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Unusual Solvent Effect on the Cycloadditions of Aromatic Nitrile *N*-Oxide with Alkyl Substituted *p*-Benzoquinones in Ethanol–Water Systems

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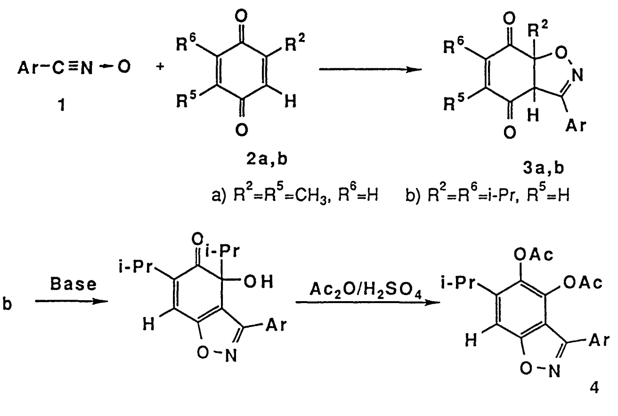
The second-order rate constants of 1,3-dipolar cycloaddition reactions of 2,6-dichlorobenzonitrile *N*-oxide (**1**) with 2,5-dimethyl-*p*-benzoquinone (**2a**) or 2,6-diisopropyl-*p*-benzoquinone in various solvents at 20 °C were determined by spectrophotometric method. The rate of **1** and **2a** in ethanol: water=60: 40 solution was 5.55×10^{-2} $dm^3\ mol^{-1}\ s^{-1}$, which was fourteen folds of that in chloroform (3.9×10^{-3} $dm^3\ mol^{-1}\ s^{-1}$). This solvent effect and the low solubility of the cycloadduct in aqueous ethanol were successfully applied to the cycloadduct synthesis.

Aromatic nitrile *N*-oxides undergo 1,3-dipolar cycloaddition with alkyl di-substituted *p*-benzoquinones (**2**) at their C=C double bond to give cyclohexenedione-fused 2-isoxazoline derivatives (**3**) in good yields.[1] Some of the cycloadducts were isomerized into isoxazole derivatives by base-induced ring system transformation,[2] and subsequently by dienone–phenol rearrangement-like reaction into isoxazole-fused catechol derivatives (**4**), which exhibit barnaclecide activity.[3]

In the synthetic pathway to the potentially useful compounds, the step of the nitrile *N*-oxide cycloaddition is desirable to enhance the reaction rate and to simplify workup processes involved. In benzene solution, the reaction had to be carried out for a day to complete the reaction. The product could be obtained after chromatographic separation and subsequent recrystallization to remove unreacted quinone. The rate constants of nitrile *N*-oxide cycloaddition in various solvents were reported mostly in the early seventies.[4] In general, there is little or only a little solvent effect on the rate, and an increase of solvent polarity causes slight decrease of the rate in the cycloaddition. Chang et al. reported[5] that the rate constant of cycloaddition of 2,4,6-trimethylbenzonitrile *N*-oxide with 1,2-bis(trifluoromethyl)fumaronitrile in acetone-d_6 was fourteen times smaller than that in benzene-d_6. This is the only report of solvent effect on the cycloaddition of nitrile *N*-oxide to a C=C double bond exhibiting over ten folds difference. Recently, Breslow and Rideout reported remarkable rate acceleration for the Diels–Alder reaction in aqueous media.[6] Therefore, it is of interest to investigate the cycloaddition reactivity of nitrile *N*-oxide in aqueous solution. As far as we know, the reactions of nitrile *N*-oxides with bases or other nucleophiles in aqueous dioxane solution were the only report of the reaction of nitrile *N*-oxides in aqueous solution[7] and no report has appeared to date as to the 1,3-dipolar cycloaddition of nitrile *N*-oxides in aqueous media.



Scheme 1. Cycloaddition reaction of nitrile *N*-oxide with alkyl substituted *p*-benzoquinones (**2a**—**b**) and subsequent ring conversion reaction of the cycloadduct **3b**.

In the present research, we have examined the cycloaddition reaction of nitrile *N*-oxide with substituted *p*-benzoquinones in aqueous ethanol or other organic solvents in order to optimize the cycloaddition conditions.

Experimental

Electronic spectra were recorded with JASCO Ubest-50 spectrometer. IR spectra of the nitrile *N*-oxide solutions were recorded with JASCO IR-700 spectrometer in KRS cell (cell length 0.1 mm). Liquid chromatography was performed with ODS column (Cica-Merck LiChrospher 100 RP-18, acetonitrile: water=70: 30, UV 254 nm). All the reactions and measurement were carried out at 20 °C.

Reagents and Solvents. 2,6-Dichlorobenzonitrile *N*-oxide (**1**) was prepared from corresponding benzaldehyde oxime by Grundmann's method[8] and recrystallized from aqueous ethanol. All the procedures were carried out keeping temperature below 40 °C to avoid isomerization. 2,5-Dimethyl-*p*-benzoquinone (**2a**) and 2,6-diisopropyl-*p*-benzoquinone (**2b**) were synthesized from corresponding alkyl-substituted phenols by oxidation using sodium dichromate-sulfuric acid.[9] Recrystallization from hexane and vacuum distillation were used for the purification of **2a** and **2b**, respectively. Organic solvents were obtained commercially and used after distillation with desiccants. Ion-exchanged water was further purified by ultrafiltration. Composition of the water–ethanol mixture was reported in volume per cent.

The Reactions of 1 with 2a; Kinetic Study. A sample solution containing **1** and **2a** (1.00×10^{-2} $mol\ dm^{-3}$ for each of the reactant) was prepared freshly, and the progress of the reaction was monitored by spectrometer at 20 °C. Amounts of the product (**3a**) were calculated from the absorbance around 380 nm, where n-π^* absorption of **3a** was observed. The rate constants k_2 were determined according to the second-order rate equation. The same procedure was applied for determination of rate constants of **1** and **2b**.

The Reactions of 1 with 2b; Syntheses of 7-(2,6-Dichlorophenyl)-1,3-diisopropyl-8-aza-9-oxa-[4.3.0]bicyclonona-3,7-diene-2,5-dione (3b). The reactions were carried out with 1.00 mmol for each of the reactant. Stirring conditions were kept at constant throughout all experiments. The progress of the reaction was followed by HPLC analyses. In all experiments, only the formation of **3b** was observed up to 60 min. The conversions were calculated from the peak intensity of unreacted **2b**. After the reaction, precipitated **3b**, if existed, was collected by filtration, dried in vacuo, and weighed.

Results and Discussion

The Kinetic Investigation of the Cycloaddition Reaction of 1 with 2a. The reactions of **1** with **2a** were carried out in various solvents. Figure 1 represents the typical spectral change during the reaction in ethanol. In all cases, isosbestic points were observed throughout the spectral change, and the time course of the reaction followed the second-order rate equation. Therefore, contribution of side reactions such as nitrile *N*-oxide isomerization or dimerization was thought negligible under these reaction conditions. IR spectra of the product isolated from the reaction mixture was identical with that of an authentic sample of **3a**. The rate constants of these reactions were summarized in Table 1.

In the case of organic solution, the reaction was slowest in chloroform and only four folds differences were observed for the solvents examined. But in ethanol : water=60 : 40 solution, over fourteen folds of acceleration compared to that in chloroform was observed. Further increase of water content resulted in precipitation of the product (**3a**) during the reaction, and the rate constants in aqueous ethanol containing more than 60 vol% could not be determined. Logarithmic plot of the rate constants vs. solvent polarity parameters, dielectric constants (ε),[10] and E_T values,[11] are shown in Fig 2.

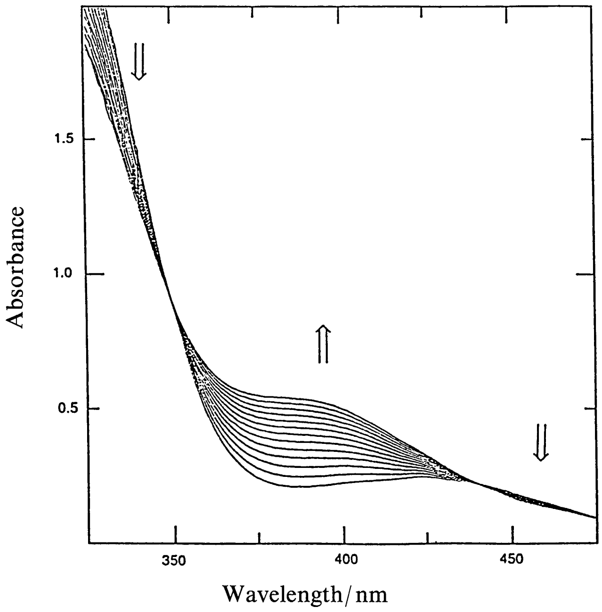


Fig. 1. Electronic spectra of **1** and **2a** in ethanol from 4 min to 64 min after the reaction was started. Substrate concentration; 1.00×10^{-2} mol dm^{-3}, Reaction temperature 20 °C.

Both curves have concave shapes, suggesting that the mode of solvent effect on the reaction is different in lower and higher region of the solvent polarity. At the lower side of the solvent polarity from cyclohexane to chloroform, the rate constants decreased as the polarity increased. In this region, rate constants exhibited normal correlation with solvent polarity.[4] But in the solvents of higher polarity, the rate constants increased as the polarity increased. Furthermore, the rate constant in ethanol : water=60 : 40 solution was fourteen times larger than that in chloroform. This solvent-induced rate acceleration is fairly large as the solvent effect on 1,3-dipolar cycloaddition reaction to C=C double bond. It is reported that the reaction of 2,4,6-trimethylbenzonitrile *N*-oxide and 1,2-bis(trifluoromethyl)fumaronitrile exhibits similar extent of solvent effect.[5] This reaction in acetone-d_6 containing water is fourteen times slower than that in benzene-d_6. In this reaction, the increase of solvent polarity caused the decrease of the rate constant. This is therefore still within the category of the normal solvent effect on 1,3-dipolar cycloaddition. However, the reaction of **1** and **2a** was accelerated in highly-polarized aqueous ethanol solvent. No other report of solvent effect exhibiting over ten folds of rate constants difference has appeared as nitrile *N*-oxide cycloaddition to C=C double or C≡C triple bond, and the results presented here are the unusual type of solvent effect on the nitrile *N*-oxide cycloaddition.

To understand this solvent effect, we tested the effect of solvation to the substrates (**1** and **2a**) and to the

Table 1. The Rate Constants of the Reactions of 2,6-Dichlorobenzonitrile *N*-Oxide (**1**) with 2,5-Dimethyl-*p*-benzoquinone (**2a**)$^{a)}$ at 20 °C

Solvents	$k_2\times10^{3\,b)}$/dm^3 mol^{-1} s^{-1}	
Cyclohexane	17.0	(4.4)
Benzene	5.5	(1.4)
o-Xylene	8.0	(2.1)
Chloroform	3.9	(≡1)
Ethyl acetate	5.4	(1.4)
Acetonitrile	7.1	(1.8)
Dimethyl sulfoxide	14	(3.5)
N,*N*-Dimethylacetamide	11	(2.8)
Ethanol	14.6	(3.8)
Ethanol : water=80 : 20	32.8	(8.5)
Ethanol : water=60 : 40	55.5	(14.2)

a) Substrate concentrations 1.00×10^{-2} mol dm^{-3}.
b) The numbers in parentheses represents the relative rate to that in chloroform.

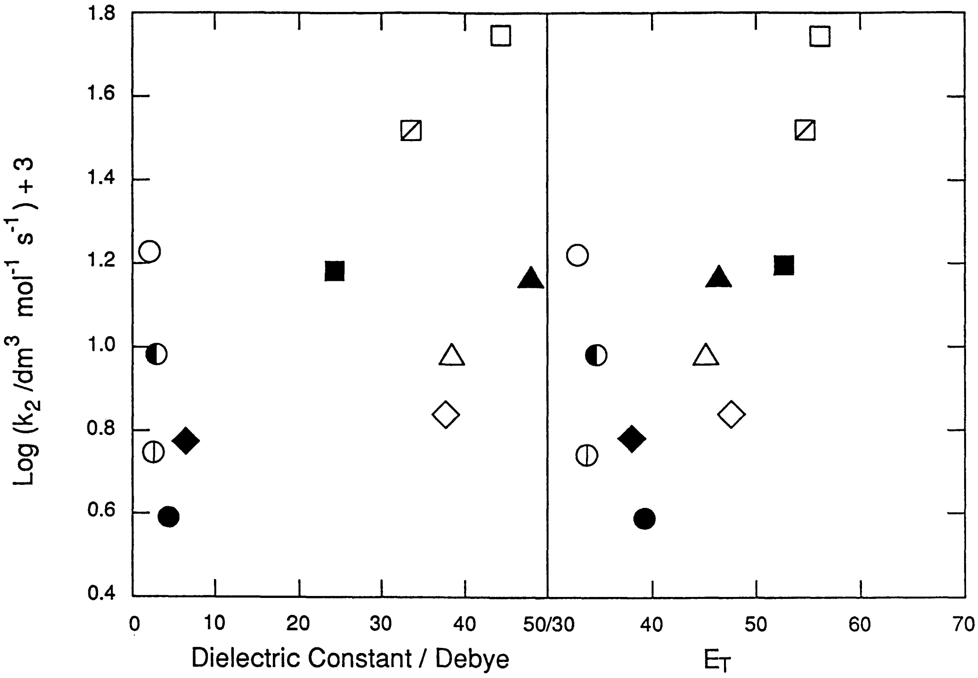


Fig. 2. The reaction of 2,6-dichlorobenzonitrile *N*-oxide (**1**) with 2,5-dimethyl-*p*-benzoquinone (**2a**); plot of $\log k_2$ vs. dielectric constant (ε) of the solvent and solvent parameters E_T.
○; cyclohexane, ⦶; benzene, ◐; *o*-xylene, ●; chloroform, ◆; ethyl acetate, ◇; acetonitrile, △; dimethyl sulfoxide, ▲; *N,N*-dimethylacetamide, ■; ethanol, ▨; ethanol : water=80 : 20, □; ethanol : water=60 : 40.

Table 2. $\nu_{\mathrm{C\equiv N}}$ of **1** in Solutions

Solvents	Wavenumber/cm^{-1}
Cyclohexane	2287
Benzene	2298.5
Chloroform	2306
Ethyl acetate	2301.5
Ethanol	2301
Ethanol : water=80 : 20	2303.5
Ethanol : water=60 : 40	2308.5
Solid (KBr pellet)	2306

Table 3. Absorption Maxima of **2a** in Various Solvents at 20 °C

Solvents	λ_{max}/nm ($\log\varepsilon$)		
Cyclohexane	446(1.39)	306(2.49)	251(4.37)
Benzene	442(1.40)	a)	a)
Chloroform	432(1.45)	317(2.46)	254(4.43)
Ethyl acetate	438(1.38)	312(2.44)	a)
Ethanol	425(1.39)	313(2.44)	251(4.32)
Ethanol : water=80 : 20	425(1.45)	318(2.46)	253(4.37)
Ethanol : water=60 : 40	424(1.46)	322(2.43)	254(4.32)

a) Could not be determined due to the absorption of solvent.

Table 4. Absorption Maxima of the *n*-π^* Band of **3a** in Various Solvents at 20 °C

Solvents	λ_{max}/nm ($\log\varepsilon$)
Cyclohexane	390 (2.10)
Benzene	389 (2.11)
Chloroform	388 (2.10)
Ethyl acetate	385 (2.10)
Ethanol	384 (2.10)
Ethanol : water=80 : 20	384 (2.07)
Ethanol : water=60 : 40	383 (2.07)

product (**3a**) by spectroscopic method. Peak positions of C≡N stretching band of **1** ($\nu_{\mathrm{C\equiv N}}$) in several solvents are summarized in Table 2, which might reflect the solvation to the nitrile *N*-oxide moiety of **1**. The $\nu_{\mathrm{C\equiv N}}$ increase monotonously as the solvent polarity increased (except for chloroform), and the direct relationship between $\nu_{\mathrm{C\equiv N}}$ and rate constants was not observed.

Absorption maxima of **2a** in different solvents are shown in Table 3. The band above 400 nm is assigned to be an *n*-π^* transition band and the stronger two bands are due to π-π^* transitions.[12] These three bands exhibited ordinary solvatochromic shifts, i.e., hypsochromic shift for *n*-π^* and smaller bathochromic shift for π-π^* as solvent polarity increased.

The effect of solvation to the product (**3a**) was examined by electronic spectroscopy. Table 4 shows the absorption maxima of *n*-π^* transition of **3a**. The band exhibited hypsochromic shift monotonously and the molar extinction coefficient of the absorption slightly decreased as solvent polarity increased. These results did not reproduce the different mode of solvent effect, and the observed rate difference could not be explained from the solvation of substrates or product. Therefore, other reasons, such as cage effect of the solvent or solvophobic effect⁽⁶⁾ of the substrates, may play a role in this unusual solvent effect.

Synthetic Application of Unusual Solvent Effect in Aqueous Ethanol Solutions. The Reaction of 1 with 2b. In an ethanol : water=50 : 50 solution, the precipitate of cycloadduct **3a** was formed soon after the solutions of **1** and **2a** were mixed, and the measurement of the time course of the reaction by electronic spectrum was unsuccessful. But this fact indicated that aqueous ethanol system offered two advantage over organic solvent systems from synthetic point of view. One is acceleration of the reaction rate and the other convenient isolation of the product. Therefore, we applied this solvent system to the cycloadduct synthesis.

For this purpose, 2,6-diisopropyl-*p*-benzoquinone (**2b**) was employed as a quinone reactant because the cycloadduct **3b** can be converted to isoxazole-fused catechol derivatives by base-catalyzed rearrangement.

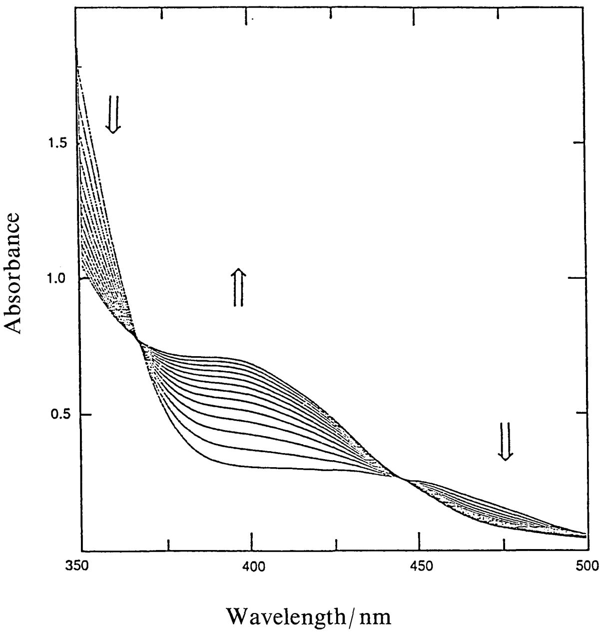


Fig. 3. Electronic spectra of **1** and **2b** in ethanol from 4 min to 64 min after the reaction was started. Substrate concentration; 1.00×10^{-2} mol dm^{-3}, Reaction temperature 20 °C.

Second order rate constants of **1** and **2b** in homogeneous media were determined by spectrophotometric method. Electronic spectra showed isosbestic points throughout the reaction, indicating the reaction proceeded without any side reactions (Fig. 3). The results are shown in Table 5. The rate constants are about twice as large as those of **1** and **2a**, and solvent effect on the rate is essentially the same as that on the reaction of **1** and **2a**. It was reported in the previous papers⁽¹³⁾ that the reactions of **1** and **2a** or **2b** were mainly controlled by HOMO(quinone)–LUMO(nitrile *N*-oxide) interaction. Therefore, the difference between the rate constants of **1** and **2a** and those of **1** and **2b** could be ascribed to the electron donating effect of isopropyl substituents of **2b**.

In this reaction, the formation of a precipitate of **3b** was observed in ethanol : water=60 : 40 system. The reaction in millimolar scale was carried out in this solvent system, and the results were shown in Table 6. Conversions determined from unreacted **2b** showed good correlation with the rate constants shown in Table 5. In the case of benzene which is frequently used as a solvent for cycloaddition of nitrile *N*-oxide, 69% of unreacted **2b** remained in the reaction mixture after 30 min. But in ethanol : water=60 : 40 solvent, the reaction almost completed within 30 min and 77% of **3b** could be isolated as a precipitate by simple filtration. The filtrate was pure **3b** containing neither unreacted quinone nor nitrile *N*-oxide, and this filtrate could be used directly for the subsequent base-induced rearrangement without further purification.

In conclusion, cycloaddition reactions of nitrile *N*-oxide with quinones exhibited unusual solvent effect and were accelerated in aqueous ethanol. In this reaction, the cycloadduct could be isolated as a precipitate in pure form. Therefore the synthesis of cycloadduct was successfully optimized.

Table 5. The Rate Constants of the Reactions of 2,6-Dichlorobenzonitrile *N*-Oxide (**1**) with 2,6-Diisopropyl-*p*-benzoquinone (**2b**) at 20 °C[a]

Solvents	$k_2\times10^3$/dm^3 mol^{-1} s^{-1}
Benzene	9.8
Ethanol	29.1
Ethanol : water=80 : 20	59.8

a) Substrate concentrations 1.00×10^{-2} mol dm^{-3}.

Table 6. The Reactions of 2,6-Dichlorobenzonitrile *N*-Oxide (**1**) with 2,6-Diisopropyl-*p*-benzoquinone (**2b**) at 20 °C[a]

Solvents	Conversions/%[b]		(Yield/%)
	30 min	60 min	
Benzene	31	54	(86%, 5 day[c])
Ethanol	52	63	
Ethanol : water=80 : 20	64	80	
Ethanol : water=60 : 40	81	87	(77% as precipitate, 1 hour)

a) Substrate concentrations 2.00×10^{-2} mol dm^{-3}. b) Calculated from unreacted **2b**. c) Ref. 1.

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