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Hydrophobic Effects in 1,3-Dipolar Cycloaddition of *C,N*-Diphenylnitrone with Dibutyl fumarate in Aqueous Solutions†

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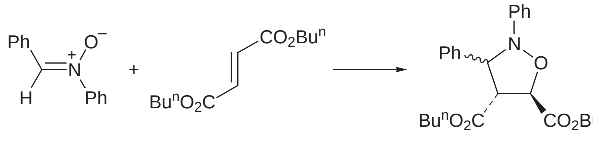
The reaction rate of 1,3-dipolar cycloaddition of *C,N*-diphenylnitrone with dibutylfumarate increases dramatically in aqueous solutions relative to other solvents.

Water is one of the least popular solvents in synthetic organic chemistry. However, the use of water as solvent has obviously environmental and economic advantages relative to other solvents. Studies in the last decade have revealed that a number of organic reactions proceed more rapidly in aqueous solutions than in organic solvents.[1,2] The Diels–Alder reaction has been most extensively studied and acceleration of this reaction in aqueous solutions has been attributed to two factors: enforced hydrophobic interactions and the hydrogen-bonding capacity of water.[3–8]

Mechanistically, 1,3-dipolar cycloadditions are related to Diels–Alder reactions, but curiously for these reactions little attention has been paid to applications of water as a solvent.[9] The reaction rate of 1,3-dipolar cycloaddition between phenylazide and norbornene in water is ten times as fast as that in propan-2-ol; this enhancement of the reaction rate is attributed to hydrophobic forces.[9]

The kinetics of the cycloaddition reaction between nitrones and dipolarophiles in aqueous solutions have not been studied and this led us to investigate the reaction of *C,N*-diphenylnitrone with dibutyl fumarate in aqueous solutions and other solvents at 65 °C (Scheme 1).



Scheme 1

Results and discussion

Second-order rate constants of the reaction between *C,N*-diphenylnitrone and dibutylfumarate were obtained in various solvents (Table 1). It is observed that the solvent effect is small and rate constants of the reaction decrease with increase of solvent polarity. This is due to the high polarity of reactants in comparison with the activated complex. Among the solvents, water has highest polarity and it might be expected that the rate constant of the reaction in water should be much less than that in ethanol. Kinetic measurements, however, show that the reaction in water is approximately 126 times faster than that in ethanol, hence it can be stated that the polarity of solvent is not an important factor for the rate of reaction in aqueous solutions. Ethylene glycol is a water-like solvent,[10] and the rate of the reaction in this solvent is approximately 18 times that in ethanol. The rate of the reaction in water increases with upon addition of 2M LiCl, NaCl or KCl and decreases with addition of 2M urea. The alkali metal salts decrease solubility of apolar solutes in water and the salting-out effect of these salts is well understood.[6] Urea, by contrast, increases the solubility of apolar solutes in water (for this reason urea is one of the denaturating materials of proteins), and hence the hydrophobicity of the reactants decreases.

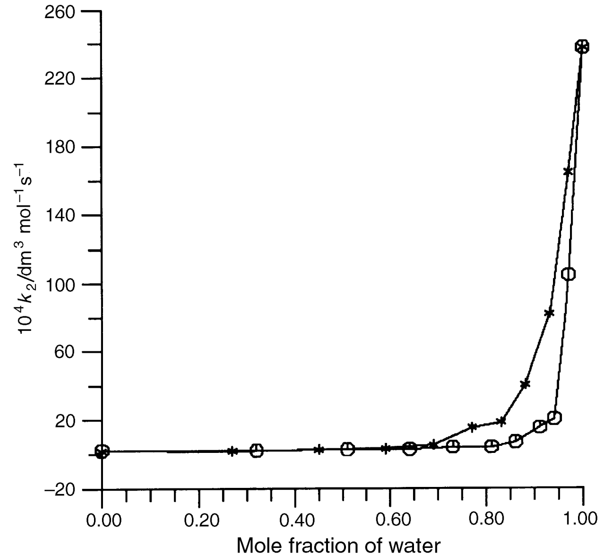


Fig. 1 Second-order rate constants of the reaction in various aqueous solutions of ethanol(*) and propan-1-ol(○) *vs*. mole fraction of water.

Table 1 Second-order rate constants of the reaction between dibutyl fumarate with *C,N*-diphenylnitrone in various solvents at 65 °C[a]

Solvent	$10^4k_2/\mathrm{dm^3\ mol^{-1}\ s^{-1}}$	E_T/kcal mol^{-1}	Solvent	$10^4k_2/\mathrm{dm^3\ mol^{-1}\ s^{-1}}$	E_T/kcal mol^{-1}
n-Hexane	19.4 ± 1.7	31	EtOH	1.9 ± 0.1	51.9
Toluene	5.8 ± 0.17	33.9	Ethylene glycol	34.9 ± 2.2	56.3
Benzene	5.6 ± 0.1	34.3	Water	237 ± 8	63.1
THF	5.9 ± 0.2	37.4	Water + 2M LiCl	985 ± 13	
DMF	2.5 ± 0.1	43.8	Water + 2M NaCl	924 ± 12	
2-PrOH	3.1 ± 0.1	48.4	Water + 2M KCl	876 ± 16	
1-PrOH	2.2 ± 0.1	50.9	Water + 2M Urea	142 ± 5.8	

[a] At least three runs were averaged: errors are standard deviations.

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Second-order rate constants of the reaction in various aqueous solutions of ethanol and propanol were obtained (Fig. 1). The increase of the reaction rate at low mole fractions of water is not rapid, since in this region water structure with high hydrogen bonding capacity is not involved. The rate of the reaction in aqueous solutions of ethanol increases more rapidly compared with the solutions in propan-1-ol. This is due to the fact that propan-1-ol increases the solubility of reactants in water (similarly to urea) more than ethanol and so the hydrophobicity of reactants in propan-1-ol is decreased more than in ethanol. The observations seen here are similar to those observed for Diels–Alder reactions.[11,12] Therefore during the activation process in the reaction of two apolar reactants, unfavorable water contacts with reagents are reduced and this is most likely a major driving force for the rate enhancement in aqueous media.

Experimental

Materials.—*C,N*-Diphenylnitrone and dibutyl fumarate were synthesized according to the literature.[13–15] All solvents of highest available purity were distilled before use. Water was redistilled in a quartz distillation unit.

Kinetic Measurements.—The rate of the reaction was studied spectrophotometrically (the spectrophotometer being coupled to a PC) by monitoring the decrease of the *C,N*-diphenylnitrone absorbance of wavelengths from 310 nm (in water) to 324 (in benzene). Thermostated water was circulated around the cell of the spectrophotometer and the temperature was maintained at 65 ± 0.1 °C. Concentrations of *C,N*-diphenylnitrone and dibutyfumarate were 7.7×10^{-5} and 8.2×10^{-4} (in water) and 1.65×10^{-1} M (in other solvents), respectively. All rate constants of the reaction were obtained by the initial rate method. In order to retard the hydrolysis of *C,N*-diphenylnitrone, the pH of aqueous solutions were adjusted to 7.[16]

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