A Hetero Retro Diels-Alder Reaction in Aqueous Solution: A Dramatic Water-Induced Increase of the Equilibrium Constant and Inhibition of Cycloreversion

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The adduct of the Diels-Alder reaction of nitrosobenzene with cyclopentadiene is not stable in solution. The equilibrium constant for the reaction depends strongly on the medium and water induces a spectacular shift to the adduct. Comparison with the bimolecular addition of nitrosobenzene to 1,3-cyclohexadiene enables separation of the effect of the 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.

Introduction

The ever growing interest in “chemistry in water” has led to the investigation of many organic transformations in aqueous media[1]. Despite practical problems, such as the low solubility or instability of organic compounds in water, a surprising number of organic reactions can be successfully carried out in aqueous solvents. Undoubtedly, pericyclic reactions are the showpiece in this field of research, because in organic solvents these reactions are rather insensitive to a change of medium[2,3], and water appears to be one of the very few solvents that can actually promote them[4]. Diels-Alder (DA) reactions[4-5] and Claisen rearrangements[6-8] have been particularly well-documented. Many synthetic applications have been reported and kinetic and thermodynamic investigations have shed light on the origin of these water-promoted cycloadditions[4,5]. Water efficiently stabilizes the activated complex of both reactions and the bimolecular DA reaction is additionally promoted by enforced hydrophobic interactions[4,5], due to the reduction of the water-accessible surface area on going from the reactants to the activated complex. By selecting two reactions in which either hydrogen bonding or enforced hydrophobic interactions are of negligible importance, it is possible to separate and quantify the two contributions[7,8]. Hydrogen bonding of water has a pronounced influence on the magnitude of the “aqueous accelerations” and therefore the number of substituents and their susceptibility to hydrogen-bond interactions are of immediate importance.

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 studies have shown that the homo retro DA reaction of a substituted anthracenedione is facilitated by protic solvents[10], and since water is an excellent hydrogen-bond donor this cycloreversion proceeds rapidly in aqueous media[11]. Grieco has reported efficient water-promoted retroaza DA reactions and demonstrated that N-alkyl-2-azonorbornenes readily decompose in water, whereas in organic solvents rigorous reaction conditions are required[11].

Scheme 1

In this paper we describe a hetero Diels-Alder (HRDA) reaction in water. The adduct of the Diels-Alder reaction of nitrosobenzene 2 with cyclopentadiene 3a is unstable and cycloreverts in solution, thereby establishing an equilibrium between the reactants and adduct[12,13] (Scheme 1). In organic solvents the cycloreversion follows perfect first-order kinetics at low concentrations, because the bimolecular reaction does not interfere. Therefore, we were particularly interested when we found deviating kinetics upon monitoring this retro cycloaddition in water. $^1$H-NMR spectroscopy revealed that in highly aqueous media the equilibrium constant ($K$) is remarkably increased, so that under our experimental conditions both reactants and adduct are present in solution. The equilibrium constants can be determined more easily using UV/Vis spectroscopy, because at 308 nm only nitrosobenzene has an absorbance.

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

**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\textsuperscript{[2]} 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\textsuperscript{[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\textsuperscript{[a]} for the cycloreversion of 1a in organic solvents and in water at 25.0°C.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(K) (s(^{-1}))</th>
<th>(10^4, k_2) (s(^{-1}))</th>
<th>(10^4, k_1) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>6.6</td>
<td>[21]</td>
<td>-</td>
</tr>
<tr>
<td>Toluene</td>
<td>12.5</td>
<td>0.96</td>
<td>7.68</td>
</tr>
<tr>
<td>Chloroform</td>
<td>24.0</td>
<td>1.18</td>
<td>4.92</td>
</tr>
<tr>
<td>Ethanol</td>
<td>35.3</td>
<td>1.10</td>
<td>3.12</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>36.1</td>
<td>1.25</td>
<td>3.46</td>
</tr>
<tr>
<td>Methanol</td>
<td>43.1</td>
<td>1.10</td>
<td>2.55</td>
</tr>
<tr>
<td>DMSO</td>
<td>59.1</td>
<td>2.51</td>
<td>4.25</td>
</tr>
<tr>
<td>Formamide</td>
<td>219</td>
<td>6.83</td>
<td>3.12</td>
</tr>
<tr>
<td>TFE\textsuperscript{[c]}</td>
<td>618</td>
<td>3.74</td>
<td>0.61</td>
</tr>
<tr>
<td>HFIP\textsuperscript{[d]}</td>
<td>-</td>
<td>5.27</td>
<td>-</td>
</tr>
<tr>
<td>Water</td>
<td>5775</td>
<td>42.5</td>
<td>0.74</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} The ratio \((k_2/K)\) is defined as the apparent first-order rate constant of the cycloreversion (see text). \textsuperscript{[b]} Deviations from first-order kinetics were observed for the addition of 2 to 3b, which prevented reliable determination of the rate constant. \textsuperscript{[c]} 2,2,2-Trifluoroethanol. \textsuperscript{[d]} 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 \((K = k_2/k_1)\)\textsuperscript{[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\textsuperscript{[14]}. The Gibbs energy of activation of Diels-Alder reactions can be dramatically reduced in fluorinated alcohols\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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 \(\rho\)-value of +2.57 for the addition of 2 to 3b\textsuperscript{[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\textsuperscript{[20]}. Hydrogen bonding results in a new, broad band at a lower frequency than the free OH vibration and the \(\nu_{OH}\)-shift correlates with the enthalpy of hydrogen bonding. In the presence of 1b, two \(\nu_{OH}\)-shifts (at 229 and 422 cm\(^{-1}\)) are observed\textsuperscript{[21]}, which confirms that the adduct is a better hydrogen-bond acceptor than 2 (110 cm\(^{-1}\))\textsuperscript{[17]}. This is in agreement with the fact that isoxazolines are strong bases with \(pK_a\) values of around 4-5\textsuperscript{[22]}, whereas 2 has a \(pK_a\) of around 0\textsuperscript{[23]}. The inhibition of the HRDA reaction is in sharp contrast with the promotion of homo RDA reactions in water\textsuperscript{[10]} 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\textsuperscript{[24]}.
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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 ($X_{1-PrOH} \approx 0.05$, $X_{tBuOH} \approx 0.025$)$^{[4,7,8]}$. 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.

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 accelerations 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$^{[27]}$.

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 nitrosoben- zene 2 and 1.0 g of freshly distilled cyclohexane 3a were mixed in 25 ml of anhydrous diethyl ether. After the characteristic blue colour of the nitrosobenzene had vanished, the ether and excess cyclohexane 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 ad- duct 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 3.35 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).

$^1$H-NMR Spectroscopy: Solutions of 1a in CDCl$_3$ and D$_2$O/CD$_3$OD (X$_{D_2O}$ = 0.95) showed the presence of 3a (δ = 3.0 (CH$_3$), 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)].


