

Substrate Dependence in Aqueous Diels-Alder Reactions of Cyclohexadiene Derivatives with 1,4-Benzoquinone

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Abstract: A reactivity difference based on the position of substituents on cyclohexa-1,3-diene was observed for the title reaction. The effect of water as solvent was more distinct for 1-methyl-4-isopropylcyclohexa-1,3-diene than for 2-methyl-5-isopropylcyclohexa-1,3-diene or non-substituted cyclohexa-1,3-diene. The effect of NaCl (salting-out) and guanidium chloride (salting-in) was also large for 1-methyl-4-isopropylcyclohexa-1,3-diene.

Keywords: Diels-Alder reaction, aqueous, cyclohexadiene, substrate dependence

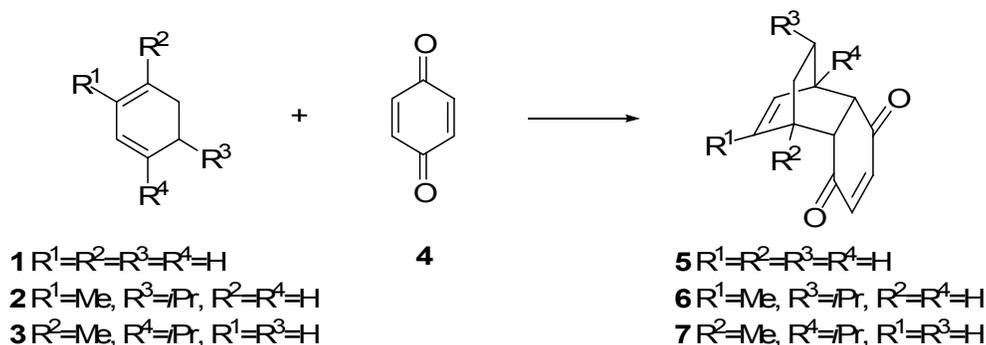
Introduction

Recently, the development of organic reactions in aqueous media has been remarkable [1], especially in light of the interest in “green chemistry”. Among the various reactions, the Diels-Alder reaction is well documented [2,3]. The effect of micelles [4] or Lewis acids [5], including Lewis acid-surfactant combinations [6] have also been studied for the aqueous Diels-Alder reaction. In contrast to the reaction in organic solvents, the water-based reaction proceeds with higher endo/exo selectivities [7]. On the other hand, substrate specificity is one of the fundamental features of enzyme or other biochemical reactions which takes place in water. In such reactions, a simple alkyl substituent sometimes plays an important role. We have studied the substrate dependence of the aqueous Diels-Alder reaction, and here report that the position of the substituents is an important factor in the aqueous Diels-Alder reaction of cyclohexadiene derivatives.

Results and Discussion

In the present study, cyclohexa-1,3-diene (**1**), 2-methyl-5-isopropylcyclohexa-1,3-diene (α -phellandrene, **2**), and 1-methyl-4-isopropylcyclohexa-1,3-diene (α -terpinene, **3**) were chosen as the dienes, and their Diels-Alder reaction with 1,4-benzoquinone (**4**) was studied (Scheme 1).

Scheme 1.



When the reaction of **1** and **4** was carried out in water, the adduct was separated as a precipitate, which was collected after 2 days of stirring at room temperature to afford **5** [8] in 67% yield (Table 1; Entry 1). The dienes having alkyl substituents, **2** and **3**, were also treated under the same reaction conditions giving **6** [9] and **7** [10], respectively (Entries 2,3). In order to clarify the effect of the aqueous media, the reaction in organic solvents such as toluene and THF were also carried out under similar reaction conditions (r.t., 2 days, Entries 4-9) for comparison. From these results, it is obvious that the product yields in water are better than that in organic solvents for all three dienes.

Table 1. Diels-Alder reaction of cyclohexadienes **1-3** and benzoquinone **4** in various solvents.^a

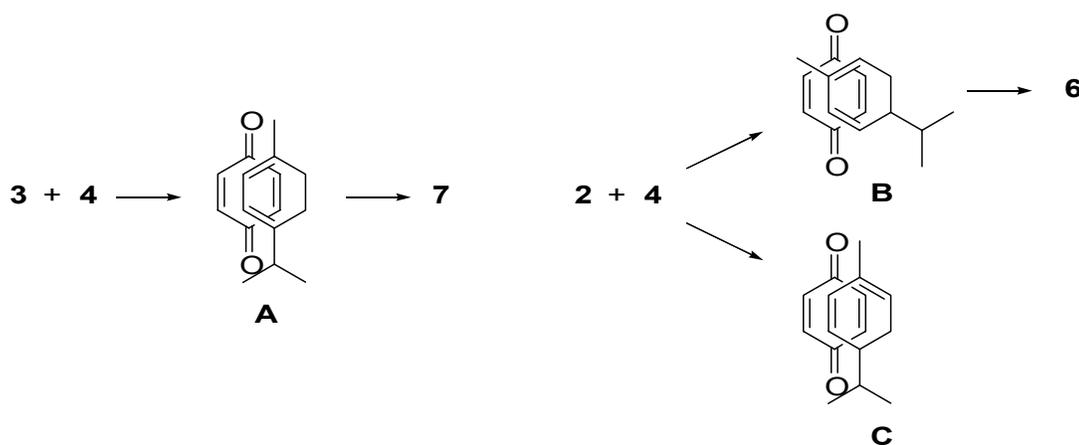
Entry	Diene	Solvent	Product	Yield
1	1	H ₂ O	5	67
2	2	H ₂ O	6	27
3	3	H ₂ O	7	28
4	1	toluene	5	15
5	2	toluene	6	15
6	3	toluene	7	3
7	1	THF	5	6
8	2	THF	6	9
9	3	THF	7	3
10	1	none	5	57
11	2	none	6	27
12	3	none	7	7

^a All reactions were carried out at room temperature for 2 days with 1:1 molar amount of diene and dienophile. The concentration of the each reactant was ca. 0.1 M.

Although the yield of **7** was lower than that of **5**, it was found that the effect of aqueous media was relatively distinct for the reaction of **3** yielding **7**. Namely, the yield of **7** in water was nine times higher than that using the organic solvent conditions.

Since dienes **1-3** are insoluble in water, the reaction under neat conditions was examined as a reference (Entries 10-12). The results indicate again that the advantage of water solution was large for precursor **3**, which is the least reactive diene among the three. In contrast, no benefit of aqueous media was observed for the reaction of **2**, since the adduct **6** was obtained in the same yield under the neat conditions. The relative yields of **5**, **6**, and **7** in H₂O/neat conditions were 1.2, 1.0, and 4.0, respectively. The only difference between **2** and **3** is the position of the substituents, with the latter having two substituents on the reactive carbon. This observed increase in yield for **3** but not for **2** can be rationalized as follows (Scheme 2): in the reaction of **3** and **4**, the reactants must approach each other as shown in **A**, which is a ‘compact’ association and therefore is relatively more favorable in aqueous media than in organic solvents because of the hydrophobic effect. In contrast, the reaction of **2** proceeds through association **B**, however the hydrophobic effect facilitates the more ‘compact’ association **C**. In organic solvents, **B** is favored over **C** or **A** because of steric interactions, which explains the very low yield of **7** in THF or toluene.

Scheme 2.



Breslow and Rizzol studied the salt effect in the aqueous Diels-Alder reaction of anthracene derivative with ethyl maleimide, and reported that the reaction is faster after addition of LiCl and slower after addition of guanidium chloride (GnCl) [11,12]. Kumar *et al.* observed a related phenomenon and explained it in terms of salting-out and salting-in effects [13]. We then examined the salt effect of the present reaction using NaCl and GnCl as the salting-out and salting-in additives [2b], respectively. The effect of NaCl was studied first and the results are shown in Table 2.

Table 2. Yield of the Diels-Alder products in NaCl aq. ^a

Entry	Diene	Conc. of NaCl (molality)	Product	Yield
1	1	2	5	74
2	1	saturated	5	69
3	2	2	6	28
4	2	saturated	6	25
5	3	2	7	16
6	3	saturated	7	13

^a See footnote a of Table 1.

A distinct retardation was observed for the reaction of **3** (Entries 5,6), while the effect of NaCl was small for both **1** and **2** (Entries 1-4). The yields of the adducts in saturated solution were of a similar value to the case of neat condition, which can be considered as the result of a salting-out effect of water-soluble benzoquinone.

The results in GnCl solution are summarized in Table 3. Here again, the effect of the additive was distinct for the reaction of **3**. Namely, in contrast to NaCl, the reaction proceeded smoothly giving the adduct **7** in better yields (Entries 10-12), and after a longer reaction time, **7** was obtained in 76% yield without heating. The yield of **6** was also improved in concentrated GnCl aq. (Entries 6-8), while almost no salt effect was observed for the reaction of **1**, except that **5** was obtained in slightly higher yield in concentrated salt solution (Entry 4). These results are in contrast to Breslow's and Kumar's observation, in which the reaction was activated by LiCl and retarded by GnCl, although the substrates and the conditions are different.

Table 3. Yield of the Diels-Alder products in GnCl aq. ^a

Entry	Diene	Conc. of GnCl (molality)	Product	Yield
1	1	2	5	69
2	1	5	5	69
3	1	10	5	79
4	1	15	5	83
5	2	2	6	32
6	2	5	6	46
7	2	10	6	52
8	2	15	6	52
9	3	2	7	38
10	3	5	7	54
11	3	10	7	54
12	3	15	7	67 ^b

^a See footnote a of Table 1; ^b 76% yield After 2 weeks.

In order to clarify the role of GnCl , related additives were examined for the reaction of **3** yielding **7**. The results are listed in Table 4. When urea, an analogue of guanidium chloride with no charge, was added, the yield of **7** increased (Entries 1-4) but the effect was much smaller than GnCl . Similar results were obtained in acetone (Entries 5-8). These data imply that the simple solvation effect against hydrocarbon **3** is small. A possible explanation of the effect of GnCl is hydrogen-bonding with 1,4-benzoquinone. In mixed solvent system of acetone/water, water is a much important solvent than acetone, since the yield of **7** in acetone without water was only 2%.

Table 4. Yield of **7** in water with related additives.^a

Entry	Additive	Conc. of additive (molality)	Yield
1	urea	2	28
2	urea	5	30
3	urea	10	35
4	urea	15	38
5	acetone	2	31
6	acetone	5	39
7	acetone	10	44
8	acetone	15	46 ^b

^a See footnote a of Table 1; ^b 2% yield in acetone only.

Conclusions

It was found that the effect of water in the aqueous Diels-Alder reaction of cyclohexadiene derivatives with 1,4-benzoquinone is more distinct for the compound having two alkyl substituents on the reacting carbon. The effect of an additive was also large for the same compound with regards to both acceleration and retardation. Therefore, the position of alkyl substituents is an important factor in the aqueous Diels-Alder reaction. A favorable compact association was proposed as the explanation.

Experimental

General

Melting points were measured on a Laboratory Devices Mel-Temp apparatus. IR spectra were recorded on a Jasco FT/IR-230 spectrometer. Both ^1H - and ^{13}C -NMR spectra were measured on a Jeol GSX-400 spectrometer (400 MHz for ^1H ; 100 MHz for ^{13}C). Chemical shifts are reported on the δ scale (ppm) with tetramethylsilane as an internal standard. Both low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a Jeol SX-102A, JMS-DX303, CMATE II, or Shimadzu GCMS-QP5050 mass spectrometer with the EI method. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 or C-300 was used for column chromatography. Anhydrous Na_2SO_4 or MgSO_4 was used for drying the extracted organic layers. For the reagents and chemicals, 1,4-benzoquinone, 2-methyl-5-isopropylcyclohexa-1,3-diene

(α -phellandrene), and 1-methyl-4-isopropylcyclohexa-1,3-diene (α -terpinene) were purchased from Tokyo Kasei Kogyo, Japan; cyclohexa-1,3-diene, GnCl , and urea were purchased from Kanto Chemical, Japan, and all were used without further purification.

Typical experimental procedure (Entry 1 of Table 1)

In an 25 mL round-bottomed flask, *p*-benzoquinone (54.3 mg, 0.50 mmol), 1,3-cyclohexadiene (39.9 mg, 0.50 mmol), and water (5.4 mL) were mixed together. After stirring for 2 days at room temperature, the mixture was extracted with AcOEt, and the organic layer was dried over Na_2SO_4 . Evaporation of the solvent followed by silica gel (8 g) column chromatography using hexane/Et₂O (3:2) as eluent afforded **5** (62.9 mg, 71%); mp. 94-96 °C (lit. mp. 98 °C [9]).

Identification

For spectral data of compounds **5**, **6**, and **7**, see refs. [8], [9], and [10], respectively.

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Sample Availability: Samples are not available.

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