

Solvophobic Acceleration of a Diels–Alder Reaction in True Solutions in Organic Solvents

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ABSTRACT: The rate of Diels–Alder reaction of diene 9,10-bis(hydroxymethyl)anthracene with dienophile N-ethylmaleimide was studied in a series of solvents with different polarity and hydrogen-bonding ability. Enthalpies and entropies of activation were determined from the temperature dependences of the rate constants. Rate acceleration in nonaqueous protic solvents such as glycerol, propylene, and ethylene glycols was observed. In addition, enthalpy versus entropy of activation plots show a compensation pattern different from the other considered solvents, which can be linked with the solvophobic effects observed in polyhydric alcohols. However, the solvophobic acceleration was not as strong as the hydrophobic acceleration in water. Hydrogen bonding of the reactants and transition state with solvent also influences the reaction rate. The studied reaction is slightly promoted in hydrocarbon solvents in comparison with aprotic polar solvents. This was explained by hydrogen bonding of the hydroxyl groups of diene with dienophile in transition state, which requires prior breaking of the hydrogen bonds of these groups with polar solvent molecules. © 2018 Wiley Periodicals, Inc. *Int J Chem Kinet* 50: 319–324, 2018

INTRODUCTION

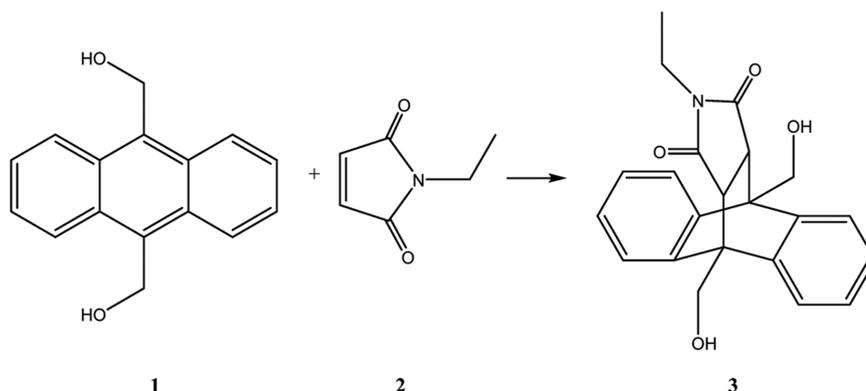
The enhancement of the rate and selectivity of Diels–Alder reactions in water is now a well-recognized and extensively studied phenomenon. It is agreed that the hydrophobic effect plays a crucial role in this acceleration.

Besides water, there are other solvents that are characterized by low solubility of apolar species and ability to support self-assembly of amphiphilic molecules

into micelles and other supramolecular structures. The most prominent examples are polyhydric alcohols, acid amides, and ionic liquids [1–3]. These solvents are described as exhibiting “solvophobic effects,” which are a generalization of the term “hydrophobic effect.” Thermodynamic studies reveal common nature of the solvophobic and hydrophobic effects. At the same time, the influence of the solvophobic effects in nonaqueous media on kinetics of chemical reactions and, in particular, of the Diels–Alder reaction, was studied quite scarcely. Acceleration of Diels–Alder reactions in ethylene glycol and formamide was described by Breslow and Guo [4], Jenner and Gacem [5]. Fluorinated hydrocarbons also can significantly speed up

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Scheme 1 Reactants and products of the studied Diels–Alder reaction.

cycloaddition, which was called “fluorophobic” acceleration [5,6]. Recently, dramatic acceleration of the rate of the Diels–Alder reaction was observed at the interface of *n*-hexane with imidazolium-based ionic liquids [7].

A solvent-induced increase in the rate of cycloaddition can be caused by different types of interactions. In ionic liquids, it was attributed [7] to stabilization of transition state by hydrogen bonding and ion–dipole interactions, whereas in perfluorocarbons it can be explained by reduction of the solvent-accessible surface area engaged in unfavorable interactions with the solvent upon formation of the transition state. In aqueous solutions, hydrogen bonds formed by reactants and transition state with water undoubtedly influence the reaction rate [8], but the proof of the key role of the hydrophobic effect arises [9] from the observations that (1) in water, the Diels–Alder reaction can be many times faster in comparison with other H-donor solvents such as methanol; (2) additives that are known to strengthen the hydrophobic effect speed up cycloaddition, whereas those suppressing the hydrophobic effect such as guanidinium chloride slows down the reaction. The solvents exhibiting well-expressed solvophobic effects such as polyhydric alcohols and acid amides have strong H-donor and H-acceptor ability that is comparable to water, but the solvophobic effects in all of them are much weaker than the hydrophobic effect in water and should lead to less prominent acceleration of the Diels–Alder reaction rates. Some authors [10] even denied the role of the solvophobic effect in such solvents as ethylene glycol and linked the observed moderate rate acceleration with the hydrogen-bonding ability of a solvent.

To extend our knowledge about the solvophobic acceleration of cycloaddition processes, in the present work, we study kinetics of the Diels–Alder reac-

tions of 9,10-bis(hydroxymethyl)anthracene **1** with *N*-ethylmaleimide **2** (Scheme 1) in various protic and some aprotic organic solvents. Possible factors governing the solvent effect on the reaction rate constants are considered. Huge UV extinction coefficient of **1** and sufficient solubility of both reactants in a wide range of protic and aprotic solvents make this reaction attractive for the study of the solvent effect on the reaction rate. Previously, we have reported [11] the rate constants and activation parameters of this reaction in the mixtures of water with 1,4-dioxane and concluded that suppression of the hydrophobic effect with addition of 1,4-dioxane leads to a decrease in the reaction rate. Unlike numerous studies of the reaction rates in suspensions or emulsions “on solvent” [12,13], all our experiments were conducted in true solutions. Thus, possible micellar [14] and interface effects on the rate constants are avoided.

EXPERIMENTAL

Materials

Compound 1 was synthesized using a previously reported procedure [15]. Mp 285°C (decomp.) (lit. [15] 287–290°C). The molar UV absorption coefficient of **1** in solution in 1,4-dioxane at $\lambda = 393$ nm was $9650 \text{ cm}^{-1} \cdot \text{M}^{-1}$ which is in a good agreement with literature ($\epsilon = 9550 \text{ cm}^{-1} \cdot \text{M}^{-1}$ [16]). *N*-ethylmaleimide **2** (99%; Acros Organics) was used as purchased. The solvents were purified by known methods [17].

Kinetic Measurements

The rate of reactions at ambient pressure was monitored using a Hitachi U–2900 spectrophotometer

Table I Rate Constants ($\times 10^{-2} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$) of Reaction **1** + **2** = **3** in Different Solvent Media at Various Temperatures and their Standard Uncertainties

Solvent	<i>T</i> (K)									
	298.15		303.15		308.15		313.15		318.15	
	<i>k</i> ₂	<i>u</i> (<i>k</i> ₂)	<i>k</i> ₂	<i>u</i> (<i>k</i> ₂)	<i>k</i> ₂	<i>u</i> (<i>k</i> ₂)	<i>k</i> ₂	<i>u</i> (<i>k</i> ₂)	<i>k</i> ₂	<i>u</i> (<i>k</i> ₂)
Water ^a	25.4	0.3	32.5	0.3	42.9	0.5	51.1	0.5	63.6	0.7
Formamide	1.60	0.02	2.25	0.01	2.97	0.03	3.71	0.04	4.70	0.04
Ethylene glycol	2.15	0.02	2.89	0.01	3.96	0.03	5.00	0.05	6.62	0.03
Propylene glycol	2.65	0.03	3.69	0.04	4.87	0.03	6.26	0.04	7.99	0.04
Diethylene glycol	1.34	0.02	1.69	0.02	2.44	0.03	2.89	0.02	3.97	0.04
Triethylene glycol	1.03	0.01	1.35	0.03	1.85	0.03	2.31	0.05	2.98	0.05
2-Methoxyethanol	0.63	0.01	0.87	0.01	1.20	0.01	1.58	0.01	2.02	0.02
2-Ethoxyethanol	0.74	0.01	1.02	0.01	1.47	0.01	1.98	0.01	2.51	0.01
2-Buthoxyethanol	0.96	0.01	1.33	0.01	1.89	0.01	2.39	0.01	3.38	0.01
2-Phenoxyethanol	0.68	0.01	0.96	0.01	1.34	0.01	1.83	0.01	2.48	0.01
Methanol	0.90	0.01	1.16	0.01	1.52	0.01	2.07	0.03	2.77	0.04
Benzyl alcohol	0.83	0.01	1.12	0.01	1.51	0.01	1.99	0.01	2.61	0.01
<i>N</i> -Methylformamide	0.68	0.01	0.89	0.01	1.22	0.01	1.56	0.01	1.99	0.02
Dimethyl sulfoxide	0.63	0.01	0.88	0.01	1.12	0.01	1.62	0.01	2.11	0.02
1,4-Dioxane ^a	0.41	0.01	0.54	0.01	0.79	0.01	1.03	0.01	1.38	0.01
Trichloromethane	0.59	0.01	0.84	0.01	1.20	0.01	1.65	0.01	2.13	0.01
Acetone	0.36	0.01	0.50	0.01	0.67	0.01	0.92	0.01	1.19	0.01
Glycerol	5.0	1.0								
Benzene	0.94	0.01								
Toluene	1.07	0.01								

^aThe rate constants in water and in 1,4-dioxane at 298.15, 308.15, and 318.15 K were reported previously [11].

according to the change in the UV absorption of **1** near the absorption maximum (390–395 nm). Freshly prepared solutions of reagents were mixed and put into a quartz cell (optical path length 1 cm), sealed with a glass stopper, and placed into the thermoblock of the cell compartment. Temperature accuracy was within ± 0.1 K. The initial concentrations of diene **1** were in the range $(4\text{--}10) \times 10^{-5} \text{ mol}\cdot\text{L}^{-1}$, except the solutions in water, benzene, and toluene, in which **1** is poorly soluble. In the latter cases, saturated solutions with lower concentrations were prepared. The concentrations of dienophile **2** were 100–500 times higher. **2** is known to undergo solvolysis in some of the considered solvents, but its rate is very small in comparison with that of cycloaddition. The values of the pseudo-first-order reaction rate constants k_1 were obtained from the plots of $\ln(D_t - D_\infty)$ against time t , where D_t is the measured absorbance at time t and D_∞ is the absorbance after the reaction is finished (no more significant change in absorbance). The true rate constant k_2 corresponding to the bimolecular reaction **1** + **2** = **3** is given by $k_2 = k_1 / [\mathbf{2}]$, where $[\mathbf{2}]$ is the concentration of **2**. Results are reported in Table I.

Solubility Measurements

In a typical experiment, **1** was dispersed in 3–5 mL of a solvent, sealed in a vial, thoroughly shaken and vortexed, then kept several days in a constant temperature water bath at 298 ± 0.1 K. For each solvent, three vials were prepared to check the repeatability. 100 μL aliquots of saturated solutions were taken and diluted with 2.9 mL of 1,4-dioxane. The concentration of solutions was determined using spectrophotometry. Saturated solutions in dimethyl sulfoxide were diluted two times due to very high solubility of **1**. Saturated solutions in water, benzene, and toluene have not been diluted due to very low solubility of **1**. The solution in glycerol has also not been diluted because of its high viscosity and formation of a very stable dispersion. The solubilities in these solvents were estimated assuming that the molar absorbance at the maximum absorption wavelength is roughly the same as in 1,4-dioxane. This assumption was supported by monitoring the changes in absorbance upon dilution of solutions of **1** in pure 1,4-dioxane with these solvents. The value of the maximum absorption wavelength is slightly different in

Table II Solubilities of **1** in Different Solvents at $T = 298.15$ K and Their Standard Uncertainties

Solvent	c_{sat} (M)	$u(c_{\text{sat}})$ (M)	x_{sat}
Water	1.43×10^{-6}	1.0×10^{-7}	2.60×10^{-8}
Formamide	5.10×10^{-4}	7.3×10^{-6}	2.03×10^{-5}
Ethylene glycol	5.78×10^{-4}	2.9×10^{-5}	3.21×10^{-5}
Propylene glycol	5.51×10^{-4}	9.0×10^{-6}	4.04×10^{-5}
Diethylene glycol	1.79×10^{-3}	1.6×10^{-5}	1.70×10^{-4}
Triethylene glycol	2.26×10^{-3}	4.0×10^{-5}	3.01×10^{-4}
2-Methoxyethanol	1.62×10^{-3}	1.4×10^{-5}	1.28×10^{-4}
2-Ethoxyethanol	1.06×10^{-3}	1.7×10^{-5}	1.02×10^{-4}
2-Butoxyethanol	5.12×10^{-4}	8.0×10^{-6}	6.73×10^{-5}
2-Phenoxyethanol	1.53×10^{-3}	2.0×10^{-5}	1.92×10^{-4}
Methanol	4.94×10^{-4}	1.8×10^{-5}	2.00×10^{-5}
Benzyl alcohol	1.09×10^{-3}	1.5×10^{-5}	1.13×10^{-4}
<i>N</i> -Methylformamide	4.39×10^{-3}	8.0×10^{-5}	2.56×10^{-4}
Dimethyl sulfoxide	7.63×10^{-2}	8.2×10^{-4}	5.44×10^{-3}
1,4-Dioxane	1.57×10^{-3}	1.3×10^{-5}	1.34×10^{-4}
Acetone	3.89×10^{-4}	5.0×10^{-6}	2.87×10^{-5}
Glycerol	2.01×10^{-4}	1.5×10^{-6}	1.47×10^{-5}
Benzene	7.37×10^{-6}	5.0×10^{-7}	6.55×10^{-7}
Toluene	5.56×10^{-6}	6.0×10^{-7}	5.91×10^{-7}

each pure solvent. To prove the proper equilibration, in the second experiment, the solutions in the same set of solvents were prepared in a different way. Vials containing **1** and solvent were heated in an ultrasound bath up to 40°C , shaken, then cooled down to room temperature and kept several days at 298 ± 0.1 K. Both experiments led to essentially the same results. Measured concentrations c_{sat} and mole fractions x_{sat} of **1** in saturated solutions are given in Table II.

RESULTS AND DISCUSSION

Results show that no one of considered solvents can compare with water in its ability to accelerate the Diels–Alder reaction. In glycerol, the studied reaction is five times slower than in water; in propylene glycol, ethylene glycol, and formamide, it is, respectively, 9.6, 11.8, and 15.9 times slower than in water. These ratios are quite close to those observed for the previously studied [4] reaction of cyclopentadiene with methyl vinyl ketone, which is 9.2 times faster in water than in ethylene glycol and 13.8 times than in formamide. However, the rate constant of reaction **1** + **2** = **3** does not drop dramatically in aprotic solvents. In acetone, it is only 4.4 times less than in formamide. Moreover, in toluene the reaction goes three times faster than in acetone.

Previously, attempts were made to find a correlation of the rate of Diels–Alder reactions in different solvents

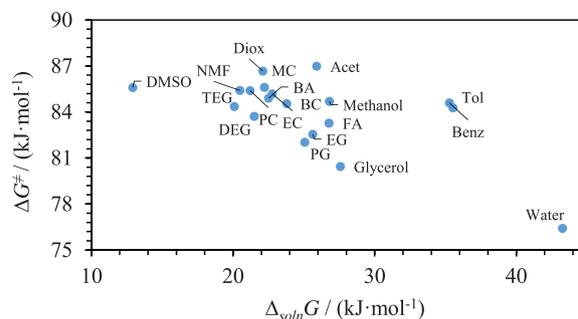


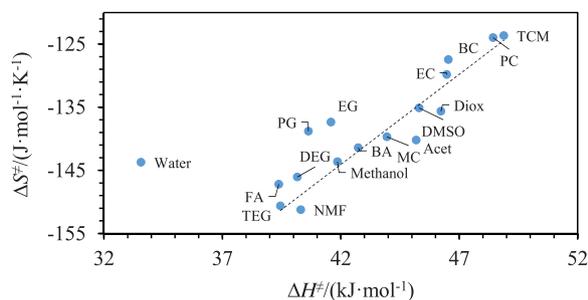
Figure 1 Plot of the Gibbs free energy of activation of reaction **1** + **2** = **3** versus standard Gibbs free energy of dissolution of **1** in different solvents at $T = 298.15$ K (see Table III for abbreviations of solvents). [Color figure can be viewed at wileyonlinelibrary.com]

with the solubility of diene in these solvents [6,18]. In Fig. 1, the values of the Gibbs free energy of activation ΔG^\ddagger of considered reactions in different solvents are plotted against the standard Gibbs free energy of dissolution $\Delta_{\text{soln}}G$ of **1** in the same solvents. ΔG^\ddagger can be calculated from the Eyring equation relating it to the rate constants: $k = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger}{RT}}$. $\Delta_{\text{soln}}G$ is given by $\Delta_{\text{soln}}G = -RT \ln x_{\text{sat}}$, where x_{sat} is the molar fraction solubility of **1** (Table II). There is no single correlation line between the two quantities.

Enthalpies and entropies of activation were determined by fitting the experimental data to the linearized form of the Eyring equation $\ln \frac{k}{T} = -\frac{\Delta H^\ddagger}{R} \frac{1}{T} + \frac{\Delta S^\ddagger}{R} + \ln \frac{k_B}{h}$. They are given in Table III.

Table III Thermodynamic Functions of Activation for Reaction **1** + **2** = **3** in Different Solvents at $T = 298.15$ K

Solvent	Abbreviation	ΔG^\ddagger (kJ·mol ⁻¹)	ΔH^\ddagger (kJ·mol ⁻¹)	ΔS^\ddagger (J·mol ⁻¹ ·K ⁻¹)
Water	–	76.4	33.6	-144
Formamide	FA	83.3	39.4	-147
Ethylene glycol	EG	82.5	41.6	-137
Propylene glycol	PG	82.0	40.6	-139
Diethylene glycol	DEG	83.7	40.2	-146
Triethylene glycol	TEG	84.4	39.4	-151
2-Methoxyethanol	MC	85.6	44.0	-140
2-Ethoxyethanol	EC	85.2	46.5	-130
2-Butoxyethanol	BC	84.5	46.5	-127
2-Phenoxyethanol	PC	85.4	48.4	-124
Methanol	–	84.7	41.9	-144
Benzyl alcohol	BA	84.9	42.7	-141
N-Methylformamide	NMF	85.4	40.3	-151
Dimethyl sulfoxide	DMSO	85.6	45.3	-135
1,4-Dioxane	Diox	86.7	46.2	-136
Trichloromethane	TCM	85.8	48.9	-124
Acetone	Acet	87.0	45.2	-140
Glycerol	–	80.4		
Benzene	Benz	84.3		
Toluene	Tol	84.6		

**Figure 2** Compensation plot of entropy versus enthalpy of activation for reaction **1** + **2** = **3** in different solvents at $T = 298.15$ K (see Table III for abbreviations of solvents). [Color figure can be viewed at wileyonlinelibrary.com]

A plot of the entropy against enthalpy of activation is shown in Fig. 2. A close-to-linear compensation is observed for most of the solvents except water, propylene glycol, and ethylene glycol. The latter solvents follow a different compensation pattern. On the other hand, data points for ethylene glycol and propylene glycol form a cluster with those for methanol, diethylene glycol, triethylene glycol, formamide, and *N*-methylformamide, all of which are protic solvents with strong intermolecular hydrogen bonds.

The difference in activation parameters in various solvents is determined by the difference in the thermodynamic functions of solvation of transition state and reactants. A different enthalpy–entropy compen-

sation for solvation processes in protic self-associated solvents rather than in aprotic polar and apolar solvents is a characteristic feature of the solvophobic effects [1]. Higher values of the entropy of activation in propylene and ethylene glycols in comparison with other solvents having similar enthalpies of activation support the hypothesis about the key role of the solvophobic effects, which are known to be entropy driven in these solvents [19,20]. It is also supported by the fact that in methanol, which has a similar polarity and H-donor ability as ethylene glycol, but much weaker solvophobic effects, the reaction goes slower. Thus, we conclude that solvophobic acceleration of the studied reaction takes place in polyhydric alcohols.

The solvophobic effects make unfavorable only the solvation of apolar parts of molecules, whereas polar fragments gain energy due to formation of the strong hydrogen bonds with protic solvents. Thus, the solubility of the reactants that contain both polar and apolar parts does not correlate with the reaction rate, as clearly seen from Fig. 1. Higher solubility of **1** in polar solvents than in hydrocarbons is explained by formation of the hydrogen bonds between hydroxyl groups and polar solvent molecules. The difference between the free energies of hydrogen bonding of the transition state and reactants with the solvent is another factor that contributes to the overall solvent effect on the reaction rate. The product of reaction **3** has two intramolecular hydrogen bonds (Fig. 3), which are likely to be

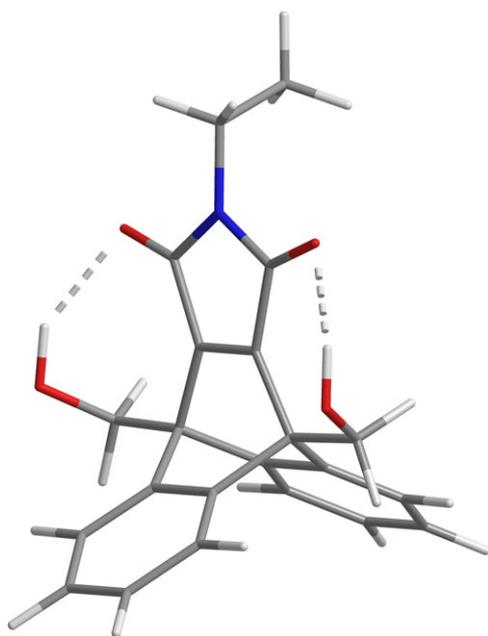


Figure 3 Geometry-optimized (B3LYP/6-31G*) structure of the reaction product **3** with hydrogen bonds shown in dashes. [Color figure can be viewed at wileyonlinelibrary.com]

present as well in the transition state. To form these bonds, in polar aprotic solvents intermolecular hydrogen bonds with the solvent donated by OH-groups of diene **1** should be broken. This obviously leads to an increase in the free energy of activation and lower rate constants in such solvents as dioxane and acetone than in hydrocarbons. Such an effect is similar to the previously reported Diels-Alder reaction rate enhancement in perfluorocarbons [6] and distinct from solvophobic acceleration in water, glycerol, or other protic self-associated solvents.

CONCLUSIONS

9,10-Bis(hydroxymethyl)anthracene is a diene that provides a balance between sufficient solubility in protic solvents due to the presence of hydroxyl groups and well-expressed acceleration of the rate of the Diels-Alder reaction in true solutions in water, glycerol, and glycols caused by the solvophobic effects favoring formation of the transition state from the reactants. Water is the most powerful catalyst, and glycerol wins the second place. The considered reaction with *N*-ethylmaleimide is also slightly accelerated in apolar hydrocarbon solvents in comparison with aprotic polar solvents due to the hydrogen bonds of hydroxyl groups

of diene with polar solvents stabilizing the initial state. In a general case, the solvent effect on the rates of reactions is a combined effect from different types of interactions of solvent with reactants and the transition state and cannot be correlated with solvation properties of only one of the reactants or a single solvent descriptor.

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