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A hetero retro Diels-Alder reaction in aqueous solution

Wijnen, J.W; Engberts, J.B.F.N.

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Department of Organic and Molecular Inorganic Chemistry, University of Groningen,
Nijenborgh 4, NL-9747 AG Groningen, The Netherlands
Fax: (internat.) +31(0)50/3634296
E-mail: J.B.F.N.Engberts@chem.rug.nl

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aqueous medium on the rate constants for the forward and reverse reaction. In water, the former reaction is accelerated and the latter is retarded. The deceleration of the retro reaction in water is due to hydrogen-bond stabilization of the adduct. The influence of cosolvents and micelles on the cycloreversion is discussed.

As part of our efforts to grasp the molecular origin of the aqueous accelerations we have examined cycloreversions^[3,9]. These processes are the reverse of bimolecular cycloadditions, but due to their unimolecular nature they are relatively insensitive to hydrophobic effects. Previous

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Several reports on DA reactions of nitroso compounds in water have been published. The bimolecular process is accelerated in water^[14]. An elegant application of aqueous hetero DA methodology was reported by Kibayashi. Despite their susceptibility to hydrolysis, acylnitroso compounds can be intramolecularly trapped and in water this process proceeds more efficiently and with high diastereoselectivity^[15].

Results and Discussion

Table 1 lists the equilibrium constants (K) of the HRDA reaction in a number of solvents. The results are in poor agreement with data of Ahmad and Hamer^[12], but we attribute this to the high concentrations used in their study. However, the observation that K increases in polar and protic solvents is consistent with previous findings^[12,13]. The exceptional effect of water resembles data for bimolecular DA reactions. The equilibrium constant is lowest in *n*-hexane and, amongst the organic solvents, is highest in 2,2,2-trifluoroethanol (TFE). However, the value of K determined in water far exceeds that found in any of the other media.

Table 1. Equilibrium constants for the HRDA reaction of **1a**, second-order rate constants for the cycloaddition of **2** with **3b** and the apparent first-order rate constants^[a] for the cycloreversion of **1a** in organic solvents and in water at 25.0°C

Solvent	K (M ⁻¹)	$10^2 \cdot k_2$ (M ⁻¹ s ⁻¹)	$10^4 \cdot k_{-1}^{app}$ (s ⁻¹)
Hexane	6.6	^[b]	-
Toluene	12.5	0.96	7.68
Chloroform	24.0	1.18	4.92
Ethanol	35.3	1.10	3.12
1-Propanol	36.1	1.25	3.46
Methanol	43.1	1.10	2.55
DMSO	59.1	2.51	4.25
Formamide	219	6.83	3.12
TFE ^[c]	618	3.74	0.61
HFIP ^[d]	^[e]	5.27	-
Water	5775	42.5	0.74

^[a] The ratio (k_2/K) is defined as the apparent first-order rate constant of the cycloreversion (see text). - ^[b] Deviations from first-order kinetics were observed for the addition of **2** to **3b**, which prevented reliable determination of the rate constant. - ^[c] 2,2,2-Trifluoroethanol. - ^[d] 1,1,1,3,3,3-Hexafluoroisopropyl alcohol. - ^[e] No equilibrium was established due to an unidentified side reaction. Since both **2** and **3a** are stable in HFIP we conclude that **1a** also decomposes in another way.

Equilibrium constants are the ratio of the rate constants of the forward and reverse reaction ($K = k_2/k_{-1}$)^[16] and consequently the high K -value in water could be the result of either a fast forward reaction or a slow cycloreversion (or a combination of these factors). Due to the reverse reaction the second-order rate constants for the addition of **2** to **3a** could not be determined and therefore the addition of **2** to 1,3-cyclohexadiene **3b** was used as a model. In this way, the “apparent” first-order rate constant of the HRDA can be estimated ($k_{-1}^{app} = k_2/K$). These rate constants are also compiled in Table 1. The data show that the large K -value in water is indeed the result of both a fast bimolecular cycloaddition and a slow retro reaction.

The effect of the medium on the cycloaddition of **2** to **3b** follows the familiar pattern found for DA reactions, with polar solvents promoting the reaction and water providing maximum acceleration. This is in accord with previous studies on this system^[14]. The Gibbs energy of activation of Diels-Alder reactions can be dramatically reduced in fluorinated alcohols^[4,8], but in the present study the effect is rather modest, and this may be attributed to the poor ability of **2** to act as a hydrogen-bond acceptor^[17]. Formamide is the best organic solvent for the cycloaddition, and this suggests that the cohesive energy density (CED) of the solvent plays an important role in this hetero DA reaction. The high rate constant of the bimolecular reaction in water significantly contributes to the high K . However, **3b** is more hydrophobic than **3a** and therefore the “aqueous acceleration” for the DA reaction of **2** with **3a** is expected to be less dramatic than that for the model reaction. Consequently, the “apparent” first-order rate constant of the cycloreversion of **1a** underestimates the retardation of the cycloreversion in water.

Interestingly, the HRDA reaction responds inversely to a change of solvent. It is clearly retarded in water, and the decomposition proceeds most efficiently in nonpolar solvents. This may be attributed to the smaller water-accessible surface area of the adduct, which is about 62% of the surface area of the reactants^[18]. However, the reaction rate is determined by the difference in Gibbs energy between the reactants and the activated complex. Since the activated complex will surely resemble the adduct, it will have a similar water-accessible surface area. Furthermore, it is known that this activated complex is quite polar, as indicated by the Hammett ρ -value of +2.57 for the addition of **2** to **3b**^[19]. Therefore, we contend that hydrophobic interactions are unlikely to affect the HRDA. These results indicate that the adduct is stabilized in water (relative to the activated complex), presumably as a result of hydrogen bonding of water which hinders the cycloreversion. The hydrogen-bond accepting ability of a solute can be easily assessed by studying the IR spectrum of phenol in tetrachloromethane in the presence of the relevant compound^[20]. Hydrogen bonding results in a new, broad band at a lower frequency than the free OH vibration and the ν_{OH} -shift correlates with the enthalpy of hydrogen bonding. In the presence of **1b**, two ν_{OH} -shifts (at 229 and 422 cm⁻¹) are observed^[21], which confirms that the adduct is a better hydrogen-bond acceptor than **2** (110 cm⁻¹)^[17]. This is in agreement with the fact that isoxazolidines are strong bases with pK_a values of around 4–5^[22], whereas **2** has a pK_a of around 0^[23]. The inhibition of the HRDA reaction is in sharp contrast with the promotion of homo RDA reactions in water^[8] and this demonstrates that hydrogen bonding of water can either facilitate or hinder pericyclic reactions. The hetero RDA reaction appears to be one of the few examples of a pericyclic reaction that is inhibited by water. We have found that the rate constants for 1,3-dipolar cycloadditions of aromatic nitrones or nitrile oxides to electron-poor dipolarophiles are also reduced in water^[24].

Figure 1 shows that upon addition of alcohols to water, the reduction of K parallels the effect of alcohols on the rate constants of bimolecular DA reactions^[4]. Hydrophobic alcohols induce a reduction of K at low mole fractions. A notable difference with the bimolecular DA reaction is the absence of maxima in the K -value at specific low mole fractions of alcohol ($X_{1-\text{PrOH}} \approx 0.05$, $X_{t\text{BuOH}} \approx 0.025$)^[4,7,8]. In the bimolecular DA reactions, an additional acceleration is observed at these mole fractions of hydrophobic cosolvents, which has been attributed to enhanced enforced hydrophobic interactions^[4]. However, these cosolvents do not further increase the K -value for the HRDA reaction, confirming the notion that hydrophobic interactions are not the dominant factor in determining the equilibrium constant.

Figure 1. Equilibrium constants of the HRDA reaction of **1a** in water/alcohol mixtures at 25.0°C: cosolvents: MeOH (■), EtOH (○), 1-PrOH (▼), *t*BuOH (Δ)

In Figure 2, the equilibrium constant, the second-order rate constant for the bimolecular process and the “apparent” first-order rate constants in water/1-propanol mixtures are compared. The data suggest that in these media essentially the same factors are operative as in the pure solvents: higher concentrations of water induce a rate enhancement of the bimolecular process and a retardation of the HRDA reaction. The overall effect thus leads to the high K in pure water. The Gibbs energy for this equilibrium changes most significantly in the highly aqueous media.

The problem of the low solubility of reactants in water can be overcome by the use of micellar solutions. It has been shown that the rate constants of bimolecular DA reactions are of roughly the same order in such media as in water^[7,8,25,26]. The specific hydrogen-bond activation of the reactants by water is reduced in micellar solutions, but for bimolecular reactions this is largely compensated by the increased local concentration of reactants in the micelle. Figure 3 shows that in solutions containing sodium *n*-dodecyl sulfate (SDS) micelles, the formation of the adduct is promoted. Both the forward addition and the cycloreversion are promoted in these media. Since the effect of the bimolecular process is dominant, the overall result is an increased K . The rate enhancement of the cycloaddition is impressive and is much larger than previously reported ac-

Figure 2. Gibbs energy for the equilibrium of the HRDA reaction of **1a** (■) (displaced upwards by 100 kJ mol⁻¹ for clarity), Gibbs energy of activation for the addition of **2** to **3b** (○) and the cycloreversion of **1a** (Δ) in water/1-PrOH solutions at 25.0°C

celerations of 10-20% for neutral DA reactions^[8,25]. It is likely that the interaction of **1a** with the micelles leads to a decreased hydrogen bonding of water to the adduct, thus facilitating decomposition. It is noteworthy that the reproducibility of the kinetic data becomes rather poor when the SDS concentration is just above the critical micelle concentration (CMC). This could be due to a sensitivity of the rate constants to the exact composition of the reaction medium, i.e. the ratio of reactants to surfactant. It is known that the properties of the micelles are very susceptible to small variations of this ratio^[27].

Figure 3. Relative equilibrium constant of the HRDA reaction of **1a** (■), relative second-order rate constants of the addition of **2** to **3b** (○) and relative first-order rate constant of the cycloreversion of **1a** (Δ) in SDS solutions at 25.0°C

Conclusions

The equilibrium constant for the cycloreversion of **1a** is dramatically increased in water. This is due to *both* an acceleration of the bimolecular DA reactions *and* an inhibition of the hetero cycloreversion relative to organic solvents.

Experimental Section

Synthesis and Product Analysis: All reagents and solvents were purchased from Aldrich. 3,6-Dihydro-1,2-oxazine **1a** was synthe-

sized by following a known procedure^[12,28]; 300 mg of nitrosobenzene **2** and a large excess of freshly distilled cyclopentadiene **3a** were mixed in 25 ml of anhydrous diethyl ether. After the characteristic blue colour of the nitrosobenzene had vanished, the ether and excess cyclopentadiene were removed in vacuo. The remaining oil was dissolved in *n*-pentane and the resulting solution was slowly cooled to -80°C, thereby affording **1a** as a white solid, m.p. 33°C (lit.^[28]: 32-34 °C).

Kinetic Experiments: Water was twice distilled and the organic solvents were either analytical grade or distilled before use. Determinations of the equilibrium constants of the HRDA reaction were carried out by injecting a known amount of a stock solution of **1a** in acetonitrile into cuvettes that contained a known amount of solvent. The reaction was followed in a thermostatted (25 ± 0.1 °C) cell holder (1 cm) using a UV/Vis spectrometer (Perkin-Elmer Lambda 2, 5 or 12). The formation of **2** was monitored at 308 nm. After establishing that **1b** does not absorb at this wavelength, the extinction coefficients of nitrosobenzene in all solvents were measured, using three different concentrations (reproducibility ±2%). Most equilibrium constants were determined by preparing the adduct **1a** in situ by mixing known amounts of **2**, **3a** and acetonitrile (typically 0.01 g of **2**, 0.02-0.1 g of **3b** in 1 ml of acetonitrile) and injecting 5-10 µl of this stock solution into cuvettes containing 3-3.5 ml of solvent. This procedure led to results with a reproducibility of ±4%. Similarly, the second-order rate constants of the addition of **2** to (distilled) **3b** were determined at 308 nm. An excess of **3b** ensured pseudo-first-order conditions. The reproducibility was within ±2%. The reproducibility of the data in the micellar solutions containing 10 and 20 mM of SDS was ±10% (see text).

¹H-NMR Spectroscopy: Solutions of **1a** in CDCl₃ and D₂O/CD₃OD (*X_w* ≈ 0.95) showed the presence of **3a** [δ = 3.0 (CH₂), 6.47 and 6.58 (CH)], **2** [δ = 7.58-7.94] and the adduct **1a** [δ = 1.80 (d, 1H), 2.18 (d, 1H), 5.00 (s, 1H), 5.18 (s, 1H), 5.96 (m, 1H), 6.38 (m, 1H), 6.88-7.24 (m, 5H)].

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