Solvent Effects on the Mechanism and Selectivities of Asymmetric Diels–Alder Reactions

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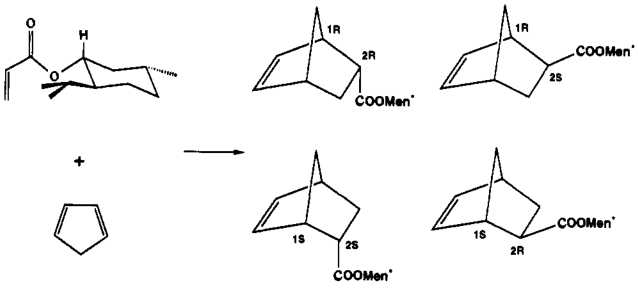
Abstract: The electrostatic effect of the solvent on the reaction of cyclopentadiene with methyl acrylate has been studied with the help of a Self-Consistent Reaction Field model by means of *ab initio* computations. The effect on the reaction mechanism, *endo*/*exo* selectivity, and activation energy has been analyzed. Moreover, the computations allow a discussion of the solvent effect on the diastereofacial selectivity when chiral acrylates are used and a comparison with experimental data for the reaction of cyclopentadiene with (–)-menthyl acrylate. The results are in agreement with the experimentally observed increase of the *endo*/*exo* and diastereofacial selectivities as a function of solvent polarity, but hydrophobic effects and hydrogen-bond formation are necessary to account for changes in reaction rates.

1. Introduction

Solvent effects on Diels–Alder reactions are well known[1] and have attracted much attention especially in the last few years because of the noticeable improvement in these reactions achieved by the use of aqueous solvents.[2] Correlations with empirical parameters have been discussed for the reaction rates[3,4] and *endo*/*exo* selectivities,[4,5] and the solvent effect has been interpreted in different ways. Among the numerous asymmetric Diels–Alder reactions studied, that of cyclopentadiene with (–)-menthyl acrylate, shown in Scheme I, has become a benchmark for asymmetric induction in cycloaddition processes,[6] and recently, the solvent effect on its rate and selectivities has been studied.[7] The *endo*/*exo* and diastereofacial selectivities are well correlated with polarity parameters for the solvents used, suggesting that the electrostatic part of the solute–solvent interactions plays an important role.[4,5a,7] On the other hand, solvophobicity parameters have been shown to be well correlated with rate variations.[7] These correlation studies have substantially clarified the role of the solvent on asymmetric Diels–Alder reactions, but their main limitation is due to intercorrelations between the empirical parameters which render the elucidation of the precise role of each solute–solvent interaction term difficult. We have then envisaged the study of these reactions in solution by means of *ab initio* computations.

Scheme I



In the last decade, some effort has been devoted to the theoretical treatment of solvation effects in reactivity studies. In most of the published work, S_N2 reactions have been considered. A special case of these S_N2 processes is the Menshutkin reaction, in which the reactants are uncharged and there is a separation of charge along the reaction coordinate so that solvent effects are expected to be very large. Indeed, the solvent has been shown to have a dynamic effect, which arises from the coupling of the reactant dynamics with fluctuations of the solvent, and accordingly, its coordinates participate with the reaction coordinate.[8] In other processes, such as the Diels–Alder reactions, the role of the solvent has been assumed to be static,[9] that is, its effect is roughly given through the contribution of the solvation energy to the total free energy of the reactants and the transition states. Though the direct participation of solvent molecules in the reaction coordinate is in this case unlikely, the electric field created by the solvent changes the shape of the potential energy surface and can modify the position of the stationary points. The reaction path itself can be perturbed. An extreme situation of this kind has been found for the ketene + imine reaction in which the reaction mechanism changes from a one- to a two-step cycloaddition in going from a vacuum to a low polar solvent.[10] Hence, a theoretical study of the electrostatic solvent effect on the reaction mechanism of Diels–Alder cycloadditions is interesting.

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Since our main aim is to analyze the role of the solvent on the reaction coordinate and selectivities, which are expected to be dependent, above all, on the electrostatic interactions, a continuum model has been used in this work to represent the liquid. It is based on a Self-Consistent Reaction Field approach previously described[11] and outlined in section 2. The main advantage of this model, compared, for instance, to statistical simulation models, is that the solvent effect on the electronic distribution of the solute (the reagents, the transition states, and the products) may be easily obtained and polarization effects discussed. Moreover, the method allows a detailed analysis of the geometrical changes induced by the solvent in the reaction path.

We also discuss solvent effects on reaction rates. As mentioned above, experimental data correlate well with solvophobicity parameters, which is not surprising considering the fact that in these reactions, there is a substantial decrease of the activation volume, as illustrated by their large pressure dependence,[12] and consequently, cavitation energy must be an important factor. Nevertheless, solvophobicity and polarity are correlated properties, and the role of pure electrostatic interactions on activation barriers needs to be clarified. Specific interactions, such as hydrogen bonds with water molecules, may also be important, but it should be noticed that this kind of interaction has a large electrostatic character, and an average effect is included in the continuum model. Besides, electrostatic interactions are present in all reaction media (including apolar and aprotic solvents), and it is important to get a deeper insight on their influence.

Ab initio calculations at the MP2/6-31G**//3-21G level have been carried out to study the reaction of cyclopentadiene with methyl acrylate. This reaction is also used to model the reaction of cyclopentadiene with (–)-menthyl acrylate, in order to maintain the computational cost within reasonable limits. Methyl acrylate is obviously not a chiral dienophile, but in the asymmetric Diels–Alder reactions of prochiral 1,3-dienes with chiral acrylates, the diastereomeric excess (de) obtained depends on the shielding effect of the chiral auxiliary and, given that *s-cis* and *s-trans* conformers display reversed topocity in their top and bottom faces, on the conformational equilibrium of the acrylate. Thus, modification of the de through the solvent effect may be related to a change in the relative stability of the possible conformations of the transition states (TS) which can be studied in the case of methyl acrylate.

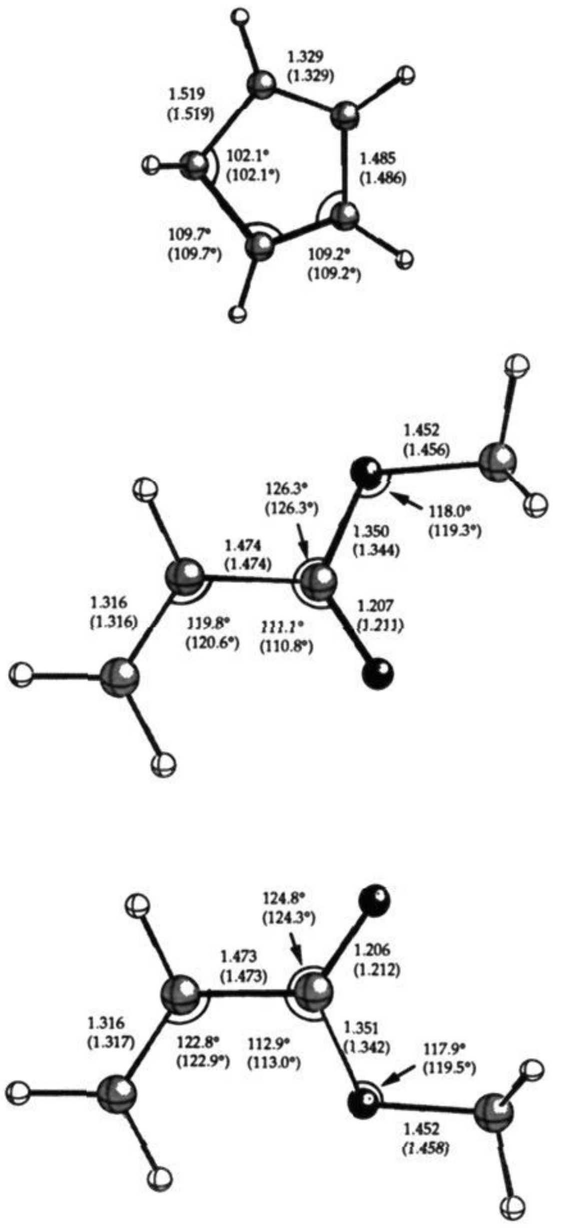

Figure 1. Optimized geometries for the reagents at the RHF/3-21G level for the isolated and the solvated (in parentheses) molecules.

2. Computational Model

The computation of reaction paths in solution requires an approximate method to take into account the solute–solvent interactions. The average effect of the reaction field, *i.e.*, the electrostatic potential created by the solvent in the region occupied by the solute, may be computed through the use of continuum models.[11,13–24] In these models, the liquid is represented by a dielectric continuum characterized by a macroscopic constant, usually the dielectric relative permittivity ϵ. A cavity, in which the solute is placed, is created in the continuum, after some cavitation energy was spent. The electronic distribution of the solute polarizes the continuum which in turn creates an electric field inside the cavity. Accordingly, the electronic distribution and the geometry of the solute will change until the equilibrium is reached. Classical electrostatics lead to the following expression for the electrostatic free energy of the solvation process:[11]

$$\Delta A_{\rm solv} = -\frac{1}{2}\sum_{l,l'}\sum_{m,m'} M_l^m f_{ll'}^{mm'} M_{l'}^{m'} \qquad (1)$$

Here, M_l^m represents a multipole moment of the solute evaluated at the center of the cavity, and $f_{ll'}^{mm'}$ is a constant depending on the dielectric properties of the medium and on the definition of the cavity surface. Indices l vary from 0 to ∞ and m from $-l$ to l, but good convergence of the series is in general obtained at $l = 6$. Note that when this sum is limited to the dipole moment, $l = 1$, and the cavity shape is taken as a sphere, Onsager's formula[25] is obtained. However, it is well known that higher multipoles may play a crucial role in many cases, even for polar systems, and neglecting their contribution to the solvation energy could lead to unreliable results. Besides, the use of a spherical cavity may be criticized. General cavity shapes may be used, but they increase the computational cost. In our work, we have assumed an intermediate approximation and considered an ellipsoidal cavity shape with three independent axes. This has the advantage of leading to analytical expressions for the solvation energy[11,26] and for the derivatives of the solvation energy with respect to the nuclear coordinates,[27] which

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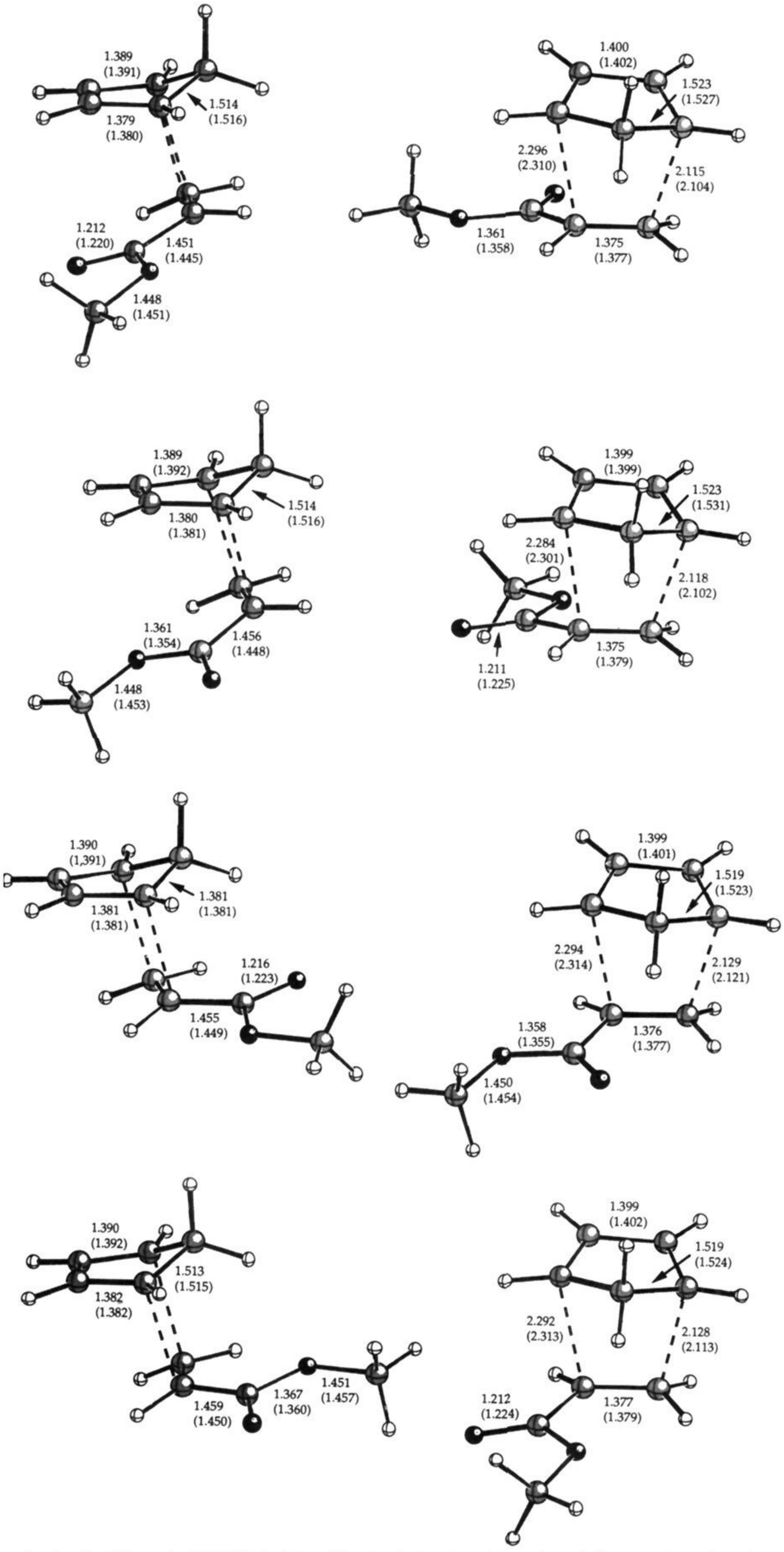

Figure 2. Optimized geometries for the TSs at the RHF/3-21G level for the isolated and the solvated (in parentheses) molecules. From top to bottom: *endo s-cis*, *endo s-trans*, *exo s-cis*, and *exo s-trans*.

substantially simplify the geometry optimization of a solvated molecule. The volume and the axes of the cavity are defined as previously proposed.[28] Thus, the volume is constrained to be equal to the average molecular volume in the liquid and is estimated from the expression $1.48V_{\mathrm{vdW}}^{\mathrm{corr}} + 0.42$ Å^3, where $V_{\mathrm{vdW}}^{\mathrm{corr}}$ is a corrected van der Waals volume computed by multiplying the atomic van der Waals radii by a factor of 1.105. (This expression has been deduced to fit experimental molecular volume data at 20 °C.[27]) The axes of the cavity are related to the three principal axes of inertia of a solid of uniform density limited by the van der Waals surface.

Assuming that the main changes of the free energy of solvation are due to electrostatic interactions, the wave function of the solvated molecule is obtained by minimizing, both in the SCF procedure and in the geometry optimization, the sum of the intrinsic molecular energy of the solute plus the free energy of solvation given by (1). It may be useful to separate the total solvation energy in a pure electrostatic term, which corresponds to the solvation energy computed using (1) and the geometry and electronic distribution of the isolated molecule, and an induction term, which is the difference between this energy and the total solvation energy for the fully relaxed (electronically and geometrically) solute molecule.

Cavitation and dispersion energies are also included in this model. Since the possible transition-state structures for the reaction studied have quite similar geometries, these contributions, which are not very sensitive to conformational equilibria, are not expected to play a major role on the modification of the selectivities by the solvent. Nevertheless, these contributions do change in proceeding from the reagents to the TSs, and their effect on the activation barriers can be substantial and will be analyzed here.

Full geometry optimization at the RHF/3-21G level[29a] has been carried out for all the species considered in this paper. Transition states have been located at this computational level using Schlegel's algorithm.[29b] The same methods were used for the solvated molecules; the second derivatives of the solvation energy, which are required for locating the TSs, were obtained numerically using analytically computed first derivatives. Using these geometries, MP2/6-31G** single-point calculations[29c] have been carried out to obtain total energies. Counterpoise corrections are neglected. This computational scheme is basically the same as that used by Houk et al.[30] in the study of similar reactions (except that polarization functions are added on the hydrogen in our calculations) and has been shown to give similar results to limited MCSCF computations[31] for the concerted mechanism of the butadiene + ethylene reaction. Note, however, that the latter have also predicted a biradical TS to lie above the concerted TS. This biradical mechanism has not been examined in the present work. Note, finally, that the use of an unpolarized basis set for the geometry optimization in the case of the solvated species probably underestimates the geometrical perturbations due to the solvent, especially for the TS structures.

The computations have been carried out using the GAUSSIAN88[32] program with an extra link[33] added to compute solvent effects as described above.

3. Results

We present below the results obtained for the geometries and energies of the reagents and TSs in a vacuum (*i.e.*, for the isolated molecules) and in water solution ($\epsilon = 78.4$), and we discuss the effect of the solvent on these quantities. Note that the electrostatic effect of a solvent with a smaller relative permittivity than that of water is predicted to go in the same direction but to be less intense.

Table I. Total Energies (in a.u.)[a] for the Reagents and the TS at Different Computational Levels

sample	RHF/3-21G	RHF/6-31G**// RHF/3-21G	MP2/6-31G**// RHF/3-21G
	Vacuum		
cyclopentadiene	−191.717080	−192.802035	−193.471134
methyl acrylate *s-cis*	−302.982025	−304.688528	−305.580541
methyl acrylate *s-trans*	−302.980811	−304.687367	−305.579018
TS *endo s-cis*	−494.660528	−497.432682	−499.046985
TS *endo s-trans*	−494.657854	−497.430353	−499.044807
TS *exo s-cis*	−494.661867	−497.432043	−499.046534
TS *exo s-trans*	−494.659205	−497.428759	−499.043674
	Solution		
cyclopentadiene	−191.720520	−192.804668	−193.473289
methyl acrylate *s-cis*	−302.989038	−304.694983	−305.584962
methyl acrylate *s-trans*	−302.988782	−304.694965	−305.584096
TS *endo s-cis*	−494.668140	−497.438417	−499.051171
TS *endo s-trans*	−494.667782	−497.438103	−499.050630
TS *exo s-cis*	−494.668810	−497.437417	−499.050490
TS *exo s-trans*	−494.668429	−497.436499	−499.049185

[a] 1 a.u. = 627.5 kcal mol^{-1}.

Equilibrium Geometries and Total Energies. The parent Diels–Alder reaction of butadiene with ethylene has been extensively studied, and its mechanism has been the subject of some controversy. However, it is now well established that this reaction is concerted and synchronous,[31,34] although, as pointed out above, a less favorable biradical mechanism has also been studied.[31] Loncharich et al.[35] performed the first *ab initio* computation on a reaction of butadiene with an unsymmetrical dienophile (acrolein) and drew the conclusion that the reaction goes through a concerted pathway but, as expected, with some degree of asynchronicity. The theoretical study by Houk et al.[30] of the reaction of cyclopentadiene with ethylene and with acrylonitrile, which is similar to the reaction studied in our work, also led to the conclusion that a concerted mechanism is operative.

The main parameters of the optimized geometries (at the RHF/3-21G level) for the reagents and for the four transition states (*endo s-cis*, *endo s-trans*, *exo s-cis*, and *exo s-trans*) are presented in Figures 1 and 2. In Table I, the total energies at the RHF/3-21G, RHF/6-31G**//RHF/3-21G, and MP2/6-31G**//RHF/3-21G levels[29d] are summarized.

The predicted geometries for the transition states correspond to a concerted although slightly asynchronous reaction, in good agreement with the results obtained for the TS of the Diels–Alder reaction between cyclopentadiene and acrylonitrile at the RHF/3-21G level reported by Houk et al.[30] The CC bond lengths obtained by these authors for the bonds being formed are 2.289 and 2.131 Å (difference of 0.158 Å) for the *endo* conformation and 2.293 and 2.134 Å (difference of 0.159 Å) for the *exo* conformation, the largest value corresponding always to the bond which carries the CN group. Our values in Figure 2 for the isolated molecules are quite close to those obtained by these authors, although some remarks may be made. In Table II, the differences between the CC bond lengths for the bonds being formed are given. Note that the asynchronicity for the reaction of cyclopentadiene with methyl acrylate is slightly greater than

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Table II. Differences in CC Bond Lengths (in Å) for the Bonds Being Formed in the Four Possible Transition-State Structures

structure	vacuum	solution	structure	vacuum	solution
endo s-cis	0.181	0.206	*exo s-cis*	0.169	0.194
endo s-trans	0.166	0.199	*exo s-trans*	0.164	0.199

Table III. Mayer Bond Orders[36] for the CC Bonds Being Formed in the Transition States

structure	CC bond[a]	vacuum	solution
endo s-cis	a	0.386	0.397
	b	0.273	0.267
endo s-trans	a	0.382	0.400
	b	0.281	0.271
exo s-cis	a	0.379	0.386
	b	0.277	0.267
exo s-trans	a	0.379	0.394
	b	0.282	0.267

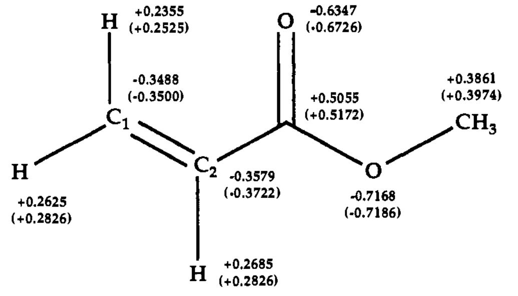
[a] b corresponds to the bond of the carbon carrying the carbomethoxy group.

in the case of acrylonitrile. For the isolated molecules, the differences between the CC bond lengths lie between 0.164 Å for the *exo s-trans* TS and 0.181 Å for the *endo s-cis* TS. For a given conformation of methyl acrylate, the asynchronicity is higher for the *endo* TS as opposed to the results obtained for acrylonitrile. Finally, the asynchronicity for the *s-cis* structures is higher than for the corresponding *s-trans* structures.

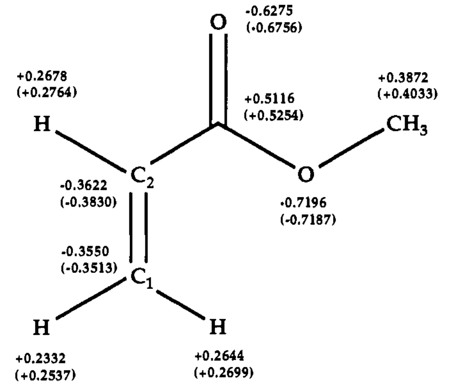
The main solvent effect on the geometry of the transition states is found for the length of the new CC bonds (see Figure 2). For the bond carrying the carbomethoxy group, which is, as pointed out, the longest one, the length increases through the solvent effect while it decreases for the other CC bond so that the asynchronicity is enhanced in solution (see Table II). The difference in bond length varies now from 0.194 Å for the *exo s-cis* TS to 0.206 Å for the *endo s-cis* TS. The change in CC distance in going from a vacuum to the solution is accompanied by a modification of the corresponding CC bond orders[36] which are given in Table III and decrease for the bond of the carbon carrying the carbomethoxy (whose bond length increases in solution), the opposite being obtained for the other CC bond.

The remaining geometrical parameters in the TS are not much perturbed by the solvent, but it is interesting to point out that the length of the other bonds participating in the reaction slightly increases in solution (see values in Figure 2).

The fact that the asynchronicity of the reaction is favored by the interactions with the solvent may be explained by considering the solvent effect on the reagents and analyzing how their electronic properties change under the influence of the solute–solvent interactions. Apart from the stabilization of the molecular orbital levels, which may modify the HOMO–LUMO interaction, the interactions with the solvent induce a polarization of the solute's electronic distribution which is expected to be substantial in the case of the dienophile because of its relative large polarity and polarizability. Mulliken populations for the *s-cis* and *s-trans* conformations of methyl acrylate, in a vacuum and in solution, are given in Figure 3. The geometry used in the computation of these populations is the same in both media and corresponds to that optimized in a vacuum. The values show that there is a large polarization of the molecule which may be roughly represented by a polarization of the electronic density of the CO bond toward the oxygen atom and of the CC bond toward the C_2 atom, *i.e.*, the carbon carrying the carbomethoxy group. This effect may be analyzed in terms of the perturbation of the molecular orbitals through the interaction with the reaction field. Fixing our attention on the CC π bond, the HOMO, our results show that the electronic distribution in solution is polarized from C_1 to C_2. Thus, for instance, in the case of the *s-trans* conformation at the gas-phase equilibrium geometry, the HOMO electronic density on the C_1 and C_2 atoms changes from 0.197 and 0.240 to 0.192 and 0.255, respectively, in going from the isolated to the solvated system. A similar effect, although slightly smaller, is found in the case of the *s-cis* conformation, too. The electronic polarization of the π bond implies a "polarization" in the opposite direction of the corresponding antibonding orbital, the LUMO, which is in fact the most important orbital on which the reactivity of the dienophile depends. For this molecular orbital, the coefficient of the p_z atomic orbitals decreases for both carbon atoms but the change is more important for C_2, which is also the atom having the smaller coefficient. Taking again the example for the *s-trans* conformation, the "density" of the LUMO on the C_1 and C_2 atoms changes from 0.479 and 0.255 to 0.470 and 0.230, respectively, from a vacuum to the solution. Accordingly, the solvent modifies the dienophile–diene orbital interaction, the formation of the CC_1 bond, relative to CC_2, is favored, and the asynchronicity is enhanced.



s-cis



s-trans

Figure 3. Net atomic charges for the two conformations of methyl acrylate computed at the RHF/3-21G level for the isolated and the solvated (in parentheses) molecules with the equilibrium geometry in a vacuum.

We note that the change of TS location in solution, as compared to the gas phase, moves the atoms along a coordinate which is an antisymmetric linear combination of the CC bond lengths, whereas the reaction coordinate in a vacuum is essentially a symmetric linear combination of these interatomic distances. The reaction coordinate in solution is thus expected to be slightly more asymmetric than in the gas phase. This has been confirmed by examination of the eigenvector corresponding to the negative eigenvalue of the Hessian matrix which shows that the difference between the new CC bond coefficients increases in going from a vacuum to the solution. The conclusion of this analysis is that the reaction path in solution cannot be deduced from the reaction path in a vacuum by simply adding the solvation energy and that a full geometry (and electronic) relaxation of the solvated TS structures is required.

Detailed analysis of the computations shows that the change of the TS geometry due to the solvent effect causes all the multipole moment contributions to the solvation energy to increase. This is a consequence of the asynchronicity enhancement because it

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(36) Mayer, I. *Chem. Phys. Lett.* **1983**, *97*, 270.

Table IV. Solvation Energies (kcal mol^{-1}) and Dipole Moments (D, in parentheses) for the Isolated Species at Different Computational Levels

species	RHF/3-21G	RHF/6-31G**// RHF/3-21G	MP2/6-31G**// RHF/3-21G
cyclopentadiene	−2.16 (0.39)	−1.65 (0.30)	−1.35
methyl acrylate *s-cis*	−4.40 (1.38)	−4.05 (1.65)	−2.77
methyl acrylate *s-trans*	−5.00 (2.34)	−4.77 (2.54)	−3.19
TS *endo s-cis*	−4.78 (2.16)	−3.60 (2.32)	−2.63
TS *endo s-trans*	−6.23 (3.03)	−4.86 (3.28)	−3.65
TS *exo s-cis*	−4.36 (1.63)	−3.37 (1.95)	−2.48
TS *exo s-trans*	−5.79 (2.78)	−4.86 (3.06)	−3.46

Table V. Multipole Contributions and Total Values of the Pure Electrostatic Solvation Energy (in kcal mol^{-1}) Using the RHF/6-31G** Calculations at the Gas-Phase Geometry with the Gas-Phase Electronic Distribution

species	*l* 1	2	3	4	total
cyclopentadiene	−0.02	−0.80	−0.28	−0.24	−1.50
methyl acrylate *s-cis*	−0.55	−1.16	−0.57	−0.78	−3.68
methyl acrylate *s-trans*	−1.16	−1.21	−0.60	−0.65	−4.13
TS *endo s-cis*	−0.60	−0.86	−1.27	−0.45	−3.71
TS *endo s-trans*	−1.13	−1.49	−1.35	−0.54	−5.05
TS *exo s-cis*	−0.40	−0.86	−1.31	−0.18	−3.31
TS *exo s-trans*	−1.06	−1.28	−1.28	−0.48	−4.75

leads to conformations in which the carbomethoxy group is far away from the cavity center and, due to the large dipole moment of the carbonyl group, the multipoles of the molecule evaluated at the center of the cavity increase.

Solvation Energies. The solvation energies for the reagents (cyclopentadiene and methyl acrylate) and for the four possible TS structures (*endo s-cis*, *endo s-trans*, *exo s-cis*, and *exo s-trans*) are collected in Table IV. Note that, although the absolute values of the solvation energies are sensitive to the quality of the basis set and to the inclusion of correlation effects, the relative values of these energies, which determine the solvent effect on the selectivities, are less dependent on the computational level. Looking at methyl acrylate, one sees that the solvation energy is greater for the *s-trans* conformation. For the transition states, it is also larger for the *s-trans* conformations (compared to the corresponding *s-cis* structures) and, for a given conformation of the dienophile, it is larger for the *endo* structures. We also give in Table IV the values of the dipole moment for the isolated species to show that the differences in the solvation energy may in general by explained by the values of the dipole moment. Nevertheless, an analysis of the multipole moment series, which is made in Table V, is quite interesting.

In the case of methyl acrylate, the first nonzero term of the multipole development ($l = 1$), which corresponds to the dipole contribution, is much greater for the *s-trans* conformation, which has a larger dipole moment. The other contributions contribute substantially to the solvation energy, although they do not change much with the conformation. Note that for both conformations, the leading term arises from the quadrupole moment. Indeed, for all the species, the quadrupole contribution is larger than the dipole contribution. Note also that in cyclopentadiene, the dipole term is very small and that the TS structures have very large octupole contributions, which are again greater than those arising from the dipole moment. In particular, for the *s-cis* structures, whose dipole moments are small compared to those of the *s-trans* structures, the main electrostatic interaction is due to the octupole moment. Though the multipole contributions in our work are probably overestimated in some cases because of the use of a crude cavity shape, it is clear from the computed values that a quantitative analysis of the solvation energy cannot be limited to dipole terms, as in the Onsager method.

Table VI. Relative Stabilities (kcal mol^{-1}) of the TS in a Vacuum and in Solution[a]

sample	RHF/3-21G	RHF/6-31G**// RHF/3-21G	MP2/6-31G**// RHF/3-21G
		Vacuum	
TS *endo s-cis*	0.00	0.00	0.00
TS *endo s-trans*	1.68	1.46	1.37
TS *exo s-cis*	−0.84	0.40	0.28
TS *exo s-trans*	0.83	2.40	2.08
		Solution	
TS *endo s-cis*	0.00	0.00	0.00
TS *endo s-trans*	0.22	0.20	0.34
TS *exo s-cis*	−0.42	0.63	0.43
TS *exo s-trans*	−0.18	1.20	1.25

[a] The *endo s-cis* has been taken as the reference.

Comparison of the pure electrostatic energies in Table V with the total solvation energies in the second column of Table IV shows that induction energy contributions (given by the difference of the two values) are not negligible. They are slightly stabilizing, except in the case of the *endo* TS structures.

4. Discussion

Endo/Exo and Diastereofacial Selectivities. A detailed analysis of the solvent effect on the *endo*/*exo* and diastereofacial selectivities may be now made using the computed solvation energies for the different TS conformations.

In order to simplify the discussion, the relative stabilities of the TS, in a vacuum and in solution, are given in Table VI. We have arbitrarily chosen the energy of the *endo s-cis* TS as the reference value. As shown, the relative stability of the TSs depends on the basis set used, the RHF/3-21G computations predicting that the *endo* structures are less stable than the corresponding *exo* ones while the contrary is predicted at the higher calculation levels. MP2 results do not change the relative stabilities much with respect to the SCF results since the correlation energy is similar for the different conformations of the TSs. Experimentally, the *endo* adduct is preferentially obtained in a series of solvents for the reaction of cyclopentadiene with methyl acrylate[4] or with (−)-menthyl acrylate,[7] in agreement with the RHF/6-31G** results. Previous computations at the RHF/3-21G level for the reaction of cyclopentadiene with acrylonitrile[30] predicted the *exo* TS to be more stable, although experimentally the *endo* is favored by 0.2 kcal mol^{-1}. The authors[30] suggested that the discrepancy between theory and experiment could be due to the fact that the CC bonds are too short in RHF/3-21G calculations. However, although we cannot exclude this hypothesis in our case, the improvement of the basis set (but using the RHF/3-21G geometry) seems to lead to correct results.

The calculated solvation energies, summarized in Table IV, show that the electrostatic effect of the solvent favors the *endo* with respect to the *exo* isomers, in agreement with the experimentally observed increase of the *endo*/*exo* selectivity as a function of solvent polarity for the reaction of cyclopentadiene with methyl acrylate[4] or (−)-menthyl acrylate.[7]

Solvent effects on the diastereoselectivity of the reaction of cyclopentadiene with (−)-menthyl acrylate have also been reported.[7] The diastereoselectivity of this reaction is governed by the chirality of the menthyl group. The experimental results show that the (1*R*,2*R*)-cycloadduct in Scheme I is preferentially obtained in a series of solvents, which requires a preferential approach of the diene on the *si* face of the dienophile. As this face is less shielded for the *s-trans* conformation (see Scheme II), one may expect that a stabilization of the *s-trans* with respect to the *s-cis* TS will increase the de. Experimental data show that the de increases with solvent polarity so that one may expect the *s-trans* TS to be more stabilized by the solvent than the *s-cis* TS. This is indeed what is predicted by our results for the electrostatic solvation energies (see Table IV). Note, however, that the

Scheme II

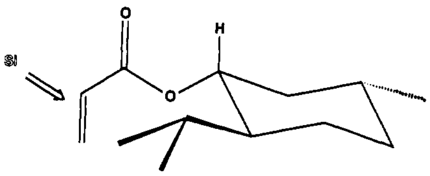

Table VII. Computed RHF/3-21G Thermodynamic Quantities (Temperature in K in parentheses) for the Reaction between Cyclopentadiene and Methyl Acrylate in a Vacuum

sample	$E_{vib}(0)^a$	$\Delta E_{vib}(298)^a$	$S(298)^b$
cyclopentadiene	62.80	0.04	−64.43
methyl acrylate *s-cis*	64.55	1.62	−78.89
methyl acrylate *s-trans*	64.56	1.61	−78.82
TS *endo s-cis*	129.46	3.69	−97.17
TS *endo s-trans*	129.47	3.66	−96.70
TS *exo s-cis*	129.59	3.65	−96.66
TS *exo s-trans*	129.62	3.64	−96.46

[a] kcal mol^{-1}. [b] cal mol^{-1}·K.

Table VIII. Experimental Activation Parameters at 298.15 K for the Reaction between Cyclopentadiene and Methyl Acrylate Carried Out in Toluene and in a Mixture of Methanol/Water (50/50)

solvent	$\Delta H^{\ddagger}(298)^a$	$\Delta S^{\ddagger}(298)^b$	$\Delta G^{\ddagger}(298)^a$
toluene	15.1	−29.7	23.9
methanol/water	10.2	−40.9	22.4

[a] kcal mol^{-1}. [b] cal mol^{-1}·K.

preference for the *s-cis* conformation predicted in the gas phase is not counterbalanced in solution (see Table VI).

It is interesting to point out that computation (at the RHF/3-21G level) of the entropy and the zero-point and thermal vibrational contributions to the gas-phase free energy does not modify the relative order of the TS energies. The computed values are given in Table VII. The lowest vibrational frequencies for the TSs are 69 cm^{-1} for the two *s-cis* structures and 82 and 84 cm^{-1} for the *exo* and *endo s-trans* structures, respectively. The zero-point energy correction, $E_{vib}(0)$, and the entropy are slightly smaller for the *endo* structures (compared to the corresponding *exo*) and for the *s-cis* conformations (compared to the corresponding *s-trans*).

Solvent effects on de may also be analyzed, at least qualitatively, in terms of solvent effects on the reagents, namely by looking at the change of the conformational equilibrium *s-cis*/*s-trans* for methyl acrylate. For isolated methyl acrylate, we predict the *s-cis* conformation to be more stable than the *s-trans* conformation, in agreement with previous computations[37] and with experimental data in the gas phase.[38] The differences in total energy at the MP2/6-31G**//3-21G level decrease from 0.96 kcal mol^{-2} in a vacuum to 0.54 kcal mol^{-1} in solution because of the greater solvation energy of the *s-trans* conformation. Thus, the electrostatic interactions in solution displace the *s-cis*/*s-trans* equilibrium toward the *s-trans* conformation.[39] The effect may be compared to that produced by Lewis acids whose effect on the de of asymmetric Diels–Alder reactions has been explained through modification of the conformational equilibrium of the acrylate.[37] Hydrogen bonding of the carbonyl with a water molecule can be considered as a simple model of a catalyzed reaction, and one expects that it modifies the equilibrium in the same way that electrostatic interactions do, *i.e.*, by favoring the *s-trans* conformation and increasing the de.[7] This has been confirmed by TS–H_2O supermolecule computations at the RHF/6-31G**//RHF/3-21G level. The *endo s-trans* and *exo s-trans* TSs are stabilized by 0.3 kcal mol^{-1} more than the corresponding *s-cis* structures.

Activation Barriers. We now consider the activation energy. In order to compare theoretical results with experimental data, kinetic measurements were carried out at several temperatures for the reaction between methyl acrylate and cyclopentadiene in toluene and in a mixture of methanol/water (50/50).[40] The results obtained are gathered in Table VIII.

Computed thermodynamic quantities in the gas phase, obtained using the MP2/6-31G**//RHF/3-21G total energies and the RHF/3-21G zero-point energy corrections, are summarized in Table IX. As shown, the calculated activation enthalpies and free energies are too small (compared, for instance, to experimental data in toluene) which is probably due to the overestimation by MP2 calculations of the effect of correlation energy on activation energies, as already pointed out.[41] We have also carried out some MP3/6-31G**//RHF/3-21G calculations. Because of computer-time limitations, only the *endo s-trans* activation energy has been considered. The corresponding total energies for the reagents (cyclopentadiene and *s-trans* methyl acrylate) and the *endo s-trans* TS are −193.507271, −305.605475, and −499.085521 a.u., respectively. With these values and the RHF/3-21G thermal corrections, an activation enthalpy of 19.6 kcal mol^{-1} is now predicted which agrees much better with the experimental value in toluene (15.1 kcal mol^{-1}).

It is a well known experimental result that the reaction of cyclopentadiene with methyl or (−)-menthyl acrylate is accelerated in highly solvophobic media.[3a–c,4] This is illustrated by the experimental data in Table VIII which shows a decrease of 1.5 kcal mol^{-1} in $\Delta G^{\ddagger}$ in going from toluene to the more solvophobic methanol/water solvent. However, owing to the fact that the most solvophobic solvents are also the most polar, correlations with polarity parameters have also been observed. Hence, in order to gain a deeper insight into the solute–solvent effects on the reaction kinetics, it is interesting to make an estimation of the influence of electrostatic and hydrophobic effects on the barriers.

If one compares the computed electrostatic solvation energy of the reagents (cyclopentadiene + methyl acrylate) with that of the TSs (see Table IV), one sees that the former is slightly greater so that electrostatic interactions cannot account for the observed decrease in $\Delta G^{\ddagger}$ upon going from toluene to a 50/50 water/methanol mixture (Table VIII). This result is not expected to change, even if higher-order Moller–Plesset contributions would be considered.

The role of hydrophobic interactions may be estimated from solubility data for hydrocarbons. Using experimental data[42] for the reaction of 1,3-butadiene + ethylene → cyclohexene, Blake and Jorgensen[9] have made an estimation of the hydrophobic effect for the Diels–Alder cyclopentadiene + methyl vinyl ketone reaction, which is similar to that studied in the present work.

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(37) Loncharic, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(38) Carmona, P.; Moreno, J. *J. Mol. Struct.* **1982**, *82*, 177.

(39) This is what is experimentally observed. However, IR data in solution (George, W. O.; Hassid, D. V.; Maddams, W. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 400) is compatible with a greater preference for the *s-trans* conformation. We have verified that the computed preference for the *s-cis* conformation is overestimated by the use of 3-21G geometries and MP2 calculations. A more accurate theoretical study of this problem will be published elsewhere.

(40) Cyclopentadiene and methyl acrylate are commercial products and were used without further purification. Toluene and methanol were dried and purified according to standard procedures. Water was deionized and doubly distilled in an all-glass apparatus. The following kinetic procedure was carried out: a solution of freshly distilled cyclopentadiene (396 mg, 6 mmol) in the corresponding reaction medium (2 mL) was added to thermostated (−5 × 0.1, 15 × 0.1, and 30 × 0.1 °C) solutions of methyl acrylate (172 mg, 2 mmol) in the same solvent or solvent mixture (2 mL). The solution was magnetically stirred and the reaction monitored by gas chromatography (FID from Hewlett–Packard 5890 II, cross-linked methyl silicone column, 23 mm × 0.2 mm × 0.33 μm; helium as carrier gas 17 psi; injector temperature 230 °C, detector temperature 250 °C; oven temperature program, 50 °C (3 min) – 25 °C/min – 100 °C (9 min); retention times, methyl acrylate 2.7 min, *exo*-cycloadduct 12.7 min, *endo*-cycloadduct 12.9 min). All reactions were repeated three times and followed second-order kinetics.

(41) (a) Bach, R. D.; McDouall, J. J. W.; Schlegel, H. B.; Wolber, G. J. *J. Org. Chem.* **1989**, *54*, 2931. (b) Gonzalez, J.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3031.

(42) Hine, J.; Mookerjee, P. K. *J. Org. Chem.* **1975**, *40*, 292.

Table IX. Computed (MP2/6-31G**//RHF/3-21G) Thermodynamic Quantities at 298.15 K for the Activation Barriers of the Cyclopentadiene + Methyl Acrylate Reaction in a Vacuum

transition state	ΔE_{elec} (0 K)[a]	ΔE_{vib} (0 K)[a]	ΔH(298)[a]	ΔH^{*}(298)[a]	ΔS^{*}(298)[b]	ΔG^{*}(298)[a]
endo s-cis	2.94	2.11	−0.34	4.71	−46.15	18.46
endo s-trans	3.35	2.12	−0.36	6.06	−46.62	19.97
exo s-cis	3.23	2.24	−0.37	5.08	−46.66	19.00
exo s-trans	5.02	2.27	−0.39	6.90	−46.86	20.88

[a] kcal mol^{-1}. [b] cal mol^{-1}·K.

These authors concluded that the hydrophobic term stabilizes the TS with respect to the reagents by ca. −1.5 kcal mol^{-1} in going from a vacuum to a water solution. Accordingly, it favors an increase in reaction rate.

In protic solvents, the activation barriers could be further modified through the effect of hydrogen-bond interactions. Indeed, since the carbonyl group is polarized from the reagents to the TS, an increase of the oxygen proton affinity is expected. We have estimated this effect by computing the stabilization energy produced by the interaction with a water molecule for the methyl acrylate *s-trans* and for the TSs. In all cases, the resulting hydrogen bond stabilizes the TS structures more than the acrylate molecule. For instance, the TS *endo s-trans* is stabilized by 6.9 kcal mol^{-1} whereas methyl acrylate is stabilized by 5.3 kcal mol^{-1} (these values were obtained at the RHF/6-31G**//RHF/3-21G level). Hence, this specific interaction tends to lower the barrier by an amount close to the hydrophobic term.

Another estimation of aqueous acceleration of Diels–Alder reactions has been reported[43] using the semiempirical AM1-SM2 solvation model[44] which accounts well for hydrophobic effects and hydrogen-bond formation. The authors obtained a smaller acceleration than that found in Monte Carlo simulations using RHF/6-31G* charges[9] and explained this through the fact that AM1 predicts less polar transition states than RHF/6-31G* computations.

In summary, our results predict an increase of the reaction rate in going from a vacuum to water solution which would be mainly due to hydrophobic interactions and hydrogen-bond formation, in agreement with previous results.[9] In principle, nonpolar aprotic solvents would modify the gas phase reaction rate less since electrostatic and solvophobic effects should be smaller and proceed in opposite directions anyway.

5. Conclusions

This study shows that the electrostatic solvent effect on the Diels–Alder reactions of cyclopentadiene with methyl and (−)-menthyl acrylate is substantial. We have shown that the geometry of the transition structures and the reaction path itself are modified in solution. In particular, the asynchronicity of the reaction is enhanced by the solvent effect, and the reaction coordinate becomes more asymmetric. This is due in part to polarization effects on the methyl acrylate molecule and, in particular, to the perturbation induced on the LUMO. Experimental data for the variation of the *endo/exo* selectivity and the de through an increase of solvent polarity for the reaction of cyclopentadiene with (−)-menthyl acrylate have been interpreted in terms of electrostatic interactions. The solvent favors the *endo* conformations of the TSs over the *exo* ones. It also favors the reaction going through *s-trans* transition states. The electrostatic solvent effect tends to increase the transition barriers, although the effect is not very large. The observed increase of the reaction rate by aqueous solvents can be mainly explained by hydrophobic effects and hydrogen-bond formation.

The main conclusion of this work is that a correct description of the solute–solvent interactions and their influence on these reactions requires taking into account induction effects on the electronic distribution and on the geometry of the TSs as well. Though the Self-Consistent Reaction Field method used here is only an approximate method for treating the intermolecular interactions in a liquid, it represents a convenient first approach to the problem and has the advantage of leading to computations which are not more costly than similar computations for isolated molecules.

Acknowledgment. Computing facilities at the CIRCE (Orsay, France) are acknowledged. We also thank C. Henriet (CRAY-FRANCE) for allowing us to run MP3 calculations at CRAY-Research.

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(43) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794 (see p 8799).

(44) Cramer, C. J.; Truhlar, D. G. *Science* **1992**, *256*, 213.