Structural Aspects of Catalytic Activities of Thiazolium Salts in Benzoin Condensation Reaction in Methanol

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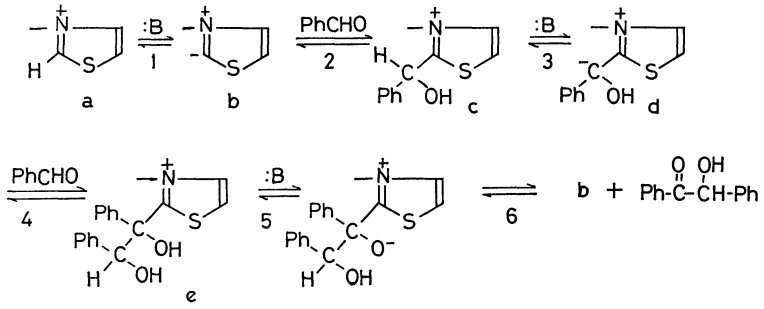
The rates of benzoin condensation catalyzed by thiazolium salts of varying structures have been determined in methanol containing triethylamine as the base by the method of gas chromatography. The condensation activity was observed not to be linearly correlated with the acidities of 2-position of catalyst thiazolium ring. The dimethylamino substituent was found not to act as an internal base for benzoin condensation, but rather exerted an inhibitory effect. In general, the effects of *N*-substituent on the rate of benzoin condensation were small. However, a large steric hindrance was observed for 3-methyl-4-menthylthiazolium perchlorate.

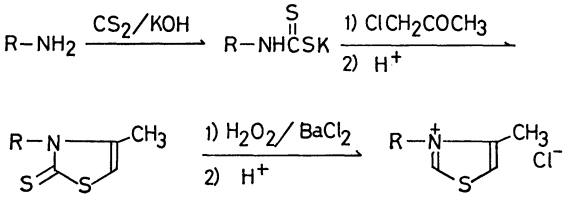
The mechanism of benzoin condensation catalyzed by a thiazolium salt is generally accepted as to involve multistep reaction pathways shown in Scheme 1.[1,2] In Scheme 1 are involved three ionization steps 1, 3, and 5, of which steps 1 and 5 were investigated and considered to be subject to lyate ion catalysis.[1c,3] However, the mechanism of base catalysis in step 3 has remained uncertain until recently as to whether it is subject to general base or lyate ion catalysis, although it has been demonstrated that the α-proton of 2-(1-hydroxyethyl)thiamine (analog of **c**) is exchangeable with solvent proton at pH 8.1.[4] Very recently, it has been shown that carbanion formation from 2-(1-hydroxyethyl)- and 2-(1-hydroxybenzyl)-thiazolium ions (analog of **c**) proceeds *via* a general base catalysis in aqueous buffer solutions.[5]



Scheme 1.

Meanwhile, we have observed general base catalysis in the H–D exchange reactions of 2,3,4-trimethylthiazolium iodide in methanol in the presence of amine.[6] This exchange reaction may also be the model of the above step 3 ionization process. Then one may expect an improved catalytic activity by attaching an appropriate basic group to the thiazolium ring which can act as an internal base. Another aspect of interests is the steric effect which we have also noted to be a determining factor for the asymmetric synthesis of benzoin.[7]

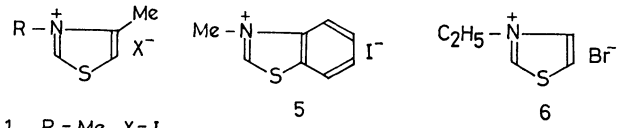
In this paper, we describe the kinetics of benzoin condensation in methanol containing triethylamine. The study was concerned with the structure-reactivity relationship of thiazolium salt catalysts such as mentioned above. It is surprising that there has been no report on the overall kinetics of benzoin formation from benzaldehyde catalyzed by thiazolium salt, although the kinetics of cyanide ion catalysis was studied in detail by Schowen and the coworkers.[8]



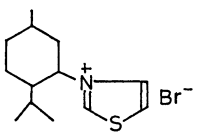
Scheme 2.

Results and Discussion

Synthesis of Thiazolium Salts. The thiazolium salts, **1**, **2**, **4**, **5**, and **6** were prepared by reacting the corresponding halides with thiazoles. 3-Phenyl (**3**), 3-[2-(dimethylamino)ethyl] (**9**), and 3-[3-(dimethylamino)propyl] (**10**) derivatives were synthesized from the corresponding amines, as shown in Scheme 2.[9] The preparation of menthyl derivatives, **7** and **8**, was described in a previous paper.[7]



1 R = Me, X = I
2a R = $PhCH_2$, X = Cl
2b R = $PhCH_2$, X = ClO_4
3 R = Ph, X = Cl
4 R = n-$C_{12}H_{25}$, X = Br
9 R = $Me_2NCH_2CH_2$, X = Cl
10 R = $Me_2NCH_2CH_2CH_2$, X = Cl



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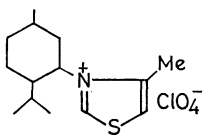

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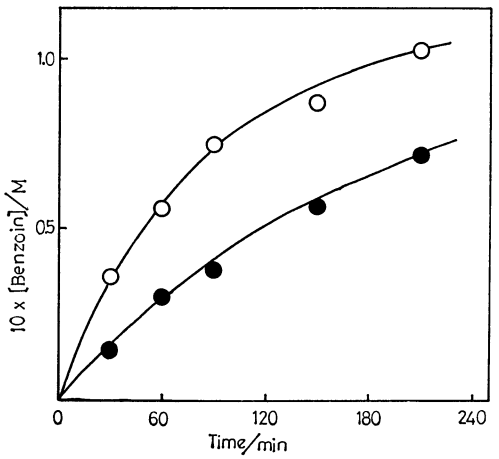


Fig. 1. Plots of benzoin yields *vs.* time, PhCHO= 0.31 M, catalyst=0.06 M, Et_3N=0.06 M, ●; **1**, ○; **2a**.

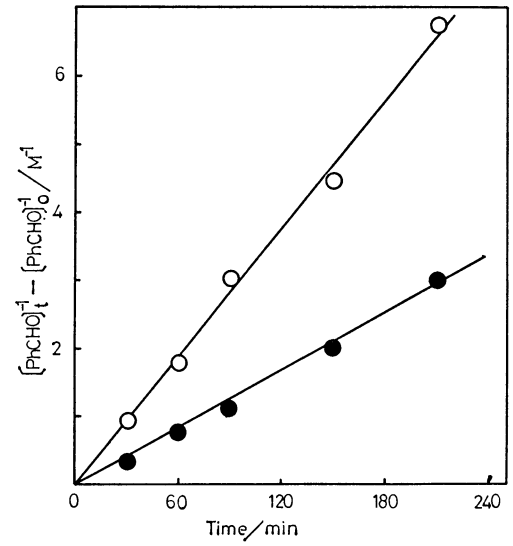
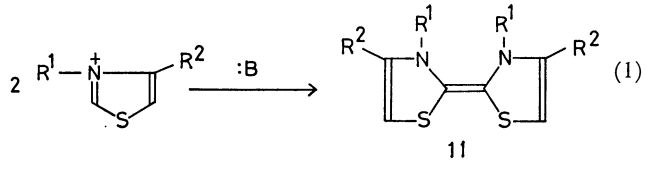


Fig. 2. Second order plots (see Fig. 1), ●; **1**, ○; **2a**.

Rates of Benzoin Condensation. In the cyanide ion-catalyzed benzoin condensation in methanol, Schowen *et al.* employed spectrophotometric method to follow the formation of benzoin at 320 nm.[8a] Unfortunately, however, in the thiazolium ion-catalyzed condensation in methanol containing triethylamine, the partial dimerization of thiazolium ion to form *N,N'*-disubstituted 2,2'-bithiazolinylidene[10] (**11**, Eq. 1) was encountered



(1)

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which disturbed the absorbance measurement at 320 nm. Therefore, we were forced to employ gas chromatography for the analysis of product benzoin by using 1,2-diphenylethane as an internal standard. The time courses of benzoin formation are illustrated in Fig. 1. The corresponding second order rate plots ($[PhCHO]_t^{-1}$ $-[PhCHO]_0^{-1}=k_{obsd}t$) are shown in Fig. 2. Good linear plots were obtained up to more than 50% of the reaction for **1** and 70% for **2a**, although deviations were noted at the later half or one third of reaction due to the partial loss of catalytic activity by the dimerization of catalyst.

Table 1. The rate constants and benzoin yield after 20 h at 51 °C

Catalyst	$10^2 k_{obsd}$ / l mol^{-1} min^{-1}	k_{rel}	Benzoin yield / %
1	1.4[a]	1	66
2a	3.2[a]	2.3	79
2b	2.9[a]	2.0	67
3	1.3[a]	0.9	45
4	1.1[a]	0.8	67
5	≈0.03[a]	0.02	10
6	1.1[a]	0.8	61
	0.6[b]		—
	0.30[c]		46
7	0.94[a]	0.7	62
8	≈0.01[a]	0.01	3

a) PhCHO=0.31 M, catalyst=0.06 M, Et_3N=0.06 M. b) Et_3N=0.03 M. c) Et_3N·HCl(0.06 M) was added.

The gas chromatographic method may be less accurate than the spectrophotometric method. Nevertheless, fairly reproducible second order rate constants were obtained. The results are listed in Table 1. In general, the rates are not very much sensitive to the *N*-substituent. Aliphatic methyl (**1**), ethyl (**6**), dodecyl (**4**), menthyl (**7**), and aromatic phenyl (**3**) substituents have almost the same effect. The effect of benzyl substituent is the largest one for the rate enhancement, but only 2—3 fold. The effect of the counter anion is also small as seen in **2a** and **2b**. The values for **5** are not accurate because of considerable decomposition of the catalyst . The activity of **8** is unusually low which is difficult to account for simply by the electronic effect, since the activity of **7** appears to be normal. As discussed in the previous paper,[7] CPK molecular model suggests that steric repulsion between 4-Me of thiazolium ring and isopropyl groups of *N*-menthyl part constrains the thiazolium ring to an unfavorable conformation for the catalysis.

Acidity of 2-Hydrogen. For several thiazolium salts, the rate constants of H–D exchange of 2-hydrogen were determined by NMR in D_2O buffered by 0.1 M acetate (mostly, pD=4.80) at 40 °C. The results are listed in Table 2.

The $k_{OD^-}=5.84\times10^5$ l mol^{-1} s^{-1} (40 °C) for **1** is reasonable in agreement with the value of 5.0×10^5 l mol^{-1} s^{-1} (38 °C) reported by Haake *et al.*[3a] Such relative rates in Table 2 appear to be accounted for in terms of the electronic effects (inductive and resonance) except for that of **4**. An enhanced rate of **4** is apparently due to the micellar effect, as we had reported in a previous communication that **4** is highly active in water for benzoin condensation.[11] The salt **4** forms micelles at concentrations of the NMR measure-

TABLE 2. THE RATE CONSTANTS OF H-D EXCHANGE OF 2-HYDROGEN OF THIAZOLIUM SALT AT 40 °C

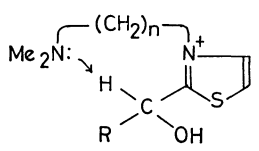
Thiazolium[a]	k_{OD^-}/l mol^{-1} s^{-1} [b]	k_{rel}
1	5.84×10^5	1
2a	2.30×10^6	3.9
3	7.94×10^6	13
4[c]	9.34×10^6	16
5	2.33×10^7	40

a) [salt]=0.4—0.5 M. b) pK_w(D_2O); 14.39 was used; A. K. Covington, R. A. Robinson and R. G. Bates, *J. Phys. Chem.*, **70**, 1820 (1966). c) Under micellar conditions.

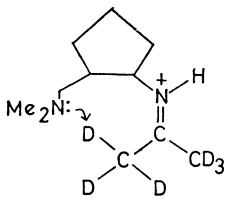
ment which are much higher than the CMC of **4** (3.3×10^{-3} M in water). The micellar effect, of course, does not operate in methanol. Hence the rate constant for **4** in Table 1 is nearly the same as those of non micelle forming **1** and **6**, *etc.*

At any rate, Tables 1 and 2 indicate a poor correlation between the relative rates of H–D exchange of 2-hydrogen and those of benzoin condensation. Presumably, a ylide formed from **5** may be stabilized too much and lose activity for condensation.

Effect of Internal Base for Benzoin Condensation. We have suggested a possibility of general base catalysis by externally added base for the abstraction of α-hydrogen of the intermediate **c** (step 3 in Scheme 1).[5,6] Such general base catalysis would be much more favored when the reacting groups are arranged in appropriate intramolecular positions. Thus we have examined the catalytic activities of **9** and **10** for the benzoin condensation, where the dimethylamino group was expected to act as internal base as illustrated in the structure **12** for the addition intermediate. Meanwhile, Hine *et al.* demonstrated a remarkable bifunctional catalysis by 3-(dimethylamino)propylamine and 2-(dimethylaminomethyl)cyclopentylamine in dedeuteration of acetone-d_6.[12] These primary amines catalyze the reaction through the formation of iminium ion intermediate as illustrated in the structure **13** for the latter amine. Hine *et al.* proposed that the intramolecular general base catalysis by dimethylamino group occurs favorably when the reacting groups can be held in an eight-membered cyclic transition state, in which the carbon-deuterium bond being broken is in a plane nearly perpendicular to the plane of the iminium double bond as depicted in the structure **14**. The structural analogy between **12b** and **13** appears to be almost perfect if one ignores the difference of α-C–OH and α-C–D bond.



12a n=2
12b n=3



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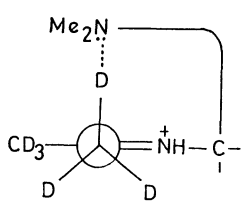

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TABLE 3. THE RATE CONSTANTS OF BENZOIN CONDENSATION CATALYZED BY **9** AND **10**[a]

[Et_3N]/[cat]	$10^2 k_{obsd}$/l mol^{-1} min^{-1}	
	9	**10**
1	— (trace)	— (5.6)
2	0.06 (12)[a]	0.14 (15)
3	0.14 (15)	0.20 (22)
4	0.24 (21)	0.29 (29)

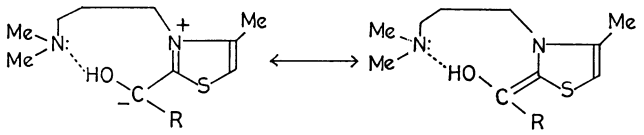
a) PhCHO=0.31 M, catalyst=0.06 M. The number in parenthesis are the benzoin yields/% after 20 h.

The pK_a values of the conjugated acids of dimethylamino group of **9** and **10** in water were determined to be 6.1 and 8.1 respectively by the NMR method.[13] They are very close to the pK_a values of the first ionization of 1,2-(dimethylamino)ethane (5.85[14]) and 1,3-(dimethylamino)propane (7.9[15]) in water. Thus it appears that the positive charge effect of thiazolium ring on the ionization of nearby protonated amino group is nearly the same as that of protonated dimethylamino group. At any rate, these pK_a values suggest the dimethylamino group, at least of **10**, to be basic enough for the ionization of α-CH bond.

Naturally, the hydrochlorides of **9** and **10** showed no activity of benzoin condensation in methanol. When an equimolar amount of triethylamine was added, the formation of benzoin was observed, but the yields of benzoin were trace for **9** and 5.6% for **10** after 20 h reaction. The increase of triethylamine concentration increased the rates and yields of benzoin formation as shown in Table 3. However, their values were unexpectedly low.

The pK_a of triethylamine is 10.78 in water[16] which is 3—5 units larger than the pK_a of **9** and **10**. These pK_a differences in water may also exist in methanol since a linear relationship is known between the pK_a values of amines in water and methanol.[17] Therefore, the dimethylamino group of **9** or **10** should be completely free in the presence of equimolar amounts of triethylamine, as verified qualitatively by NMR spectra. Yet the activity of both **9** and **10** was negligibly small. Meanwhile, as shown in Table 1, the rate constant for 3-ethyl analogue (**6**) was reduced from 1.1×10^{-2} to 0.3×10^{-2} l mol^{-1} min^{-1} in the presence of the equimolar amount of triethylamine hydrochloride (*i.e.*, Et_3N=$Et_3N\cdot HCl$=0.06 M). Thus the low activity of **9** and **10** appears partly due to this salt effect. For example, the addition of twice molar amount of free Et_3N over the catalyst hydrochloride should give a mixture of equimolar amounts of Et_3N, $Et_3N\cdot HCl$, and free dimethylamino group. However, with this salt effect alone, it seems difficult to account for such low activity. Namely, the rates of **9** and **10** are only about one fourth of that of **6** in spite of the same salt concentration. The use of **10** with partially free

amino group did not increase the rate appreciably. Electron-withdrawing inductive effect of free dimethylamino group should be small (σ_I=0.10). The CPK molecular model indicates no such steric hindrance for both **9** and **10** as noted for **8**. Both of **9** and **10** were quite stable under the present experimental conditions as far as the NMR spectra indicate. Thus we are unable to offer any reasonable explanation for the above low reactivity of **9** and **10**. However, it may be conceivable that the dimethylamino group in **9** and **10** can in fact act as internal general base as in **12b**, but the resulting carbanion loses reactivity for further condensation due to stabilization by charge delocalization which is favored to occur by ring formation involving hydrogen bonding (**12c** and **12d**).



12c 12d

Experimental

NMR was recorded by a Varian A-60 spectrometer. Triethylamine was distilled on sodium hydroxide pellets, and methanol was refluxed with calcium oxide overnight and distilled. Benzaldehyde was distilled under N_2 prior to use.

Preparation of Thiazolium Salts. *3,4-Dimethylthiazolium iodide (**1**)* was prepared by reaction of 4-methylthiazole[18] with excess methyl iodide in ethanol, mp 119—121 °C (ethanol–ether) (lit,[19] mp 119—120 °C).

*3-Benzyl-4-methylthiazolium chloride (**2a**)* was prepared from benzyl chloride and 4-methylthiazole, mp 190 °C (lit,[3a] mp 191—192 °C).

*3-Benzyl-4-methylthiazolium perchlorate (**2b**)* was obtained by anion exchange of (**2a**) with silver perchlorate in ethanol. Recrystallized from ethanol–ether, mp 111—113 °C. Found: C, 45.50; H, 4.19; N, 4.84%. Calcd for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18; N, 4.83%.

*3-Dodecyl-4-methylthiazolium bromide (**4**)* was prepared from 4-methylthiazole and dodecyl bromide in ethanol, mp 102—104 °C (ethanol–ether). Found: C, 55.00; H, 8.56; N, 3.98%. Calcd for $C_{16}H_{30}BrNS$: C, 55.15, H, 8.68; N, 4.02%.

*3-Methylbenzothiazolium iodide (**5**)* was prepared from benzothiazole and methyl iodide in ethanol, mp 210 °C, (lit,[10] mp 208—210 °C).

*3-Ethylthiazolium bromide (**6**)* was prepared from thiazole and ethyl bromide, mp 160—161 °C (ethanol–ether). Found: C, 30.81; H, 4.33; N, 7.10; S, 16.39%. Calcd for C_5H_8BrNs: C, 30.94, H, 4.15; N, 7.22; S, 16.52%.

3-Phenyl-4-methyl-4-thiazoline-2-thione. To a stirred solution of ammonium phenyldithiocarbamate[20] (10 g, 58 mmol) in methanol (100 ml) was added chloroacetone (5.4 g, 58 mmol) dropwise at room temperature and stirring was continued overnight. Then, 3—4 drops of concd hydrochloric acid was added and the solution refluxed for 30 min. Methanol was evaporated and water (100 ml) was added. After neutralization with $NaHCO_3$ solid, the solution was extracted with ether. The ether layer was dried over $MgSO_4$ and was evaporated to dryness. The crude crystals were recrystallized from methanol, yield 8.0 g (67%), mp 146—148 °C, NMR (CCl_4) δ 2.08 (3H, d, J=1.6 Hz) 6.50 (1H, d, J=1.6 Hz), 7.28—7.80 (5H, m).

*3-Phenyl-4-methylthiazolium Chloride (**3**).* A mixture of the above thione (2 g, 9.66 mmol), 30% hydrogen peroxide (4.4 g, 38.6 mmol) and one drop of concd hydrochloric acid in H_2O (20 ml) was stirred for 30 min at room temperature. $BaCl_2 \cdot 2H_2O$ (2.36 g, 9.66 mmol) was added and stirring was continued overnight. The precipitate ($BaSO_4$) was separated by centrifugation. The solution was evaporated to dryness. The crystals were recrystallized from ethanol–ether, yield 1.3 g (60%), mp 205—210 °C (dec). NMR (D_2O) δ 2.4 (3H, s), 7.55—7.88 (5H, m), 8.06 (1H, s), 10.10 (1H, s). Found: C, 56.70; H, 4.50; N, 6.45%. Calcd for $C_{10}H_{10}ClNS$: C, 56.73; H, 4.76; N, 6.62%.

3-[2-(Dimethylamino)ethyl]-4-methyl-4-thiazoline-2-thione. To a stirred solution of potassium 2-(dimethylamino)ethyldithiocarbamate (5.0 g, 25 mmol), which was prepared from the corresponding amine, potassium hydroxide and carbon disulfide in methanol (150 ml) was added chloroacetone (2.3 g, 25 mmol) at room temperature. Stirring was continued overnight and concd hydrochloric acid was added until the solution became acidic and stirred further for 30 min. Enough ether was added to give precipitates. The precipitates were filtered and recrystallized from ethanol–ether, yield 4.2 g (82% as HCl salt), mp 200—205 °C NMR (D_2O) δ 2.40 (3H, d, J=1.6 Hz), 3.09 (6H, s), 3.58 (2H, t, J=8.0 Hz), 4.72 (2H, t, J=8.0 Hz), 6.77 (1H, d, J=1.6 Hz).

*3-[2-(Dimethylamino)ethyl]-4-methylthiazolium Chloride (**9**).* The above thione (3.0 g, 13 mmol) and $BaCl_2 \cdot 2H_2O$ (3.1 g, 12.7 mmol) were dissolved in 10 ml of water with one drop of concd HCl and 30% hydrogen peroxide (4.9 g, 43 mmol) was added under ice-cooling. Stirring was continued overnight at room temperature. The precipitate was separated by centrifugation. The water layer was evaporated to dryness. The residue was dissolved in methanol (5 ml) and treated with charcoal and ether was added to give crystals. The crystals thus formed were recrystallized from methanol–ether, 2.6 g (84%), mp 200 °C (dec). NMR (CD_3OD) δ 2.75 (3H, s), 3.09 (6H, s), 3.84 (2H, t, J=8.0 Hz), 5.12 (2H, t, J=8.0 Hz), 8.07 (1H, m), 10.44 (1H, d, J=2.7 Hz). Found: C, 39.55; H, 6.60; N, 11.75%. Calcd for $C_8H_{16}Cl_2N_2S$: C, 39.51; H, 6.63; N, 11.52%.

3-[3-(Dimethylamino)propyl]-4-methyl-4-thiazoline-2-thione was prepared by the same procedures as described for the above 3-[2-(dimethylamino)ethyl]-4-methyl-4-thiazoline-2-thione. Yield 35%, mp 205 °C (as HCl salt). NMR (D_2O) δ 2.00—2.50 (2H, m), 2.42 (3H, d, J=1.6 Hz), 2.99 (6H, s), 3.37 (2H, t, J=7.5 Hz), 4.40 (2H, t, J=7.5 Hz), 6.80 (1H, d, J=1.6 Hz).

*3-[3-(Dimethylamino)propyl]-4-methylthiazolium Chloride (**10**).* was synthesized by the same manner as described for **9**. The yield was 61% from the corresponding thione, mp 200 °C (dec). NMR (CD_3OD) δ 2.30—2.80 (2H, m), 2.73 (3H, s), 3.00 (6H, s), 3.43 (2H, t, J=7.0 Hz), 4.70 (2H, t, J=7.5 Hz), 8.07 (1H, m), 10.50 (1H, d, J=3.0 Hz). Found: C, 42.00; H, 7.13; N, 10.88%. Calcd for $C_9H_{18}Cl_2N_2S$; C, 42.03; H, 7.05; N, 10.90%.

Kinetics of H–D Exchange of 2-Hydrogen. Deuterium oxide (99.75%, Merck) was used. The pH was measured on a Horiba (F-7DE) pH meter. The pD was then calculated by adding 0.40 to the observed pH.[21] The exchange was followed by the NMR method. The solutions for kinetics were prepared by weighing thiazolium salt (0.25 mol) in a NMR tube and by adding 0.5 ml of 0.1 M acetate buffer solution. The rate constants were calculated from the integrated areas of 2-hydrogen and those of non-exchangeable hydrogens (4-methyl, 5-hydrogen or phenyl).

pK_a *Determination.* The pK_a values of dimethylamino group of **9** and **10** in water were determined by NMR method described by Grunwald.[12] Namely, chemical shifts of dimethyl group from tetramethylammonium bromide (internal standard) were measured at seven pH's from pH 3 to 7.62 (0.2 M, citric acid–Na_2HPO_4 buffer). The pK_a values were calculated by the best fit of experimental points by using equation: $pH=pK_a+\log(\delta_{obsd}-\delta)/(\delta_{H^+}-\delta_{obsd})$, where δ_{H^+}, δ_{obsd}, δ are the chemical shifts from internal standard of fully protonated, partially dissociated at a given pH and free dimethylamino groups which were estimated because of instability of thiazolium ring at higher pH, respectively.

Kinetics of Benzoin Condensation. Into a 5 ml of septum-rubber capped flask were placed 2 ml of 0.62 M benzaldehyde, 0.5 ml of 0.48 M triethylamine and 1 ml of 0.30 M 1,2-diphenylethane (internal standard for GLC analysis). The flask was bubbled with N_2 saturated with methanol vapor for 10 min. After temperature equilibration at 51 °C for 10 min, 0.5 ml of 0.48 M solution of given catalyst was added under N_2 with appropriate time intervals, *ca.* 0.2 ml of reaction mixture was pipetted out by syringe and poured into a mixture of 2 ml of H_2O and 0.5 ml of benzene. After vigorous shaking, benzene layer was dried over $MgSO_4$. This layer was subjected to GLC analyses (column; 5% DMCS on Cromosorb WAW, 2 m, 200 °C). The amount of benzoin was determined by comparing the relative peak area of benzoin *vs.* internal standard with those of the calibration chart.

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