Asymmetric Benzoin Condensation Catalyzed by Optically Active Thiazolium Salts in Micellar Two-phase Media

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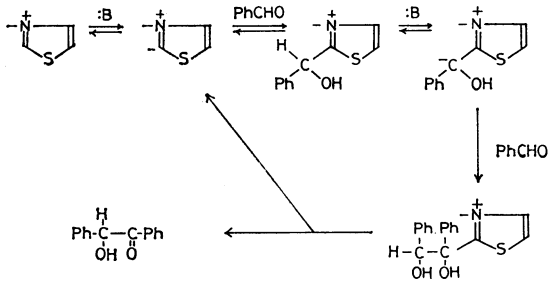
Three thiazolium salts, 3-[2-(*l*-3-*p*-menthyloxy)ethyl]thiazolium bromide (**1**), 3-(*l*-3-*p*-menthyl)thiazolium halides (**2**), and 3-(*l*-3-*p*-menthyl)-4-methylthiazolium perchlorate (**3**) have been examined for the catalysis of benzoin condensation in micellar two-phase media. The catalytic activities on the chemical yields of benzoin were observed to be high for **1** and **2** but low for **3**. On the contrary, for the asymmetric induction, **3** gave much higher optical purity of 35.3% than in the cases of **1** and **2** (0.8—3.5%). These results are discussed in terms of micellar and conformational effects.

Thiazolium salts are well known to catalyze the benzoin condensation (Scheme 1).[1] The catalytic activity, however, is generally not large in aqueous media. Therefore, the catalysts are commonly used in organic solvents such as in methanol for the purpose of synthesis.[2] Meanwhile, we have found that *N*-(long chain alkyl)thiazolium salts are highly active catalysts when used in aqueous two-phase system.[3] We consider that such enhanced activity was produced by combined effects of micellar[4] and phase transfer[5] catalyses. For the past decade, these catalytic systems have been extensively studied as the enzyme models, and some success appears to have been achieved in the simulation of enzymic rate enhancement. However, relatively little success has been achieved in the simulation of enzymic stereospecificity, although there have been some interesting examples of stereospecific micellar[6] and phase transfer[7] reactions.

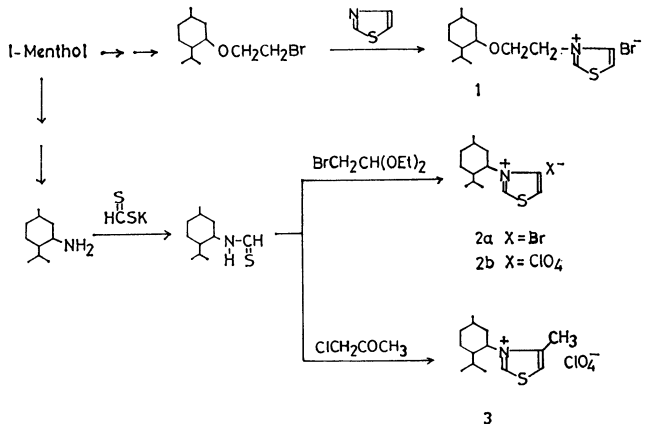


Scheme 1.

In the meantime, Sheehan and the coworkers have already studied the asymmetric benzoin condensation and obtained fairly high optical purity of 52% by using some optically active thiazolium salt of highly constrained structure.[8] Unfortunately, they examined the reactions only in methanol. Therefore, we have reexamined similar asymmetric benzoin condensation, but under micellar conditions in aqueous media.

Results and Discussion

Synthesis of the Catalysts. All catalysts were prepared starting from crystalline *l*-menthol, as outlined in Scheme 2. Synthetic procedures for **1** involve no disturbance of asymmetric center. Whereas in the syntheses of **2** and **3**, the chirality of the 3-position of *l*-menthol was once destroyed by the oxidation leading



Scheme 2.

to *l*-menthone. However, this and the subsequent transformations to (*l*-3-*p*-menthyl)amine are well established procedures.[9] The conversions of (*l*-3-*p*-menthyl)-amine to **2** and **3** were carried out according to the method of Sheehan *et al.*[8]

Benzoin Condensation. The reactions were carried out in a Thunberg tube under the nitrogen atmosphere at room temperature. The reaction mixture was homogeneous when carried out in methanol containing triethylamine. While it was heterogeneous when carried out in aqueous phosphate buffer (pH 8) because of insolubility of benzaldehyde. Each catalyst was soluble in aqueous buffer, but when stirred in the presence of benzaldehyde it was extracted nearly completely from the aqueous phase to the liquid benzaldehyde phase. The benzoin thus formed was isolated by column chromatography on silica gel. The results are compiled in Table 1.

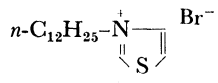
Table 1 indicates the following features: (a) In all the cases, the benzoin yield is higher in water (heterogeneous) than in methanol (homogeneous). The yield is also higher with bromide (**2a**) than with perchlorate (**2b**). (b) Racemization of the product benzoin occurs to some extent for a prolonged reaction duration. (c) The catalyst **2a** gave rotation of opposite sign to that given by **1** and **3**. (d) The 4-methyl substituent in **3** caused the highest optical purity, but the lowest benzoin yield.

The higher benzoin yield in water has already been observed for the catalyst (**4**).[3] The **4** forms micelle (CMC$=3.3\times10^{-3}$ M in H_2O) and its H-D exchange

Table 1. Thiazolium salt catalysis of benzoin condensation[a)]

Catalyst	Solvent	Time h	Benzoin yield[b)] %	$[\alpha]_D^{20}$ °	Optical purity[c)] %
1	H_2O[d)]	2	78	−5.43	3.3
	H_2O[d)]	24	77	−3.00	1.8
	MeOH[e)]	24	38	−5.67	3.5
2a	H_2O[d)]	2	26	+5.34	3.2
	H_2O[d)]	24	82	+1.27	0.8
	MeOH[e)]	24	20	+3.00	1.8
2b	H_2O[d)]	40	61	+2.85	1.8
3	H_2O[d)]	41	20	−57.5	35.3
	MeOH[e)]	41	trace		

a) PhCHO=2.8 mmol, cat=0.15 mmol, under N_2, at room temp. b) Isolated yields by column chromatography (silica gel, $CHCl_3$). c) (*R*)-Benzoin,[10)] $[\alpha]_D^{20}$ −163.04° (*c* 1.0, MeOH) was used. d) 0.5 M Phosphate buffer (pH 8), 10 ml. e) MeOH (10 ml), Et_3N (0.16 mmol).



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rate at the 2-position is 16 fold faster than that of non-micelle forming 3-methyl analogue.[3,11)] The incorporation of **4** into benzaldehyde phase during the catalysis is also the same as observed for **1**, **2**, and **3**. Therefore, the micellar or phase transfer activation may be appropriate to account for the reactivities of these salts. The effect of counter anion (**2a** *vs.* **2b**) is also consistent with the micellar effects, since it is known that the perchlorate anion is bound more tightly to cationic micelle than bromide ion and a tighter binding causes a stronger inhibition of micellar reactivity.[4)]

The 4-methyl group in **3** showed profound effects on both chemical and optical yields of benzoin. These effects may be understood in the following way. Namely, the conformations of **2** and **3** can be drawn as in the following formula **A** and **B**.[12)] The CPK molecular model indicates that the isopropyl group enforces the plane of thiazolium ring to assume the conformations in such a way to bisect the plane of cyclohexane ring (C_1–C_3–C_5 and C_2–C_4–C_6). The interconversion between **A** and **B** is relatively easy when R=H (**2**), but severely restricted when R=Me (**3**) favoring **A** much more than **B**. On the other hand, the condensation should be easier through **B** than **A** since the reaction

A B

R: H, Me

at 2-position of thiazolium ring is shielded by cyclohexane ring in **A**. Thus **2** should be more reactive (more in the reactive **B**) than **3** (more in the less reactive **A**). Meanwhile, the accounting for stereospecificity is not easy, since there are two addition steps to create two asymmetric carbons (see Scheme 1), both of which should be important, although the asymmetry of the first carbon (or carbanion) is lost after the condensation. Only we can suspect is that stereochemical confinement may be more stringent for more conformationally frozen **3** than **2**.

The above observation that the highest optical purity was obtained with the lowest yield is rather disappointing, since in the enzymic catalyses the rate enhancement and stereospecificity appear to be inseparable in the same catalytic mechanism.[13)] For the present micellar two-phase system, the hydrophobic interaction between the catalyst and the substrate is considered to be important for the rate enhancement. However, some more special hydrophobic or multifunctional interactions are necessary for enzymic stereospecificity.

Experimental

3-[2-(l-3-p-menthyloxy)ethyl]thiazolium Bromide (1). The salt was synthesized starting from *l*-menthol *via* the following intermediates successively: (*l*-3-*p*-menthyloxy)acetic acid, ethyl(*l*-3-*p*-menthyloxy)acetate, 2-(*l*-3-*p*-menthyloxy)ethanol, and 2-(*l*-3-*p*-menthyloxy)ethyl bromide. The last bromide 1 g (3.8 mmol) and thiazole 0.35 g (4.1 mmol) was heated (100 °C) in a sealed tube for 44 h. Crystals formed were collected and recrystallized from ethanol–ether, yield 0.74 g (56%), mp 188—189 °C, $[\alpha]_D^{20}$ −54.3° (*c* 0.97, MeOH). Found: C, 51.46; H, 7.53; N, 4.05%. Calcd for $C_{15}H_{26}BrNOS$: C, 51.71; H, 7.54; N, 4.02%.

(l-3-p-Menthyl)amine Hydrochloride. *l*-Menthol was converted to *l*-menthone by chromium trioxide oxidation followed by further conversion to *l*-menthone oxime. This oxime was reduced by metallic sodium in ethanol according to the literature procedures to give (*l*-3-*p*-menthyl)amine which was isolated as the hydrochloride, mp 255 °C, $[\alpha]_D^{20}$ −35.5° (*c* 2.0, H_2O) [lit,[9)] $[\alpha]_D^{20}$ −36.1° (*c* 2.0, H_2O)].

N-thioformyl-(l-3-p-menthyl)amine was prepared by the same procedures as reported by Sheehan *et al.*[8)]

3-(l-3-p-menthyl)thiazolium Bromide (2a). To a stirred solution of *N*-thioformyl-(*l*-3-*p*-menthyl)amine (5 g, 25 mmol) in benzene (40 ml) was added α-bromoacetaldehyde diethyl acetal (5 g, 25 mmol) in benzene (10 ml). The mixture was stirred overnight at room temperature. After benzene was evaporated, ether (20 ml) was added and neutralized with $NaHCO_3$ and extracted with ether to remove unreacted materials. The aqueous layer was evaporated to dryness. The residue was recrystallized from acetone–ether, 4.2 g (52%), mp 201—203 °C, $[\alpha]_D^{20}$ −31.8° (*c* 1.0, MeOH). Found: C, 51.72; H, 7.53; N, 4.64; S, 10.10%. Calcd for $C_{13}H_{22}BrNS$: C, 51.30; H, 7.30; N, 4.60; S, 10.54%.

3-(l-3-p-menthyl)thiazolium Perchlorate (2b). To a stirred

solution of **2a** 0.5 g (1.64 mmol) in methanol (5 ml) was added silver perchlorate 0.34 g (1.64 mmol). Silver bromide precipitated was filtered off and methanol was evaporated. The residue was dissolved in acetone and the insoluble silver bromide was again removed. Acetone was removed and the crystalline residue was finally recrystallized from ethanol–ether, yield 0.45 g (84%), mp 113—115 °C, $[\alpha]_D^{20}$ −32.1° (*c* 0.62, MeOH). Found: C, 48.05; H, 6.71; N, 4.28; S, 9.86%. Calcd for $C_{13}H_{22}ClNO_4S$: C, 48.21; H, 6.86; N, 4.33; S, 9.90%.

3-(l-3-p-Menthyl)-4-methylthiazolium Perchlorate (3). To a stirred solution of *N*-thioformyl-(*l*-3-*p*-menthyl)amine (4.1 g, 20.5 mmol) in benzene (40 ml) was added chloroacetone (1.9 g, 20.5 mmol) in benzene (20 ml). The mixture was stirred for 24 h and finally refluxed for 15 min. Benzene was evaporated, water was added, and neutralized with sodium carbonate (pH 7—8). The aqueous layer was extracted with ether to remove the unreacted materials. The water was evaporated to dryness. The residue was dissolved in dichloromethane to remove sodium chloride. The dichloromethane layer was dried over sodium sulfate. The dichloromethane was removed to give pasty residue. This paste was dissolved in acetone and treated with silver perchlorate in acetone. Silver chloride precipitated was filtered off and ether was added to the filtrate to give crystalline precipitates. The crystalline precipitates were collected and recrystallized from ethanol–ether, yield 0.16 g (16%), mp 199—200 °C, $[\alpha]_D^{20}$ −57.0° (*c*, 1.00, MeOH). Found: C, 50.10; H, 7.35; N, 4.07; S, 9.50%. Calcd for $C_{14}H_{24}ClNO_4S$: C, 49.76; H, 7.17; N, 4.15; S, 9.49%.

Asymmetric Benzoin Condensation. In a Thunberg tube, the solvent (10 ml) containing a catalyst (0.15 mmol) was bubbled with nitrogen for 20 min. The reaction was initiated by mixing the solvent with benzaldehyde (2.8 mmol) which was placed with a stirring rod in the upper flask of Thunberg tube. Stirring was continued at room temperature for a given time. The reaction mixture was extracted with ether, and the ether layer was dried over anhydrous magnesium sulfate. The ether was evaporated to dryness and the residue was chromatographed on a silica gel column with chloroform. The fraction containing benzoin was collected and the solvent was removed. Further recrystallization was noted to be unnecessary.

Optical rotation was recorded with a JASCO-SL automatic polarimeter, the precision of reading to be within ±0.002°.

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