Retro-Diels−Alder Reaction in Aqueous Solution: Toward a Better Understanding of Organic Reactivity in Water

Jan W. Wijnen and Jan B. F. N. Engberts*

Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Received December 11, 1996[⊗]

The retro-Diels−Alder (RDA) reaction of anthracenedione **1a** proceeds considerably faster in aqueous solutions than in organic solvents. Addition of organic solvents to water retards the reaction, whereas glucose induces a modest acceleration. SDS micelles induce a considerable retardation, but even at high concentrations of surfactant (complete micelle−substrate binding), the cycloreversion is not fully inhibited. Correlation with data for solvatochromic indicators strongly suggest that the origin of the water-induced acceleration involves primarily enhanced hydrogen bonding of water to the activated complex for the RDA reaction of **1a**. Activation parameters support this view. A comparison of the present results with previous kinetic data for bimolecular and intramolecular Diels−Alder reactions provides insights into the contributions of hydrogen-bond and hydrophobic interactions to the aqueous accelerations of the latter two types of reactions.

Introduction

Water is an unconventional solvent for organic reactions. Besides obvious economical and environmental advantages, water can have a surprisingly beneficial effect on organic reactions, and this notion has popularized water as a reaction medium.[1] Presently almost every type of organic reaction has been studied in water, and a considerable number of these reactions are actually promoted by an aqueous reaction medium, most notably pericylic reactions like the Claisen rearrangement,[2] 1,3-dipolar cycloadditions,[3] and particularly the Diels−Alder (DA) reaction.[4,5] Successful attempts to catalyze organic reactions in aqueous solutions have extended the potential of water as a reaction medium.[6]

By far the most intriguing issue associated with water entails hydrophobic interactions.[7] These rather complex phenomena are governed by the limited ability of water to dissolve apolar molecules through the formation of hydrophobic hydration shells. Overlap of these hydration shells leads to association of apolar species. However, the strong focus on hydrophobic interactions often outshines other unique properties of water, which may also affect organic reactivity. One of these properties is the ability to act as a very efficient hydrogen-bond donor as well as acceptor.[8] The high acceptor number (AN), E_T(30)-value, and Kamlet−Taft's α-parameter show that water is one of the best hydrogen-bond-donating solvents, only surpassed by much more acidic solvents like formic acid. Presumably, this quality is partly due to the small size of the water molecule, which enables water to interact effectively and multimolecularly with Lewis bases. In water, organic reactions are often promoted by these interactions.

The bimolecular Diels−Alder reaction has been thoroughly studied in aqueous solutions,[4,5] and it has become apparent that nearly all different types of this cycloaddition benefit from an aqueous reaction medium. By now it is widely accepted that two factors are primarily responsible for the 'aqueous acceleration': (i) stabilization of the transition state relative to the initial state due to enhanced hydrogen bonding of water to the polarized activated complex and (ii) substantial reduction of the hydrophobic surface area of reactants during the activation process ('enforced hydrophobic interactions').[4,9,10]

Since the debate on the origins of the water-induced acceleration of DA reactions appears to be settled, the discussion has shifted to the intriguing but rather troublesome problem of separating and quantifying both factors.[4,9,10] This is a considerable challenge since nearly all common DA reagents are hydrophobic *and* possess activating substituents that are susceptible to hydrogen bonding. The dimerization of cyclopentadiene looks like a perfect example of a DA reaction in which hydrogen-

---

[⊗] Abstract published in *Advance ACS Abstracts*, March 15, 1997.

[1] (a) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (b) Li, C. *Chem. Rev.* **1993**, *93*, 2023. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741.

[2] (a) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515. (b) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849. (c) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966. (d) Gao, J. *J. Am. Chem. Soc.* **1994**, *116*, 1563. (e) Gajewski, J. J.; Brichford, N. L. *J. Am. Chem. Soc.* **1994**, *116*, 3165.

[3] (a) Dignam, K. J.; Hegarty, A. F.; Quain, P. L. *J. Org. Chem.* **1978**, *43*, 388. (b) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079. (c) Rohloff, J. C.; Robinson, J.; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113. (d) Wijnen, J. W.; Steiner, R. A.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1995**, *35*, 5389.

[4] (a) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1992**, *114*, 5440. (c) Otto, S.; Blokzijl, W.; Engberts, J. B. F. N. *J. Org. Chem.* **1994**, *59*, 5372. (d) Wijnen, J. W.; Zavarise, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1996**, *61*, 2001.

[5] (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137. (c) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (d) Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265.

[6] (a) Kalck, P.; Monteil, F. *Adv. Organomet. Chem.* **1992**, *34*, 219. (b) Herrmann, W. A.; Kohlpainter, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (c) Kobayashi, S. *Synlett* **1994**, 689. (d) Papadogianakis, G.; Sheldon, R. A. *New J. Chem.* **1996**, *20*, 175. (e) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7002. (f) Loh, T.-P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2315.

[7] Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.

[8] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Cambridge, 1990.

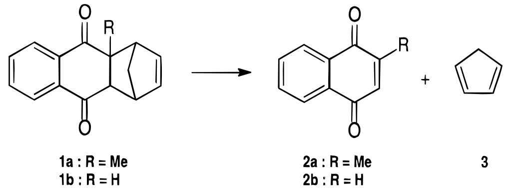
[9] (a) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (b) Blake, J. F.; Lim, D.; Jorgensen, W. L. *J. Org. Chem.* **1994**, *59*, 803. (c) Jorgensen, W. L.; Blake, J. F.; Lim, D.; Severance, D. L. *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1727.

[10] Furlani, T. R.; Gao, J. *J. Org. Chem.* **1996**, *61*, 5492.

[11] (a) Sangwan, N. K.; Schneider, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223. (b) Breslow, R.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9923.

S0022-3263(96)02320-1 CCC: $14.00

Scheme 1



bond interactions can be neglected. Unfortunately kinetic studies are experimentally precarious, and indeed there is some dispute about the exact rate constants.[9c,11] Recently we have investigated another reaction in which hydrogen-bond interactions are of minor importance: the cycloaddition of cyclopentadiene to acridizinium bromide.[12] This reaction is only modestly accelerated in water.

Computational methods have been successfully applied to investigate the origins of the 'aqueous acceleration' of cycloadditions.[9,10] They indicate that hydrogen-bond interactions often are the dominant contribution to the rate enhancements in water.

In this paper we present the results of a kinetic study of a reaction in which contributions of hydrophobic effects are negligible, thus providing an opportunity to quantify the influence of hydrogen bonding on cycloadditions. The retro-Diels−Alder (RDA) reaction of **1a** seems a suitable candidate[13] (Scheme 1). According to frontier molecular orbital theory (FMO) RDA reactions are mechanistically comparable to DA reactions. Thus, RDA reactions are accelerated by electron-withdrawing substituents on the (future) dienophile and electron-donating substituents on the (future) diene.[14,15] RDA reactions are dominated by the enthalpy of activation, the entropy of activation usually being small.[13,14,16,17] But compared to DA reactions, the volume of activation ($\Delta^{\ddagger}V^{\theta}$) of a RDA is markedly smaller, in fact, close to zero.[13,17] Furthermore, due to the unimolecular nature of the RDA reaction, no substantial dehydration of the reactant has to take place during the activation process (in contrast to bimolecular reactions in aqueous solutions) and also aggregation of reactants is excluded. This means that contributions of 'enforced hydrophobic interactions' are negligible, since no significant change of solvent-accessible surface area takes place during the activation process.

In organic solvents, medium effects on DA and RDA reactions are small. Both reactions are modestly promoted by protic solvents.[8,18] Desimoni and co-workers[16] reported reaction rates of the cycloreversion of anthracenedione **1a** and elegantly demonstrated that in organic solvents the DA and RDA reactions are dominated by the same solvent properties.

The RDA reaction is an organic transformation that allows the stereospecific formation or regeneration of an unsaturated bond, but often high reaction temperatures are a major drawback as they may reduce the selectivity of the reaction. Therefore several techniques have been developed that have rendered this cycloreversion more applicable. Flash vacuum thermolysis[19] is most frequently used, but also examples of acid catalysis,[20] antibody catalysis,[21] silica gel[22] or alumina[23] catalysis, and Lewis acid catalysis[24] are known. Grieco[25] has reported efficient water-promoted retro-aza DA reactions and demonstrated that *N*-alkyl-2-azanorbornenes readily decompose in water, whereas in organic solvents rigorous reaction conditions are required.

Table 1. First-Order Rate Constants and Gibbs Energies of Activation for the RDA Reaction of 1a in Organic Solvents and in Water at 40.0 °C

entry	solvent	$10^8 \times k_1$ (s^{-1})	$\Delta^{\ddagger}G^{\theta}$ (kJ mol^{-1})	$E_T(30)^a$	AN^b
1^c	*n*-hexane	2.6	122.3	31.0	0
2^c	benzene	6.6	119.9	34.3	8.2
3^c	DMSO	23	116.6	45.1	20.4
4^c	2-PrOH	27	116.2	48.4	33.6
5^c	acetic acid	62	114.0	51.7	52.9
6	TFE	161	111.5	59.8	53.3
7	water	359	109.5	63.1	54.8
8	HFIP	469	108.8	65.3	

[a] From ref 8. [b] Acceptor number; see ref 8. [c] Calculated from data in ref 16.

In this study we present kinetic data on a homo-RDA reaction in water and in mixed aqueous solutions. It will be shown that water facilitates this reaction, despite the fact that hydrophobic interactions are of negligible importance. The efficient hydrogen-bond-donating ability of water appears to govern the increased reactivity by stabilizing the polarized activated complex.

Results and Discussion

Kinetics of the Cycloreversion in Water and Organic Solvents. Rate constants for the cycloreversion of **1a** were determined at 40.0 °C in water and in several fluorinated alcohols (Table 1) and are compared with rate constants calculated from previously reported activation parameters[16] (Table 1). The fluorinated alcohols were chosen because they are excellent hydrogen-bond donors.

The RDA reaction proceeds exceptionally fast in water compared to organic solvents, its rate only being faster in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). These results are striking and important because they clearly show that water can greatly accelerate pericylic reactions through hydrogen-bond interactions with hydrophobic effects playing no significant role. This water-induced acceleration of the RDA reaction is similar to the promotion of the Claisen rearrangement in aqueous solvents.[2] The data confirm the efficiency of water as a hydrogen-bond donating solvent and its ability to stabilize the polar activated complex.

---

(12) Van der Wel, G. K.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1996**, *61*, 9001.

(13) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(14) (a) Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1986**, *51*, 2851. (b) Chung, Y.-S.; Duerr, B.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1988**, *53*, 1334. (c) Chung, Y.-S.; Duerr, B. F.; McKelvey, T. A.; Nanjappan, P.; Czarnik, A.W. *J. Org. Chem.* **1989**, *54*, 1018.

(15) Jurczak, J.; Kawczynski, A. L.; Kozluk, T. *J. Org. Chem.* **1985**, *50*, 1106.

(16) Desimoni, G.; Faita, G.; Pasini, D.; Righetti, P. P. *Tetrahedron* **1992**, *48*, 1667.

(17) Jenner, G.; Papadopoulos, M.; Rimmelin, J. *J. Org. Chem.* **1983**, *48*, 748.

(18) Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283.

(19) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121.

(20) Bunnelle, W. H.; Shangraw, W. R. *Tetrahedron* **1987**, *43*, 2005.

(21) Bahr, N.; Güller, R.; Reymond, J.-L.; Lerner, R. A. *J. Am. Chem. Soc.* **1996**, *118*, 3550.

(22) Chantarasiri, N.; Dinprasert, P.; Thebtaranonth, C.; Thebtaranonth, Y.; Yenjai, C. *J. Chem. Soc., Chem. Commun.* **1990**, 286.

(23) Pagni, R. M.; Kabalka, G. W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* **1993**, *49*, 6743.

(24) (a) Marchand, A. P.; Vidyasagar, V. *J. Org. Chem.* **1988**, *53*, 4412. (b) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008. (c) Grieco, P. A.; Abood, N. *J. Chem. Soc., Chem. Commun.* **1990**, 410.

(25) (a) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859. (b) Grieco, P. A.; Clark, J. D. *J. Org. Chem.* **1990**, *55*, 2271.

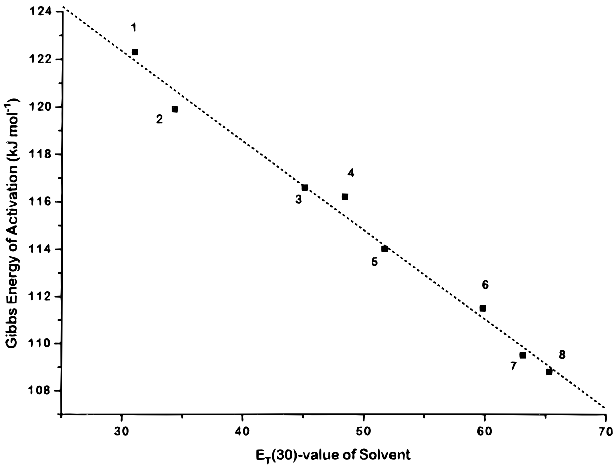


Figure 1. Gibbs energy of activation for the RDA reaction of **1a** vs the E_T(30)-value of the solvents. Numbers correspond to entries in Table 1.

Table 2. Gibbs Energy of Activation for the RDA[a] Reaction of 1a, the IMDA[b] Reaction of 4, and the Bimolecular DA[c] Reaction of 2b with 3 in Organic Solvents and in Water

solvent	$\Delta^{\ddagger}G^{\theta}_{\mathrm{RDA}}$ (kJ mol^{-1}) (at 40.0 °C)	$\Delta^{\ddagger}G^{\theta}_{\mathrm{IMDA}}$ (kJ mol^{-1}) (at 25.0 °C)	$\Delta^{\ddagger}G^{\theta}_{\mathrm{DA}}$ (kJ mol^{-1}) (at 25.0 °C)
hexane	122.3	94.6	90.5
propanol	116.2	93.2	83.2
TFE	111.5	87.6	77.9
water	109.5	82.0	69.4
HFIP	108.8		

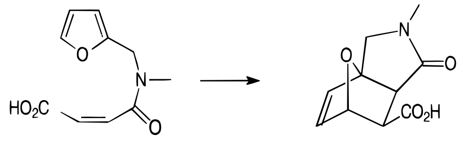
[a] Partly taken from ref 16. [b] Taken from ref 26. [c] Taken from refs 4c and 26.

Figure 1 shows a remarkable correlation between the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction and the solvatochromic parameter E_T(30) of the solvents. The latter parameter is an accepted indicator of the polarity and hydrogen-bond-donating capacity of solvents;[8] therefore, this observation supports the importance of the notion that the $\Delta^{\ddagger}G^{\theta}$ of this type of reaction is largely governed by these solvent properties. Likewise, the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction decreases with increasing AN of the solvents, but the correlation is less accurate.

No detailed experimental data on a RDA reaction in water are available, but Jorgensen[9a] and Furlani and Gao[10] simulated the cycloaddition of methyl vinyl ketone (MVK) to **3** in water along the entire reaction path. The studies also included a calculation of the change in Gibbs energy of hydration, on going from the transition state to the product, which in effect is the change of Gibbs energy of activation of the RDA reaction of that system. Jorgensen computed a $\Delta\Delta^{\ddagger}G^{\theta}$ of 13 kJ mol^{-1} for the RDA reaction, and Furlani and Gao obtained a value of 2.5 kJ mol^{-1}. These results seem quite inconsistent, although a correction of Jorgensen[9c] on the Gibbs energy of hydration of the transition state somewhat reduces the discrepancy. Comparison of these data with our experimental results is obscured by the fact that in the former case the substrate only possesses one activating carbonyl group, but two in the latter case. Still, a water-induced reduction of the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction of 6–8 kJ mol^{-1} per carbonyl group seems reasonable.

Comparison with Other DA Reactions. In Table 2 our kinetic data for the RDA reaction of **1a** and previously reported data[4a,26] for the bimolecular DA reaction (**2b** + **3** → **1b**) (Scheme 1) and the intramolecular DA reaction (IMDA) of *N*-furfuryl-*N*-methylmaleamic acid (Scheme 2) are compared. The different features of these reactions enable an analysis of the factors that govern the respective reactivities in water. In organic solvents RDA reactions have a $\Delta^{\ddagger}V^{\theta}$ close to zero.[17] The exact $\Delta^{\ddagger}V^{\theta}$ for the cycloreversion of **1a** is unknown, but it appears likely that also in this case $\Delta^{\ddagger}V^{\theta}$ is small. A point of concern is the solvent effect on $\Delta^{\ddagger}V^{\theta}$. For the bimolecular DA reaction it is known that $\Delta^{\ddagger}V^{\theta}$ is more negative in water than in organic solvents,[27] which has been attributed to electrostriction as a result of an increased solvation of the activated complex (increased hydration of the relatively polar activated complex). In water, the $\Delta^{\ddagger}V^{\theta}$ for the RDA reaction may be similarly affected. However, we envisage that even in water the $\Delta^{\ddagger}V^{\theta}$ for the RDA of **1a** is much smaller than the $\Delta^{\ddagger}V$ of the bimolecular DA reaction. Furthermore it is obvious that in the case of the bimolecular DA reaction both reactants must be at least partly stripped of their hydration shells before C–C bond formation can take place, whereas this is not necessary in the case of the RDA reaction, since in a geometrical sense the activated complex resembles the reactant (**1a**). Consequently the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction will be hardly affected by 'enforced hydrophobic interactions', whereas this factor does affect the DA and IMDA reactions since these reactions are accompanied by a reduction of the solvent-accessible surface area during the activation process.

Scheme 2



4 5

The extent to which water can affect a reaction through hydrogen-bond interactions naturally depends on the number and the hydrogen-bond-accepting capability of the substituents in the substrate. In the case of **1a** the two carbonyl groups enable protic solvents to exert this stabilizing effect efficiently. A direct comparison of the DA and RDA reactions is justified as follows: according to the principle of microscopic reversibility, the DA and the RDA reactions possess the same transition state and the extent of polarization of all chemical bonds is identical. Therefore we contend that the hydrogen-bond-induced reduction of the Gibbs energy of activation for the RDA reaction of **1a** affects the aqueous acceleration of the bimolecular DA reaction of **2b** with **3** similarly. Also comparison with the IMDA reaction seems reasonable because the dienophilic part of the IMDA probe contains two activating groups.

The data in Table 2 show that on going from the apolar and aprotic *n*-hexane to water the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction is reduced by nearly 12.8 kJ mol^{-1}. The contribution of hydrogen bonding to the bimolecular DA reaction is assumed to be similar (as a matter of fact, it seems likely that it is even more dominant, since water can interact better with the transition state of **1b**: the methyl group of **1a** surely hampers hydrogen bonding of

---

(26) (a) Blokzijl, W. Ph.D. Thesis, University of Groningen, Groningen, The Netherlands, 1991. (b) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823.

(27) Isaacs, N. S.; Maksimovic, L.; Laila, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 495.

Table 3. First/Second-Order Rate Constants and Relative Rate Constants[a] for the RDA Reaction of 1a (at 40.0 °C) and the Bimolecular DA Reaction[b] of 2b with 3 (at 25.0 °C) in Highly Aqueous Solutions[c]

solvent	$10^6 \times k_1^{RDA}$ (s^{-1})	k^{rel} (RDA)	k_2^{DA} ($M^{-1}\,s^{-1}$)	k^{rel}(DA)
water	3.59	1	4.48	1
WM95	3.20	0.89	4.29	0.96
WM90	2.74	0.76	3.80	0.85
WE95	3.04	0.85	4.73	1.06
WE90	2.28	0.64	3.89	0.87
WP95	2.69	0.75	5.14	1.15
WP90	1.33	0.37	1.52	0.34
WB95	1.75	0.49	4.39	0.98
WB90	0.91	0.25	0.90	0.20
WU95	3.44	0.96	3.82	0.85
WU90	3.38	0.94	3.46	0.77
WG95	4.08	1.14	7.40	1.65

[a] See text. [b] Partly taken from ref 4a. [c] WM, WE, WP, WB, WU, and WG: aqueous mixtures of methanol, ethanol, 1-propanol, *t*-butyl alcohol, urea, and glucose, respectively. WM95 indicates a water–MeOH solution containing 95 mol % of water.

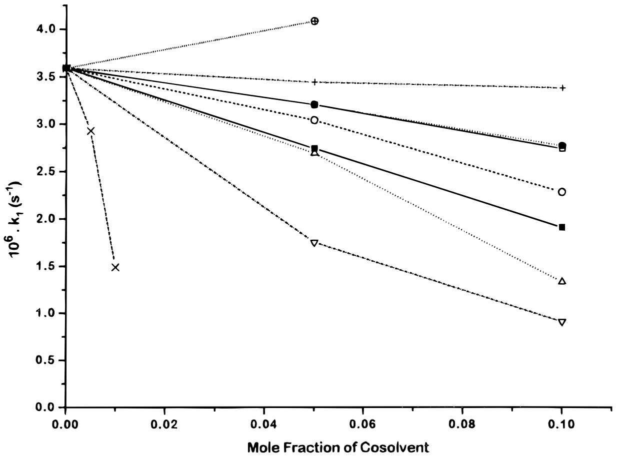


Figure 2. First-order rate constant (×10^6; 40 °C) of the RDA reaction of **1a** vs mole fraction of organic cosolvents: MeOH (□), EtOH (□), 1-PrOH (△), *t*-BuOH (▽), formamide (●), acetonitrile (■), 1-cyclohexyl-2-pyrrolidinone (×), urea (+), and glucose (⊕).

water), which would mean that hydrophobic interactions are responsible for a reduction of the $\Delta^{\ddagger}G^{\theta}$ by 8.3 kJ mol^{-1}. Going from hexane to water, the $\Delta^{\ddagger}G^{\theta}$ for the IMDA reaction is reduced by 12.6 kJ mol^{-1}, and this suggests that also in this case hydrogen-bond interactions play a pivotal role.

Using computational techniques, Jorgensen[9] has also quantified the contributions of hydrogen-bond and hydrophobic interactions to the rate enhancements of the 'aqueous DA reaction'. In the case of the DA reaction of **3** with MVK, enhanced hydrogen bonding of water to the carbonyl substituent is shown to be largely responsible for the accelerations in water. Depending on the geometry of the MVK–water complex, this interaction may account for up to 8.2 kJ mol^{-1}. Hydrophobic interactions are thought to account for 4–6.5 kJ mol^{-1}. In a subsequent calculation the hydrogen-bond stabilization is computed to be less efficient, which suggests that both contributions are roughly similar. Furlani and Gao conclude that hydrogen bonding contributes about 4.2–6.7 kJ mol^{-1} to the acceleration of the same reaction in water.[10] Taking into account the fact that **1a** contains two carbonyl groups whose interactions with water are hampered by steric hindrance, the computed hydrogen-bond-induced reduction of the $\Delta^{\ddagger}G^{\theta}$ and our results are reasonably consistent.

Effect of Cosolvents on the RDA Reaction in Water. A curious feature of the DA reaction in water is the fact that small concentrations of hydrophobic organic cosolvents lead to an additional acceleration.[4,26] The extent of this acceleration and the specific mole fraction where maximum acceleration is observed depend on the hydrophobicity of the cosolvent, *e.g.*, addition of small amounts of methanol hardly affects the rate constant, whereas about 5 mol % of propanol or about 2–3 mol % of *t*-butyl alcohol actually provides additional accelerations. Previously, this phenomenon has been attributed to increased 'enforced hydrophobic interactions'.[4,26]

We examined the effect of small mole fractions of cosolvents on the rate constant of the RDA reaction in water, and the results are compiled in Table 3 and Figure 2. The second-order rate constants for the bimolecular DA reaction (**2b** + **3** → **1b**) are also included, while k^{rel}(RDA) and k^{rel}(DA) indicate the relative acceleration/deceleration of the reactions compared to pure water as the solvent. The data show that nearly all organic cosolvents decrease the rate of the RDA reaction. This is opposite to the effect of small concentrations of these cosolvents on the DA reaction. Hydrophobic cosolvents induce the most significant retardation of the RDA reaction, the impact of 1-cyclohexyl-2-pyrrolidinone being most dramatic. The decelerating effect of the alcohols parallels their hydrophobicity. Also acetonitrile induces a substantial rate inhibition, whereas the effect of formamide (which shares some characteristics of water) is quite modest.

Urea and glucose behave quite differently as additives: apparently substantial concentrations of these compounds do not interfere with the hydrogen-bond-donating capacity of water. This is in accord with previous studies.[28] Even 10 mol % of urea hardly affects the RDA reaction in water, whereas addition of 5 mol % of glucose slightly accelerates the reaction. In this case the effects of urea and glucose on the RDA reaction and the bimolecular DA reaction are very similar. Also the latter reaction is insensitive to large concentrations of urea but is accelerated by glucose.

Under the assumption that the water-induced accelerations of bimolecular DA reactions are caused by both a hydrogen-bond effect and enforced hydrophobic interactions, we can now discuss the effects that cosolvents exert on bimolecular DA reactions. The kinetic data of the RDA reaction reveal that the hydrogen-bond activation of water is decreased upon addition of alcohols to water. Consequently the observed acceleration of the bimolecular DA reaction in the presence of small amounts of alcohol is predominantly caused by enhanced enforced hydrophobic interactions. Addition of urea to water hardly affects the RDA and bimolecular DA reactions;[4a] therefore, we conclude that urea does not alter the hydrogen-bond capacity of water (as the RDA results show) and only slightly reduces the hydrophobic interactions.[28] Finally, the glucose-induced acceleration of bimolecular DA reactions[4a] seems to be partly caused by enhanced hydrogen bonding of water to the electron-withdrawing substituents of the dienophile, although

---

(28) (a) Finney, J. L.; Soper, A. K. *Chem. Soc. Rev.* **1994**, 1. (b) Posthumus, W.; Engberts, J. B. F. N.; Bijma, K.; Blandamer, M. J. *J. Mol. Liq.*, in press.

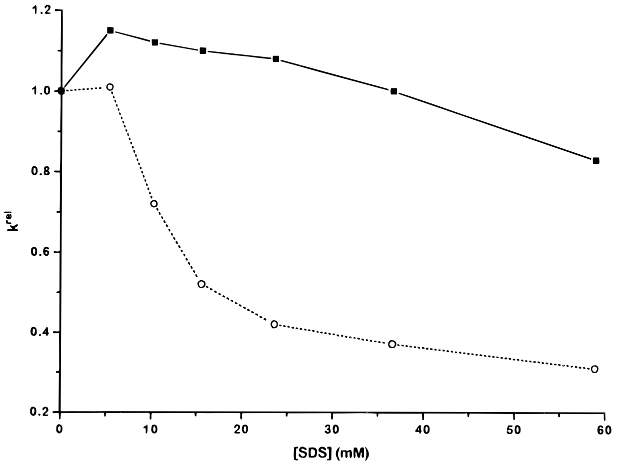


Figure 3. Relative rate constant of the RDA reaction (○) and the DA reaction (■) in SDS solutions (see text).

Table 4. First-Order Rate Constants for the RDA Reaction of 1a (at 40.0 °C) and Second-Order Rate Constants for the Bimolecular DA Reaction of 2b with 3 (at 25.0 °C) in SDS Solutions

solvent	$10^6 \times k_1$(RDA) (s^{-1})	k_2(DA) (M^{-1} s^{-1})
water	3.59	4.48
SDS 5.4 mM	3.61	5.21
10.3 mM	2.59	5.09
15.6	1.86	5.00
23.6 mM	1.49	4.83
36.6 mM	1.32	4.54
58.9 mM	1.11	3.78

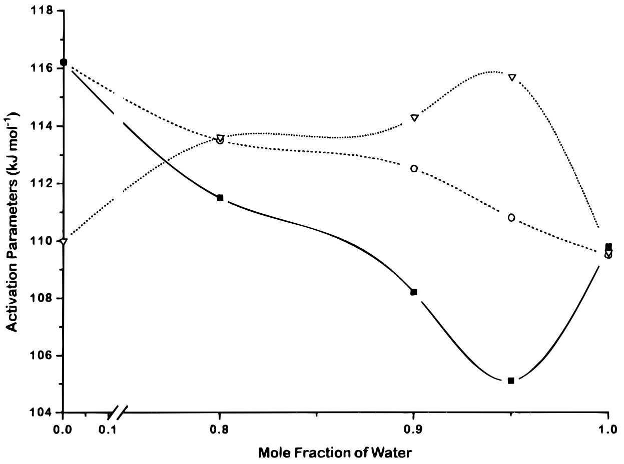


Figure 4. Activation parameters of the RDA reaction of **1a** in water/1-PrOH mixtures vs mole fraction of water: $\Delta^{\ddagger}G^{\theta}$ (○), $\Delta^{\ddagger}H^{\theta}$ (■), and $-T\Delta^{\ddagger}S^{\theta}$ (▽). The $T\Delta^{\ddagger}S^{\theta}$ plot has been displaced upward by 110 kJ mol^{-1} for clarity.

Table 5. Activation Parameters for the RDA Reaction of 1a (at 40.0 °C) in Water/Propanol Mixtures

solvent	$\Delta^{\ddagger}G^{\theta}$ (kJ mol^{-1})	$\Delta^{\ddagger}H^{\theta}$ (kJ mol^{-1})	$-T\Delta^{\ddagger}S^{\theta}$ (kJ mol^{-1})
water	109.5 (±0.1)	109.8 (±1.9)	-0.3 (±1.8)
water/1-PrOH ($X_w = 0.95$)[a]	110.8 (±0.2)	105.1 (±2.2)	5.7 (±2.0)
($X_w = 0.90$)[a]	112.5 (±0.1)	108.2 (±2.1)	4.3 (±2.0)
($X_w = 0.80$)[a]	113.5 (±0.1)	111.5 (±1.7)	3.6 (±1.6)
2-PrOH[b]	116.2 (±0.1)	116.2 (±4.3)	0 (±4.2)

[a] X_w is mole fraction of water. [b] Taken from ref 16.

enhanced hydrophobic interactions again seem to be the dominant cause of the acceleration of the bimolecular DA reaction.

Effect of Micelles on the RDA and DA Reactions in Water. In Table 4 and Figure 3 is recorded the effect of SDS micelles on the RDA (at 40.0 °C) and DA (at 25.0 °C) reactions. In Figure 3, k^{rel} is defined as the ratio of the (first- or second-order) rate constants in SDS solution to that in pure water ($k^{rel} = k^{SDS}/k^0$). The cycloreversion is gradually retarded above the CMC of this surfactant (8.56 mM at 40 °C[29]), but even at [SDS] = 58.9 mM it still proceeds rather fast. Note that in these SDS solutions the rate constant is still much larger than that in propanol. This is of interest because (under our experimental conditions) at this [SDS] all solute molecules (**1a**) certainly interact with micelles (the ratio SDS/**1a** is more than 200 while the aggregation number of SDS is about 88[30]). Apparently this does not prevent water from activating **1a**, which is in accord with the notion that water can still interact with molecules that are bound to micelles.[31]

Contrary to the above results, the bimolecular DA reaction is slightly accelerated by SDS. This already occurs at 5.4 mM SDS, suggesting that 2−3 mmol of **3** (or the propanol which is used as the solvent for the stock solution) induces the formation of some sort of mixed SDS/**3** aggregates, which promote the reaction. This is a well-documented phenomenon.[32] Only at high concentrations of SDS is a decrease of the rate constant observed. These results are in agreement with previously reported kinetic data on the effect of micelles on aqueous DA reactions. Both the cycloaddition of **3** to MVK[4a,26] and the cycloaddition of **3** to fumaronitrile[33] are retarded at relatively high concentrations of SDS, although the 10−20% decrease of the rate constant (similar to our results) is certainly not dramatic.

Combining the results of the RDA and DA reactions, it appears that micelles substantially reduce the hydrogen-bond activation by water. However, in the case of the bimolecular DA reaction this ‘deactivation’ is largely compensated, presumably by the local increase of substrate concentrations in the micelle, leading to the modest deceleration of the bimolecular DA reaction.

Activation Parameters. Activation parameters shed more light on the origin of the acceleration of the RDA reaction of **1a** in water. These parameters were determined in pure water and in water/1-propanol mixtures and may be compared with previously reported values for this reaction[16] (Table 5 and Figure 4). Even in pure water the entropy of activation is close to zero, supporting the view that hydrophobic effects are of minor importance for this reaction and also that solvent rearrangement is rather small. The higher reactivity of **1a** in water is completely accounted for by a reduction of the enthalpy of activation (relative to organic solvents), most likely reflecting an increased interaction of water with the activated complex. Addition of 1-propanol leads to enthalpy−entropy compensating behavior.[34] When 5 mol % of 1-propanol is added to water, the modest increase of the $\Delta^{\ddagger}G^{\theta}$ of the RDA reaction is the result of an

---

[29] Moroi, Y.; Nishikido, N.; Uehara, H.; Matuura, R. *J. Colloid Interface Sci.* **1975**, *50*, 254.

[30] Hayter, J. B.; Penfold, J. *Colloid Polym. Sci.* **1983**, *261*, 1022.

[31] Lissi, E.; Abuin, E. in *Solubilization in Surfactant Aggregates*; Christian, S. D., Scamehorn, J. F., Eds.; Marcel Dekker: New York, 1995; p 297.

[32] Magid, L. In *Surfactants in Solution;* Mittal, K. L., Ed.; Plenum Press: New York, 1977; Vol. 1, p 427.

[33] Hunt, I.; Johnson, C. D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1051.

[34] Lumry, R.; Rajender, S. *Biopolymers* **1970**, *9*, 1125.

unfavorable $\Delta^{\ddagger}S^{\theta}$, which is largely compensated by a more favorable $\Delta^{\ddagger}H^{\theta}$. On increasing the concentration of propanol, $\Delta^{\ddagger}S^{\theta}$ drops back to zero and the reaction is again completely enthalpy-controlled. This compensation effect also strongly indicates that water directly participates in the reaction under study.[34]

The activation parameters for the bimolecular DA reaction of **3** with MVK also exhibit this curious compensating effect. In this case and when 1,4-naphthoquinone is used as dienophile, the reduction of the $\Delta^{\ddagger}G^{\theta}$ (going from 1-propanol to water) is almost equally accounted for by the more favorable entropy *and* enthalpy of activation.[4c]

Concluding Remarks

The results of this study illustrate how water can increase the reactivity of vinylic compounds by exerting an activating effect on their substituents. It therefore seems reasonable that water may also promote other organic reactions in a similar fashion. It is indeed striking that a large number of the water-promoted organic reactions have been carried out with reagents that possess polarizable, electron-withdrawing substituents.[1] Undoubtedly all these reactions are affected by hydrophobic interactions, which can provide a unique driving force for organic reactivity, but the hydrogen-bond activation by water which we have studied in detail in this paper seems to provide at least an equally important contribution to the beneficial effect of water as a reaction medium.

Experimental Section

Synthesis and Product Analysis. 1,4,4a,9a-Tetrahydro-4a-methyl-(1α,4α,4aα,9aα)-1,4-methanoanthracene-9,10-dione (**1a**) was synthesized according to a literature procedure[16] and crystallized several times from cyclohexane, mp 97 °C (lit.[16] mp 96 °C). On a synthetic scale the RDA reaction was carried out as follows: 50 mg of **1a** was dissolved in 5 mL of acetonitrile, and this solution was added dropwise to 200 mL of water. The slightly turbid solution was stirred overnight at 70−80 °C. After cooling, the yellow solution was extracted several times with chloroform, the organic layer dried with sodium sulfate, and finally the solvent removed. ^{1}H NMR analysis only revealed the presence of **2a**.

Kinetic Experiments. Rate constants were determined using UV/vis spectroscopy. Water was twice distilled in an all-quartz distillation unit. Solvents were of the best available quality and were distilled before use. The RDA reaction was monitored at 340 nm, and the first-order rate constant was determined using the initial rate method.[35] This method is less accurate than conventional pseudo-first-order kinetics, but it enables determination of a large number of rate constants for slow reactions. The technique requires determination of the extinction coefficient of both **1a** and **2a**. In the highly aqueous solutions these were nearly identical to those in water. A few microliters of a stock solution of **1a** dissolved in propanol was added to the cuvettes; initial concentrations of **1a** were 0.2−20 mM. The first-order rate constants are the average of at least five independent experiments and were reproducible to within 4%. Activation parameters were calculated from rate constants at four different temperatures in the range 30−49 °C.

The DA reaction (**2a** + **3** → **1a**) does not affect the kinetics of the RDA reaction: addition of a large excess of acrylonitrile (to scavenge **3**) does not change the observed rate constants. The rate constants of the bimolecular DA reaction were determined as described previously.[4]

Acknowledgment. Mr. Evert van Rietschoten and Mr. Frans Wessels are gratefully acknowledged for carrying out the initial experiments of this work and for valuable comments and discussion.

JO9623200

---

(35) (a) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, 1961; p 45. (b) Scheiner, P.; Schomaker, J. H.; Deming, S.; Libbey, W. J.; Nowack, G. P. *J. Am. Chem. Soc.* **1965**, *87*, 306.