obtained for log *k* and log [**3**/**4**] versus E_T^N and *Sp* are in good agreement with those previously described for the reaction between methyl acrylate and cyclopentadiene.[3] In both cases E_T^N and *Sp* have statistically significant coefficients (a cut-off of 95% of probability is used throughout the work). The normalized coefficients [0·456 for E_T^N and 0·490 for *Sp* in log *k*, and 0·579 for E_T^N and 0·453 for *Sp* in log [**3**/**4**] show that both parameters are of similar importance in log *k* and E_T^N is slightly more important in log [**3**/**4**].

The lack of information about the influence of the solvent on diastereofacial selectivities increases the interest of these experimental results. Unfortunately, the regression model for log [**3a**/**3b**] is worse than those obtained for reaction rate and *endo*/*exo* selectivity. In spite of this, the lack of significance of the *Sp* coefficient seems to show that *de* tends to increase when the E_T^N of the solvent increases.

The colinearity between E_T^N and *Sp* remains very high ($r > 0{\cdot}80$) despite the inclusion of highly polar solvents of medium solvophobicity[16] such as fluorinated alcohols. This makes the discussion of the physicochemical factors that influence the reaction course difficult.

In view of this, we tested a different empirical approach. The Abboud–Abraham–Kamlet–Taft (AAKT) model[17] avoids in principle the above-mentioned problem by the use of quasi-independent parameters, namely π^*, δ, α and β, which account for the dipolarity–polarizability and HBD–HBA abilities, respectively. Given that these parameters are not known for several aqueous mixtures, the set of solvents is now reduced to 17 (Table 1). The regression models obtained for log *k*, log [**3**/**4**] and log [**3a**/**3b**] are given in Table 2.

The use of the AAKT model for log *k* shows that only the α coefficient is statistically significant. In fact, a regression model of log *k* vs. α gives almost the same result, which agrees with the results previously reported by Desimoni and co-workers[5] using the *AN* parameter.

Both dipolarity–polarizability and the HBD properties of the solvent influence the *endo*/*exo* selectivity. The normalized regression coefficients (0·533 for π^*, –0·325 for δ and 0·574 for α) provide a clearer view of the relative influence of each parameter, showing that both solvation mechanisms are of similar importance.

A poorer result is again obtained for the diastereo facial selectivity, but the model clearly shows that log [**3a**/**3b**] tends to increase in HBD solvents.

In summary, the use of the AAKT model shows that α plays the most significant role in determining the reaction course. This is not incompatible with the results of similar quality obtained using the E_T^N and *Sp* parameters, because of the strong correlation between E_T^N and α ($r = 0{\cdot}93$) and *Sp* and α ($r = 0{\cdot}70$).

The former correlation was expected because of previous knowledge about the nature of E_T^N, which consists of a blend of dipolar and HBD properties.[15] However, the use of π^* and δ in the AAKT model enables us to decide about the relative influence of both solvation mechanisms.

On the other hand, there was no previous report about the correlation between *Sp* and α, although

Table 2. Regression model result of rate, *endo*/*exo* and diastereofacial selectivities with several empirical solvent parameters

	n	*r*	*s*	Intercept	E_T^N	*Sp*	π^*	δ	α	β
Log *k*	17	0·912	0·151	–4·646	0·520 ± 0·243	1·354 ± 0·590	–	–	–	–
	15	0·975	0·078	–4·654	–	–	0·104 ± 0·103	0·117 ± 0·063	0·491 ± 0·042	0·137 ± 0·084
	15	0·947	0·099	–4·489	–	–	–	–	0·446 ± 0·042	–
Log(**3**/**4**)	20	0·986	0·030	0·415	0·320 ± 0·040	0·432 ± 0·069	–	–	–	–
	17	0·963	0·054	0·328	–	–	0·332 ± 0·064	–0·093 ± 0·042	0·176 ± 0·029	0·080 ± 0·058
	17	0·957	0·056	0·345	–	–	0·367 ± 0·061	–0·121 ± 0·038	0·163 ± 0·028	–
Log(**3a**/**3b**)	20	0·791	0·026	0·050	0·142 ± 0·034	–0·089 ± 0·059	–	–	–	–
	20	0·758	0·027	0·053	0·099 ± 0·020	–	–	–	–	–
	17	0·894	0·023	0·060	–	–	0·017 ± 0·027	0·021 ± 0·017	0·067 ± 0·012	–0·024 ± 0·024
	17	0·832	0·026	0·103	–	–	–	–	0·060 ± 0·006	–

judging from the nature of both parameters it was to be expected. This makes a clear interpretation of the role of solvophobicity difficult. The use of Hildebrand's δ_H^2 parameter,[17,18] included in the AAKT model, should lead, at least in theory, to a correct interpretation of the relative importance of each solvation mechanism. Unfortunately, as this parameter is not defined for the aqueous mixtures, which present the highest solvophobicities, it therefore cannot be used in our case to assess the importance of this solvent property.

As a consequence, the influence of solvophobicity on reaction rates cannot be discounted, because the reaction is faster in the more solvophobic solvents, which are not the most HBD in the series. However, the diastereofacial selectivity shows a clear dependence on solvent HBD ability. In this case, the most HBD solvents lead to the greatest increase in *de*, in spite of the fact that these solvents are not the most solvophobic.

As this is the best possible result from an empirical viewpoint and the establishment of the physicochemical factors influencing the course of asymmetric Diels–Alder reactions is of prime importance for further work in this area, we considered a different approach from a theoretical point of view.

The pure electrostatic solute–solvent interactions may be introduced into SCF procedures[19] and make it possible to compute a reaction path for a solvated system. The comparison between the transition state (TS) energies calculated as isolated species and in a dielectric continuum enables us to estimate the solvation energies. In this way, the electrostatic influence of the solvent on the *endo*/*exo* and diastereofacial selectivities can be studied, at least in a qualitative manner.

The specific effects of the solvent can also be considered by means of the well-known supermolecule approach. One or several molecules of the solvent are explicitly considered to interact with the solute molecule. The solvation energy is usually calculated by the difference in the energies between the supermolecule and the isolated species. This methodology is computationally expensive but, in most cases, the use of a single solvent molecule is enough to show the solvation trend of the system.

Given that (−)-menthyl acrylate is a large molecule and the complete study of the reactive system must include eight TSs (two *endo s-cis*, two *endo s-trans*, two *exo s-cis* and two *exo s-trans*), we chose methyl acrylate as a simpler model of the reaction studied. An AM1 study showed that the dipole moments of the *s-cis* and *s-trans* conformers of methyl acrylate are similar to those of the corresponding conformers of (−)-menthyl acrylate so that the electrostatic solute–solvent interactions should lead to comparable effects. The calculated conformational equilibria in the gas phase are also similar for both dienophiles (Table 3). Further, the solvents affect the *endo*/*exo* selectivity of the reactions of both dienophiles with cyclopentadiene in approximately the same way.

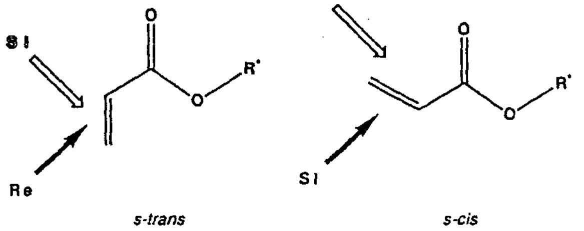
Table 3. Dipole moments and heats of formation of methyl and (−)-menthyl acrylates in the *s-cis* and *s-trans* conformations, as calculated by AM1

Dienophile	ΔH_f (kcal mol^{-1})[a]	μ (D)
Methyl acrylate *s-cis*	−70·0	1·60
Methyl acrylate *s-trans*	−69·6	2·32
(−)-Menthyl acrylate *s-cis*	−112·6	1·52
(−)-Menthyl acrylate *s-trans*	−112·2	2·27

[a] 1 kcal = 4·184 kJ.

Methyl acrylate is obviously not a chiral dienophile, but in the asymmetric Diels–Alder reactions of prochiral 1,3-dienes with chiral acrylates, the *de* obtained depends on the shielding effect of the chiral auxiliary and, given that *s-cis* and *s-trans* conformers display reversed topicity in their top and bottom faces, on the conformational equilibrium of the acrylate (Scheme 2).[20]

In our study the chiral auxiliary does not change, so it can be concluded that variations in *de* depend on the nature of the solvent and are mainly related to the change in conformational equilibrium in the TS induced by the solvent. This equilibrium can be studied in the case of methyl acrylate.



Scheme 2

Computational analyses

We first used a cavity model to represent the solvent. In this model, the molecule is placed in an ellipsoidal cavity surrounded by an infinite polarizable and dielectric continuum, characterized by its dielectric permittivity ε. The charge distribution of the molecule polarizes the continuum, which in turn creates an electric field inside the cavity. The Hamiltonian of the electric interactions is added to the Hartree–Fock operator and a complete SCF calculation is made so that polarization effects are also taken into account. The total free energy of solvation (electrostatic plus induction) is given by the simple expression[19]

$$A = -\frac{1}{2}\sum_{l=0}^{\infty}\sum_{m=-l}^{l}\langle R_l^m\rangle\langle M_l^m\rangle$$

where M_l^m is a component of the multipole moment operator of order l and R_l^m its corresponding reaction field component, which in the linear response approximation is given by

$$\sum_{l'm'} f_{ll'}^{mm'} M_{l'}^{m'}$$

The components $f_{ll'}^{mm'}$ depend on the cavity axes and the dielectric permittivity ε only.

The solvation energy contains other terms (dispersion, cavitation) which are not included in this model. Their role will be discussed below.

The definition of the cavity is a crucial point in this model and we have used a procedure described elsewhere.[21,22] It consists of the determination of an ellipsoid which fits as best as possible the isodensity surface enclosing a volume equal to the molecular volume. Computations were carried out with the GEOMOS[23] and GAUSSIAN 86[24] programs for the semi-empirical and *ab initio* parts, respectively.

Semi-empirical computations were performed with the AM1[25] and PM3[26] methods. *Ab initio* computations were carried out at the minimal basis set STO-3G level. After inspecting the potential energy surfaces, the transition state (TS) structures were located by using Powell's algorithm[27] as implemented in the MOPAC 5.0 program[28] (for the semi-empirical calculations) and Schlegel's algorithm[29] as implemented in GAUSSIAN 86 (for the *ab initio* calculations). The TS structures were checked and characterized by the presence of only one negative eigenvalue of the Hessian matrices. A complete optimization of the molecular geometries was performed for the isolated molecules. In the case of the solvated species, we retained the same geometry but checked that there were no large modifications in the equilibrium geometry for the reagents. In STO-3G calculations we also used a recently reported algorithm which enables us to search for TSs in the cavity.[30] There are no significant differences between the TS structures obtained by this method and those obtained in vacuum.

The pure electrostatic and HBD effects of the solvents were analysed by comparing the results obtained for the isolated molecules with those obtained with the cavity model in a polar solvent (we shall arbitrarily take $\varepsilon = 78$, i.e. the dielectric permittivity of water) and those obtained by means of the supermolecule approach (considering a single water molecule solvating the carbonyl oxygen), respectively.

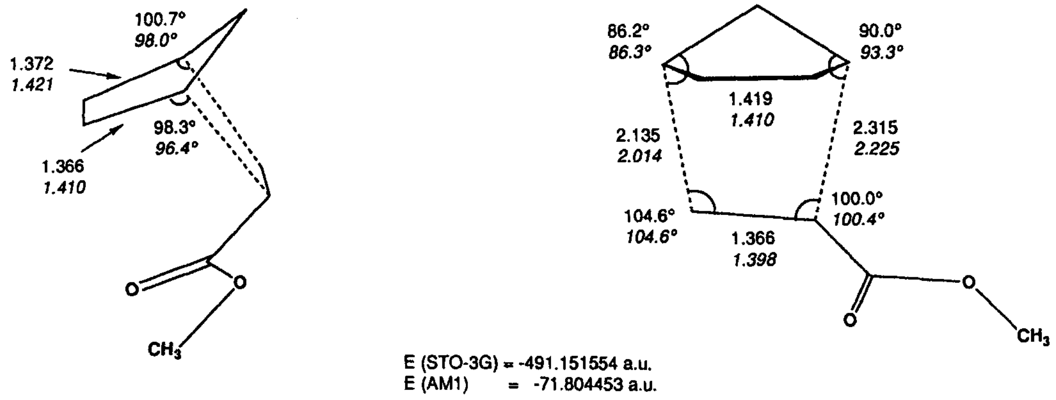
The geometrical structures and the energies of the TSs, as predicted by the AM1 and STO-3G calculations, are given in Figure 1. The structural results are in good agreement with those obtained previously[31] for the TSs of similar Diels–Alder reactions at 3–21G level. The AM1 structures are slightly more asynchronous than the STO-3G structures and the C—C distances (for the bonds created) are slightly shorter. Both methods predict a longer distance for the C—C bond which carries the carbomethoxy group. It can also be seen that (a) the STO-3G structures present a greater asynchronicity for the *endo* configurations, in accordance with previous results, but the AM1 results show similar asynchronicity for the various TS structures, (b) the *exo* structures do not change much from the *s-cis* to the *s-trans* conformations, (c) the TS structures are approximately half way between the reagents and products and (d) the TS energies calculated by both methods show a preference for the *s-cis* over the *s-trans* forms. The STO-3G calculations show a preference of the *endo* over the *exo* TSs, whereas the AM1 calculations show the reverse order.

The total energies of solvation for the reagents (cyclopentadiene and methyl acrylate) and for the four possible TS structures (*endo s-trans, endo s-cis, exo s-trans* and *exo s-cis*) are given in Table 4. Table 4 also gives dipole moments for the isolated species.

Although the solvation energies are larger for the most dipolar species, the detailed analysis of the multipolar expansion shows that the quadrupole and the

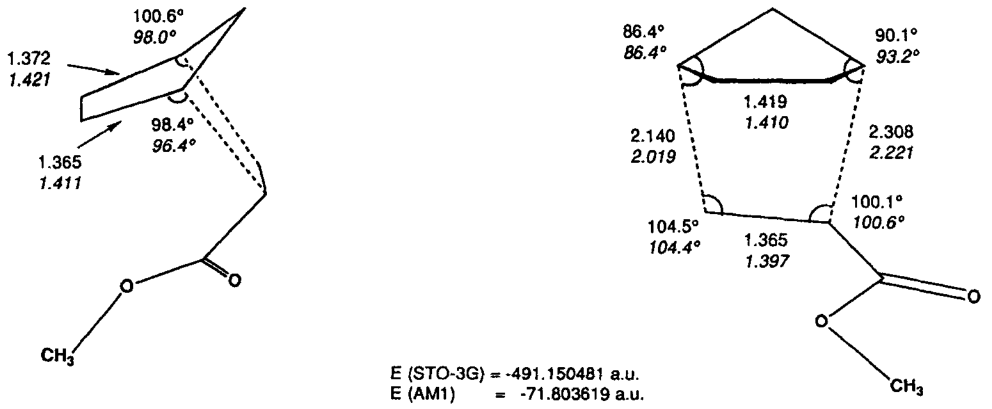
Table 4. Calculated dipole moments and free energies of solvation of the reagents and transition state structures for the reaction between methyl acrylate and cyclopentadiene

	AM1		STO-3G		PM3:
	μ (D)	E_{solv} (kcal mol^{-1})	μ (D)	E_{solv} (kcal mol^{-1})	E_{solv} (kcal mol^{-1})
Reagents					
Cyclopentadiene	0·53	−1·06	0·38	−0·50	–
Methyl acrylate *s-cis*	1·60	−3·22	1·37	−1·56	−3·85
Methyl acrylate *s-trans*	2·32	−3·67	2·33	−1·70	−3·97
Transition states					
endo s-cis	2·61	−3·24	1·66	−1·88	−3·75
endo s-trans	2·88	−3·81	1·96	−2·34	−4·95
exo s-cis	1·85	−2·79	1·08	−1·62	−3·92
exo s-trans	2·79	−3·66	1·81	−2·22	−4·47



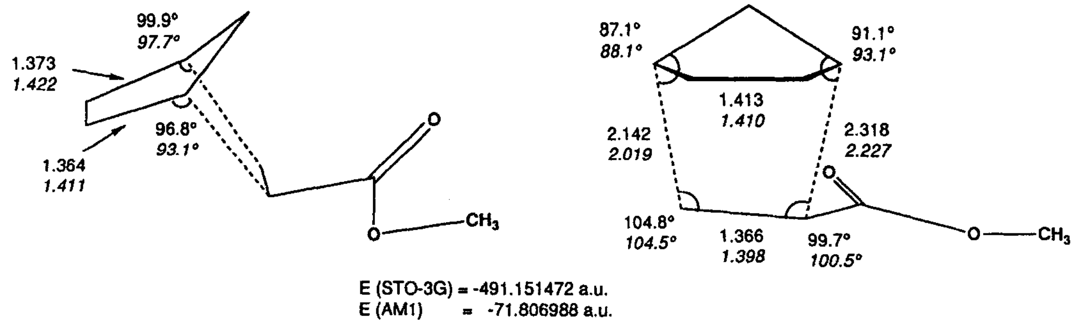
E (STO-3G) = -491.151554 a.u.
E (AM1) = -71.804453 a.u.

endo s-cis



E (STO-3G) = -491.150481 a.u.
E (AM1) = -71.803619 a.u.

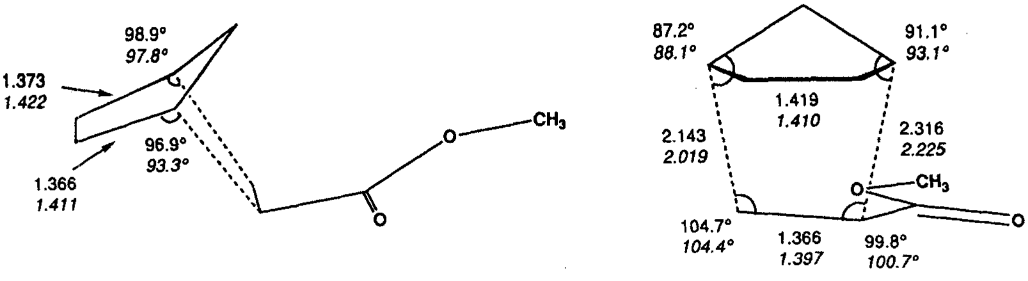
endo s-trans



E (STO-3G) = -491.151472 a.u.
E (AM1) = -71.806988 a.u.

exo s-cis

Figure 1. Side and front views of the *endo s-cis, endo s-trans, exo s-cis* and *exo s-trans* transition structures at the STO-3G (roman typeface) and AM1 (italic typeface) levels for the reaction between cyclopentadiene and methyl acrylate. Distances are in Å and angles are in degrees



E (STO-3G) = -491.150250 a.u.
E (AM1) = -71.805951 a.u.

exo s-trans

Figure 1. (*Continued*)

octupole moments play an important role in the solvation process. In fact, the contributions of these moments to the free energy of solutions are in some cases greater than the dipole moment contribution.

The use of the AM1 method in the supermolecule approach leads to unrealistic geometries and solvation energies. This fact is well-known, and has been documented.[32] On the other hand, it has been reported[28,32] that the semi-empirical PM3 method leads to a more correct representation of hydrogen-bonding species, so this method was finally chosen to calculate the solvation energies of reagents and TSs (Table 4). In each case, the water molecule position was fully optimized, fixing the geometry of the remainder of the supermolecule.

The supermolecule model (and, to a lesser extent, the STO-3G cavity model) predicts a decrease in the transition barrier for the *s-trans* TSs and a slight increase for the *s-cis* TSs, so these models do not account for the increase in rates found experimentally in aqueous media.

A recent theoretical study by Blake and Jorgensen[33] of the reaction between cyclopentadiene and methyl vinyl ketone has shown that the transition barriers substantially decrease when going from the vacuum to solution in protic solvents. This study was carried out using Monte Carlo simulations and showed the importance of the role played by non-hydrophobic interactions. Since our cavity calculations show that the effect of the pure electrostatic interactions on the transition barriers can be neglected, dispersion forces may be invoked to explain the differences between the reaction rates. In fact, dispersion energy is expected to be substantially different for the reagents and for the TS structures owing to the change in the number of π-electrons.[34]

However, it should be remembered that a detailed study of the reaction rates would require a further discussion of the dynamics of the process, namely the relaxation of the solvent around the species present along the reaction path. Given that the above-mentioned computations do not take this aspect of the problem into account, their conclusions have to be considered qualitatively.

On the other hand, the cavitation term of the solvation energy has to be considered. In order to obtain an approximate estimation of this term, we applied Pierotti's scaled particle theory (SPT),[35] which enables us to calculate the free energy of cavitation from the following equation:

$$G_c = k_0 + k_1 r + k_2 r^2 + k_3 r^3$$

where r is the (spherical) cavity radius and k_0–k_3 are constants depending on several solvent properties (solvent radius, density) and pressure.

The radii for the TSs were estimated from the data of the corresponding activation volumes, $\Delta V^{\neq}$,[36] and the molar volumes of the reagents. The values obtained show a decrease of *ca* 1·9 kcal mol^{-1} in the transition barrier, which agrees with a significant effect of solvophobic interactions.

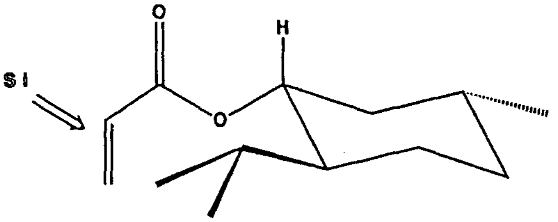
The solvation energies calculated using the cavity model lead to an increase in the *endo* preferences in the STO-3G calculation and to a decrease in the *exo* preference in the AM1 calculation. These results show that the electrostatic effect of the solvent favours the *endo* over the *exo* isomers, which agrees with the experimentally found importance of π^* on *endo*/*exo* selectivity. Further, the solvation energies obtained by means of the supermolecule approach account for the increase in *endo* selectivity in HBD solvents.

The application of the above-mentioned SPT equation using the experimental values of $\Delta\Delta V^{\neq}$ for *endo* and *exo* TSs[36] show that the differences in cavitation energies for both TSs (and, in consequence, the corresponding solvophobic effect) are negligible (<0·005 kcal mol^{-1}).

In all the previously mentioned reaction media the (1*R*, 2*R*)-cycloadduct (**3a**) is preferentially obtained, which requires a preferential approach of the diene on the *Si* face of the dienophile. Given that this face is the less shielded in the *s-trans* conformation (Scheme 3), it can be assumed that a relative stabilization of the *s-trans* with respect to the *c-cis* TS will increase the *de*.

Hydrogen bond formation clearly favours the *s-trans* conformation for the TSs and makes it possible to explain the increase of *de* in HBD solvents. It should be noticed, however, that this interaction contains a substantial electrostatic component whose average effect is included in the cavity model computations which, qualitatively, lead to a comparable effect. It can therefore be concluded that pure electrostatic interactions increase *de* slightly, whereas in the case of HBD solvents this effect is substantially enhanced.

A consideration similar to that used for the *endo*/*exo* selectivity can be invoked for the cavitation energy differences between *s-cis* and *s-trans* TSs, so a significant solvophobic effect on *de* cannot be expected.



Scheme 3

CONCLUSIONS

Combined empirical studies and theoretical studies have proved to be valuable tools for investigating the effect of the solvent on the results of an asymmetric Diels–Alder reaction. The results obtained suggest that the solvophobicity (through the cavitation energy) and the dispersion energy may play an important role in the effect of the solvent on the rate of these reactions. However, the influence of these terms on *endo*/*exo* and diastereofacial selectivities seems to be negligible. In fact, pure electrostatic and hydrogen-bonding interactions account for the changes observed in both responses.

Although the calculation levels used do not accurately reproduce the absolute energies of the TSs, they succeed in the qualitative pattern of solvation energies, which determine the modification of the *endo*/*exo* and diastereofacial selectivities induced by the solvent.

EXPERIMENTAL

Calculations. AM1 calculations for isolated systems were done using the standard AM1 method,[25] as implemented in the MOPAC[28] semi-empirical molecular orbital package. AM1 calculations for the same systems considering the solvent effect by means of the dielectric continuum theory and also PM3[26] supermolecule calculations were carried out using the GEOMOS[23] package. *Ab initio* STO-3G calculations for both isolated and solvated systems were performed using a locally modified[22] version of the GAUSSIAN-86[24] package.

General. Gas chromatographic analyses were carried out with an apparatus with a flame ionization detector, cross-linked methylsilicone column (25 m × 0·2 mm i.d. × 0·3 mm o.d.), helium as carrier gas (18 psi), injector temperature 230 °C, detector temperature 250 °C and oven temperature programmed from 190 °C (held for 1 min) at 2 °C min^{-1} to 180 °C and then at 1 °C min^{-1} to 170 °C (held for 5 min). Retention times were (−)-menthyl acrylate (**2**) 3·7 min, *exo* cycloadducts (**4**) 17·6 min, *endo* (2*S*)-cycloadduct (**3b**) 18·2 min and *endo* (2*R*)-cycloadduct (**3a**) 18·6 min. All organic solvents were dried and purified according to standard procedures. Water was deionized and doubly distilled in an all-glass apparatus.

Kinetic procedure. In a typical run, 0·396 g (6 mmol) of cyclopentadiene (**1**) dissolved in the corresponding organic solvent or organic–aqueous mixture (4 ml) was added to a thermostated (30 ± 1 °C) solution of 0·42 g (2 mmol) of (−)-menthyl acrylate (**2**) in the same solvent (28 ml) and the solution obtained was stirred magnetically. Reaction rates were determined by gas chromatographic analyses of aliquots of the reaction mixtures, following the formation of cycloadducts (**3a**, **3b** and **4**). All the reactions, which were repeated three times, followed second-order kinetics.

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