University of Groningen

Diels-Alder reactions in water

Engberts, Jan B.F.N.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1995

[Link to publication in University of Groningen/UMCG research database](#)

Diels-Alder reactions in water: Enforced hydrophobic interaction and hydrogen bonding

Jan B.F.N. Engberts

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

Abstract: Second-order rate constants have been measured for the Diels-Alder (DA) reactions of cyclopentadiene with dienophiles of varying hydrophobicity and hydrogen-bond acceptor capacity in water, in a series of organic solvents and in alcohol-water mixtures. The intramolecular DA reaction of N-furfuryl-N-alkylacrylamides was also investigated in the same reaction media. The often huge rate accelerations in water appear to be inherent in the activation process of the cycloaddition and do not originate from diene-dienophile association. A pseudothermodynamic analysis of the rate acceleration in water relative to 1-propanol and 1-propanol-water mixtures provides evidence for two factors dominating the rate enhancement in water: hydrogen-bond stabilization of the polarized activated complex and the decrease of the hydrophobic surface area of the reactants during the activation process.

Quite generally, organic chemists think that water is not a good solvent for organic reactions. Rightly so. The often limited solubility of apolar organic compounds in water and the sensitivity of many reagents and functional groups towards water are among the factors which make more apolar and inert organic solvents a better choice. On the other hand, however, the selective molecular recognition processes and chemical transformations in biological systems are confined to aqueous reaction media. Also for many mechanistic studies in organic chemistry, water is a preferred solvent, partly because complex ion-pairing phenomena can be avoided. Eversince the pioneering work of Breslow et al. (ref. 1) another factor has come to light which appears to favor water as the solvent for a whole variety of bimolecular organic reactions. In fact, it was found (largely by accident) that second-order rate constants for the Diels-Alder (DA) reactions of a series of diene/dienophile combinations are greatly enhanced in aqueous solution. This was the more surprising since DA reactions, involving isopolar activated complexes, are known (ref. 2) to exhibit only modest medium effects on their rate constants. Breslow's findings attracted great attention and the aqueous medium effect was well-used in synthetic organic chemistry, in particular by Grieco et al. (ref. 3). Interestingly, several other organic transformations were found to be accelerated substantially in water, including the aldol condensation (ref. 4), the benzoin condensation (ref. 5) and the Claisen rearrangement (ref. 6). Most attention has been focussed on carbon-carbon bond formation processes (ref. 7). The interest in water as the solvent is, of course, also stimulated by chemist's care for the environment (ref. 8).

Different explanations have been offered in the literature for the rate enhancement of DA reactions in water. These include: hydrophobic packing of diene and dienophile (ref. 9), effects of the internal pressure (ref. 4, 10) and cohesive energy density of water (ref. 11), hydrogen-bonding effects (ref. 12,

13), solvophobic effects (ref. 14) and hydrophobic *vs.* antihydrophobic effects (ref. 15). Our interest in the peculiar solvent properties of water (ref. 16) and the obvious controversies in the interpretation of the aqueous medium effects, led us to investigate in some detail the origin of the, at first sight, anomolous rate accelerations in water. We employed a physical-organic approach: kinetics in different media and variation of substrate structures. The results have been rationalized in terms of transition-state theory.

Intermolecular DA reactions. Rate constants in organic solvents and in water

The DA reactions of 5-substituted naphthoquinones (**1a-e**) with cyclopentadiene (**2**) and the corresponding reaction of **2** with methyl vinyl ketone (**3**) and methyl vinyl sulfone (**4**) (Scheme 1) have been studied in most detail (ref. 17-20). The data in Table 1 illustrate the large rate enhancements in water for the reactions of **1a-e** with **2**: $k_2(H_2O)/k_2$(n-hexane) amounts to 1180 (**1a**), 1651 (**1b**), 4583 (**1c**), 7250 (**1d**) and 12780 (**1e**). It is clear that the rate acceleration in water depends markedly on the nature of the dienophile. Another obvious conclusion that emerges from these data is, that an increase of the hydrogen-bonding donor capacity of the alcohols leads to a substantial increase of k_2 : k/HFP)/k(EtOH)= 83 (**1a**), 68 (**1b**), 114 (**1c**), 99 (**1d**) and 154 (**1e**). However, the rate increase in water, which is definitely less acidic than HFP, is the highest of all solvents: $k(H_2O)/k(HFP)$= 1.91

1a R=NO$_2$
 b R=COCH$_3$
 c R=H
 d R=CH$_3$
 e R=OCH$_3$

3 X=CO
4 X=SO$_2$
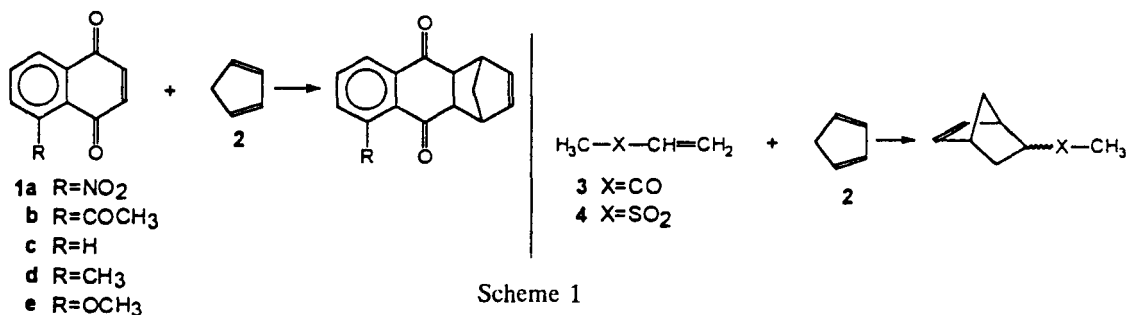
Scheme 1

(**1a**), 2.88 (**1b**), 2.93 (**1c**), 3.73 (**1d**) and 2.96 (**1e**). It should be recognized, of course, that the small size of the water molecule and the availability of two OH donor sites, in combination with the cooperative H_2O-H_2O interactions, enhances the effectiveness of water as a H-bond donor solvent.

For the slower DA reaction of **2** with **3** and **4** essentially similar results are obtained (Table 2), but the rate enhancements going to water as the solvent are smaller. The hydrogen-bonding effect is also less pronounced. Finally, the data show that the DA reaction of **2** with **3** is retarded rather than accelerated in micellar SDS and CTAB solutions.

Thermodynamic activation parameters

For organic reactions in a highly structured solvent like water, an interpretation of medium effects is usually couched in terms of transition-state theory (ref. 21). A rather informative plot is shown in Fig. 1 (ref. 20). Gibbs energies of activation for the DA reaction of **1e** with **2** show a trend with the Dimroth-Reichardt solvatochromic parameter $E_T(30)$. It appears that there is a stronger dependence on $E_T(30)$ for the protic solvents as compared with that for the aprotic solvents, but the regression coefficients for both lines are poor (r_{protic}= 0.919; $r_{aprotic}$= 0.737). Again, water is a much better solvent for the DA reaction than suggested on the basis of the trend of $\Delta^{\neq}G^{\ominus}$ *vs.* $E_T(30)$. Isobaric activation parameters for the DA reaction of **2** with **1c**, **1e**, and **3** in water and 1-propanol are listed in Table 3. The Gibbs energies of activation are 10-15 kJ.mole^{-1} more favorable in water as compared with the alcohol. Both the enthalpies and entropies of activation contribute to this reduction of $\Delta^{\neq}G^{\ominus}$ in water, but usually the entropic term is the dominating effect.

TABLE 1. Second-order rate constants for the DA reaction of **1a-e** with **2** in selected organic solvents and in water at 25°

	$10^3 \cdot k_2$ (M^{-1}s^{-1})				
Solvent	**1a**	**1b**	**1c**	**1d**	**1e**
n-hexane	21.2	5.37	1.08	0.509	0.435
acetonitrile	92.2	21.6	6.28	5.35	3.90
ethanol	158	45.0	14.8	10.0	12.2
1-propanol	228	64.9[c]	19.6	13.2[c]	14.8[c]
TFE [a]	3520	867	438	291	326
HFP [b]	13100	3080	1690	988	1880
water	25000	8870	4950	3690	5560

[a] 1,1,1-Trifluoroethanol.

[b] 1,1,1,3,3,3- Hexafluoro-2-propanol.

[c] Rate constant in 2-propanol.

TABLE 2. Second-order rate constants for the DA reaction of **3** and **4** with **2** in selected organic solvents and in water at 25°C

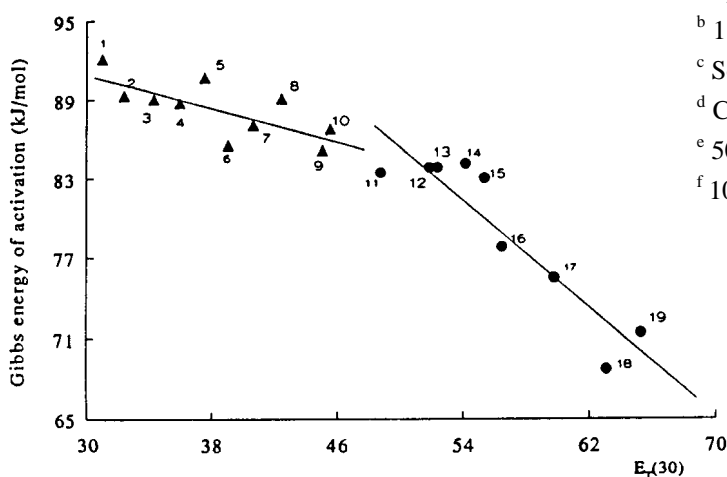|	$10^3 \cdot k_2$ (M^{-1}s^{-1})	
Solvent	**3**	**4**
acetonitrile	0.175	0.00885
ethanol	0.839	0.0200
1-propanol	0.912	0.0304
TFE[a]	8.72	0.0950
HFP[b]	17.5	0.200
water	50.8	0.629
water + SDS[c,e]	45.6	
water + SDS[c,f]	40.5	
water + CTAB[d,e]	29.5	
water + CTAB[d,f]	20.8	

[a] 1,1,1-Trifluoroethanol.

[b] 1,1,1,3,3,3-Hexafluoro-2-propanol.

[c] Sodium n-dodecylsulfate.

[d] Cetyltrimethylammonium bromide.

[e] 50 mmol in 1 kg of water.

[f] 100 mmol in 1 kg of water.

Fig. 1. Gibbs energies of activation for the DA reaction of **1e** with **2** in n- hexane (1), CCl$_4$ (2), benzene (3), 1,4-dioxane (4), THF (5), CHCl$_3$ (6), CH$_2$Cl$_2$ (7), acetone (8), DMSO (9), CH$_3$CN (10), 2-PrOH (11), EtOH (12), N-methyl- acetamide (13), N-methyl- formamide (14), MeOH (15), glycol (16), TFE (17), H$_2$O (18), HFP (19).

Endo-exo product ratios. Medium effects in alcohol-water mixtures

The endo/exo product ratios for the reaction of **2** with **3** have been determined over the whole mole fraction scale in MeOH-H$_2$O, EtOH-H$_2$O, 1-PrOH-H$_2$O and t-BuOH-H$_2$O at 25°C (ref. 17). The preference for the endo product is greatly enhanced in water: [endo]/[exo]= 10(MeOH), 7(t-BuOH) and 21 (H$_2$O). Similar results were obtained for ethyl vinyl ketone as the dienophile.

TABLE 3. Isobaric activation parameters for the DA reaction of **2** with **1c**, **1e**, and **3** in 1-propanol and water at 25°C

Dienophile	$_\Delta{}^{\#}G^{\ominus}$	$_\Delta{}^{\#}H^{\ominus}$	$-T_\Delta{}^{\#}S^{\ominus}$
	kJ.mol^{-1}	kJ.mol^{-1}	kJ.mol^{-1}
1c	83.05[a]	42.9(0.6)	40.1(0.6)
	69.42[b]	36.6(0.4)	32.8(0.5)
1e	83.44[a]	43.3(1.0)	40.2(1.0)
	68.91[b]	40.5(0.7)	28.4(0.7)
3	90.37[a]	45.1(0.7)	45.3(0.7)
	80.35[b]	39.4(0.7)	40.9(0.7)

[a] In 1-propanol. [b] In water.

TABLE 4. First-order rate constants for the IMDA reaction of N-furfuryl-N-alkylacryl-amides in different solvents

R$_1$	R$_2$	Solvent	T	k$_1$
			°C	(s^{-1})
Me	CO$_2$H	CH$_2$Cl$_2$	25	$2.36.10^{-5}$
		MeCN	25	$9.27.10^{-5}$
		EtOH	25	$3.09.10^{-4}$
		H$_2$O	25	$2.50.10^{-2}$
Me	H	EtOH	60	[a]
		H$_2$O	60	$2.05.10^{-5}$

[a] No observable conversion after a reaction time of 3 weeks.

Intramolecular DA reactions

The intramolecular DA (IMDA) reaction is an important transformation in the construction of polycyclic ring systems (ref. 22). In the substrate the diene and dienophile are already brought together and it was of particular interest to examine whether water is also a favorable medium for the unimolecular activation process. An extensive study has been made (ref. 17, 23), from which we have selected the kinetic data shown in Table 4 for the IMDA reaction of N-furfuryl-N-alkylacrylamides (Scheme 2) in different solvents. It is evident that the rate enhancements in water as compared to organic solvents resemble those for the intermolecular DA reactions. NMR studies reveal that the large rate enhancement in water cannot be attributed to a preference for the s-cis conformation of the substrate in aqueous solution. For example, for the substrate with R$_1$=Me and R$_2$=CO$_2$H, the equilibrium constants [s-cis]/[s-trans] were found to be 1.05 (CHCl$_3$), 1.03 (MeOH), 0.94 (acetone-d$_6$) and 1.2 (H$_2$O).

Evidence against diene/dienophile association in water

In previous studies it has been envisaged (ref. 9) that association of the DA reaction partners could be responsible for increased local concentrations of diene (DI) and/or dienophile (DIP) leading to acceleration of the bimolecular reaction. One can then distinguish between homotactic (i.e. DI-DI or DIP-DIP) association and heterotactic (DI-DIP) association. Similar favorable entropy effects for bimolecular processes have been identified for catalytic effects in the presence of surfactant aggregates and cyclodextrines. We contend, however, that such effects are not operative for the DA reaction of **2** with **1a-e**, **3** and **4**, at least under the conditions of the kinetic measurements. The evidence (ref. 17, 19) includes the following. (1) Vapor pressure measurements for **2** in water and in 10% (w/w) 1-PrOH-H$_2$O show nonideal behavior only at concentrations beyond 0.03M, and 0.06M, respectively. Since the concentration of **2** in the kinetic experiments was always kept below 0.002M, aggregation of **2** appears to be ruled out. (2) The DIP's **3** and **4** are highly soluble in water. During the kinetic measurements the concentration of **3** was always below 0.01M and vapor pressure measurements again display no evidence for nonideal behavior. (3) The concentration of **1a-e** in the kinetic measurements was $\leq 5.10^{-5}$M, which makes association unlikely. (4) The second-order rate constants for the DA reactions in water were independent of the substrate concentrations, even when **2** was present in a large excess. Finally, (5), we note that the large rate enhancements for the IMDA reactions are not easily reconcilable with homo- or heterotactic association.
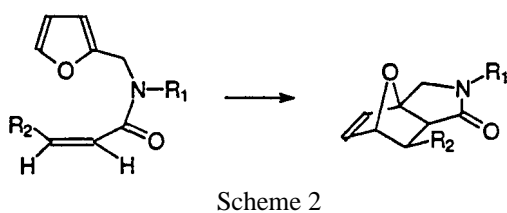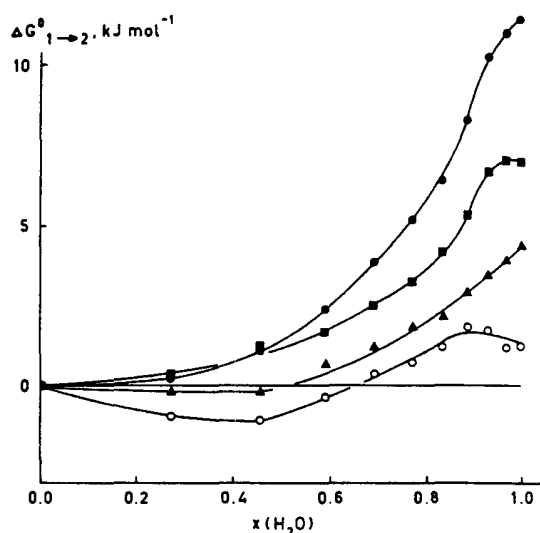
Scheme 2

Fig. 2.Standard Gibbs energies of transfer for IS and AC of the DA reaction of **2** with ethyl vinyl ketone (**5**) from 1-PrOH to 1-PrOH-H_2O mixtures as a function of the mole fraction of water; **2**, ■; **5**, ▲; IS, ●; AC, ○.

Initial state vs. transition state effects. Enforced hydrophobic interaction and hydrogen bonding

Solvent effects on rate constants reveal differences in interactions of the solvent with the initial state (IS) and the activated complex (AC). A pseudothermodynamic analysis allows a distinction between both effects. In this analysis, the difference in $_\Delta^\#G^\Theta$ for reaction in the solvents S_1 and S_2, is combined with Gibbs energies for transfer of the substrate(s) from S_1 to S_2. The results (ref. 18, 19) for the DA reaction of **2** with ethyl vinyl ketone (**5**) in 1-PrOH-H_2O over the whole mole fraction range are shown graphically in Fig. 2. Standard Gibbs energies of transfer were obtained from vapor pressure measurements using a GC technique. Similar results have been found for the reaction of **2** with **3**. The results lead to the following conclusions. The IS (**2** + **5**) is strongly destabilized in the water-rich region (x(H_2O) >0.8). This effect is dominated by the contribution of the rather hydrophobic **2**, but the hydrophobicity of **5** is revealed by the positive $\Delta G^\circ_{1\to2}$ as well. By contrast, there are only minor changes in $\Delta G^\circ_{1\to2}$ for the AC over the whole solvent composition range. These results imply that the rate acceleration in water and in the water-rich mixtures is primarily caused by destabilization of the IS relative to the AC. In the absence of substrate association (*vide supra*), we submit that two factors are of major importance in determining this difference in solvation behavior of the IS and AC. The first is hydrogen-bonding; the AC is more polarized than the IS, and the polarized carbonyl moiety of the AC will be better stabilized by hydrogen-bonding than the carbonyl group of the IS. This enhanced hydrogen-bonding of water to the AC was also proposed on the basis of Monte Carlo simulations (ref. 12) and ab initio MO calculations (ref. 13) and is in line with the relatively high rates of the DA reactions in TFE and HFP (*vide supra*). The second effect involves enforced hydrophobic interaction (ref. 17, 18, 20). The *activation process* of the concerted cycloaddition reaction involves a reduction of the hydrophobic surface area of the reaction partners, leading to a gain in Gibbs energy relative to nonaqueous solvents. This effect is not equivalent to "hydrophobic packing" of diene and dienophile in water, which may well lead to a complex with a geometry different from that of the AC. The contribution of both effects is further supported by analysis of our kinetic data for the reaction of **1d** with **2** in a series of solvents employing the KOMPH2 correlation equation (ref. 24). We like to stress that the relative contribution of both effects to the rate acceleration in water will critically depend on the nature of diene and dienophile. As argued by Jorgensen (ref. 13) small charge variations in the AC relative to the IS will induce large differences in hydrogen-bonding. The operation of the hydrophobic effect provides a rational for the preference for the endo isomer in the reaction of **2** with **3** and **5** in

water (*vide supra*) and for the small increase of k_2, relative to water, upon addition of 1-2 mole % of 1-PrOH or *t*-BuOH (ref. 17, 19). A detailed comparison of the solvent effects on the DA reaction of **2** with **3** and **4** (ref. 20) led to the unexpected result that **4** is less hydrophobic than **3** despite the fact that the sulfonyl moiety is a weaker hydrogen-bond acceptor than the carbonyl group. This finding can be rationalized by assuming that **4** accepts four hydrogen bonds in water while the carbonyl group can accept only two hydrogen-bonds.

Summary and outlook

The DA reaction is not unique in exhibiting large rate accelerations in water. The effect has now been established for a whole series of other synthetically important organic reactions. Although further detailed studies are clearly necessary, the available data gives reason to believe that the hydrophobic and hydrogen-bonding effects, operative for the (IM)DA reactions in water, are also affecting the activation process of these reactions. It is a considerable challenge to further accelerate these organic transformations in water by carefully designed (chiral) catalysts. This could lead to a highly beneficial combination of medium and catalytic effects. There seems to be no doubt that research on organic reactions in water has been revitalized.

Acknowledgement

I have summarized work that has been carried out by Dr. W. Blokzijl, S. Otto and J.W. Wijnen. I am greatly indebted to these friends for their contributions and for sharing my interest in water as a medium for organic reactions.

REFERENCES

1.   D.C Rideout and R. Breslow, *J.Am.Chem.Soc.* **102**, 7816 (1980).
2.   Ch. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim (1988).
3.   P.A. Grieco, *Aldrichim. Acta* **24**, 59 (1991).
4.   A. Lubineau, *J.Org.Chem.* **51**, 2142 (1986).
5.   E.T. Kool and R. Breslow, *J.Am.Chem.Soc.* **110**, 1596 (1988).
6.   E. Brandes, P.A. Grieco and J.J. Gajewski, *J.Org.Chem.* **54**, 517 (1989). J. Gao, *J.Am.Chem.Soc.* **116**, 1563 (1994).
7.   C-J. Li, *Chem.Rev.* **93**, 2023 (1993).
8.   E.M. Kirschner, *Chem.Eng.News* **72** (25), 13 (1994).
9.   R. Breslow, *Acc.Chem.Res.* **24**, 159 (1991).
10.   P.A. Grieco, J.J. Nunes and M.D. Gaul, *J.Am.Chem.Soc.* **112**, 4595 (1990).
11.   J.J. Gajewski, *J.Org.Chem.* , **57**, 5500 (1992).
12.   J.F. Blake and W.L. Jorgensen, *J.Am.Chem.Soc.* **113**, 7430 (1991).
13.   J.F. Blake, D. Lim and W.L. Jorgensen, *J.Org.Chem.* **59**, 803 (1994).
14.   H.J. Schneider and N.K. Sangwan, *Angew.Chem.Int.Ed.Engl.* **26**, 896 (1987).
15.   R. Breslow, ACS Symp. Series Nr. 568: Structure and Reactivity in Aqueous Solution (1994), in press.
16.   W. Blokzijl and J.B.F.N. Engberts, *Angew.Chem.Int.Ed.Engl.* **32**, 1545 (1993).
17.   W. Blokzijl, M.J.Blandamer and J.B.F.N. Engberts, *J.Am.Chem.Soc.* **113**, 4241 (1991).
18.   W. Blokzijl and J.B.F.N. Engberts, *J.Am.Chem.Soc.* **114**, 5440 (1992).
19.   W. Blokzijl, Ph.D. Thesis, University of Groningen, (1991).
20.   S. Otto, W. Blokzijl and J.B.F.N. Engberts, *J.Org.Chem.* ; 1994, in press.
21.   J.B.F.N. Engberts in *Water. A Comprehensive Treatise*, F. Franks, Ed., Plenum, New York, Ch.4 (1979).
22.   W.R. Roush, *Adv.Cycloaddit.* **2**, 91 (1990).
23.   W. Blokzijl and J.B.F.N. Engberts, to be published.
24.   J.J. Gajewski, ACS Symp. Series Nr. 568: Structure and Reactivity in Aqueous Solution (1994), in press.