

Prediction of solvent effect on the reaction rate and *endo/exo* selectivity of a Diels–Alder reaction using molecular surface electrostatic potential

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Received 7 October 2002; revised 31 January 2003; accepted 20 March 2003

ABSTRACT: Molecular surface electrostatic potential was used to predict the solvent effect on the reaction rate, *endo/exo* selectivity and diastereomeric excess of a Diels–Alder reaction. It is shown that these quantities can be expressed in terms of molecular surface electrostatic potentials of solvents which are obtained computationally by the HF/6–31++G* procedure. Regression analyses and an experimental database are used to obtain analytical representation of rate constant, *endo/exo* selectivity and diastereomeric excess. The models obtained show that the hydrogen bond donor ability of solvents on the above mentioned properties is substantial, whereas solvophobicity only affects the reaction rate and *endo/exo* selectivity of the reaction. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: solvent effect; molecular surface electrostatic potential; *endo/exo* selectivity; Diels–Alder reaction

INTRODUCTION

Most of chemical phenomena occur in condensed phases, especially in solutions in which the effects of neighboring molecules presumably need to be taken into account. Solute–solvent interactions are of particular chemical importance and a great deal of effort, with considerable success, has gone into developing theoretical models for their quantitative description.^{1,2} They have usually used solvatochromic descriptors, which are bulk properties of solvents.³ Molecular orbital (MO) calculations have also been used for developing a set of theoretical linear solvation energy relationship (LSER) parameters, which are referred to as TLSER.^{4,5}

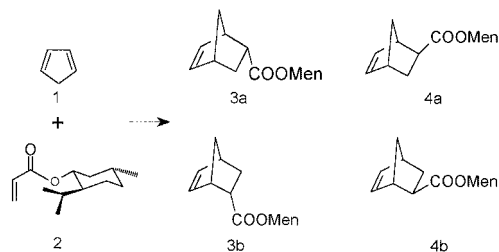
It has been shown that a variety of macroscopic properties of the condensed phase can be expressed analytically in terms of statistically defined quantities.^{4,6–8} These quantities characterize molecular surface electrostatic potentials (MSEP). The MSEP, which is created on the surface of a molecule by its nuclei and electrons, is a well-established guide to physical properties and molecular interactive behavior.^{9,10} Unlike many of the other quantities used now and earlier as indexes of physicochemical behavior, the electrostatic potential, $V(r)$, is a real physical property, one that can be determined experimentally by diffraction methods or computationally.

The MSEP approach clearly has elements in common with the previous empirical models; however, three

important point should be addressed. The previous effective models express the properties in terms of descriptors of various theoretical or empirical origins, that are intended to reflect certain specific features, e.g. hydrogen bond accepting or donating ability, polarizability, etc. In contrast, computed quantities from $V_s(r)$ are statistical measures of the variation of a single physical observable, the electrostatic potential, over a well-defined molecular surface. Also, the computed surface quantities are generally little affected by conformational changes, unless these considerably diminish the internal polarity.¹¹ Furthermore, the trends in these quantities are found to be similar by different computational procedures.¹² With the recent advances in computer technology, $V(r)$ is most commonly obtained computationally for a variety of chemical systems.

Solvent effects on Diels–Alder reactions are well known and some efforts have been devoted to the theoretical and experimental treatment of solvation effect on these reactions.³ Correlation with empirical parameters has been discussed for the reaction rate^{13,14} and *endo/exo* selectivity,^{14,15} and the solvent effect has been interpreted in different ways. For example, the asymmetric Diels–Alder reaction of cyclopentadiene with (–)-menthyl acrylate (Scheme 1) has been studied.¹⁶ Also, a detailed analysis of the solvent effect on the rate, *endo/exo* selectivity and diastereomeric excess (*de*) of the Diels–Alder reaction has been carried out by Ruiz-Lopez *et al.*¹⁷ The observed increase in the reaction rate was explained by hydrophobic effects and hydrogen bonding interactions, and the *endo/exo* selectivity and *de* of the reaction were attributed to electrostatic interactions. It

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Scheme 1

was considered that the solvophobicity of solvents cannot affect the *endo/exo* and *de* selectivity of this reaction.

The characteristics of $V(r)$ encouraged us to investigate the influence of the solvent on asymmetric Diels–Alder reactions using MSEP and regression analysis. The Diels–Alder reaction between cyclopentadiene and menthyl acrylate (Scheme 1) was selected. Statistical analysis was used in conjunction with the experimental results¹⁶ to express the rate constant, *endo/exo* selectivity and *de* in terms of the calculated electrostatic potential on the surface of solvent molecules.

EXPERIMENTAL

The electrostatic potential $V(r)$ created in the space around a molecule by its nuclei and electrons is given rigorously by

$$V(r) = \sum \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')}{r' - r} dr'$$

where Z_A is the charge on nucleus A, located at R_A and $\rho(r')$ is the electronic density. $V(r)$ was computed with the Gaussian 98 package,¹⁸ using the HF procedure and the 6–31++G* basis set. The molecular surface was taken to be the 0.001 a.u. contour of $\rho(r')$ as proposed by Bader *et al.*¹⁹

The quantities characterizing the MSEP are as follows:⁸

1. $V_{s,\max}$ and $V_{s,\min}$, the most positive and negative values of $V(r)$ on the molecular surface, respectively.
2. π , the average deviation on the surface, defined as

$$\pi = \frac{1}{n} \sum_{i=1}^n [V_s(r_i) - \bar{V}_s]$$

where \bar{V}_s is the average of $V(r)$ over the surface.

3. ν_s^+ and ν_s^- the average of positive and negative electrostatic potentials on the surface of the molecules, respectively.
4. σ_+^2 and σ_-^2 , the positive and negative variances of $V(r)$ over the surface of the molecules, respectively, which

are included in the σ_{tot}^2 , the total variances of $V(r)$ over the surface of molecules, according to

$$\sigma_{\text{tot}}^2 = \sigma_+^2 + \sigma_-^2 = \frac{1}{m} \sum_{j=1}^m (v_s^+(r_j) - \bar{v}_s^+)^2 + \frac{1}{h} \sum_{k=1}^h (v_s^-(r_k) - \bar{v}_s^-)^2$$

5. ν , the balance between the positive and negative surface potentials, defined by

$$\nu = \frac{\sigma_+^2 \sigma_-^2}{(\sigma_{\text{tot}}^2)^2}$$

The multilinear correlation regression (MLR) method was used to obtain the optimum correlations.

RESULTS AND DISCUSSION

Table 1 shows the experimentally determined rate constants along with the *endo/exo* and diastereofacial selectivity of the reaction in 15 solvents.¹⁶ Some of the key features of the molecular surface electrostatic potentials on the basis of our calculation are also listed in Table 1. These parameters are found to be relevant to the experimental data.

In seeking an analytical representation of the experimental data in Table 1, we tested a number of quantities related to $V_s(r)$, including some which are shown in Table 1. The best correlation was obtained by the equations presented in Table 2. Although these equations do not reproduce the absolute values of the experimental data, they can predict the qualitative pattern of solvation which determined the modification of the rate constant and *endo/exo* and diastereofacial selectivities induced by the solvent.

Cativiela *et al.* showed that the solvent's electrostatic effect is one of the most important factors affecting the rate constant and *endo/exo* and diastereofacial selectivity of the reaction.¹⁶ They also suggested that solvophobicity (through cavitation energy calculation) and dispersion energy may play important roles in the solvent effect on the rate of these reactions. However, they proposed that the influence of these terms on the *endo/exo* and diastereofacial selectivity is negligible and the observed changes can be explained by pure electrostatic and hydrogen bonding interactions.

The regression models using surface electrostatic potentials give the similar equations for the solvent effects on *endo/exo* selectivity and rate of reaction of cyclopentadiene with menthyl acrylate. In both models, Eqns (1) and (2) (Table 2), the dominant interactions are $\nu \sigma_{\text{tot}}^2$, $V_{s,\max}$ and volume of the solvent molecules. $\nu \sigma_{\text{tot}}^2$ has

Table 1. Molecular surface electrostatic potential properties of solvents used in the reaction of cyclopentadiene with menthyl acrylate

Solvent	Log k^a	Log3/4 ^a	Log3a/3b ^a	π^b	\bar{V}_s^b	$V_{s,max}^b$	$V_{s,min}^b$	σ_{tot}^{2c}	ν	$\nu\sigma_{tot}^{2c}$	Volume ^d
2-Propanol	-4.094	0.663	0.094	9.73	1.86	47.8	-40.48	235.4	0.204	48.01	539.07
Acetone	-4.545	0.554	0.079	15.18	3.97	25.36	-44.8	228.69	0.112	25.64	617.25
Acetonitrile	-4.408	0.638	0.081	10.50	1.717	28.855	-40.979	170.43	0.208	35.53	619.99
Benzene	-4.443	0.434	0.063	10.45	-2.17	16.56	-18.95	54.37	0.232	12.63	805.13
Benzonitrile	-4.411	0.6	0.109	5.81	0.011	24.835	-39.61	211.44	0.093	19.66	886.03
Chlorobenzene	-4.456	0.478	0.084	9.67	0.09	22.02	-15.27	57.12	0.196	11.17	1026.04
Dichloromethane	-4.473	0.564	0.07	11.15	1.29	31.16	-15.16	125.85	0.103	13.02	570.73
Dioxane	-4.47	0.493	0.063	10.99	3.14	23.19	-33.98	143.97	0.065	9.30	704.49
Ethyl acetate	-4.578	0.505	0.064	14.24	1.93	32.59	-41.94	187.16	0.200	37.46	791.52
Hexafluoroisopropanol	-3.707	0.852	0.235	5.48	5.76	190.07	-23.22	371.96	0.030	11.16	833.22
Hexane	-4.645	0.505	0.081	13.27	0.13	43.31	-48.31	300.79	0.155	46.74	1084.07
Methanol	-4.073	0.73	0.084	7.48	1.81	49.19	-38.89	255.24	0.248	63.40	341.26
Nitrobenzene	-4.296	0.582	0.119	16.19	3.41	34.88	-46.97	366.39	0.180	66.14	815.61
Toluene	-4.539	0.437	0.083	7.98	0.84	15.96	-20.49	51.96	0.217	11.26	1050.82
Trifluoroethanol	-3.697	0.818	0.164	19.29	3.02	62.93	-33.82	253.51	0.177	44.92	578.20

^a Experimental results from Ref. 16.^b kcal mol⁻¹.^c (kcal mol⁻¹)².^d Å³.

been found previously to be a key quantity for representing properties that reflect non-covalent interactions of a molecule with others of its own kind.⁸ This means that the solvent molecules tend to aggregate more, which improves the solvophobicity of the solvent. One can therefore use this quantity to show the solvophobicity interactions between solutes and solvents, and its promotion or inhibition of this specific interaction.

Hydrogen bond basicity and acidity have also been explored from a quantitative standpoint using both positive and negative regions of surface electrostatic potentials computed at the HF/6-31G* level.²⁰ Hagelin *et al.*²⁰ have shown that the $V_{s,max}$ values, associated with hydrogens of hydrogen bond donors, and the $V_{s,min}$ values, associated with hydrogen bond accepting atoms, correlate with measures of hydrogen bond acidity and basicity, respectively. Hence, according to our models, the reaction rate and *endo/exo* selectivity of the Diels–Alder reaction of cyclopentadiene with menthyl acrylate depends largely on solvophobic and hydrogen bond interactions between the solute and solvent.

From the models obtained, it seems that the molecular size of the solvent plays a role either explicitly or implicitly in the reaction rate and *endo/exo* selectivity. The negative coefficient of volume of solvent molecules [Eqns (1) and (2)] shows a reverse relationship between the molecular size of the solvent and its effect on the reaction rate and *endo/exo* selectivity. Qualitatively it can

be said that the volume of solvent molecules alters the reaction rate and *endo/exo* selectivity through changing the differences in the entropies of activation for both processes.

Cativiela *et al.* suggested that the electrostatic part of the solute–solvent interactions plays an important role in the *endo/exo* selectivity and *de*,¹⁶ and they did not obtain any effects for the solvophobic interactions on these selectivities. Whereas the experimental results show that *endo/exo* selectivity increases with solvent polarity, and as the most solvophobic solvents are also the most polar, a solvophobic interaction should exist between solute and solvent molecules, affecting the *endo/exo* selectivity.

Since the effect of solvent on *de* is small, it was analyzed qualitatively. As Eqn (3) (Table 2) shows, the diastereofacial selectivity of the reaction is a function of $\nu\sigma_{tot}^2$ (as described above) and π . It has been suggested that π can be viewed as a measure of the local polarity or internal charge separations that is present even in molecules having zero dipole moment.²¹ Hence the concluding model for diastereofacial selectivity suggests that the local polarity on the surface of solvent molecules and the hydrogen bond donor ability of the solvent increase the diastereofacial selectivity of the reaction. It has been predicted previously that hydrogen bond formation clearly favors the *s-trans* conformation and makes it possible to explain the increase in *de* in hydrogen bond

Table 2. Regression models of rate and *endo/exo* and diastereofacial selectivity in terms of MSEP of solvents

Equation	Regression coefficient
(1) $\text{Log}k = 0.00209\nu\sigma_{tot}^2 + 0.00506V_{s,max} - 0.00048(\text{volume}) - 4.243$	0.840
(2) $\text{Log}3/4 = 0.001504\nu\sigma_{tot}^2 + 0.00223V_{s,max} - 0.0002524(\text{volume}) + 0.6385$	0.915
(3) $\text{Log}3a/3b = 0.001745\pi + 0.000834V_{s,max} + 0.0407$	0.902

donor solvents.¹⁶ Also, our results confirm that the influence of solvophobicity seems to be negligible.

This study shows that the effect of hydrogen bond donor ability of solvents calculated from MSEP on the Diels–Alder reaction of cyclopentadiene with menthyl acrylate is substantial. We have shown that this property of solvents increases the rate and *endo/exo* and diastereofacial selectivity of this reaction. Also, the observed increase of the reaction rate and *endo/exo* selectivity is a function of the solvophobicity of the solvent, whereas this specific interaction does not have a substantial effect on the diastereofacial selectivity of the reaction studied. Moreover, the local polarity on the surface of solvent molecules (even for molecules having zero dipole moment) has a considerable effect on the diastereofacial selectivity of the reaction.

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