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A study of solvent effects on the stereoselectivity of Diels–Alder reactions through molecular surface electrostatic potentials

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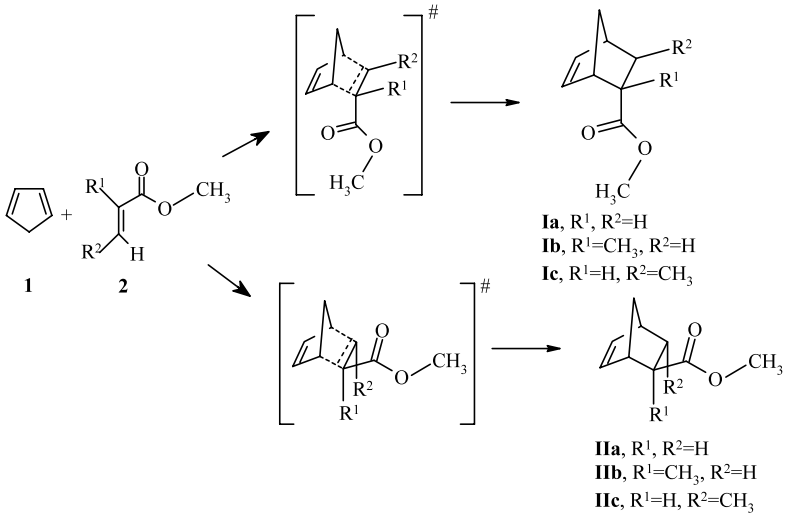
Abstract—Statistical models for the study of solvent effects on the *endo*/*exo* selectivity of Diels–Alder reactions using molecular surface electrostatic potentials was obtained. The models show that hydrogen bond interactions of solvent molecules favor the predominance of the *endo* isomer for the reaction of methyl acrylate, methyl methacrylate and methyl *trans*-crotonate with cyclopentadiene whereas the effect of solvophobicity seems to be negligible.

Solvent effects on Diels–Alder reactions are well known and have attracted much attention because of the noticeable improvement in these reactions achieved by the use of aqueous solvents.[1–5] Several explanations have been offered to account for the observed solvent effects, such as solvophobicity and enhanced hydrogen bonding to the transition state.[6,7] On the theoretical side, Jorgensen and co-workers found that enhanced hydrogen-bonding interactions at the transition state were the predominant cause of the observed rate acceleration for Diels–Alder reactions in water.[8,9] Mayoral and co-workers have suggested that pure electrostatic and hydrogen bonding interactions account for the changes observed in the *endo*/*exo* selectivity.[10] Also, a detailed analysis of ab initio computations shows that the electrostatic effects of the solvent favor the *endo* isomer with respect to the *exo* isomer in agreement with the experimentally observed increase of the *endo*/*exo* selectivity as a function of solvent polarity.[11]



Scheme 1.

Keywords: solvent effect; stereoselectivity; Diels–Alder reaction; electrostatic potential.
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Table 1. *endo*/*exo* Selectivity and differential activation parameters of Diels–Alder reactions of CPD with MA, MMA and MtC in different solvents along with MSEP properties of solvent molecules

Solvent	LogN/X (MA)	LogN/X (MtC)	LogN/X (MMA)	$\Delta\Delta H^{\neq}_{XN}$ (MA)	$\Delta\Delta H^{\neq}_{XN}$ (MtC)	$\Delta\Delta H^{\neq}_{XN}$ (MMA)	$\Delta\Delta S^{\neq}_{NX}$ (MA)	$\Delta\Delta S^{\neq}_{XN}$ (MtC)	$\Delta\Delta S^{\neq}_{XN}$ (MMA)	σ^2_+ (kcal/mol)^2	σ^2_- (kcal/mol)^2	σ^2_{tot} (kcal/mol)^2	$V_{s,max}$ (kcal/mol)	$V_{s,min}$ (kcal/mol)	$\nu\sigma^2_{tot}$ (kcal/mol)^2	π (kcal/mol)
Triethylamine	0.508	0.021	−0.526	0.54	0.68	−0.4	0.37	−2.4	−0.97	47.06	23.65	70.71	39.61	−55.57	5.67	30.06
Decaline	–	0.045	–	0.35	0.34	−0.74	1.3	−0.73	0.96	2.76	0.58	3.34	6.597	−2.94	0.14	0.998
Dimethoxy ethane	0.602	0.088	−0.46	0.64	0.66	−0.39	0.43	−2	−0.69	6.79	153.67	160.46	11.838	−43.91	6.28	4.83
Dimethyl formamide	0.652	0.12	−0.42	0.52	0.23	−0.52	1.1	−0.3	−0.11	240.05	83.8	323.85	97.55	−58.6	25.56	38.58
Pyridine	0.64	0.108	−0.417	0.76	0.24	−0.35	0.17	−0.36	−0.64	30.85	101.41	132.25	21.61	−37.97	24.88	5.24
Nitromethane	0.738	0.212	−0.357	0.64	0.58	−0.52	1	−1.1	0.23	53.43	61.05	114.47	32.86	−30.73	28.82	9.81
Acetonitrile	0.764	0.172	−0.336	0.78	0.44	−0.39	0.6	−0.75	−0.12	50.328	120.15	170.473	28.855	−40.979	35.48	10.499
Acetone	0.659	0.124	−0.393	0.73	0.44	−0.33	0.37	−0.97	−0.57	30.44	144.12	174.56	21.68	−37.98	7.04	6.39
Dichloroethane	0.641	0.104	−0.415	0.6	0.46	−0.59	0.75	−1.2	0.26	64.58	23.66	88.24	29.3	−21.6	16.58	6.74
Ethanol	0.807	0.264	−0.297	0.98	0.38	−0.27	0.14	−0.19	−0.38	434.59	50.29	484.88	159.96	−50.62	35.07	22.71
Acetic acid	0.87	0.373	−0.251	0.96	0.29	−0.44	0.5	0.66	0.46	86.37	108.11	194.49	54.21	−34.58	5.54	6.93
Methanol	0.944	0.296	−0.149	1.4	0.26	0.1	−0.9	0.53	−1.05	393.42	66.89	460.32	153.15	−37.06	45.52	22.64

N = *endo*, X = *exo*; $\Delta\Delta H^{\neq}_{NX} = \Delta H^{\neq}(N) - \Delta H^{\neq}(X)$, $\Delta\Delta S^{\neq}_{NX} = \Delta S^{\neq}(N) - \Delta S^{\neq}(X)$; $\Delta\Delta H^{\neq}_{XN} = \Delta H^{\neq}(X) - \Delta H^{\neq}(N)$, $\Delta\Delta S^{\neq}_{XN} = \Delta S^{\neq}(X) - \Delta S^{\neq}(N)$.
MA = methyl acrylate, MMA = methyl methacrylate, MtC = methyl *trans*-crotonate.

It has been shown that a variety of macroscopic properties of the condensed phase can be expressed analytically in terms of statistically defined quantities.[12–15] 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.[16,17] 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 as well as computationally. The characteristics of *V(r)* encouraged us to investigate the influence of the solvent effect on the *endo*/*exo* selectivity of Diels–Alder reactions of cyclopentadiene (CPD) with methyl acrylate (MA), methyl methacrylate (MMA) and methyl *trans*-crotonate (MtC) (Scheme 1) using MSEP and regression analysis. The statistical analysis is used in conjunction with the experimental results[18] to express the *endo*/*exo* selectivity in terms of the calculated electrostatic potentials on the surface of solvent molecules.

The electrostatic potential *V(r)* is created in the space around a molecule by its nuclei and electrons as given rigorously by Eq. (1).

$$V(r)=\sum\frac{Z_A}{|R_A-r|}-\int\frac{\rho(r')}{|r'-r|}dr' \quad (1)$$

In Eq. (1), Z_A is the charge on nucleus A, located at R_A and $\rho(r')$ is the electronic density. The *V(r)* was computed using the Gaussian 98 package,[19] using the B3P86 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.[20]

The quantities characterizing the MSEP are as follows:

1. $V_{s,max}$ and $V_{s,min}$, are the most positive and negative values of *V(r)* on the molecular surface, respectively. These quantities account for the hydrogen bond acidity and basicity of molecules.
2. π, is the average deviation of *V(r)* on the molecular surface. It is viewed as being indicative of the local polarity, or charge separation, that is present even in molecules having zero dipole moments.[21]
3. σ^2_{tot}, is the sum of the variance of the positive and negative potentials ($\sigma^2_+ + \sigma^2_-$). σ^2_{tot} has been found to be an effective indicator of a molecule's overall tendency for non-covalent interactions.[21] In some instances, it is more effective to use σ^2_+ or σ^2_- alone, which refer to tendencies for non-covalent interactions through positive and negative regions, respectively.
4. $\nu\sigma^2_{tot}$, is a key quantity for representing properties that reflect the non-covalent interactions of a molecule with others of its own kind.[21] The result of this quantity is increased aggregation of the molecules, which in the case of solvent molecules improves the solvophobicity of the solvent.

Table 1 shows the experimental *endo*/*exo* selectivity results and differences in enthalpy and entropy of activation[18] along with some of the key features of the molecular surface electrostatic potentials on the basis of our calculations. These parameters are found to be relevant to experimental data. The best correlations were obtained by the equations presented in Table 2. The resulting models show that the hydrogen bond acidity ($V_{s,max}$) of solvent molecules has a positive effect on the *endo* diastereofacial selectivity of the reactions studied. This can be induced through hydrogen bond interactions of solvent molecules with the carbonyl oxygen, which as reported by Blake and Jorgensen exist in water.[8] On the other hand, the coefficient of $V_{s,max}$ can show the relative importance of this interaction on the *endo*/*exo* selectivity for the dienophiles used. As the coefficient of $V_{s,max}$ in the models presented in Table 2 shows, for the reaction of CPD with MMA and MtC the effects of hydrogen bond acidity of the solvent molecules has diminished in comparison to the reaction of MA. This can be attributed to the additional methyl group, which is expected to shield the carbonyl group from forming efficient hydrogen bonds. Our result is in agreement with the solvation energies obtained by means of the supermolecule approach that accounts for the increase in the *endo* selectivity of the reaction of MA with cyclopentadiene in hydrogen bond donor solvents.[10]

In order to understand how the specific and nonspecific interactions of solvents change the diastereoselectivty of Diels–Alder cycloaddition reactions, we carried out a statistical analysis of MSEP on the differential activation enthalpy and the differential activation entropy that control the stereoselectivity. Recently Cainelli and coworkers have used the modified Eyring equation (2) to analyze the temperature dependency on the formation of the two diastereoisomers (*endo*/*exo*).[22] The analysis using this equation helped us determine how the solvent molecules affect the differential activation parameters of stereoselectivity. Statistical analysis of the differential activation parameters and molecular surface properties in Table 1 resulted in the models presented in Table 3.

$$\ln S=-(\Delta\Delta H^{\neq}/RT)+\Delta\Delta S^{\neq}/R \quad (2)$$

where S = stereoselectivity

Table 2. Regression models of *endo*/*exo* selectivity of Diels–Alder reactions of CPD with MA, MMA and MtC in terms of MSEP properties

Reaction	Model		Regression coefficient
MA+CPD	1	$\log N/X = 0.69+0.00397\sigma^2_- -0.0026\sigma^2_{tot}+0.00988\ V_{s,max}+0.00839\ V_{s,min}$	0.950
MMA+CPD	2	$\log N/X = -0.372+0.00319\sigma^2_- -0.00207\sigma^2_{tot}+0.00801\ V_{s,max}+0.00712\ V_{s,min}$	0.970
MtC+CPD	3	$\log N/X = 0.00795+0.00338\nu\sigma^2_{tot}-0.00855\pi-0.00257\sigma^2_+ +0.00869\ V_{s,max}$	0.973

MA = methyl acrylate; MMA = methyl methacrylate; MtC = methyl *trans*-crotonate; CPD = cyclopentadiene.

Table 3. Regression models of differential activation parameters of *endo*/*exo* selectivity of Diels–Alder reactions of CPD with MA, MMA and MtC in terms of MSEP properties

Reaction	Model		Regression coefficient
CPD+MA	4	$\log\Delta\Delta H^{\neq}_{XN} = 0.505 + 0.0073\ V_{s,min} + 0.00496\ V_{s,max} + 0.00308\sigma^2_-$	0.845
CPD+MMA	5	$\log\Delta\Delta H^{\neq}_{XN} = -0.1110 + 0.001845 v\sigma^2_{tot} + 0.00808\pi - 0.000529\sigma^2_{tot} + 0.00841\ V_{s,min}$	0.912
CPD+MtC	6	$\log\Delta\Delta H^{\neq}_{XN} = -0.383 - 0.00765 v\sigma^2_{tot} - 0.00513\ V_{s,min} + 0.00025\ V_{s,max}$	0.730
CPD+MA	7	$\log\Delta\Delta S^{\neq}_{NX} = 0.2849 + 0.04977\pi + 0.005862\sigma^2_- + 0.04498\ V_{s,min}$	0.834
CPD+MMA	8	$\log\Delta\Delta S^{\neq}_{XN} = 2.7298 - 0.0391 v\sigma^2_{tot} + 0.06032\pi + 0.07289\ V_{s,min} + 0.00192\sigma^2_{tot}$	0.946
CPD+MtC	9	$\log\Delta\Delta S^{\neq}_{XN} = -0.1218 - 0.01010 v\sigma^2_{tot} - 0.01149\sigma^2_+ + 0.0305\ V_{s,max}$	0.865

$\Delta\Delta H^{\neq}_{NX} = \Delta H^{\neq}(endo) - \Delta H^{\neq}(exo)$, $\Delta\Delta S^{\neq}_{NX} = \Delta S^{\neq}(endo) - \Delta S^{\neq}(exo)$.
$\Delta\Delta H^{\neq}_{XN} = \Delta H^{\neq}(exo) - \Delta H^{\neq}(endo)$, $\Delta\Delta S^{\neq}_{XN} = \Delta S^{\neq}(exo) - \Delta S^{\neq}(endo)$.
MA = methyl acrylate; MMA = methyl methacrylate; MtC = methyl *trans*-crotonate; CPD = cyclopentadiene.

Hydrogen bond acidity of solvent molecules ($V_{s,max}$) favors the predominance of the *endo* isomer for the reaction of MA or MtC with cyclopentadiene through $\Delta\Delta H^{\neq}$(models 4 and 6). However, the solvent $V_{s,max}$ disfavors the *endo* isomer in the reaction of MtC with CPD through $\Delta\Delta S^{\neq}$ (model 9). In the case of hydrogen bond basicity of solvent molecules, $V_{s,min}$, the *endo* isomer is favored in the reaction of MA or MMA with CPD through $\Delta\Delta H^{\neq}$ (model 4) and the positive or the negative contribution of this quantity is predictable through the models presented (Table 3). The models obtained also predict that the solvophobicity ($v\sigma^2_{tot}$) of solvents has some effect on $\Delta\Delta H^{\neq}$ or $\Delta\Delta S^{\neq}$. For example solvophobicity has a negative effect on $\Delta\Delta S^{\neq}_{XN}$ in the reaction of MA or MtC with cyclopentadiene (models 6 and 9), which drives the stereoselectivity of the reaction towards formation of the *endo* isomer. However, the total effect of this specific interaction of solvents on *endo*/*exo* selectivity appears only in the reaction of MtC (model 3). Thus, solvophobicity can change $\Delta\Delta H^{\neq}$ or $\Delta\Delta S^{\neq}$ in the studied reactions, but its influence on the stereoselectivity of these reactions seems to be negligible in comparison to other interactions of the solvents.

Furthermore, it is shown that non-covalent electrostatic interactions through negative regions of solvent molecules (σ^2_-) favor the *endo* cycloadduct whereas interactions through positive regions (σ^2_+), drive the stereoselectivity of the cycloaddition reaction of cyclopentadiene with the dienophiles towards the *exo* cycloadduct. Therefore, according to our model, non-covalent electrostatic interactions (σ^2_{tot}, σ^2_+ and σ^2_-) and local polarity (π) of the solvent molecules also play a role in determining the *endo*/*exo* selectivity of the reactions studied. Also, the effect of these interactions on $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ has been investigated (Table 3).

In conclusion, we have developed statistical models for the study of solvent effects on *endo*/*exo* selectivity using molecular surface electrostatic potentials. Hydrogen bonding interactions ($V_{s,max}$ and $V_{s,min}$) and non-covalent electrostatic interactions (σ^2_{tot}, σ^2_+ and σ^2_-) of solvents were found to generally affect the stereoselectivity of the Diels–Alder reactions of MA, MMA or MtC with cyclopentadiene. The effect of solvophobicity on stereoselectivity seems to be unimportant in the reactions studied. This maybe attributed to the existence of hydrogen bond interactions between solvent molecules and the dienophile, which diminishes the importance of solvophobicity. Further investigations concerning applications of this strategy to the kinetics of other types of reaction is currently ongoing.

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