

1,3-Dipolar Cycloadditions of Benzonitrile Oxide with Various Dipolarophiles in Aqueous Solutions. A Kinetic Study

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The second-order rate constants for the 1,3-dipolar cycloaddition of benzonitrile oxide (**1**) with various dipolarophiles (**2a–e**) were determined in aqueous media and in organic solvents to gain more insight into the influence of an aqueous medium on pericyclic reactions. 1,3-Dipolar cycloadditions with electron-poor dipolarophiles are accelerated in water and protic solvents, whereas an aqueous medium has no special effect when electron-rich dipolarophiles are involved. These observations can be explained using frontier molecular orbital theory. In all cases, enforced hydrophobic interactions promote the reaction. These results are supported by kinetic experiments in water–ethanol mixtures. Sodium dodecyl sulfate micelles accelerate the cycloaddition of **1** with both electron-rich and electron-poor dipolarophiles. More than for other systems, the present results show that hydrogen bonding and hydrophobic interactions can either cooperate or counteract each other in determining the kinetic medium effects in aqueous solutions.

Introduction

Water has never been a popular medium in organic chemistry. Chemists who use water as a solvent are often confronted with practical problems such as limited solubility of the reactants or the “aggressive” nature of water toward organic compounds. However, since the eighties, the use of water as a solvent in organic chemistry has become an active field of research.¹

One of the reasons for this rediscovery of water as a reaction medium is the search for new synthetic procedures in organic chemistry which are more environmentally friendly or can lower the cost of industrial processes. Furthermore, water is in several respects a unique solvent and can affect a chemical reaction in various ways. For example, organic reactions can be accelerated or the endo/exo ratio of the products of cycloadditions can be changed when a reaction is performed in water instead of in the usual organic solvents.^{2,3}

The special effects of water on chemical reactions are due to several interaction mechanisms.³ In particular, hydrophobic interactions, which largely stem from the limited ability of water to dissolve apolar molecules, are of importance. Also, the capacity of water to act as both a hydrogen-bond donor and a hydrogen-bond acceptor can have major effects on chemical transformations.

A growing group of organic reactions appears to benefit from aqueous media. Among them are 1,2- and 1,4-nucleophilic additions to carbonyl groups,⁴ epoxidations

of olefins,⁵ Mannich reactions,⁶ halogenations,⁷ and polymerizations.⁸ Two reactions of the class of pericyclic reactions, the Claisen rearrangement⁹ and particularly the Diels–Alder reaction,^{10–14} are the best examples of reactions that take advantage of an aqueous reaction medium.

In general, the rate of a Diels–Alder reaction is quite solvent insensitive, but in 1980, Breslow¹⁰ discovered a striking rate enhancement of this reaction in water. He attributed this acceleration to hydrophobic effects. Ever since this publication, the Diels–Alder reaction has been extensively studied in aqueous solutions^{3,11} and at present it is widely accepted that two factors contribute to these

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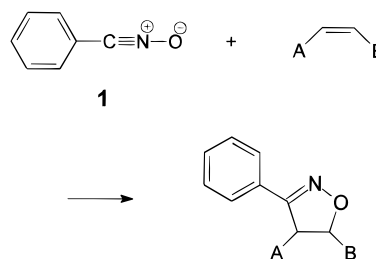
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accelerations in aqueous media. First, the enhanced hydrogen bonding of water (in combination with the polarity of water) often stabilizes the transition state compared to the initial state, thereby increasing the rate of the reaction. Second, enforced hydrophobic interactions^{3a} promote Diels–Alder reactions in water. This phenomenon is related to the fact that the water-accessible surface area of the activated complex is reduced compared to that of the hydrated reactants. Computer simulations have confirmed that the acceleration of aqueous Diels–Alder reactions is due to these two factors.¹² The magnitude of both effects depends on the nature of the reactants. Recently, Diels–Alder reactions have been examined for which either hydrogen-bond interactions¹³ or enforced hydrophobic interactions¹⁴ can be neglected. These studies revealed that enhanced hydrogen bonding of water to the activated complex is often the major factor for the aqueous accelerations of Diels–Alder reactions.

After the success of the Claisen rearrangement and the Diels–Alder reaction in aqueous solutions, it seems likely that 1,3-dipolar cycloadditions, another representative of the class of pericyclic reactions, could also benefit from water as the reaction medium. This idea is supported by the fact that 1,3-dipolar cycloadditions and Diels–Alder reactions share many mechanistic features, in particular the fact that both reactions are concerted, nearly synchronous processes with an early transition state.¹⁵ In fact, the dipolarophiles in 1,3-dipolar cycloadditions act as dienophiles in Diels–Alder reactions.

1,3-Dipolar cycloadditions with nitrile oxides yield 2-isoxazolines or isoxazoles, which are useful intermediates in organic synthesis, and still much research is focused on extending the synthetic possibilities.¹⁶ A common medium for 1,3-dipolar cycloadditions with nitrile oxides is a biphasic aqueous/organic mixture.¹⁷ In these mixtures, the 1,3-dipoles are generated *in situ*, which is necessary because of the instability of the dipole. In 1978, Hegarty¹⁸ was the first to demonstrate that water could act both as a base for the generation of the dipole from benzohydroxamoyl chloride and as a medium for the consecutive 1,3-dipolar cycloaddition. He performed the cycloadditions of *p*-nitrobenzotrile oxide with ethyl acrylate and dimethyl maleate in various media. No unusual beneficial effect of pure water on the rate of cycloaddition was observed (the rate constant in water was roughly twice the rate constant in a 1:1 mixture of water and 1,4-dioxane). However, in 1991, a 14-fold increase of the rate constant for the addition of 2,6-dichlorobenzotrile oxide to 2,5-dimethyl-*p*-benzoquinone in a mixture of ethanol and water (6:4, v/v) relative to that in chloroform was reported by Shiraishi.¹⁹ Compared to the usual solvent effects observed for 1,3-dipolar cycloadditions, this rate enhancement is rather large. No relationship between spectroscopic data of the reactants and the rate acceleration was found, and no

Scheme 1



further attempts were made to investigate the origin of this kinetic medium effect. The aqueous reaction medium also had a synthetic advantage: the product precipitates during the reaction, which facilitates isolation of the product. Yields are higher than in organic media, and recrystallization of the product is not necessary.

Another application of water as a medium for 1,3-dipolar cycloadditions was reported by Rohloff.²⁰ Dibromoformaldoxime decomposes into nitrile oxide in alkaline water, after which it smoothly and in high yields adds to dipolarophiles. In this case, also, the synthetic advantages of an aqueous medium were emphasized.

Following Grigg,²¹ Lubineau²² has studied the reaction between azomethine ylides and *N*-ethylmaleimide in aqueous solutions. In this case, a mixture of products arising from a Michael addition and a 1,3-dipolar cycloaddition is obtained. Curiously, water promotes the Michael addition and organic cosolvents are required to direct the reaction toward the desired cycloaddition pathway.

The 1,3-dipolar cycloaddition of phenyl azide with norbornene in aqueous solutions has also been studied.²³ Kinetic data revealed a remarkable rate acceleration in water-rich solutions compared with conventional organic solvents. Hydrophobic interactions were considered to be the prime accelerating factor for the rate enhancement. Herein we describe an extensive study of the kinetics of 1,3-dipolar cycloadditions of benzonitrile oxide with various dipolarophiles in several organic and aqueous media.

Results and Discussion

1,3-Dipolar Cycloadditions of Nitrile Oxides in Water and in Organic Solvents. Second-order rate constants for the 1,3-dipolar cycloadditions of benzonitrile oxide (1) with various dipolarophiles (Scheme 1) were determined using UV spectroscopy. It is known that 1,3-dipolar cycloadditions can be performed with both electron-rich and electron-poor dipolarophiles.¹⁵ We chose cyclopentene (2a) and 2,3-dihydrofuran (2b) as electron-rich dipolarophiles. In addition, we selected methyl vinyl ketone (2c), acrylonitrile (2d), and *N*-methylmaleimide (2e), which are dipolarophiles possessing electron-

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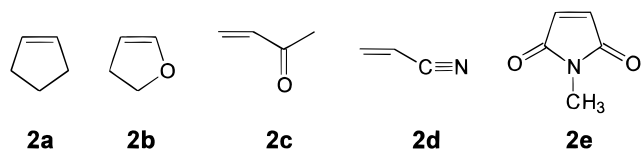
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withdrawing groups and are classified as electron-poor dipolarophiles.

The cycloadditions were studied in seven different solvents. Among them were the apolar and aprotic *n*-hexane and dichloromethane, which is used as the organic layer in the biphasic system in which 1,3-dipolar cycloadditions are generally performed. Furthermore, some protic solvents were used because hydrogen-bonding probably affects the reaction rate. We included 2,2,2-trifluoroethanol (TFE) because this solvent shows a "protic behavior" similar to that of water.²⁴ Low substrate concentrations were used in the experiments, allowing the use of water as a solvent. The kinetic results are collected in Table 1.

Comparing the second-order rate constants for the reactions in *n*-hexane and in water, it is interesting to see that the cycloadditions with the electron-rich dipolarophiles **2a** and **2b** are *accelerated* in aqueous solutions, whereas the aqueous medium has a small *rate-retarding* effect on the rate constants for the cycloadditions with the electron-poor dipolarophiles (**2c–2e**). Also of interest are the cycloadditions performed in TFE. The results of these measurements show a trend similar to that for the reactions in water: cycloadditions of nitrile oxide with electron-rich dipolarophiles **2a** and **2b** are accelerated, and cycloadditions of nitrile oxide with electron-poor dipolarophiles **2c–e** are strongly retarded in TFE, using *n*-hexane as the reference solvent. These results clearly signal the influence of hydrogen bonding of the solvent to the reactants (positive for electron-rich dipolarophiles, negative for electron-poor dipolarophiles). We contend that water affects these 1,3-dipolar cycloadditions through this mechanism.

We suggest an explanation for these results in terms of the frontier molecular orbital (FMO) theory, which has been used extensively to explain and predict reactivity in 1,3-dipolar cycloadditions.²⁵ This theory states that the Gibbs energy of activation is related to the energy gap between the (dominant) interacting HOMO and LUMO. The energies of HOMO and LUMO can be experimentally assessed (ionization potential and electron affinity, respectively) or theoretically estimated. For a number of common reactants in 1,3-dipolar cycloadditions, Houk²⁶ has calculated the energy of the FMOs. The results of these calculations are in reasonable accord with experimental studies. For most 1,3-dipolar cycloadditions, a good correlation is observed between the Gibbs energy of activation and the ionization potential of the dipolarophile, in accordance with FMO theory.²⁷ FMO theory also accounts for stereoselectivity and regioselectivity: reactions take place in the direction of maximum HOMO–LUMO overlap.²⁸

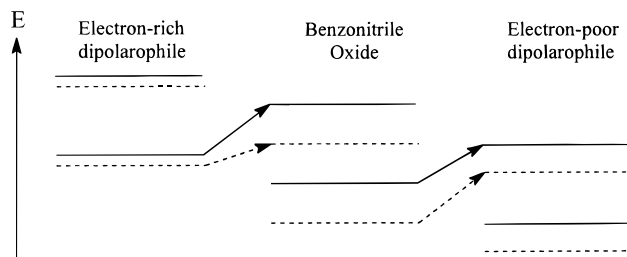


Figure 1. Schematic drawing of the levels of the FMOs of an electron-rich dipolarophile (**2a,b**, left), benzonitrile oxide (**1**, middle), and an electron-poor dipolarophile (**2a–c**, right). The solid lines depict the FMOs in *n*-hexane, and the dashed lines depict the FMOs in a protic solvent.

Table 1. Second-Order Rate Constants for the 1,3-Dipolar Cycloadditions of **1** with **2a–e** in Various Organic Solvents and in Water at 25.0 °C

	dipolarophile				
	2a $10^2 k_2$ ($M^{-1} s^{-1}$)	2b $10^3 k_2$ ($M^{-1} s^{-1}$)	2c $10 k_2$ ($M^{-1} s^{-1}$)	2d $10^2 k_2$ ($M^{-1} s^{-1}$)	2e $10 k_2$ ($M^{-1} s^{-1}$)
<i>n</i> -hexane	2.6	2.7	4.8	1.5	3.6
1,4-dioxane	1.7	3.7	1.8	1.3	1.2
dichloro- methane	1.2	2.9	0.9	0.6	0.7
dimethyl sulfoxide	2.7	10.9	2.3	3.1	3.0
2,2,2-trifluoro- ethanol	3.3	8.3	0.6	0.2	0.6
ethanol	2.3	6.3	3.3	1.4	2.2
water	8.5	30.0	3.0	1.1	2.6

The relative levels of the HOMO and LUMO of both reactants determine whether the HOMO(dipole)–LUMO(dipolarophile) interactions or the LUMO(dipole)–HOMO(dipolarophile) interactions are dominant. Furthermore, one should take into consideration that the levels of the FMOs can be affected by (de)stabilizing factors. For example, electron-withdrawing substituents stabilize the FMOs, whereas electron-donating substituents raise the FMO energy. Similarly, complexation of Lewis acids leads to a drop in FMO energy.²⁹ Hydrogen bonding is another factor that can promote cycloadditions by reducing the energies of the FMOs.³⁰

Figure 1 shows a schematic presentation of the levels of the FMOs of an electron-rich dipolarophile (left), benzonitrile oxide (**1**) (center), and an electron-poor dipolarophile (right). The solid lines represent the FMOs in hexane, and the dashed lines represent the FMOs in a protic solvent. Hydrogen-bond interactions can stabilize the FMOs of the reactants, and the magnitude depends on the susceptibility of the reactants toward such interactions. The preferred complexation of Lewis acids with nitrile oxides³¹ indicates that nitrile oxides are good Lewis bases. Therefore, the FMOs of these dipoles are substantially stabilized in protic solvents. The

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electron-rich dipolarophiles **2a** and **2b** are weak hydrogen-bond acceptors, which means that their FMOs are only slightly affected by hydrogen-bond interactions. Overall, both effects lead to a reduction of the energy gap between the interacting FMOs (in this case, the HOMO of the dipolarophile and the LUMO of the 1,3-dipole). Consequently, the Gibbs energy of activation of the reaction is reduced, and the reaction is accelerated in protic solvents, including water. For the reaction with the electron-poor dipolarophile, the dominating interaction is that between the HOMO of the 1,3-dipole and the LUMO of the dipolarophile. The electron-poor dipolarophiles are relatively good hydrogen-bond acceptors, leading to a reduction of the levels of the FMOs in protic solvents. However, we assume that this interaction is less efficient than that between the nitrile oxide and protic solvents, in view of the known examples of Lewis acid inhibition of the 1,3-dipolar cycloadditions of acrylates with aromatic nitrones^{31a} or aliphatic nitrile oxides.^{31b} This means that the Gibbs energy of activation is increased for this reaction, leading to a retardation of the cycloadditions of the nitrile oxide with electron-poor dipolarophiles in protic solvents.

However, we cannot account for all the results in Table 1; in particular, the differences in rate constants for the reactions in TFE and water (despite similar "protic" character²⁴) are not accounted for. We have to consider the fact that the (de)stabilizing influence on the FMOs is the sole solvent effect that is included in the FMO theory. Another contributor to aqueous accelerations of pericyclic reactions are enforced hydrophobic interactions.^{3a} Enforced hydrophobic interactions are a result of the reduction of the water-accessible surface area of the reactants during the activation process. For all cycloadditions in this study, this effect will exert a favorable influence on the rate of the reaction. We propose that the enforced hydrophobic interactions account for the larger rate constants in water compared to those for TFE. It is interesting to note that for cycloadditions in aqueous media hydrogen-bond interactions and enforced hydrophobic interactions can actually *counteract* each other. Because Diels–Alder reactions are controlled by the same mechanism, it is likely that these interactions also counteract in the case of specific Diels–Alder reactions in water. Indeed, the reaction of *p*-nitrostyrene with di-(2-pyridyl)-1,2,4,5-tetrazine is retarded by hydrogen-bond interactions (slow reaction in TFE), whereas this reaction is promoted by enforced hydrophobic interactions.³²

1,3-Dipolar Cycloadditions of Nitrile Oxides in Water–Ethanol Mixtures. We have also examined the cycloadditions of nitrile oxide with the five dipolarophiles in various ethanol–water mixtures. In Figure 2, the rate constants for these reactions are given relative to rate constants for the reaction in pure ethanol. All reactions show a maximum of the rate constant at a mole fraction of water of roughly 0.9. This observation is in line with similar results for Diels–Alder reactions, and for the latter reactions, this phenomenon has been attributed to cosolvent effects.³³ Small amounts of hydrophobic cosolvent increase hydrophobic interactions in water, further promoting bimolecular cycloadditions. However,

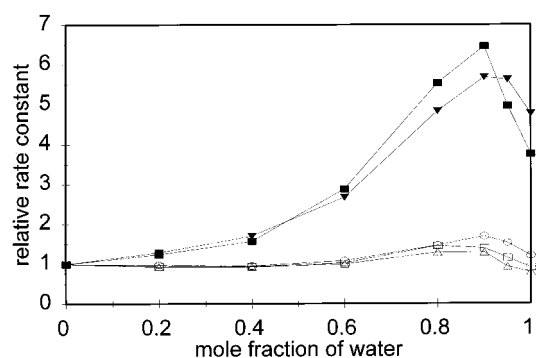


Figure 2. Second-order rate constants of the 1,3-dipolar cycloaddition of **1** with **2a** (■), **2b** (▼), **2c** (□), **2d** (△) and **2e** (○) in various ethanol–water mixtures at 25.0 °C, relative to the second-order rate constants in pure ethanol.

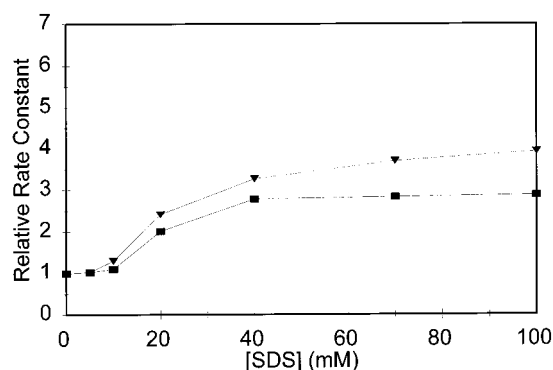


Figure 3. Second-order rate constants of the 1,3-dipolar cycloaddition of **1** with **2b** (■) and **2c** (▼) in micellar solutions of SDS at 25.0 °C, relative to the second-order rate constants in pure water.

beyond a certain concentration (about 10 mol % for ethanol) the hydrophobic hydration shells of the cosolvent molecules start to overlap significantly, which leads to the formation of cosolvent-rich domains and preferential solvation by ethanol of the reactants. Consequently, the reacting molecules no longer experience the unique driving force of hydrophobic acceleration.³⁴ This leads to a decrease of the reaction rate.

1,3-Dipolar Cycloadditions of Nitrile Oxides in Micellar Solutions. Finally, we have studied the effect of anionic micelles on the cycloaddition of **1** with **2b** and **2c**. Sodium dodecyl sulfate (SDS) with a critical micelle concentration (CMC) of 8.2 mM was used as surfactant. The results are depicted in Figure 3.

In both cases, an increase of the second-order rate constant is observed above the CMC. This is probably due to the fact that the hydrophobic dipolarophile is bound to the micellar surface. However, at higher concentrations of SDS, the rate is still increasing. Usually, the rate decreases at higher micelle concentrations because the reactants are "diluted" over an increasing number of micelles. This indicates that the binding of **1** to the micelles is relatively weak and that a high concentration of micelles is necessary for complete binding of **1**. Also, the fact that the wavelength at which maximum absorption of **1** takes place hardly shifts in the presence of micelles is indicative for the weak interactions between **1** and the micelles.

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Concluding Remarks

1,3-Dipolar cycloadditions of nitrile oxides in water illustrate how water affects bimolecular cycloadditions in general: (1) enforced hydrophobic interactions accelerate these bimolecular processes, because these interactions promote the transformation of two hydrophobically hydrated molecules into a less hydrophobic activated complex, and (2) the effect of hydrogen-bond interactions depends critically on the dominant HOMO–LUMO interaction for the reaction. Only if hydrogen bonding predominantly reduces the LUMO energy is the cycloaddition further accelerated. Consequently, an additional rate acceleration is only observed when the electron-poor reactant (usually the 2π species) is more susceptible to such interactions. Kinetic results for the 1,3-dipolar cycloaddition with nitrones in aqueous media are in line with this hypothesis.^{24,35}

Experimental Section

All compounds were purchased from Aldrich. Dipolarophiles **2a–d** were distilled before use. Solvents were either of the best quality available or distilled before use.

One 1,3-dipolar cycloaddition was performed on a synthetic scale. Thus, 1.6 g of pure benzaldoxime was added dropwise

under vigorous stirring to a solution of 1.6 g of styrene in a 50 mL household-bleach solution. The reaction mixture became warm, and a cream-colored solid spontaneously precipitated (3,5-diphenyl-2-isoxazoline; mp: 72–73 °C (lit.^{17c} 73–75 °C); ¹H NMR (CDCl₃): δ 3.34 (dd, 1H), 3.79 (dd, 1H), 5.75 (dd, 1H), 7.39 (m, 8H), 7.70 (m, 2H).³⁶

For all kinetic experiments, the following procedure was applied. Preparation of **1** was performed in a test tube by dissolving benzaldoxime in a bleach/dichloromethane two-phase system and shaking this tube for a few seconds. Several microliters of the organic phase were transferred into a quartz UV cell (1 cm) which contained the dipolarophile solution (dipolarophile in excess) and which was placed in a thermostated cell compartment of a Perkin-Elmer λ 2 spectrophotometer. The reactions were monitored at 273 nm at 25.0 °C, and pseudo-first-order rate constants were calculated using a PC fitting procedure (absorbance versus time). Starting concentrations were ca. 0.1 mM of benzonitrile oxide and 5–40 mM of dipolarophile. In all cases, isosbestic points were observed throughout the spectral change. In the absence of dipolarophile, the UV spectrum of **1** in water remained unchanged, which indicates that side reactions such as hydrolysis, isomerization, or dimerization are negligible. Each experiment was carried out at least three times. Rate constants were reproducible to within 4%.

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