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Asymmetric Michael Addition of Aromatic Thiols to 2-Cyclohexenone and Maleic Acid Esters Via Formation of Crystalline Cyclodextrin Complexes

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Abstract. The asymmetric Michael addition of aromatic thiols to 2-cyclohexenone and maleic acid esters has been carried out by utilizing their crystalline cyclodextrin complexes suspended in water. The best chiral induction, 30% enantiomeric excess (ee), was achieved in combinations of 2-cyclohexenone and octyl maleate with the crystalline β-cyclodextrin complex of benzenethiol (method **A**) to afford (*S*)-3-phenylthiocyclohexanone and (*S*)-octyl-2-phenylthiosuccinate, respectively, whereas the reaction of benzenethiol with 2-cyclohexenone included in β-cyclodextrin (method **B**) inversely induced the chiral recognition to give the (*R*)-adduct with 4–9% ee.

Key words. Asymmetric Michael addition, thiol, α,β-unsaturated carbonyl compound, cyclodextrin complex.

1. Introduction

The asymmetric Michael addition of thiols to α,β-unsaturated carbonyl compounds is one of the useful first-step reactions in syntheses of biologically active compounds such as sex pheromones [1] and terpenes [2]. Wynberg *et al.* [3, 4] and Mukaiyama *et al.* [5, 6] have already reported the asymmetric Michael addition reactions of thiols with 2-cyclohexenone and maleic acid esters which are catalyzed by chiral bases such as cinchona alkaloids and a synthetic amino alcohol; enantioselectivities being up to 67 [4] and 88% [5], respectively. In these addition reactions, the hydroxyl group of the chiral catalysts plays a significant role by assuming hydrogen bonding interactions with the carbonyl oxygen of α,β-unsaturated compounds in the enantioselective transition state [5].

Cyclodextrin (CD), a bottomless bucket-shaped cyclic oligomer composed of six or more glucopyranose units, involves both a hydrophobic cavity and peripheral hydroxyl groups that provide a chiral binding site capable of including guest molecules [7]. The hydroxyl groups of CD, particularly the secondary ones as

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efficient proton donors [7], may be brought into close proximity of the carbonyl oxygen of substrates such as Michael acceptors by their mutual hydrogen bonding interactions.

We have recently found that a chiral template-effect, using a crystalline cyclodextrin (CD), acts successfully to induce chirality into prochiral substrates included in it [8–13]. During studies of these solid state reactions, we found that association of the CD complexes of aromatic thiols in the crystalline state with α,β-unsaturated carbonyl compounds in aqueous solution resulted in enantioselective Michael addition. To date no study has been reported for asymmetric Michael addition by using CD as a chirality inducing component.

2. Experimental

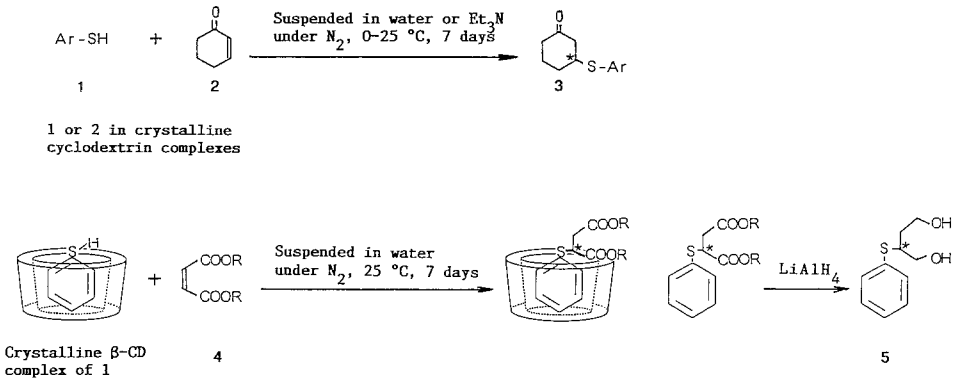
α-, β-, and γ-CDs were purchased from Sanraku-Ocean Co., and purified by recrystallization from water. Aromatic thiols (**1**) such as benzenethiol (**1a**). *p*-toluenethiol (**1b**), *p-tert*-butylbenzenethiol (**1c**), and phenylmethanethiol (**1d**), and α,β-unsaturated carbonyl compounds (**2** and **4**) such as 2-cyclohexenone (**2**) nd methyl (**4a**), ethyl (**4b**), and octyl (**4c**) maleates were distilled *in vacuo* before use.

2.1. PREPARATION OF INCLUSION COMPLEXES

The crystalline inclusion complexes were prepared by adding aromatic thiols (**1**) or 2-cyclohexenone (**2**) to a saturated aqueous solution of CD. To 100 mL of an aqueous solution containing α-CD (8×10^{-1} M), β-CD (1×10^{-1} M), or γ-CD (8×10^{-1} M) were added equimolar amounts of the guest molecules at 70°C and further dissolved by mixing at 80°C for 30 min. After stirring for 2 h at room temperature, the mixtures were cooled to 0°C over 1 day. The CD complexes were collected by filtration and used without drying *in vacuo*; their crystallinity was found to partially diminish upon dehydration [14]. The white crystalline precipitates were obtained in 85–95% yields. Stoichiometries of the complexes were determined by ^{1}H NMR spectroscopy in deuterated dimethyl sulfoxide (DMSO-d_6).

2.2. ASYMMETRIC MICHAEL ADDITION OF THIOLS TO α,β-UNSATURATED CARBONYL COMPOUNDS

The general procedure for the Michael addition of thiols (**1a–d**) to 2-cyclohexenone (**2**) or maleic acid esters (**4a–c**) using their crystalline CD complexes was as follows (Scheme 1). The crystalline inclusion compounds (2.5–3 g wet weight, 2 mmol) prepared from an aqueous solution of CD and the substrates were suspended in water (5 mL) or in triethylamine (5 mL) containing the other substrates (2 mmol) at 0 or 25°C over 7 days under nitrogen. All the reaction mixtures were heterogeneous under such conditions. The amount (mol %) of the reacted and unreacted guest molecules, released from the inclusion complex to media, was measured by UV spectroscopy of the supernatant solutions in the region of 240–430 nm. The complex was dissolved in water and the aqueous solution was



Scheme 1

extracted three times with dichloromethane and the resulting precipitated CD-solvent complex was separated. The combined organic extract was washed with aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The extract, recovered in 93–95% yields, was chromatographed on a column of Wako C-300 silica gel with dichloromethane as eluent. Chemical yields of the optically active products were calculated to be 30 to 93% by comparison of their ^{1}H NMR and IR spectra with those of authentic samples. The optical rotation was measured at 25°C in a suitable solvent. The absolute configuration and the enantiomeric excess (ee) were determined from the known values of optical rotation given in the literature. The homogeneous Michael addition of **1a** (1 mmol) to **2** or **4c** was carried out in an aqueous solution (200 mL) of β-CD (1 mmol) at 25°C over 7 days under nitrogen. Isolation of the products from the aqueous solution was carried out by procedures identical with those described above.

2.3. ANALYTICAL METHODS

Analytical and preparative high-performance liquid chromatography (HPLC) were run on Eruma ERC 8710 and ERC 8510 instruments, respectively, by using a UV detector (254 nm). ^{1}H NMR spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer in DMSO-d_6 or CCl_4 by using $(CH_3)_4Si$ as an internal reference. IR spectra were measured in the region of 400–4000 cm^{-1} on a Shimazu IR-460 spectrometer. Optical rotations were measured in benzene or methanol on a Union Giken PM-101 spectropolarimeter equipped with a 1 dm cell at 25°C.

3. Results and Discussion

3.1. INCLUSION COMPLEXES

The solid complexes of aromatic thiols (**1a–d**) and 2-cyclohexenone (**2**) were obtained as crystalline precipitates from aqueous solutions containing the individual guests and α-, β-, or γ-CD in yields over 80%. The complex formation was confirmed by X-ray powder diffraction measurements. The X-ray diffraction pat-

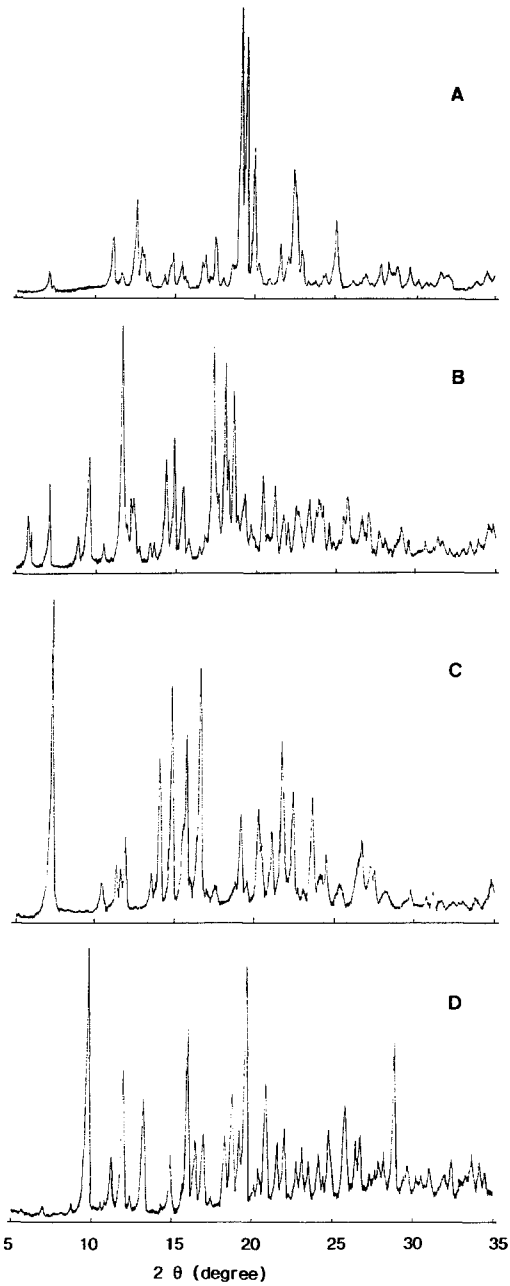


Fig. 1. X-ray diffraction patterns for the cyclodextrin complexes: **A**, α-CD complex with **1a** (2 : 1 = host : guest); **B**, β-CD complex with **1a** (1 : 1); **C**, γ-CD complex with **1a** (1 : 1); **D**, *β-CD* complex with **2** (1 : 1).

terns of these complexes indicated that they were highly crystalline and different from those for physical mixtures of CDs and substrates at the same molar ratios. Figure 1 shows typical diffraction patterns for the α-, β-, and γ-CD complexes with benzenethiol (**1a**) and the β-CD complex of **2**. β-CD formed 1 : 1 (guest : host) crystalline complexes with all the substrates. Benzenethiol formed a 1 : 2 complex with α-CD and a 1 : 1 complex with γ-CD, respectively.

3.2. ADDITION OF AROMATIC THIOLS TO 2-CYCLOHEXENONE

For the successful asymmetric Michael addition of aromatic thiols (**1a–d**) to 2-cyclohexenone (**2**) via formation of their crystalline CD complexes, the selection of suitable media for suspension of each of the solid complexes should be one of the key factors to maintain the CD complexes in the crystalline state and to keep the guest molecules inside the CD cavity during the course of the reaction. The solvent effect on the chiral induction, therefore, was studied in two combinations, **2** and the solid β-CD complex of benzenethiol (**1a**) (method **A**) or **1a** and the β-CD complex of **2** (method **B**), these being suspended in water and triethylamine at 0 and 25°C over 7 days, respectively, as shown in Table I. However, the Michael addition did not occur in an aqueous suspension containing both of the solid β-CD complexes of **1a** and **2**.

The best chiral induction, 28–30% ee, was achieved for a combination of **2** and the crystalline β-CD complex of **1a** suspended in water in the temperature range of 0–25°C under nitrogen (method **A**), which afforded (*S*)-(−)-3-phenylthiocyclohexan-1-one ((*S*)-**3a**) in high chemical yields (73–93%). The reaction with the same combination in triethylamine gave the same product, (*S*)-**3a**, in lower optical yields (4–9% ee). As for the reaction in triethylamine as a suspension solvent, the reacted and unreacted guest molecules were released in considerable amounts from the solid complex to the solvent, whereas the heterogeneous reaction in water minimized an

Table I. Asymmetric Michael addition of benzenethiol to 2-cyclohexenone with their crystalline β-cyclodextrin complexes.[a]

Guest in β-CD complex	Solvent for suspension	Temp. (°C)	Yield[b] (%)	$[\alpha]_{578}^{25}$(°) (c 1.0, benzene)	ee/%[c] (Config.)
Benzenethiol (**1a**)	H_2O	0	73	−20.3	28 (*S*)
(method **A**)		25	93	−21.7	30 (*S*)
	Et_3N	0	30	−6.5	9 (*S*)
		25	50	−2.9	4 (*S*)
2-Cyclohexenone (**2**)	H_2O	25	84	+3.0	4 (*R*)
(method **B**)	Et_3N	0	56	+6.5	9 (*R*)
1a + **2**	H_2O[d]	25	66	0	0

[a]The crystalline β-CD complexes of **1a** and **2** were suspended in solvents containing another substrate at 0 or 25°C over 7 days under nitrogen.
[b]Isolated yield.
[c]Based on the maximum specific rotation value of $[\alpha]_{578}^{21}$ + 72.4° (benzene) for the *R* enantiomer [3].
[d]A homogeneous reaction in aqueous solution.

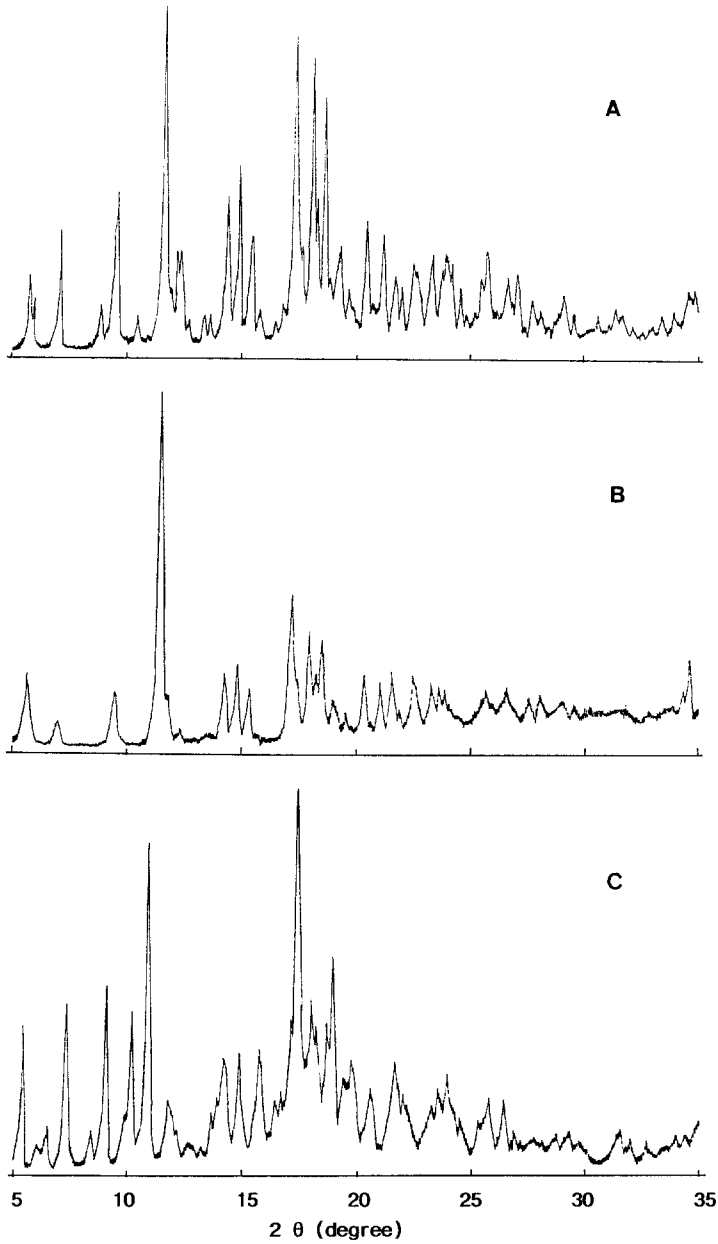


Fig. 2. Changes of X-ray diffraction patterns of the β-cyclodextrin complex of benzenethiol (**1a**) after the Michael addition to 2-cyclohexenone (**2**) and octyl maleate (**4c**): **A**, β-CD complex before the reaction; **B**, complex **A** after the reaction with **2** at 25°C over 7 days (93% convention); **C**, complex **A** after the reaction with **4c** at 25°C over 7 days (50% conversion).

amount of the guest molecule released from the complex even after 7 days of reaction (<0.5 mol %). These results show that the chiral induction is dependent on the solvent ability to hold the guest molecule rigidly in the chiral CD cavity of the crystalline state. In fact, the crystallinity of the β–Cd complex of **1a** was not greatly decreased during the reaction over 7 days, as shown in Figure 2 (**B**). In contrast, no chiral induction was observed for the homogeneous reaction of **1a** and **2** in an aqueous solution of β-CD. Interestingly, the reactions with a combination of **1a** and the β-CD complex of **2** suspended both in water and in triethylamine (method **B**) afforded a product of inverse chirality, (*R*)-**3a**, in low optical yields (4–9% ee). Thus, the results suggest that β-CD forms crystalline complexes with **1a** and **2** so that different enantioselectivities are exercised toward **2** and **1a**, respectively, to yield **3a** of opposite chiralities.

The opposite stereoselectivities were also observed between methods **A** and **B** for the addition of other aromatic thiols (**1b–d**) to **2** by the use of an aqueous suspension of the solid CD complexes, as summarized in Table II. Furthermore, the preferential chirality induced by the addition of **1b–d** to **2** is the inverse of that observed upon addition of **1a** to **2**. When the α-, β, and γ-CD complexes of **1a** reacted with **2**, the same chiral product, (*S*)-**3a**, was obtained in 1, 30, and 10% ee, respectively. The best optical yield, 30% ee, was observed for the reaction based on method **A** by using β-CD in the combination of **1a** and **2** as compared with the other combinations; **1b–d** and **2** (1–7% ee).

Although no detailed explanation of the stereochemistry of the Michael addition with the CD complex can be proposed at present because of lack of the crystalline molecular structures for these solid CD complexes, the chiral induction is reasonably explained on the basis of the CPK space-filling models depicted in Figure 3. Judging from the models for β-CD complexes of **1a** and *p-tert*-butylbenzenethiol (**1c**) (**A** and **B** in Figure 3), the thiol moiety of **1c** protrudes from the chiral frame of β-CD, in which the *p-tert*-butylphenyl moiety is included, whereas that of **1a** fits in the internal cavity of β-CD. The latter stereochemical situation favors the formation of (*S*)–**3a** in a higher optical yield (30% ee).

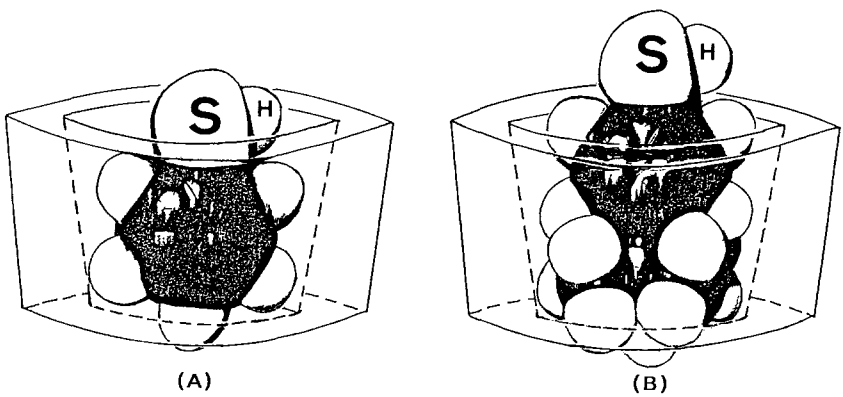
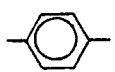
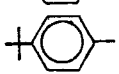


Fig. 3. Schematic representations of the β-cyclodextrin inclusion complexes of benzenethiol (**1a**) and *p-tert*-butylbenzenethiol (**1c**) on the basis of CPK molecular modeling: **A**, β-CD complex of **1a**; **B**, β-CD complex of **1c**.

Table II. Asymmetric Michael addition of aromatic thiols (**1**) to 2-cyclohexenone (**2**) with their crystalline cyclodextrin complexes[a]

	Aromatic thiol	Cyclo-dextrin	Reaction product					
			Method **A** with CD complex of **1**			Method **B** with CD complex of **2**		
	1	(CD)	Yield(%)[b]	$[\alpha]_{578}^{25}$(°)[c]	ee(%)(Config.)[d]	Yield(%)[b]	$[\alpha]_{578}^{25}$(°)[c]	ee(%)(Config.)[d]
a	 SH	α-CD	67	−0.7	1 (S)	–	–	–
		β-CD	93	−21.7	30 (S)	84	+2.9	4 (R)
		γ-CD	73	−7.2	10 (S)	–	–	–
b	 SH	β-CD	39	+4.9	7 (R)	65	−0.7	1 (S)
c	 SH	β-CD	35	+2.5	5 (R)	82	−3.1	6 (S)
d	 CH_2SH	β-CD	50	+1.7	1 (R)	61	−3.5	2 (S)

[a]The crystalline CD complexes of **1** and **2** were suspended in water containing another substrate at 25°C over 7 days under nitrogen.
[b]Isolated yield.
[c]Measured in benzene (c 1.0).
[d]Enantiomeric excess (%) was calculated from the reported rotation values, and configuration was dertermined by the sign of optical rotation given in References [3] and [5].

Table III. Asymmetric Michael addition of benzenethiol in a crystalline β-cyclodextrin complex to maleic acid esters.[a]

Alkyl maleate (**4**)		2-Phenylthio-1,4-butanediol (**5**)		
	Alkyl	Yield[b] (%)	$[\alpha]_D^{25}$(°) (c 1.0, MeOH)	ee(%)[c] (Config.)
a	Me	81	−1.2	3 (S)
b	Et	73	−2.4	6 (S)
c	Octyl	50	−12.1	30 (S)
c	Octyl	80[d]	0	0

[a]The crystalline β-CD complex of benzenethiol was suspended in water containing maleic acid esters at 25°C over 7 days under nitrogen. The adducts were reduced with $LiAlH_4$ to yield (*S*)-(−)-2-phenylthio-1,4-butanediol ((*S*)-**5**).
[b]Isolated yield.
[c]Based on the maximum specific rotation value of $[\alpha]_D^{23}$ − 40.2° (methanol) for the S enantiomer [6].
[d]A homogeneous reaction in aqueous solution.

3.3. ADDITION OF BENZENETHIOL TO MALEIC ACID ESTERS

The crystalline β-CD complex of **1a** was the best chiral nucleophile for the asymmetric Michael addition to **2**, as mentioned above (method **A**). Therefore, method **A** was applied to the addition of **1a** to maleic acid esters (**4a–c**), other α,β-unsaturated carbonyl compounds (Scheme 1), and the results are summarized in Table III. All the addition reactions afforded the optically active (−)-phenylthiosuccinates. The adducts were reduced with $LiAlH_4$ [6] to give (*S*)-(−)-2-phenylthio-1,4-butanediol ((*S*)-**5**). The best optical yield, 30% ee, was achieved with a combination of octyl maleate (**4c**) and the β-CD complex of **1a** to afford (*S*)-**5** in a moderate chemical yield. The homogeneous reaction of **1a** and **4c** in an aqueous β-CD solution showed no enantioselectivity. After the reaction was continued over 7 days, the X-ray diffraction pattern for the β-CD complex of **1a** was transformed into **C** in Figure 2, but the crystallinity of the complex was not damaged to such a great extent as observed for the reaction with **2**. The enantioselectivity of the complex as a chiral nucleophile, however, decreased by changing the octyl group of **4c** to the methyl and ethyl groups (**4a** and **4b**) to 3 and 6% ee, respectively. The reactions with the complex also induced (*S*)-chirality similar to that with **2** as a Michael acceptor.

In conclusion, the crystalline β-cyclodextrin complexes of aromatic thiols induced chirality in the course of the Michael addition of the thiols to α,β-unsaturated carbonyl compounds, even though the chiral induction was as much as 30% enantiomeric excess in the highest case.

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