for the preparation of 7, the concentrated residue was chromatographed on silica gel and hexane/CH_2Cl_2 (3:1) as an eluent to give 437 mg of **9** as a red viscous oil (39%): ESR (CH_2Cl_2, 25 °C) $g = 2.0053$, $a_{N(-O\cdot)} = 10.4$ G, $a_{H(arom)} = 1.8$ G; MS m/z calcd for $C_{40}H_{72}N_3O_3Si_2$ 698.5112, found 698.5134 (0.5), 57 (base).

Bis[3-*tert*-butyl-5-(*N*-hydroxy-*tert*-butylamino)phenyl] Nitroxide (10). A solution of 97.5 mg of **9** and 97 mg of tetrabutylammonium fluoride trihydrate in 5 mL of THF was stirred at 0 °C for 15 min and at room temperature for 15 min under argon. After aqueous workup as described above, the organic layer was chromatographed on silica gel and CH_2Cl_2 to give 37 mg of **10** as a red viscous oil (55%): ESR (benzene, 25 °C) $g = 2.0057$, $a_{N(-O\cdot)} = 9.9$ G, $a_{H(arom)} = 1.9$ G; IR (KBr disc) ν_{O-H} 3268 cm^{-1}; MS m/z 526 (M^+, 0.5), 57 (base).

Bis[3-*tert*-butyl-5-(*N*-oxy-*tert*-butylamino)phenyl] Nitroxide (4). To a solution of 33 mg of **10** in 2 mL of ether, a large excess amount (ca. 100 mg) of freshly prepared Ag_2O was added, and the mixture was stirred for 30 min at room temperature. The mixture was filtered with Celite, and the filtrate was chromatographed (alumina/CH_2Cl_2) to give 26 mg of **4** as orange solids (80%): mp 120–123 °C (from hexane); ESR (solid, 25 °C) $g = 2.0055$; (benzene, 25 °C) $g = 2.0058$, $\Delta H_{pp} = 14$ G; MS m/z calcd for $C_{28}H_{42}N_3O_3$ 468.3226, found 468.3243 (1), 57 (base); UV/vis λ 370 nm (sh, ε 1900), 430 (sh, 1500), 520 (sh, 410).

Acknowledgment. This work was supported in part by the Grant-in-Aid for Scientific Research on Priority Area No. 02230102 from the Ministry of Education, Science and Culture.

Diels–Alder Reactions in Aqueous Solutions. Enforced Hydrophobic Interactions between Diene and Dienophile

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Abstract: Second-order rate constants and isobaric activation parameters for the intermolecular Diels–Alder reactions of cyclopentadiene with alkyl vinyl ketones (**2a,b**) and 5-substituted-1,4-naphthoquinones (**3a–c**) as well as for the intramolecular Diels–Alder reaction of *N*-furfuryl-*N*-methylmaleamic acid (**4**) were determined in water, monohydric alcohols, and highly aqueous solutions containing monohydric alcohols and other organic cosolvents. The intermolecular as well as the intramolecular Diels–Alder reaction are characterized by large rate accelerations upon going from an organic solvent to water as the reaction medium. A model for solvation effects on rate constants for Diels–Alder reactions in aqueous solutions is developed. The typical, huge rate enhancements for Diels–Alder reactions in water and in highly aqueous binary mixtures are significantly sensitive to substituent effects and are discussed in terms of enforced pairwise hydrophobic interactions between diene and dienophile.

Introduction

For a wide range of solvent systems, both the rate constants and stereoselectivities of Diels–Alder reactions are only moderately sensitive to changes in the nature of the reaction medium.[1] However, the pioneering work of Breslow et al.[2] has shown that Diels–Alder reactions are dramatically accelerated in aqueous solutions. Other studies also revealed curious rate effects on different types of cycloaddition reactions in water.[3-7] Recently, Grieco et al.[8] reported a large rate enhancement for a Diels–Alder reaction in diethyl ether containing 5 M lithium perchlorate. The large rate accelerations have been tentatively explained in terms of hydrophobic packing of diene and dienophile,[2] aggregation processes[3c] and the high internal pressure of water.[8-10]

Chart I

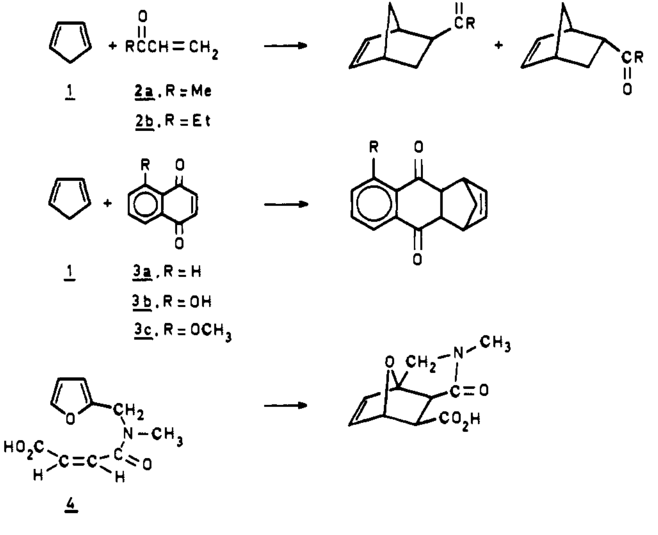

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Table I. Rate Constants and Isobaric Activation Parameters for the Diels–Alder Reaction of Cyclopentadiene (**1**) with Different Dienophiles and for the Intramolecular Diels–Alder Reaction of **4** in Water and 1-Propanol at 25 °C

diene	dienophile	k_2, $dm^3 \cdot mol^{-1} \cdot s^{-1}$	$\Delta^{\ddagger}G^{\ominus}$, $kJ \cdot mol^{-}$	$\Delta^{\ddagger}H^{\ominus}$, $kJ \cdot mol^{-}$	$-T\Delta^{\ddagger}S^{\ominus}$, $kJ \cdot mol^{-}$
1	**2a**	$51.9 \times 10^{-3\,a}$	80.35	39.4 (0.7)	40.9 (0.7)
		$0.912 \times 10^{-3\,b}$	90.37	45.1 (0.7)	45.3 (0.7)
1	**2b**	$48.9 \times 10^{-3\,a}$	80.50	41.5 (0.6)	39.0 (0.6)
		$0.762 \times 10^{-3\,b}$	90.82	45.8 (0.5)	45.0 (0.6)
1	**3a**	4.28^{a}	69.42	36.6 (0.4)	32.8 (0.5)
		$17.6 \times 10^{-3\,b}$	83.05	42.9 (0.6)	40.1 (0.6)
1	**3b**	4.33^{a}	69.39	44.2 (0.8)	25.2 (0.8)
		$32.2 \times 10^{-3\,b}$	81.54	44.2 (0.5)	37.3 (0.6)
1	**3c**	5.26^{a}	68.91	40.5 (0.7)	28.4 (0.7)
		$14.9 \times 10^{-3\,b}$	83.44	43.3 (1.0)	40.2 (1.0)
	4	$26.7 \times 10^{-3\,a,c}$	82.00		
		$0.260 \times 10^{-3\,b,c}$	93.49		

[a] In water. [b] In 1-propanol. [c] First-order rate constant (s^{-1}).

Here we report a detailed study of the intermolecular Diels–Alder reactions of cyclopentadiene (**1**) with alkyl vinyl ketones (**2a**,**b**) and 5-substituted-1,4-naphthoquinones (**3a–c**) as well as of the intramolecular Diels–Alder reaction of *N*-furfuryl-*N*-methylmaleamic acid (**4**) in aqueous media (Chart I).

The second-order rate constants for the cycloaddition of dienophiles **2a**,**b** and **3a–c** with diene **1** in water are, respectively, about 200 and 5800 times larger than those in *n*-hexane. The intramolecular cycloaddition of **4** appears to be accelerated in water similarly. In order to analyze the origin of these unexpectedly large rate effects, we have determined the effect of different substituents in the dienophiles on the observed medium effects. Rate constants as well as activation parameters for the Diels–Alder reactions have also been measured in 1-propanol and in mixtures of water with monohydric alcohols. The rate constants in the highly aqueous media are analyzed by a novel quantitative treatment based on pairwise Gibbs function interaction parameters.[11]

The stereoselectivity of cycloadditions in aqueous media is also significantly different from that in conventional organic solvents.[2,5,12] We have measured the stereoselectivity of the Diels–Alder reactions of **1** with **2a** and **2b** in water and in mixtures of water with monohydric alcohols. The endo product, which is already the most dominant product in organic solvents,[13] is even more favored in water.

Results and Discussion

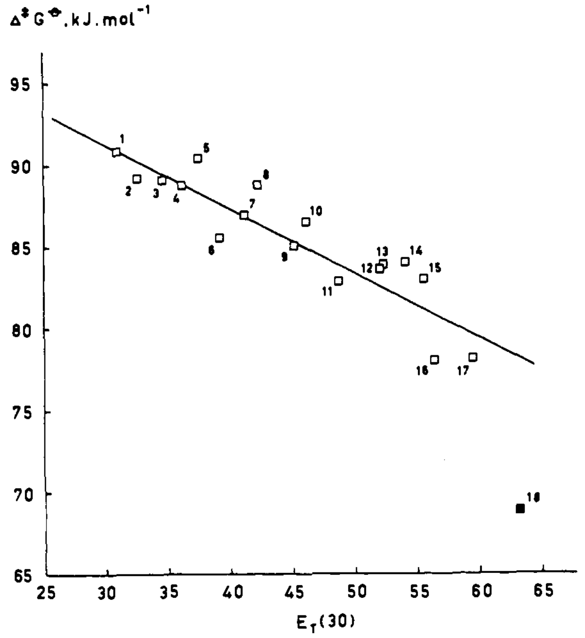

Figure 1. Free energy of activation (25 °C) for the Diels–Alder reaction of **1** with **3c** in *n*-hexane (1), tetrachloromethane (2), benzene (3), *p*-dioxane (4), THF (5), chloroform (6), dichloromethane (7), acetone (8), DMSO (9), acetonitrile (10), 2-propanol (11), ethanol (12), *N*-methylacetamide (13), *N*-methylformamide (14), methanol (15), glycol (16), trifluoroethanol (17), and water (18).

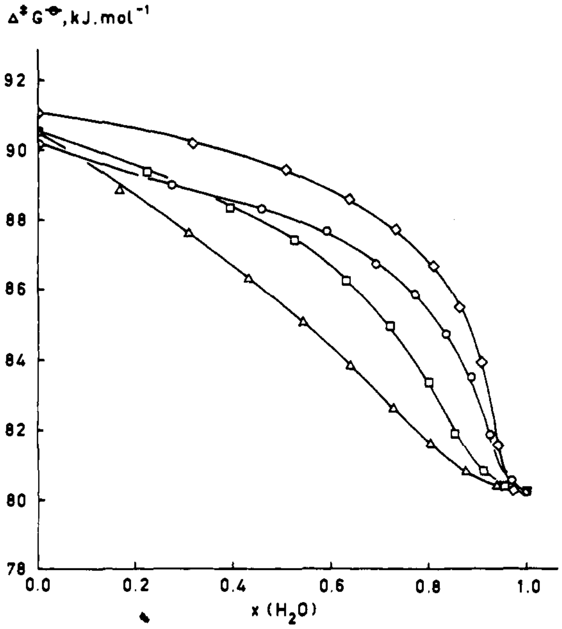

Figure 2. Free energy of activation (25 °C) for the Diels–Alder reaction of **1** with **2a** in mixtures of water and methanol (△), ethanol (□), 1-propanol (○) and 2-methyl-2-propanol (◇) as a function of the mole fraction of water.

Second-order rate constants, as well as isobaric activation parameters for the intermolecular Diels–Alder reactions of diene **1** with dienophiles **2a**,**b** and **3a–c** and the intramolecular Diels–Alder reaction of **4** in water and in 1-propanol, are listed in Table I. The order of reactivity of the 5-substituted-1,4-naphthoquinones in 1-propanol can be understood in terms of a frontier molecular orbital approach, reported by Houk et al.[14] The second-order rate constant for the Diels–Alder reaction of **3c** with diene **1** increases with increasing solvent polarity. The Gibbs energy of activation ($\Delta^{\ddagger}G^{\ominus}$) shows an approximately linear correlation with the $E_T(30)$ value for a series of organic solvents (Figure 1). Interestingly, Diederich[15] has shown that the free energy of

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(10) Some authors have reported correlations of rate constants of Diels–Alder reactions with emperical solvent parameters like the $E_T(30)$ value (see ref 6), the polarity parameter (Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297), and the solvophobicity parameter S_P (Reference 6; Cativiela, C.; Mayonal, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1990**, *3*, 414). Solvent effects of Diels–Alder reactions of butadiene with naphthoquinones have also been analyzed by using frontier molecular orbital approaches (Desimoni, G.; Faita, G.; Righetti, P.; Tornaletti, N.; Visigalli, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 437). Previous reference[8,9] to the "high" internal pressure of water is incorrect (Dack, M. J. R. *Chem. Soc. Rev.* **1975**, *4*, 211) and should be replaced by cohesive energy density.

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(13) Endo/exo ratios have been correlated with the polarity of the solvent (Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297) but also with the free energy of activation, external pressure, and the presence of catalysts (Segushi, K.; Sera, A.; Otsuki, Y.; Manuyama, K. *Bull Chem. Soc. Japan* **1975**, *48*, 3641 and references cited therein).

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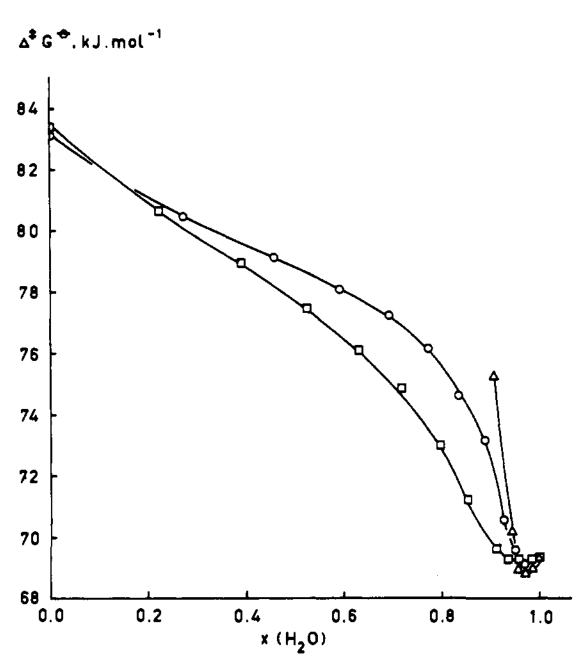

Figure 3. Free energy of activation (25 °C) for the Diels-Alder reaction of **1** with **3a** in mixtures of water with ethanol (□), 1-propanol (○), and 2-methyl-2-propanol (△) as a function of the mole fraction of water.

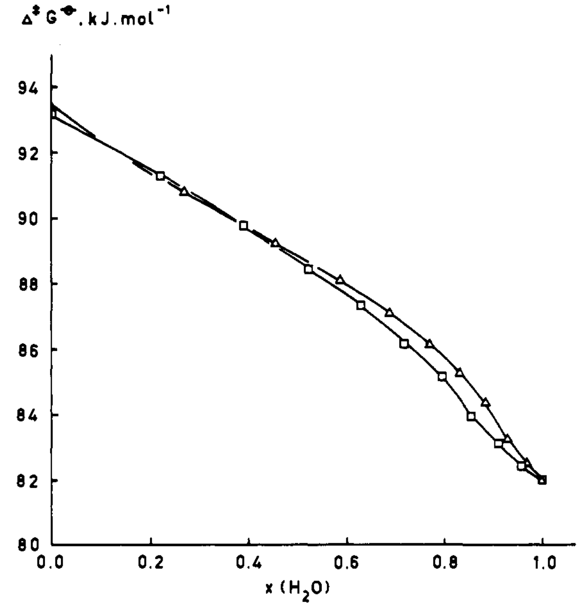

Figure 4. Free energy of activation (25 °C) for the intramolecular Diels-Alder reaction of compound **4** in mixtures of water with ethanol (□) and 1-propanol (△) as a function of the mole fraction of water.

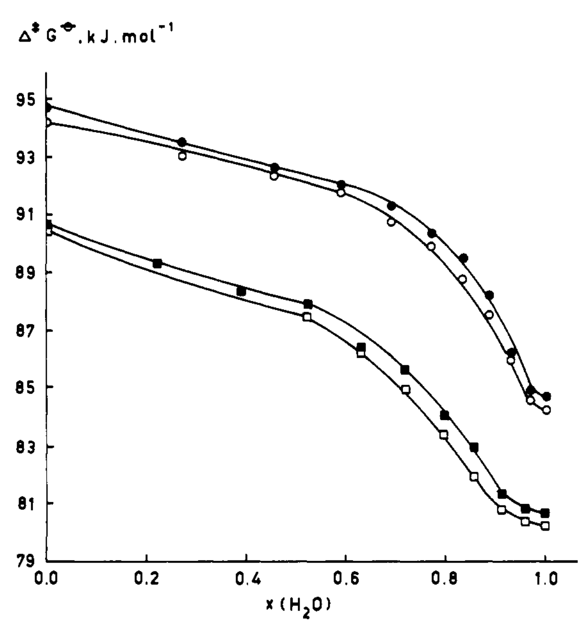

Figure 5. Free energy of activation (25 °C) for the Diels-Alder reactions of **1** with **2a** in mixtures of water with ethanol (□) and 1-propanol (○) and **1** with **2b** in mixtures of water with ethanol (■) and 1-propanol (●) as a function of the mole fraction of water. The $\Delta^{\ddagger}G^{\ominus}$ for 1-propanol-water mixtures has been displaced upwards by 4 kJ·mol^{-1} for clarity.

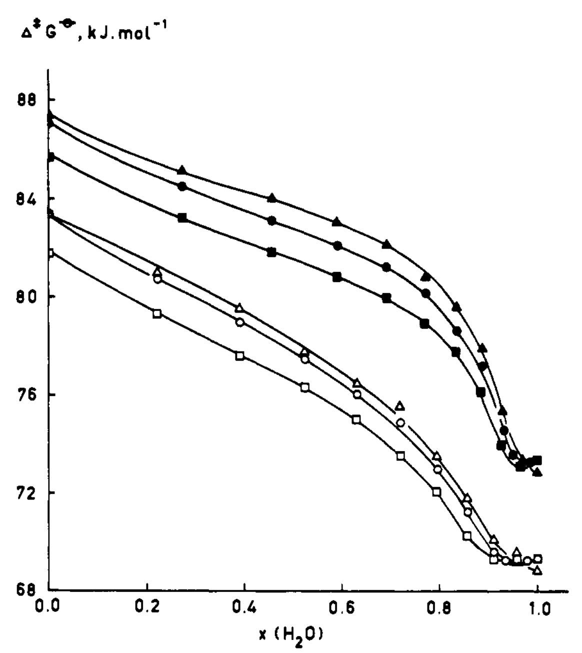

Figure 6. Free energy of activation (25 °C) for the Diels-Alder reactions of **1** with **3a** (circles), **3b** (squares), and **3c** (triangles) in mixtures of water and ethanol (unfilled symbols) and 1-propanol (filled symbols) as a function of the mole fraction of water. The $\Delta^{\ddagger}G^{\ominus}$ for 1-propanol-water mixtures has been displaced upwards by 4 kJ·mol^{-1} for clarity.

molecular complexation in various organic solvents, including water, correlates very well with the $E_T(30)$ value. However, the data point for water in Figure 1 deviates dramatically from the observed trend, which stresses the difference between molecular complexation of apolar molecules in cavities and a bimolecular cycloaddition reaction in water. In addition, the observation that the rate constant for reaction in water is larger than that for reaction in the more acidic trifluoroethanol precludes an explanation for the high reactivity in water in terms of hydrogen bonding to the carbonyl moiety of the dienophile.

Based on the experimental results, the changes of the rate constants of Diels-Alder reactions in binary mixtures of water and monohydric alcohols are characterized by two critical mole fractions of water, $x(H_2O)$, which separate three different ranges of solvent composition.

Alcohol-Rich Solutions. In these media the free energies of activation for the Diels-Alder reactions decrease gradually and almost linearly with the mole fraction of added water (Figures 2-6). The enthalpy and the entropy of activation of the cycloaddition of **1** with **3b** in 1-propanol-water mixtures also change gradually. The increase of the already highly unfavorable $\Delta^{\ddagger}S^{\ominus}$ is almost totally compensated by the decrease of $\Delta^{\ddagger}H^{\ominus}$ (Figure 8). Finally, the endo/exo product ratio for the Diels-Alder reaction of **1** with dienophiles **2a,b** changes smoothly in favor of the endo product at higher water concentrations (Figure 7).

Nonideal Alcohol-Water Mixtures. At critical mole fractions of water, which are about 0.6, 0.7, and 0.8 in mixtures of water with ethanol, 1-propanol, and 2-methyl-2-propanol, respectively, the $\Delta^{\ddagger}G^{\ominus}$ for all cycloadditions studied starts to decrease more

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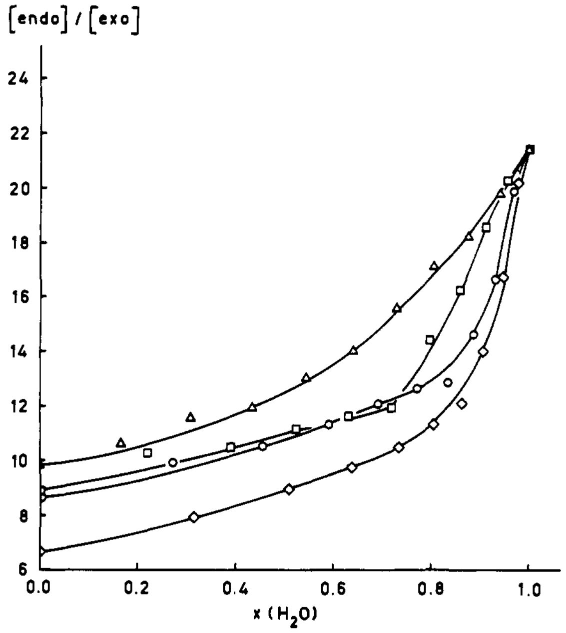

Figure 7. Endo/exo product ratio (25 °C) for the Diels–Alder reaction of **1** with **2a** in mixtures of water with methanol (△), ethanol (□), 1-propanol (○), and 2-methyl-2-propanol (◇) as a function of the mole fraction of water.

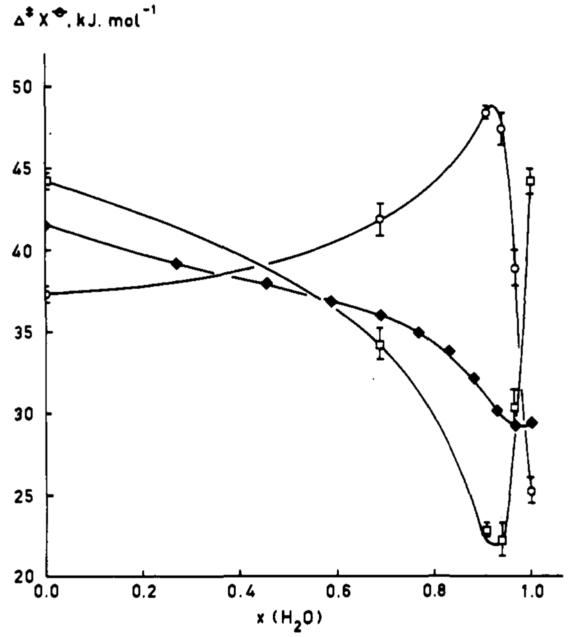

Figure 8. Activation parameters (25 °C) for the Diels–Alder reaction of **1** with **3b** as a function of the mole fraction of water in mixtures of water with 1-propanol: $\Delta^\ddagger G^\ominus$ (◆), $\Delta^\ddagger H^\ominus$ (□), and $-T\Delta^\ddagger S^\ominus$ (○). The values of $\Delta^\ddagger G^\ominus$ have been displaced downward by 40 kJ·mol⁻¹.

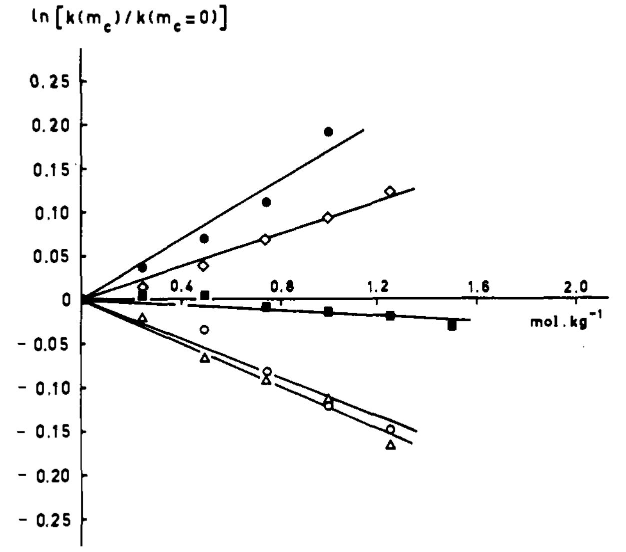

Figure 9. Plots of ln $[k(m_c)/k(m_c{=}0)]$ against the molality of urea (■), 2-methyl-2-propanol (○), D-glucose (●), glycerol (◇), and *p*-dioxane (△) for the Diels–Alder reaction of **1** with **2a** in highly aqueous solutions at 25 °C.

rapidly. It is also at these particular mole fractions that the endo/exo product ratio begins to change more dramatically. Figure 8 shows that the $\Delta^\ddagger H^\ominus$ as well as the $\Delta^\ddagger S^\ominus$ for the cycloaddition of **1** with **3b** in mixtures of water and 1-propanol start to change more dramatically at $x(H_2O) = 0.7$. $\Delta^\ddagger H^\ominus$ becomes extremely small whereas $\Delta^\ddagger S^\ominus$ changes to even more negative values.

Highly Aqueous Solutions. In highly aqueous reaction media, i.e., from about $x(H_2O) = 0.95$ to $x(H_2O) = 1.00$, the activation parameters for the Diels–Alder reactions again show a significantly different behavior. In this context we refer to a theoretical approach for the analysis of medium effects of chemically inert cosolvents on hydrolysis reactions in highly aqueous solutions that we have developed recently.[11] The observed rate effects are interpreted in terms of pairwise Gibbs function interaction parameters, describing the respective interactions of the cosolvent molecules with the initial state and the activated complex of the reaction. The rate constants were shown to be linearly correlated with the molality of the added cosolvent. Extending our analysis to a bimolecular process, the medium effect of cosolvents C on Diels–Alder reactions in highly aqueous media can be described in terms of pairwise Gibbs function interaction parameters *g*(P↔Q) describing the interaction between molecules P and Q (ac denotes the activated complex).[11b]

$$\ln [k(m_c)/k(m_c{=}0)] = 1/(RTm_0^2)\{g(\text{diene}\leftrightarrow\text{C}) + g(\text{dienophile}\leftrightarrow\text{C}) - g(\text{ac}\leftrightarrow\text{C})\}m_c$$

For an intramolecular cycloaddition a similar relation can be derived in which diene and dienophile are combined in one single molecule. In these equations, $k(m_c)$ and $k(m_c{=}0)$ are the second-order rate constants (kg·mol⁻¹·s⁻¹) in aqueous solution in the presence of m_c mol·kg⁻¹ of a cosolvent C and in pure water, respectively; m_0 is 1 mol·kg⁻¹ and represents a necessary scale conversion factor.

In Figure 9 ln $[k(m_c)/k(m_c{=}0)]$ is plotted as a function of the molality of a series of cosolvents for the reaction of diene **1** with dienophile **2a**. The results show that in the water-rich media the free energy of activation for the Diels–Alder process is only moderately affected by the addition of cosolvent. Thus, the sum of the free energies associated with the pairwise interactions of the cosolvent with the diene and the dienophile almost equals the pairwise interaction of the cosolvent with the activated complex. The same situation applies for all the Diels–Alder reactions examined in the present study. Rate constants for, e.g., the reactions of **1** with dienophiles **3a** and **3b** are even increased by the addition of a few mole percent of an apolar cosolvent. This rate increase is particularly noticeable when the cosolvent is 2-methyl-2-propanol (Figure 3).

In contrast to $\Delta^\ddagger G^\ominus$, $\Delta^\ddagger H^\ominus$ and $\Delta^\ddagger S^\ominus$ are dramatically affected by the addition of relatively small amounts of 1-propanol to water (Figure 8). The effects are, however, almost completely compensating, with a sharply decreasing value of the $\Delta^\ddagger H^\ominus$ and a similar increase of the already unfavorable $\Delta^\ddagger S^\ominus$. Interestingly, in pure water the rate-accelerating effect (12 kJ·mol⁻¹ relative to 1-propanol) is almost entirely entropic in origin, whereas in the presence of ca. 10 mol % of 1-propanol the rate-accelerating effect is nearly the same but is now due entirely to enthalpic contributions ($\delta\Delta^\ddagger H^\ominus$; 22 kJ·mol⁻¹) which overcome an unfavorable entropy contribution ($\delta T\Delta^\ddagger S^\ominus$; 10 kJ·mol⁻¹).

A Pairwise Interaction Model. A bimolecular reaction necessarily involves the formation of a direct, solvent-unseparated complex of both reactants during the activation process. If two relatively apolar reactants are involved in this process, and the medium is highly aqueous, we might speak of an "enforced pairwise hydrophobic interaction". The term "enforced" is introduced here, in order to distinguish this associative process from hydrophobic interactions between the reactants that do not lead to the activated complex; hydrophobic interactions can lead to solvent-separated complexes, and moreover, the geometry of the complexes formed might not lead to further reaction. In order to account for the large effect of water on the Diels–Alder reactions, the enforced solvophobic binding process needs to be more favorable in water than in conventional organic solvents.

In general, the Gibbs energy associated with enforced solvophobic interaction will be given by[16]

$$\Delta G(R) = U_{DD}(R) + \delta G^{Sl}(R)$$

The first term represents the direct diene–dienophile pair potential, which is the work required in the process of bringing diene and dienophile from an infinite separation to a distance R in vacuum. The second term takes account of the solvent effect on the same associative process. The diene as well as the dienophile are quite polarizable molecules and will strongly interact in a solvent-unseparated complex. Now, Diels–Alder reactions are characterized by a large, negative volume of activation.[17] The distance between the diene and the dienophile in the activated complex will be significantly smaller than R, and in highly aqueous media, the "enforced pairwise hydrophobic interaction" will be accompanied by an additional decrease of the molecular volume that has to be hydrated.

During the activation process of the Diels–Alder reaction, solute–solvent interactions are replaced by solute–solute interactions and the solvent molecules will rearrange themselves around the activated complex and in the bulk. Water has an extremely low molecular polarizability. As a consequence, London dispersion interactions between the reactants and the solvent molecules will be enthalpically much more favorable in conventional organic solvents than in water. Due to this contribution, the $\Delta^{*}H^{\ominus}$ for the Diels–Alder reaction in water will be markedly smaller.

The rearrangement of water molecules accompanying the enforced hydrophobic interaction must be discussed in terms of the process of hydrophobic hydration.[16] In conventional organic solvents, solvation of an apolar solute will be accompanied by small entropy and enthalpy changes. Recent theoretical approaches to the phenomenon of hydrophobic hydration have established that the formation of a cavity in water to accommodate an apolar solute molecule is entropically as well as enthalpically highly unfavorable.[18] This is mainly the result of the extremely small molecular volume of the water molecules and the strongly hydrogen-bonded solvent structure. The formation of a hydrophobic hydration shell, however, appears to be an enthalpically favorable process, in which the enthalpy needed for the creation of the cavity is more than compensated by the formation of a structured hydration shell. However, in this process the entropy of the water molecules is reduced even more, leading to an overall unfavorable Gibbs energy.

We submit that the reduction of the hydrophobic surface and hydrated volume during the activation process of the Diels–Alder reaction leads to a large gain of entropy as well as a large loss of enthalpy of the water molecules. Consequently, the differences in the isobaric activation parameters for the Diels–Alder reactions in water and in 1-propanol (Table I) will be a result of an entropy-dominated cavity contribution and an enthalpy-dominated polarizability contribution. The data in Table I reveal that the reduction of the free energy of activation is indeed caused by both a favorable enthalpy contribution and a larger, favorable entropy contribution.

Hydrophobic packing between diene and dienophile, which is often suggested to be the major cause for the rate accelerations of Diels–Alder reactions in water,[2] is difficult to reconcile with the large rate acceleration observed for the intramolecular cycloaddition of **4** in water, which is of the same magnitude as those found for the intermolecular Diels–Alder reactions. Instead, we submit that intramolecular Diels–Alder reactions are also accompanied by a significant decrease of the molecular volume and a concomitant decrease of the solvent-accessible surface during the activation process.[17,19,20] Accordingly, enforced hydrophobic interactions provide a likely explanation for the rate enhancement. In the case of a moderately polar character of the activated complex,[1] the stabilizing effect due to addition of 1-propanol to water will be reduced. This may provide a further consideration in explaining the rate enhancement in water.

The Diels–Alder reactions of **1** with the dienophiles **3a–c** exhibit a more pronounced rate effect in water than the corresponding cycloadditions of the alkyl vinyl ketones. This is largely a result of a more favorable entropy contribution, due to the larger reduction of the apolar molecular surface area during the activation process. The substituent effects on the rate enhancements for both types of Diels–Alder processes in aqueous media appear to be moderate but significant. The reduction of the hydrophobic surface during the activation process for the cycloaddition of alkyl vinyl ketones with cyclopentadiene is only slightly affected by the change in substituent. However, the substituent effects on the Diels–Alder reactions of the 5-substituted-1,4-naphthoquinone with diene **1** are more pronounced, and the rate enhancement increases with increasing hydrophobicity of the substituent.

The preference for the endo product in highly aqueous media can be easily rationalized. The activated complex leading to the endo product is significantly more compact than that for the exo product, which, in water, leads to a favorable entropy contribution during the activation process.

The addition of apolar cosolvents to water gives rise to a number of additional interactions. First of all, in highly aqueous solutions, water becomes even more structured by the formation of hydrophobic hydration shells surrounding the apolar cosolvent molecules. As a result, hydrophobic interactions will become entropically slightly more favorable. In addition, pairwise interactions with the cosolvent will stabilize the initial state more than the activated complex. These pairwise hydrophobic interactions result in the well-known $\Delta^{*}H^{\ominus}/\Delta^{*}S^{\ominus}$ compensation behavior involving a dominant entropy contribution.[21] However, the small but favorable cavity term may even overcompensate the unfavorable pairwise interaction term, and the reactions can be even accelerated by addition of structure-promoting cosolvents (Figure 3).

At a critical concentration of apolar cosolvent molecules, the critical hydrophobic interaction concentration (chic[22]), bulk hydrophobic interactions become important, leading to the formation of highly dynamic clusters of apolar cosolvent molecules. At these mole fractions large concentration fluctuations start to occur,[23] with water gradually losing its typically aqueous character. The diene and the dienophile will become more and more preferentially solvated by the apolar cosolvents, and the driving force for the dramatic rate effect in water will be lost. Finally, beyond the mole fraction of cosolvent where the concentration fluctuations are at their maximum, the binary mixtures start to behave like a conventional organic solvent, leading to smooth changes in rate and activation parameters upon variation of the solvent composition.

Conclusion

The often dramatic rate accelerations for intermolecular as well as intramolecular Diels–Alder reactions in water and in highly aqueous binary solvent mixtures can be explained in terms of

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"enforced hydrophobic interactions". The term "enforced" is used to distinguish the hydrophobic bonding of the diene and the dienophile during the activation process for the cycloaddition from hydrophobic interactions that lead to complexes of different geometry and complexes in which the components may be separated by water molecules. It is anticipated that organic reactions of neutral substrates that are accompanied by a significant reduction of the molecular volume, as well as a reduction of the solvent-accessible surface area during the activation process, will be considerably accelerated in aqueous reaction media. Changes in the hydrophobicities of the reactants will induce only moderate rate effects. The rate enhancements found for intermolecular as well as intramolecular Diels–Alder reactions reflect the unique solvent properties of water.

Experimental Section

Materials. 1,4-Naphthoquinone (**3a**) and 5-hydroxy-1,4-naphthoquinone (**3b**) were commercially available (Aldrich) and were recrystallized from methanol. 5-Methoxy-1,4-naphthoquinone (**3c**) was prepared from **3b**, as reported in the literature,[24] and recrystallized from methanol; mp 185–186 °C (lit.[24] mp 187 °C). Methyl vinyl ketone (**2a**) and ethyl vinyl ketone (**2b**) (Janssen) were freshly distilled before use. Cyclopentadiene (**1**) was prepared from its dimer immediately before use.

Demineralized water was distilled twice in an all-quartz distillation unit. All cosolvents were of the highest purity available.

***N*-Furfuryl-*N*-methylmaleamic acid (4)** was synthesized as described previously.[25] However, after hydrogenation and extraction of the acidified reaction mixtures with ether, the aqueous layer was made basic with 40% NaOH and extracted with chloroform instead of ether, leading to a greatly improved yield (81%) of pure *N*-furfuryl-*N*-methylamine. Finely powdered maleic anhydride (60 mg, 0.60 mmol) was dissolved in freshly distilled *N*-furfuryl-*N*-methylamine (120 mg, 1.08 mmol) on a ceramic plate. The solution deposited compound **4** upon standing, and the solid was repeatedly washed with ether. Compound **4** cannot be isolated in analytically pure form and will undergo intramolecular cyclization even in the solid state (see also ref 20).

Kinetic Measurements. Pseudo-first-order rate constants were determined by following the change in absorbance at appropriate wavelengths in a quartz UV cell (1 cm) that was placed in a thermostated cell compartment of a Perkin-Elmer λ2 spectrophotometer, equipped with a standard personal computer. For reactions of cyclopentadiene, the UV cuvettes were carefully sealed in cases where the half-lives were longer than 10 min in order to prevent evaporation of cyclopentadiene. Evaporation of cyclopentadiene may otherwise seriously hamper the kinetic measurements and can lead to dramatic errors in the determined rate constants, especially in highly aqueous reaction media.

Reactions of cyclopentadiene with dienophiles **2a** and **2b** were followed by monitoring the decrease of absorbance of cyclopentadiene at 250–255 nm (dependent on the reaction mixture in which the reaction was followed), using an excess of the alkyl vinyl ketone. About 5–8 μL of a concentrated stock solution of cyclopentadiene in 1-propanol was added to the reaction medium (3 cm^3) that contained a known concentration of alkyl vinyl ketone. Typical concentrations used for determination of the rate constants are 1×10^{-4} M of cyclopentadiene and 3.5×10^{-2} M of alkyl vinyl ketone.

Reactions of dienophiles **3a–c** with cyclopentadiene were followed by monitoring the decrease of absorbance of the 5-substituted-1,4-naphthoquinones at, respectively, 333, 426, and 400 nm, with an excess of cyclopentadiene. Especially in highly aqueous media it was appropriate to add cyclopentadiene in a very concentrated stock solution just before the measurement, followed by addition of 5–8 μL of a stock solution of the dienophile. After addition of the two reactants, the solution was stirred briefly with an external microstirrer. Typical concentrations used in the kinetic runs are 6–8 $\times 10^{-3}$ M cyclopentadiene and 5×10^{-5} M 5-substituted-1,4-naphthoquinone.

The intramolecular cycloaddition of **4** was followed by determining the decrease of absorbance at 225 nm. Finely powdered maleic anhydride (20 mg, 0.20 mmol) was dissolved in freshly distilled *N*-furfuryl-*N*-methylamine (40 mg, 0.36 mmol) on a ceramic plate. The solution deposited compound **4** upon standing, and the solid was carefully and repeatedly washed by ether. The compound was immediately dissolved in 1-propanol. The first-order Diels–Alder reaction is followed after injection of 8–10 μL of this stock solution into the reaction medium that contained about 5×10^{-2} M HCl. The stock solution must be freshly prepared before each measurement.

All reactions were followed for at least 5 half-lives and were perfectly first-order. A total of 200–600 data points were collected and pseudo-first-order rate constant were calculated by a fitting program. Rate constants were reproducible to within 1%, except for those Diels–Alder reactions of cyclopentadiene with compounds **3a–c** in highly aqueous reaction media, which were reproducible to within 3%. Isobaric activation parameters were calculated with the Eyring equation, for kinetic data obtained at at least six different temperatures. In highly aqueous media, eight to ten temperatures were used. To prevent evaporation of cyclopentadiene, rate constants were measured in the temperature range 10–35 °C. Plots of ln (k/T) against $1/T$ were perfectly linear, and $\Delta^{\ddagger}H^{\ominus}$ was calculated by least-squares regression.

Product Analysis. To obtain endo/exo ratios, the reaction mixtures, after the reactions were allowed to go to completion, were analyzed by gas chromatography (Hewlett-Packard 5890 instrument, equipped with a 15 m wide bore HP1 fused silica column). Retention times of endo and exo products were significantly different, and the relative peak areas allow for determination of the endo/exo ratio. Products of all reactions were analyzed by NMR. No side reactions were observed.

Acknowledgment. We thank the Research Board (University of Leicester) for a travel grant to M.J.B.

Supplementary Material Available: Tables of second-order rate constants (at 25 °C) for all Diels–Alder reactions reported in this paper (4 pages). Ordering information is given on any current masthead page.

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