



## 1,3-Dipolar Cycloaddition of Phenyl Azide to Norbornene in Aqueous Solutions

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**Abstract** : Second-order rate constants for the cycloaddition of phenyl azide to norbornene were determined in aqueous solutions. In organic solvents this reaction shows a very small solvent effect. In highly aqueous media, however, remarkable accelerations are observed. The solvent dependence of the rate constants on solvent composition in mixed aqueous solutions resembles those observed for Diels-Alder reactions, most likely because both types of cycloadditions are mechanistically related.

Water is one of the least popular solvents in synthetic organic chemistry. This is not only due to the rather low solubility of many organic compounds in water, but also because of the rather aggressive nature of this solvent : numerous compounds are readily hydrolysed in aqueous solution. However, the use of water has obvious environmental and economic advantages and recent studies have revealed a number of organic reactions that proceed more rapidly and efficiently in aqueous solution than in organic solvents<sup>2</sup>. Particularly pericyclic reactions have drawn considerable attention, because these types of reactions were notoriously solvent-insensitive. The Diels-Alder reaction has been most extensively studied and the acceleration of this reaction in aqueous solution has been attributed to two factors<sup>3</sup>. The hydrogen-bonding capacity of water leads to polarisation of the substituents of the dienophile, comparable to the activating effect of Lewis acids. Secondly, enforced hydrophobic interactions increase the reaction rate. During the activation process the hydrophobic surface of the reactants is reduced, thereby minimizing unfavorable interactions between the apolar reactants and water.

The use of water as a solvent for Diels-Alder reactions allows mild reaction conditions, thus avoiding formation of side-products. Aqueous Diels-Alder reactions generally lead to high yields and a number of reactions have been reported that only proceed efficiently in aqueous solutions<sup>2</sup>. Therefore it would be synthetically interesting to investigate whether aqueous media have similar advantageous effects on other cycloadditions.

Mechanistically 1,3-dipolar cycloadditions are related to Diels-Alder reactions, but curiously very little attention has been paid to applications of water as a solvent for these reactions. 1,3-Dipolar cycloadditions are widely used for the synthesis of five-membered heterocycles<sup>4</sup>. Like the Diels-Alder reaction it is described by the designation  $[\pi^4_s + \pi^2_s]$  and both transformations share a number of features. The two reactions are reversible and are characterized by a concerted, nearly synchronous reaction mechanism with an early, highly ordered transition state, a negative volume of activation and a high stereospecificity. Frontier Molecular

Orbital theory has been successfully applied to explain many intriguing aspects of these reactions.

The effect of different organic solvents on 1,3-dipolar cycloadditions is as characteristic as the one observed for Diels-Alder reactions : usually reaction rates hardly differ on changing the solvent<sup>4,5</sup>. The small solvent effect seems to be dependent on the nature of the reactants since rate constants can either increase or decrease with increasing solvent polarity.

In 1991 Shiraishi<sup>6</sup> reported an unusual acceleration of the 1,3-dipolar cycloaddition of 2,6-dichlorobenzonitrile N-oxide to 2,5-dimethyl-p-benzoquinone. The second-order rate constant increases by an unusually large factor of fourteen on changing the medium from chloroform to an ethanol-water mixture (60:40 (v:v)). Comparison with kinetic data for conventional organic solvents demonstrates that this acceleration is unusually large. Except for the rate increase, the use of the aqueous solvent has another practical advantage, since precipitation of the product facilitates work-up procedures. These kinetic data may be compared with the results of Hegarty<sup>8</sup> which revealed an increase of the second-order rate constant of the cycloaddition of p-nitrobenzonitrile N-oxide to ethyl acrylate or dimethyl maleate of less than a factor of two on changing the solvent from 1:1 water-dioxane to water. Previously Kadaba<sup>7</sup> had already observed an acceleration of the diazomethane addition to N-arylidenearylamines when small amounts of water were added to the organic solvent.

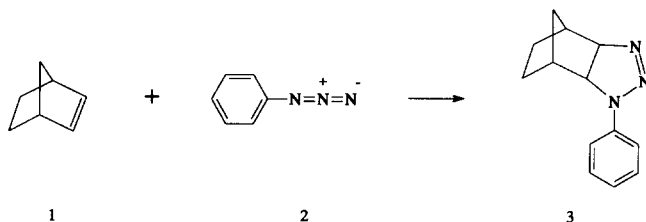


Fig. 1

In this communication we wish to report kinetic data that show that 1,3-dipolar cycloadditions are markedly accelerated in water-rich solutions. The reaction of norbornene **1** and phenyl azide **2** yields triazoline **3** (Figure 1). Detailed kinetic studies by Scheiner<sup>9</sup> have confirmed the typical mechanistic features of a 1,3-dipolar cycloaddition for this reaction.

The kinetics of this reaction have been studied in organic solvents and in water-alcohol mixtures (using water of pH 12 to prevent nitrogen elimination of the triazoline)<sup>10</sup>. The data in Table 1 demonstrate the small sensitivity of the rate constant of this reaction towards different organic solvents. In highly aqueous media, however, the cycloaddition is significantly accelerated. In water containing 1 mol % of 1-cyclohexyl-2-pyrrolidinone (NCP) an unprecedented increase of the reaction rate by a factor of 53 (relative to n-hexane) is observed. It is obvious that rate enhancements of this magnitude may be exploited in organic synthesis.

The dependence of the second-order rate constants on the mole fraction of water in water-alcohol mixtures

**Table 1 :** Second-order rate constants for the cycloaddition of phenyl azide to norbornene at 40.3°C in various solvents<sup>a</sup>

Solvent	$10^5 \cdot k_2$ ( $M^{-1}s^{-1}$ )	Solvent	$10^5 \cdot k_2$ ( $M^{-1}s^{-1}$ )
n-Hexane	4.7	EtOH	7.4
THF	5.3	2-PrOH	8.2
$CHCl_3$	6.8	t-BuOH	8.0
$CCl_4$	5.5	H <sub>2</sub> O/MeOH (75:25)	35
$CH_3CN$	7.7	H <sub>2</sub> O/EtOH (75:25)	37
DMSO	17.5	H <sub>2</sub> O/2-PrOH (92:8)	83
DMF	11.3	H <sub>2</sub> O/t-BuOH (94:6)	72
MeOH	7.3	H <sub>2</sub> O/NCP <sup>b</sup> (99:1)	250

<sup>a</sup> Rate constants were determined using the initial rate method as described by Scheiner<sup>9</sup>. Second-order rate constants are the average of at least three kinetic runs. The molar ratio of the aqueous mixtures is indicated between brackets. <sup>b</sup> NCP = 1-cyclohexyl-2-pyrrolidinone.

is akin to that for aqueous Diels-Alder reactions (Figure 2). The initial addition of water to alcohol enhances the reaction rate moderately, but at higher water concentrations a more marked increase of the reaction rate is observed. The specific mole fractions of water at which the water-induced accelerations become clearly apparent increase in the order MeOH < EtOH < 2-PrOH < t-BuOH, which reflects the increasing

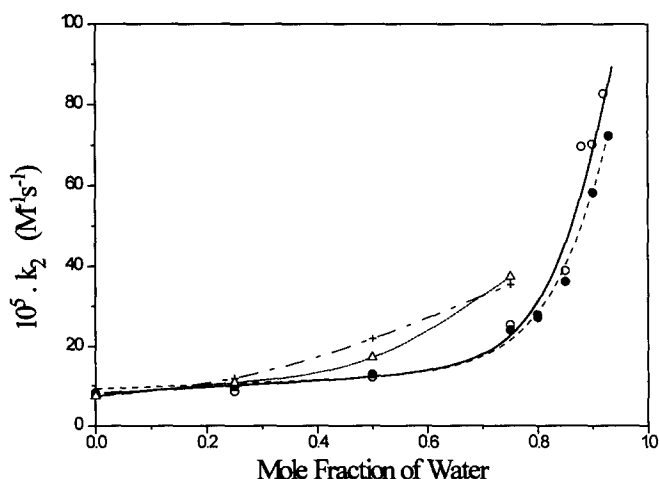


Fig. 2. Second-order rate constants for the cycloaddition of 1 to 2 in alcohol-water mixtures at 40.3°C. + : MeOH;  $\Delta$  : EtOH;  $\circ$  : 2-PrOH;  $\bullet$  : t-BuOH

hydrophobicity of the alcohols. Numerous studies have revealed that above these specific mole fractions solute-solute interactions are largely governed by hydrophobic effects<sup>11</sup>. We note that reaction of the two apolar reactants reduces the unfavorable water contacts during the activation process and this is most likely a major driving force for the rate enhancement in aqueous media. It is unlikely that this 1,3-dipolar cycloaddition is accelerated by hydrogen-bonding interactions. Unfortunately the limited solubility of the reactants prevented kinetic studies in pure water. However, further mechanistic studies are in progress to elucidate the detailed nature of the observed aqueous acceleration of this reaction and to determine how general this phenomenon is for 1,3-dipolar cycloadditions.

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10. The reaction has also been performed on a synthetic scale in ethanol and aqueous ethanol. <sup>1</sup>H NMR-analysis showed that the only product was the triazoline **3**, m.p. 101°C (lit.<sup>9</sup> 101-102°C)
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