Diels–Alder Reactions in Water. Effects of Hydrophobicity and Hydrogen Bonding

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In order to check whether the activated complex for the Diels–Alder reactions of 5-substituted 1,4-naphthoquinones **1a–e** with cyclopentadiene (**2**) is more polar in water than in other solvents, we have determined the substituent effects in seven different solvents. The substituent effects gradually decrease with increasing rate of the reaction in a specific solvent, indicating that the charge separation in the activated complex in water is not much different from that in the other solvents. We also compared solvent effects on the Diels–Alder reaction of methyl vinyl ketone (**3**) with cyclopentadiene with effects on the corresponding reaction of methyl vinyl sulfone (**4**). The medium effects were separated into effects on initial state and activated complex. The destabilization of the initial state by water and the stabilization of the activated complex by 2,2,2-trifluoroethanol were less pronounced for the sulfone than for the ketone. These results further underline the importance of enforced hydrophobic interactions and changes in hydrogen bonding during the activation process in explaining the acceleration of Diels–Alder reactions in water.

Introduction

Recently there has been much discussion about the mechanism of the Diels–Alder (DA) reaction.[1] Although reactions proceeding through zwitterionic[2] and biradical[3] intermediates are known, it is now generally accepted that DA reactions are normally (nearly) synchronous and concerted processes.[4] The reactions are characterized by modest solvent effects,[1a,5] indicating small changes in charge on going from the reactants to the activated complex. Breslow's observation that DA reactions can show huge accelerations in water[6] was therefore surprising, intriguing, and even synthetically promising.[7] It soon became clear that the DA reaction was not the only process showing a large and unexpected rate enhancement on going from organic solvents to water; also accelerations of, inter alia, the Claisen rearrangement,[8] the aldol condensation,[9] and the benzoin condensation[10] in water have been reported (for a recent review see ref

7i). Most of these bimolecular reactions involve hydrophobic reaction partners and are characterized by negative volumes of activation.

In the case of the DA reaction, different explanations have been proposed for the rate enhancement in water. The first suggestion was hydrophobic packing of diene and dienophile,[10b,11] but since intramolecular DA reactions (in which the reactants are already "packed") are also considerably faster in water than in organic solvents,[12] aggregation phenomena,[7a,b] as far as they occur at all, cannot be held responsible for the observed effects. Most significantly, vapor pressure measurements on the reaction partners have indicated that no aggregation takes place at the concentrations of diene and dienophile used in most kinetic experiments.[13] Furthermore it was shown that micellar catalysis leads to a rate retardation compared to the reaction in pure water.[6b,13,14] Several authors[9,15] tried to explain the rate enhancement in terms of the solvent's internal pressure $(p_i = (\partial E/\partial V)_T)$,[16] which was proposed to influence the rate in the same way external pressure does.[17] However, the internal pressure of water is very low[5b] and consequently cannot explain

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the effect of water. On the other hand, the cohesive energy density of the solvent[18] (ced $= (\Delta H_{vap} - RT)/V_M)^{16}$ has been succesfully used by Gajewski,[18b] describing the solvophobicity in a multiparameter equation. It was also shown that solvent polarity has a marked influence on the rate of some Diels–Alder reactions. But since correlations with solvent polarity parameters over a broad span of solvents are usually poor,[19] polarity alone cannot explain the acceleration in water. It was noted that hydrogen bonding can play an important role,[20,21] probably in the same way as Lewis acid catalysis does.[22] This has been stressed by Desimoni et al.[23] who found a hyperbolic relationship between the rates of DA reactions and the acceptor number (AN)[24] of the solvent. As pointed out before,[12,25] solvophobic interactions[26] appear to play an important role. Correlations of DA reaction rates and selectivities with the Sp parameter[27] have been reported,[19a,b] but are not normally observed within a broad series of solvents.[19d,28]

In this paper we make an endeavor to provide further insight into the factors responsible for the acceleration of the DA reaction in water. In our previous studies[12,25] it has been concluded that the acceleration of DA reactions in water is mainly a result of a combination of enforced hydrophobic interactions and hydrogen bonding. The term "enforced" is used to distinguish the hydrophobic bonding of the reactants during the activation process from hydrophobic interactions not dictated by the activation process, which may lead to complexes of different geometry. Interestingly, the activated complex of the DA reaction was shown to be remarkably solvent-adaptable.[25] Therefore it seemed likely that the activated complex in water might have a more polar character than in other solvents. In order to check this possibility we studied the substituent effects on the reaction between naphthoquinone, substituted at the 5-position (**1a–e**), and cyclopentadiene (**2**) (Chart 1) in seven different solvents. In

Chart 1

1a R=NO₂
b R=COCH₃
c R=H
d R=CH₃
e R=OCH₃

3 X=CO
4 X=SO₂
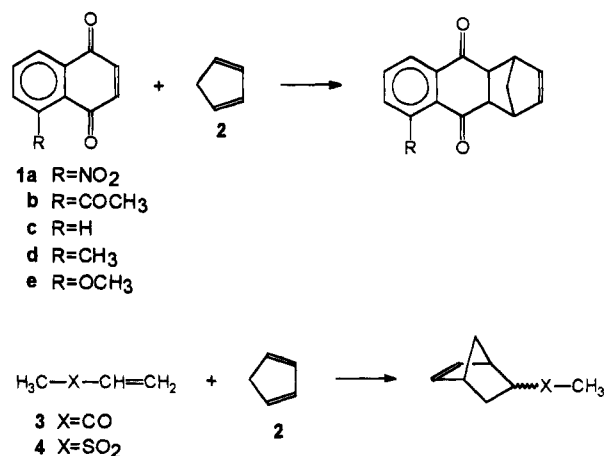
order to assess the influence of hydrogen bonding we also compared the DA reaction of **2** and methyl vinyl ketone (**3**) with the reaction of the corresponding sulfone (**4**). The second-order rate constants were determined in six solvents. For these reactions the Gibbs energies of transfer of the reagents from acetonitrile to several other solvents, including water, were determined in order to separate medium effects on the initial state and the activated complex.

Results and Discussion

A Polar Activated Complex? As reported previously,[12,25] the DA reactions between 5-substituted-1,4-naphthoquinones and **2** show a large acceleration in water relative to organic solvents. We chose this system for an analysis of the substituent effects on the reaction in water, in comparison with those in a series of organic solvents. The range of solvents was chosen as broad as possible (from *n*-hexane to water), including two fluorinated alcohols, 1,1,1-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), since these solvents are strong hydrogen-bond donors. If the observed substituent effects would be markedly larger in water than in the other solvents, this would be consistent with a significantly larger buildup of charge in the activated complex in water. If, on the other hand, the differences in charge buildup in the different solvents are relatively small, one expects the reaction in polar protic solvents like water to be less sensitive to substituent effects than in more weakly interacting solvents like *n*-hexane.

Figure 1 shows the Hammett plots for the reaction of **1a–e** with **2** in *n*-hexane, HFP, and water. A linear Hammett plot was only obtained for the reaction in *n*-hexane ($\varrho = 1.6$; $r = 0.997$). For the other solvents acetonitrile gave the best fit ($\varrho = 1.3$; $r = 0.977$). Taking into account that the substituents are three bonds away from the reacting double bond, the ϱ-values are rather large for a DA reaction,[1a] thus providing evidence for a rather polar activated complex. Hammett correlations in the protic solvents (particularly water and HFP) are strongly nonlinear. Particularly the methoxy substituent effect showed unexpected solvent-dependent behavior. Being an electron-donating group, it slows down the reaction in *n*-hexane. But in water and HFP, **1e** reacts faster than the parent **1c**. This might reflect a solvent-mediated interaction between the substituent and the nearby carbonyl group (see Figure 2), rendering the latter with a greater electron-withdrawing ability.

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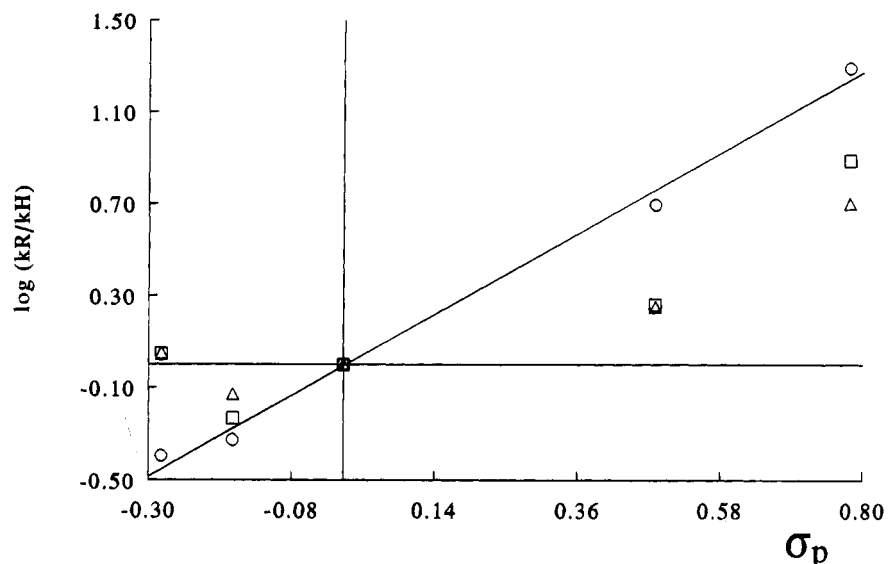
Figure 1. Hammett plot for the DA reaction of **1a–e** with **2** in *n*-hexane (○), water (△), and HFP (□).
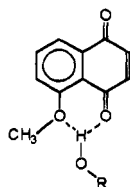

Figure 2. Solvent-mediated interaction between the methoxy substituent and the nearby carbonyl group of **1e**.

Table 1. Rate Constants for the DA Reaction of 1a and 1c with 2 in Different Solvents at 25 °C

	k_2 (M^{-1} s^{-1})		
solvent	**1a**	**1c**	$k_2(1a)/k_2(1c)$
n-hexane	2.12×10^{-2}	1.08×10^{-3}	19.6
acetonitrile	9.22×10^{-2}	6.28×10^{-3}	14.7
ethanol	0.158	1.48×10^{-2}	10.7
1-propanol	0.225	1.96×10^{-2}	11.5
TFE	3.52	0.438	8.04
HFP	13.1	1.69	7.75
water	25.0	4.95	5.05

Table 1 shows the acceleration of the reaction of **1a** with **2** relative to that of the parent compound in a range of solvents. Clearly the effect of the nitro substituent decreases gradually with increasing rate of the reaction in the specific solvent. We contend that the charge separation in the activated complex in water is not much, if at all, different from that in the other solvents.

The importance of Hydrogen Bonding—Gibbs Energies of Activation. In the second part of our study, we made an attempt to asses the importance of hydrogen bonding in the activation process of the aqueous DA reaction. A strong indication that hydrogen bonding could be an important factor comes from Figure 3, showing the dependence of the rate of the DA reaction between **1a** and **2** on the $E_T(30)$ value of the solvent.[5b] It appears that two lines can be drawn, one for the protic solvents and one for the aprotic ones. Although the regression coefficients are noticeably poor ($r_{protic} = 0.919$; $r_{aprotic} = 0.737$), the greater slope of the former suggests that the DA reaction is more sensitive to hydrogen
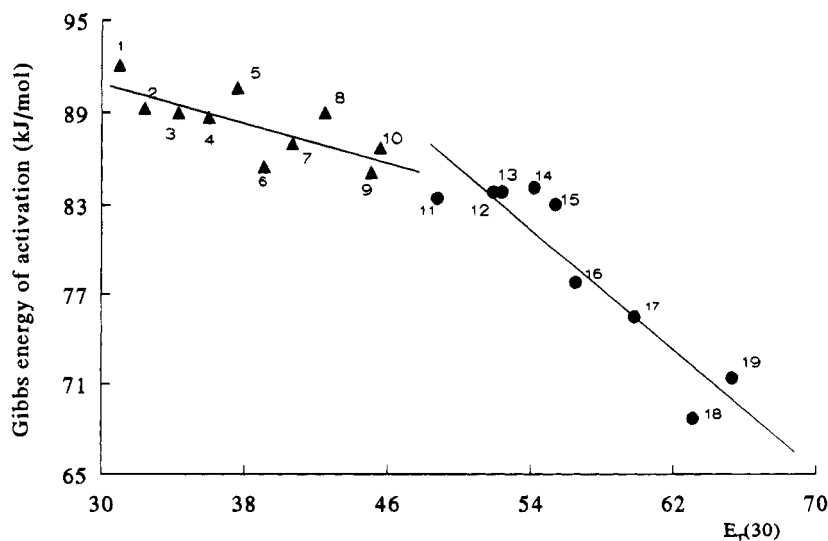

Figure 3. Gibbs energy of activation for the DA reaction of **1e** with **2** in (1) *n*-hexane, (2) carbon tetrachloride, (3) benzene, (4) 1,4-dioxane, (5) THF, (6) chloroform, (7) dichloromethane, (8) acetone, (9) DMSO, (10) acetonitrile, (11) 2-propanol, (12) ethanol, (13) *N*-methylacetamide, (14) *N*-methylformamide, (15) methanol, (16) glycol, (17) TFE, (18) water, and (19) HFP as a function of the $E_T(30)$ value of the aprotic (▲) and protic (●) solvents.

Table 2. ^{13}C **Chemical Shifts (ppm) of 3 and 4 in CDCl$_3$ and D$_2$O at 30 °C**

	CH$_2$	CH	CH$_3$
3			
CDCl$_3$	128.70	137.18	26.07
D$_2$O	132.43	136.64	25.78
Δδ	*3.73*	*−0.54*	*−0.29*
4			
CDCl$_3$	129.20	137.32	42.05
D$_2$O	130.91	136.19	41.51
Δδ	*1.71*	*−1.13*	*−0.54*

Table 3. Rate Constants and Gibbs Energies of Activation for the DA Reactions of 3 and 4 with 2 in Different Solvents at 25 °C

	second-order rate constant (M^{-1} s^{-1})		Gibbs energy of activation (kJ/mol)	
solvent	**3**	**4**	**3**	**4**
water	5.08×10^{-2}	6.29×10^{-4}	80.3	91.2
HFP	1.75×10^{-2}	2.00×10^{-4}	83.0	94.0
TFE	8.72×10^{-3}	9.50×10^{-5}	84.7	95.9
1-propanol	9.12×10^{-4}	3.04×10^{-5}	90.3	98.7
ethanol	8.39×10^{-4}	2.20×10^{-5}	90.5	99.5
acetonitrile	1.75×10^{-4}	8.85×10^{-6}	94.4	101.7

Table 4. Gibbs Energies of Transfer (kJ/mol) for 2, 3, and 4 from Acetonitrile to Other Solvents at 25 °C

solvent	**2**	**3**	**4**
acetonitrile	0	0	0
1-propanol	0.65	4.44	5.93
TFE	2.00	−5.33	−1.23
water	9.58	6.54	2.78

bonding than the $E_T(30)$ probe (which is a zwitterion). Recent computer simulations by Jorgensen et al.[21] also stress the importance of hydrogen bonding in the activation process of the DA reaction.

In order to quantify the role of hydrogen bonding, we compared the DA reaction of **2** with two structurally related dienophiles: methyl vinyl ketone (**3**) and methyl vinyl sulfone (**4**). From IR studies of the pairwise interaction using phenol as a hydrogen-bond donor in carbon tetrachloride, it is known that sulfones are weaker hydrogen-bond acceptors than ketones.[29] Furthermore the sulfonyl group is less capable of stabilizing an adjacent negative charge by resonance than a carbonyl group.[30] This is consistent with the ^{13}C chemical shift data shown in Table 2. The methylene carbon atom of **3** shows a large deshielding upon changing the solvent from CDCl$_3$ to D$_2$O. The corresponding effect is much smaller for **4**. These results suggest that (a) **4** is a weaker H-bond acceptor than **3** and (b) **4** is less efficient than **3** in transferring the electronic effect of a hydrogen bond to the rest of the molecule.

From the above results we anticipated that the acceleration of the DA reaction on going from acetonitrile to water would be smaller for **4** than for **3**. This was indeed borne out in practice. The acceleration for **4** is four times smaller than that for **3** (Table 3). However, a more detailed consideration of the data in Table 3, in particular the Gibbs energy of activation for the reaction in TFE and HFP relative to that in water, shows that the situation is more complicated. The relatively fast reactions in the fluorinated alcohols can probably almost totally be ascribed to their strong H-bond donating capacities, whereas the reaction in water also benefits from enforced hydrophobic interactions. Therefore it could be anticipated that the difference between the Gibbs energy of activation in water and that in TFE and
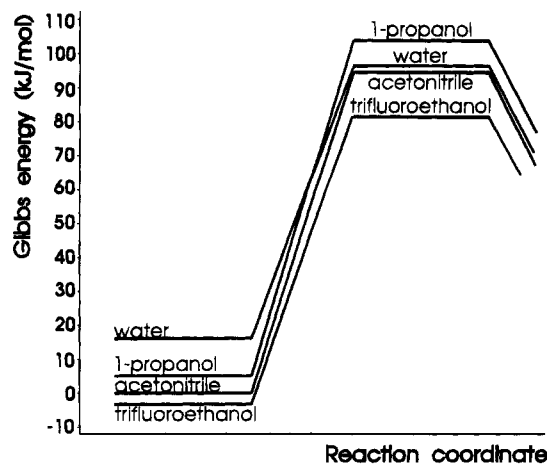
Figure 4. Relative positions of the Gibbs energies of the initial state and the activated complex of the DA reaction between **3** and **2** in water, 1-propanol, acetonitrile, and TFE.
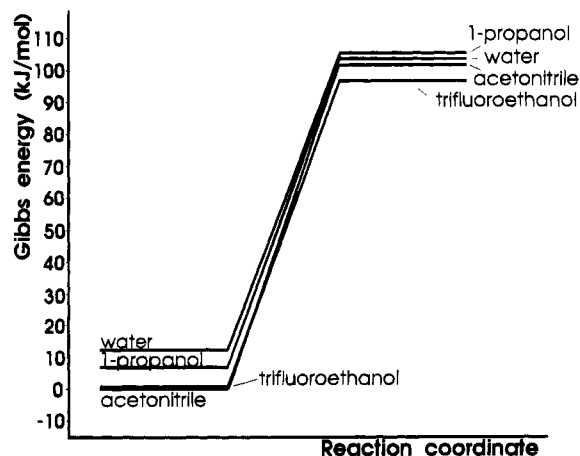
Figure 5. The relative positions of the Gibbs energies of the initial state and the activated complex of the DA reaction between **4** and **2** in water, 1-propanol, acetonitrile, and TFE.

HFP should be larger for the DA reaction of the sulfone than for the reaction of the ketone. The data in Table 3 show that this is not the case. The increase in Gibbs energy of activation upon going from water to TFE or HFP is almost equal for **3** and **4**.

The Importance of Hydrogen Bonding—Gibbs Energies of Transfer. At this stage we note that Gibbs energies of activation alone do not provide enough information to rationalize the above kinetic medium effects, since they only quantify the differences between the Gibbs energies of the initial state and the activated complex in each solvent and not their relative positions. It would be more informative to have access to the differences in the Gibbs energies for the initial state and the activated complex separately in the different solvents. Therefore, we determined the Gibbs energies of transfer of the initial state, $\Delta G_t(IS)$, from acetonitrile to three other solvents (water, TFE, and 1-propanol) from vapor pressure measurements. The results are shown in Table 4. Combining these data with the Gibbs energies of activation (Table 3) provides the relative Gibbs energies of the activated complex. Figures 4 and 5 show the differences in Gibbs energies of the initial state and the activated complex in different solvents. At first sight the acceleration of the DA reactions in water seems to be caused largely by a hydrophobic destabilization of the

initial state. However, the fact that the activated complex is not also significantly destabilized by water suggests a stabilizing interaction between water and the activated complex. This is probably due to a hydrogen-bonding effect. Evidence comes from the large stabilization of the activated complex observed in TFE in the case of the carbonyl dienophile. The fact that hydrogen bonding stabilizes the activated complex more than the initial state means that the functional group that accepts the hydrogen bonds is more polarized in the activated complex than in the initial state. The same conclusions have been reached in recent computer simulations by Jorgensen et al.[21]

The data in Table 4 indicate that, in comparison with **3**, **4** is more destabilized in 1-propanol and less stabilized in TFE. This is what one would expect on the basis of the rather poor H-bonding acceptor capacity of the sulfonyl group. However, in water, **4** is less destabilized than **3** and, therefore, **4** is less hydrophobic than **3**. This rather unexpected result might find its origin in the greater overall polarity of the sulfonyl compound, possessing two polarized S=O bonds. Futhermore a sulfonyl moiety allows the formation of four hydrogen bonds to the small water molecules, whereas a carbonyl group accepts only two hydrogen bonds.

We propose that the low Gibbs energies of activation for the DA reaction of **4** in TFE and HFP relative to water (Table 3) are a consequence of the diminished hydrophobic acceleration of the reaction of **4** in water.

Conclusions

The acceleration of the DA reaction between cyclopentadiene (**2**) and 5-substituted-1,4-naphthoquinones **1a**−**e** or methyl vinyl ketone (**3**) can be explained in terms of hydrophobic destabilization of the initial state accompanied by a stabilization of the activated complex by hydrogen bonding to the activating group of the dienophile. Substituent effects on the reaction of **2** with **1a**−**e** in water and in six organic solvents cannot be reconciled with an enhanced charge separation in the activated complex in aqueous solution. For the DA reaction between **2** and methyl vinyl sulfone (**4**), the acceleration in water is less pronounced than that with **3** as the dienophile. This is consistent with **4** being less hydrophobic than **3** and with Gibbs energies of transfer of **3** and **4** from acetonitrile to water.

Experimental Section

Materials. 5-Nitro-,[31] 5-acetyl-,[32] 5-methyl-,[33] and 5-methoxy-1,4-naphthoquinone[34] were synthesized as reported in the literature. 1,4-Naphthoquinone was obtained from Aldrich and recrystallized form methanol. Methyl vinyl ketone (Janssen) was distilled immediately before use. Methyl vinyl sulfone was purchased from Aldrich. Cyclopentadiene was prepared from its dimer (Merck−Schuchardt) immediately

before use. Demineralized water was distilled twice in a quartz distillation unit. All solvents used were of the highest purity available.

Kinetic Measurements. Second-order rate constants of the reaction of **2** with the **1a**−**e** and with **3** were determined by UV spectroscopic techniques following procedures described earlier.[12] All rate constants were measured at least three times and were reproducible to within 3%.

The second-order rate constants for the reaction of **2** with **4** were determined with GC by following the decrease in the concentration of **2** in the vapor phase above a solution containing a small concentration of **2** and an excess of **4**. At low concentrations the partial pressure of **2** is linearly related to the concentration of **2** in the solution. Injecting a constant volume of vapor makes usage of an internal standard superfluous and, in combination with the fact that the vapor pressure of **2** is very high, leads to more accurate results than when a small volume of liquid is injected. The method has been succesfully tested for the reaction of **2** with **3**, for which rate constants determined by the UV spectrophotometric method are available. The reactions were carried out in 5-mL round-bottomed flasks containing 3 mL of a solution of **4** (concentrations ranging from 1.6 M in acetonitrile to 0.4 M in water) and **2** (concentration never larger than 0.005 M). The flasks were sealed with a rubber septum cap and placed in a thermostated waterbath at 25 (±0.1) °C. To prevent condensation on the inside of the septum cap, which has a dramatic effect on the reproducibility, the parts of the flasks above the water surface were insulated using foam rubber. For each reaction a constant volume (either 100 or 250 μL) of vapor was withdrawn from the flasks about 25 times over a timespan of 4 half-lives using a gas-syringe. The samples were analyzed by chromatography using a Hewlet-Packard 5890A gas chromatograph with a HP1 cross-linked methyl silicone gum column (15 m × 0.53 mm × 2.65 μm film thickness). The column temperature was 25 °C, and the injector and the detector (f.i.d.) were kept at 55 °C and 250 °C, respectively. The peak areas of **2** were determined by integration. Pseudo-first-order rate constants were calculated using a fitting program. Every rate constant was determined at least two times. Measurements were reproducible within 4%.

^{13}C-NMR Measurements. The ^{13}C chemical shifts (relative to TMS) of **3** and **4** in D_2O and $CDCl_3$ were measured on a Varian VXR 300 NMR spectrometer at 30 °C. The concentration of **3** and **4** was 0.67 M in each sample.

Gibbs Energies of Transfer. The Gibbs energy of transfer of a solute from one solvent to another can be determined by measuring the vapor pressures of the solute for the different solvents and using the equation:

$$\Delta G_t(1\rightarrow2) = -RT \ln[m(1)p(2)/m(2)p(1)]$$

where m(1) is the molarity of the solute in solvent 1 and p(1) is the vapor pressure of the solute in that (ideal) solution.[13,14] The vapor pressures can be obtained from GC peak areas, using the same apparatus and following the same procedures as described above for the kinetics of the reaction of **4** with **2**. For **3** the injector temperature had to be raised to 85 °C. For **4** a suitable retention time was obtained with an injection temperature of 270 °C and a column temperature of 95 °C. For each solute in each solvent the vapor pressures were determined for at least four different concentrations. For each concentration the vapor above the solution was chromatographed at least three times. Especially in the case of **4**, where peaks were small, sometimes up to ten runs were needed in order to get reliable data. Plots of the vapor pressures versus the concentration were perfectly linear, indicating that the solutions can be regarded as ideal. The slopes of the plots were calculated using a least squares method and were subsequently used for calculating the Gibbs energies of transfer.

Supplementary Material Available: Table of second-order rate constants for the DA reactions of **1b**, **1d**, and **1e** with **2** in water, HFP, TFE, 2-propanol, ethanol, acetonitrile, and *n*-hexane (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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