

A Computational Study on the Mechanism of the Formose Reaction Catalyzed by the Thiazolium Salt

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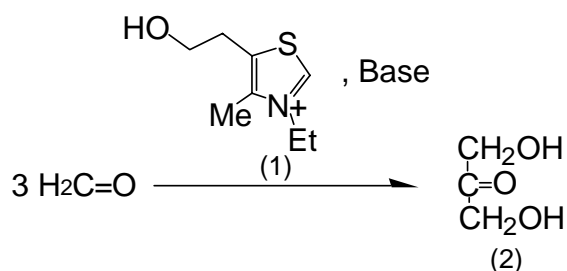
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The mechanism of the formose reaction catalyzed by thiazolium salt was investigated by MOPAC-PM3 semi-empirical molecular orbital (MO) method in order to elucidate the factor(s) stabilizing the reaction intermediates. We assumed that one factor was the formation of an ion pair with the ammonium ion in the reaction medium. Based on this assumption, possible intermediates were examined, including their structures and the heats of formation were calculated. It was suggested that the formation of an ion pair between the zwitterion intermediate (**II**^{*}) and an ammonium ion and the subsequent formation of the intermediate, 2-hydroxymethyl-3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium (**II**^{**}), were crucial for the reaction. A more plausible mechanism for the initial stage of the formose reaction is proposed based on calculation results.

Keywords: MOPAC-PM3, Formose reaction, Thiazolium salt, Reaction mechanism, Ion pair formation

1 Introduction

Recent studies on the formose reaction have shown that the thiazolium salt serves as a catalyst to produce 1,3-dihydroxyacetone, a simple C3 carbohydrate, from formaldehyde in the presence of amines [1–11] (Scheme 1). The reaction mechanism has been proposed based on the structures of the isolated reaction intermediates [5] and has been generally accepted [4]. However, the detailed argument for the stability of the intermediates has not been made.



Scheme 1. Formose reaction catalyzed by the thiazolium salt (**1**)

Recently, molecular orbital calculations have been examined for complicated reaction systems which are difficult to study experimentally. However, only limited calculation has been done with the thiazolium salts and their analogues, presumably due to the complication of this species, especially due to the positively charged nitrogen and sulfur atoms. For instance, the computational analyses of the structures (bond length, bond angle, and partial charge distribution) using semi-empirical methods (extended-Huckel calculation for thiamine derivatives [12] and AM1 calculation for thiamine [13]) have been reported. For thiazole and pyrimidine that are the component of thiamine, the most suitable calculation method has been discussed by the comparison between the results of the semi-empirical methods (MNDO, AM1, PM3) [14] or those of the non-empirical ones (RHF/STO-3G, 3-21G, 3-21G*, and 6-31G* levels) [15]. As a former example, Shaffer and Wierschke reported that the PM3 program has given the best semi-empirical results for 4-methylthiazole in comparison with MNDO, AM1, and the Benson method [14]. In terms of the geometry of the positive species, an ab initio study has been made for protonated heteroatomic rings such as imidazole, oxazole and thiazole [16]. However, only the proton affini-

ties have been reported. Thus, although several computational studies of the thiazole and thiazolium species have been done, no discussion has been had on the stability of thiazolium ions and on the reaction mechanism with respect to the role of the thiazolium ions. The discussion of the stability of the intermediates is important to further elucidate the mechanism.

There is a computo-chemical argument of an analogous reaction, that is, the Wittig reaction. Both Wittig and formose reactions include the reaction of an “ylide” with an aldehyde. In a report on the Wittig reaction, PM3 calculation was used [17], and the results were in good agreement with the experimental results.

In this study, we examined the intermediates of the formose reaction catalyzed by thiazolium salts, using a semi-empirical method (MOPAC-PM3), to afford the mechanistic insight of the formose reaction by discussions on the stability of the intermediates and energies of the transition state.

2 Computational Methods

The MOPAC-PM3 semi-empirical MO method was used in the CAChe Work System (Fujitsu) on Apple Power Macintosh G3. In order to simplify calculations, 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium (**1**) was used as the model for thiazolium catalysts, and trimethylamine (**3**) was adopted as the model base. Although the thiazolium has a counter-ion, an anion, as the first stage, the anion was assumed to affect the reaction intermediates uniformly in the reaction, and thus the anion was not included in the calculations for simplicity. The effect of solvent was not taken into consideration, either.

The starting geometries for all of these semi-empirical calculations were at first minimized with the MM2 method in CAChe Work System. The optimized geometries of **1** and **3** were confirmed in terms of vibrational analysis. The transition state for each step was located using the SADDLE routine implemented in MOPAC. No arbitrary assumptions were imposed on finding the most likely geometries for the transition state in each case. Further refinement of some transition state geometries was carried out with the NLLSQ algorithm. In this calculation, geometries optimization was carried out for the starting and final geometries of the reaction path beforehand. The resulting geometries of the transition states were confirmed by vibrational analysis.

3 Results and Discussion

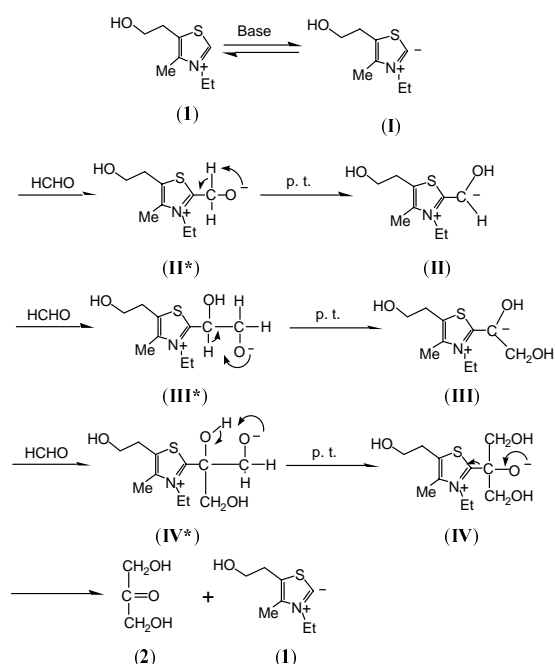
3.1 Generally accepted mechanism

The outline of the generally accepted mechanism of the formose reaction catalyzed by thiazolium salts is shown

in Scheme 2 [4, 18–20]. First, the base removes the proton on the C2 position of the thiazolium (**1**) (Step a), and then the intermediate **I** is formed. Next, formaldehyde adds to **I**, and the addition gives the zwitterion intermediate **II*** with a negative charge on the oxygen atom (Step b). Subsequently, the proton transfers from the C1' position to the negatively charged oxygen atom in **II*** (Step c). Steps between b and c are repeated until three molecules of formaldehyde are added. The 1,3-dihydroxyacetone (**2**) finally generates and the catalyst **I** is reproduced. Thus, this reaction is a condensation of aldehyde which proceeds via a carbanion and an intermediate with a negative charge on the oxygen atom. In the mechanism, the formation of the intermediates with a negative charge on the oxygen atom is an important step.

The proton, which is removed from the C2 position by the base, can connect with the negative charge on the zwitterion intermediate **II***, **III***, or **IV***. If the zwitterion intermediate binds to the proton, however, the resulting intermediate can not separate to **1** and the carbohydrate. The corresponding compound has been observed in the reaction medium [5].

This reaction is generally considered to follow a reaction path similar to the “benzoin condensation” catalyzed by the cyanide ion. Actually, benzoin is known to be formed in the reaction of benzaldehyde catalyzed by the thiazolium salt [18]. However, the existence and the stability of the other intermediates in the formose reaction are still ambiguous. Thus, based on this mechanism, geometry optimization was executed for each intermediate, and then the transition state was examined for each reaction step.



Scheme 2. Generally accepted mechanism of the formose reaction

3.2 Geometry optimization of the model catalyst

The model catalyst, 3-ethyl-(2-hydroxyethyl)-4-methyl-thiazolium (**1**), was used as the reference in energy in every discussion of the intermediates on the formose reaction. Thus the geometry optimization of **1** was first executed. The optimized results are shown in Figure 1 and are summarized in Table 1. The literature data were also summarized in Table 1 for comparison.

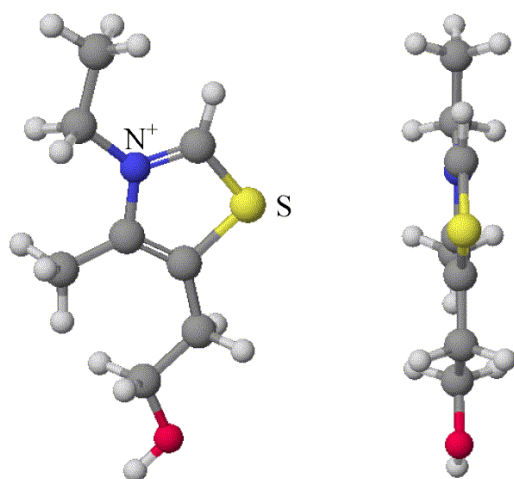


Figure 1. Result of geometry optimization of **1**

Table 1. Calculation data of **1**

Compound (Method)		Thiazolium (PM3)	Thiazolium (AM1)*	Thiazole (PM3)**
bond length	S1-C2	1.691	1.674	1.748
	C2-N3	1.358	1.321	1.324
	N3-C4	1.428	1.394	1.409
	C4-C5	1.382	1.352	1.368
	C5-S1	1.748	1.727	1.675
bond angle	S1-C2-N3	114.25	112.3	114.16
	C2-N3-C4	111.78	114.1	111.55
	N3-C4-C5	111.97	111.8	113.38
	C4-C5-S1	111.19	110.4	111.85
	C5-S1-C2	90.82	91.5	89.06
Atomic Charge	S1	+573.8	+864	+280.8
	C2	-391.9	-373	-236.1
	N3	+460.7	-51	-59.4
	C4	-194.2	-8	-106.8
	C5	-196.6	-408	-332.0
	H(C2)	+209.2	+245	+191.4
heat of formation		130.8	no data	40.28

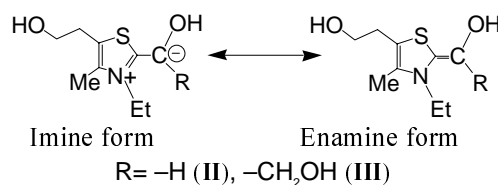
* Reference 13, ** Reference 14

The structure of **1** was planar, and all the carbon atoms of the substituents were put on the same plane with respect to the thiazolium ring. All bond lengths and bond angles nearly conformed to those of thiazole and previous data. This result indicates that the molecule has no appreciable strain in the heterocyclic ring. The atomic charge of S was more positive than that of N⁺ (N3) for the calculation result. A counter-anion may approach the

S atom, since the space surroundings the S atom is sterically open. AM1 calculations usually give the poorest results for most five-membered aromatic heterocycles with one nitrogen [14] and thus, the N3 atom of thiamine may have positive charge. The heat of formation was calculated to be 130.8 kcal/mol. The positive charge of the C2-proton (H(C2)) was similar in magnitude to that of proton of the hydroxyl group, suggesting that the C2-proton has very high acidity and is easily removed. Therefore, the corresponding carbanion **I** is very readily formed from the thiazolium ion **1**.

3.3 Geometry optimization of intermediates and validity of the generally accepted mechanism

Geometry optimization of the intermediates in the formose reaction was executed. The geometry optimization of the carbanion intermediates (**I**, **II**, and **III**) was successfully completed, and the heat of formation (ΔH_f) was evaluated as 6.6, -65.0, and -109.5 kcal/mol, respectively. It should be noted that the intermediates **II** and **III** are more stable than **I** in terms of the heat of formation. The bond order of C-C⁻ bond was 1.764 for **II** and 1.739 for **III**, and the bond length was about 1.35Å for both **II** and **III**, indicating that the C-C⁻ bond in **II** and **III** is similar to the C-C double bond. Based on these results, the stability of **II** and **III** will be explained with the existence of enamine forms as shown in Scheme 3. Since such an enamine form does not exist in **I**, the latter will become less stable than **II** and **III**.



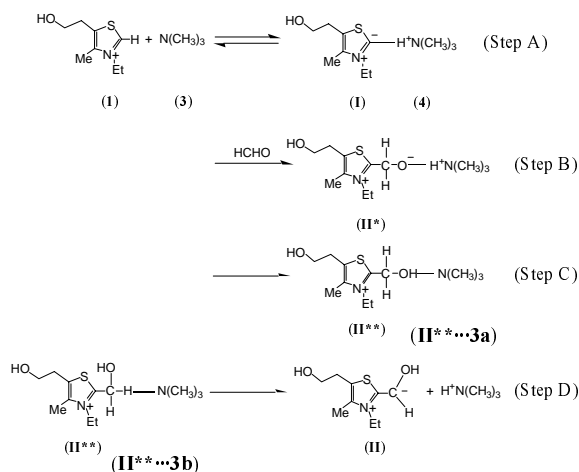
Scheme 3. Imine and enamine forms of the intermediates **II** and **III**

On the other hand, geometry optimization of the intermediates with a negative charge on the oxygen atom (**II**^{*}, **III**^{*}, **IV**^{*}, and **IV**) was unsuccessful. In all the optimized geometries of these zwitterion intermediates, the length of the C-C bond, which should adjoin the anionic oxygen, was extremely long as if there exists no bond between these atoms. Actually, the bond order of the C-C bond was almost zero. In the geometry optimization, the zwitterion intermediates revert to the preceding intermediates (**II** and **III**). For example, geometry optimization of **II**^{*} gave the same geometry as that of **I** and formaldehyde coexisting. These results imply that all the intermediates (**II**^{*} to **IV**^{*}) with an anionic oxygen, which should be the key intermediates in the generally accepted

mechanism, are actually unstable and that the addition of formaldehyde to the carbanion does not give these intermediates. In other words, it is inappropriate to consider the mechanism via the intermediates like **II***, **III***, and **IV*** for the present, suggesting that some stabilizing factor is necessary for the zwitterionic intermediates, especially around the anionic oxygen atom, to participate in the formose reaction.

3.4 The role of the ammonium ion

The tertiary amine in the reaction medium reacts with the proton at the C2 position of the thiazolium ion to form the corresponding ammonium ion. As one of the plausible pathways, the positive charge in the ammonium ion may stabilize the negative charge on the oxygen atom in the intermediates through the formation of an ion pair. The ammonium ion in the reaction medium will serve as a stabilizing factor for the intermediates.



Scheme 4. Mechanism of the formose reaction with contribution of ammonium ion

By considering the contribution of the ammonium ion to the proton transfer process, the reaction mechanism can be redrawn as shown in Scheme 4, where trimethylamine is used as a model base. First, the base reacts with the proton at the C2 position of **1** to form the ion pair of **I** with the ammonium ion **4** (Step A). Next, formaldehyde binds to the anionic C2 of **I** in the ion pair, to form the ion pair of the intermediate (**II***) with **4** (Step B). Then, the ammonium ion **4** donates its proton to the anionic oxygen of **II*** to form 2-hydroxy-methyl-3-ethyl-5-(2-hydroxyethyl)-4-methyl-thiazolium (**II****) (Step C). Finally, the proton at the C1'-position of **II**** is extracted

by the base to give the intermediate **II** (Step D). The steps from B to D are repeated until three molecules of formaldehyde are consumed. These steps correspond to the proton transfer process in the generally accepted mechanism. Formation of the intermediate **II**** is a possible pathway. It is because the reaction intermediate isolated by Saimoto and co-workers has the structure in which the *N*-substituted group, for example the *N*-ethyl group in the model molecule **1**, is removed from **II**** [5].

In order to confirm the mechanism including the contribution of an ammonium ion, geometry optimization was executed for the intermediates in these steps.

3.4.1 Step A: Extraction of the proton at the C2 of the thiazolium

Step A was considered first. This step is presumably in equilibrium in the presence of the base. Here, we do not argue about the equilibrium in detail. However, since the geometry of each molecule in this step becomes the reference to the species in the consecutive steps, it is necessary to execute the geometry optimization exactly. The geometry optimization of **1** and **I** had already been successfully completed as described in the above sections. Thus, the geometry optimization was executed for other species (**3** and **4**) in Step A. The heat of formation (ΔH_f) of the optimized structures of **3** and **4** was -10.8 and 151.3 kcal/mol, respectively.

The thiazolium **1** and the intermediate **I** coexist with **3** or **4** in the reaction medium. Thus, using the above calculation results, the geometry optimization of the species in the left side of Step A (**1+3**) and the right side (**I...4**) was also executed, and was successfully completed. The ΔH_f of **1+3** and **I...4** was 105.0 and 120.5 kcal/mol, respectively. The optimized structure is shown in Figure 2. The carbon atom at C2 position of the thiazolium, hydrogen atom, and the nitrogen atom of the base were linearly located in each state. The geometries of **1+3** and **I...4** are almost identical except for the location of the hydrogen atom at C2. The ΔH_f of **1+3** (105.0 kcal/mol) was about 15 kcal/mol lower than the sum of the ΔH_f of **1** and **3** (130.8 + (-10.8) = 120.0 kcal/mol). Similarly, **I...4** was about 37 kcal/mol more stabilized (6.6 + 151.3 = 157.9 kcal/mol vs. 120.5 kcal/mol). These results show that these intermediates are stabilized by some interaction between each species. In the case of **1+3**, the major stabilizing factor will be the coordinate bond between the hydrogen atom at C2 position of **1** and the nitrogen atom of **3**. The formation of the ion pair (Coulombic interaction) between **I** and **4** will be the major stabilizing factor for **I...4**.

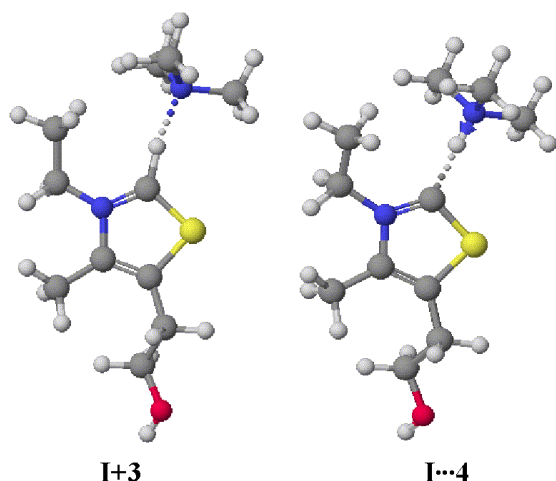


Figure 2. Optimization geometries of intermediates in Step A

3.4.2 Step B: Addition of Formaldehyde in the presence of the ammonium ion

In this step and thereafter, the reaction mechanism differs from the generally accepted one in terms of the contribution of the ammonium ion. Geometry optimization of the intermediate Π^* in the generally accepted mechanism was not successful, as described before. This is the first step in which the zwitterion intermediate appears in the reaction mechanism. To confirm the role of the ammonium ion in stabilizing the intermediate, geometry optimization was executed for the intermediates in Step B.

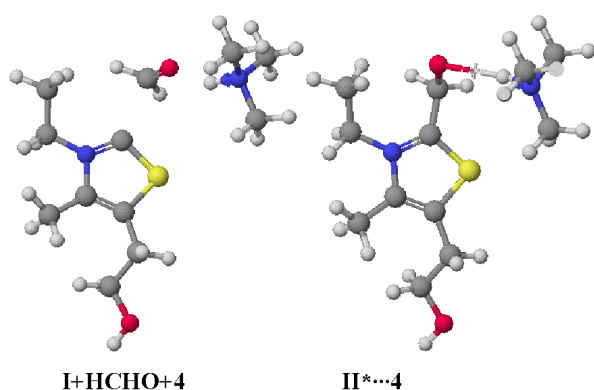


Figure 3. Optimized geometries of the intermediates in Step B

The geometry optimization of the intermediate Π^* in the presence of the ammonium ion ($\Pi^*\dots 4$) was successfully completed. The optimized geometry of $\Pi^*\dots 4$ is shown in Figure 3. An ion pair seems to be formed between Π^* and **4**, and the structure of Π^* was stabilized

with the ionic bond, for it is not stable in the absence of **4**. These results are very interesting because they suggest that the intermediates with a negative charge on the oxygen atom can only exist with the formation of the ionic bond. The ΔH_f of $\Pi^*\dots 4$ was estimated to be 95.5 kcal/mol.

Next, geometry optimization of $I\dots 4$ in the presence of formaldehyde ($I+HCHO+4$) was also executed. In the optimized result, an HCHO molecule was placed close to $I\dots 4$. The ΔH_f of $I+HCHO+4$ was 96.3 kcal/mol. The geometries of $I+HCHO+4$ and $\Pi^*\dots 4$ are fundamentally identical except for the distance between C2 of the thiazolium and C1' of formaldehyde.

Searching of the transition state between $I+HCHO+4$ and $\Pi^*\dots 4$ was executed, but the transition state was not found. In addition, the vibrational analysis of $I+HCHO+4$ showed that it was not the transition state. Note that no appreciable transition state exists in this step. That is, $I+HCHO+4$ is transformed very smoothly to $\Pi^*\dots 4$.

Based on the above results, Figure 4 summarizes the energy diagram along the reaction coordinate toward step B. The initial energy is 85.9 kcal/mol, which corresponds to the sum of ΔH_f s for **1**, **3**, and **HCHO**. The energy necessary for the formation of $\Pi^*\dots 4$ from **1**, **3**, and **HCHO** is estimated to be 10.4 kcal/mol by subtracting the initial energy from the ΔH_f of $I+HCHO+4$. The opposite reaction, from $\Pi^*\dots 4$ to $I+HCHO+4$, needs only an energy of 0.8 kcal/mol. These results indicate that the intermediate $\Pi^*\dots 4$ will easily revert to the intermediate, $I\dots 4$, **HCHO**.

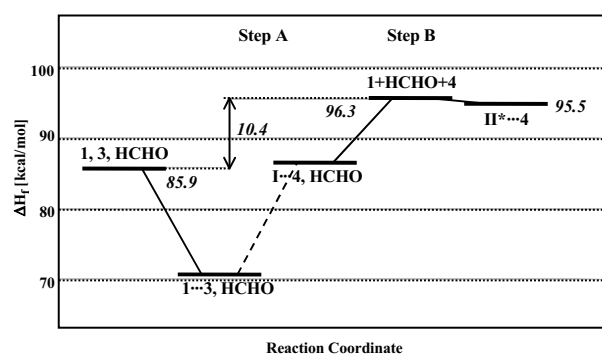


Figure 4. Energy diagram of Steps A to B

3.4.3 Steps C and D: Proton transfer

The Steps C and D are regarded as proton transfer processes via *N*-substituted 2-hydroxymethyl-5-(2-hydroxyethyl)-4-methylthiazolium (Π^{**} ; *N*-substituent is the ethyl group in the model species). The presence of the intermediate Π^{**} is crucial in the possible mechanism. As shown in Scheme 4, there are two possible sites in Π^{**}

for the base **3** to react with. One is the proton on the C1'-oxygen of \mathbf{II}^{**} ($\mathbf{II}^{**}\cdots\mathbf{3a}$ is formed), and the other is the proton on the C1' position ($\mathbf{II}^{**}\cdots\mathbf{3b}$ is formed). Thus, geometry optimization was executed for \mathbf{II}^{**} , $\mathbf{II}^{**}\cdots\mathbf{3a}$, $\mathbf{II}^{**}\cdots\mathbf{3b}$, and $\mathbf{II}\cdots\mathbf{4}$ in Steps C and D. The initial geometries of $\mathbf{II}^{**}\cdots\mathbf{3a}$ and $\mathbf{II}^{**}\cdots\mathbf{3b}$ were prepared from the optimized geometry of \mathbf{II}^{**} .

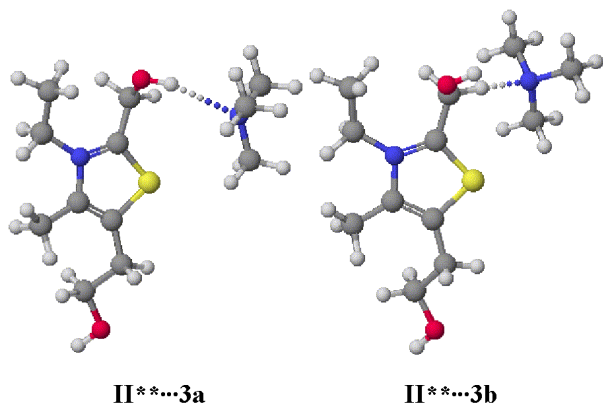


Figure 5. Optimization geometries of intermediates in Steps C and D

The geometries of all these species were successfully optimized. The geometries of $\mathbf{II}^{**}\cdots\mathbf{3a}$, and $\mathbf{II}^{**}\cdots\mathbf{3b}$ are shown in Figure 5. The ΔH_f s of \mathbf{II}^{**} , $\mathbf{II}^{**}\cdots\mathbf{3a}$, $\mathbf{II}^{**}\cdots\mathbf{3b}$, and $\mathbf{II}\cdots\mathbf{4}$ were 87.0, 69.7, 71.1, and 71.9 kcal/mol, respectively.

Since the ΔH_f of **3** is -10.8 kcal/mol, both the ΔH_f of $\mathbf{II}^{**}\cdots\mathbf{3a}$ and $\mathbf{II}^{**}\cdots\mathbf{3b}$ are lower than the sum of that of \mathbf{II}^{**} and **3**. This is because the hydrogen bond between \mathbf{II}^{**} and **3** contributes to the stabilization of the intermediates, $\mathbf{II}^{**}\cdots\mathbf{3a}$ and $\mathbf{II}^{**}\cdots\mathbf{3b}$. The difference in ΔH_f between $\mathbf{II}^{**}\cdots\mathbf{3a}$ and $\mathbf{II}^{**}\cdots\mathbf{3b}$ is only 1.4 kcal/mol, indicating that the difference in the position where \mathbf{II}^{**} interacts with **3** has only small influence on the heat of formation. Both of these species would exist in the reaction system.

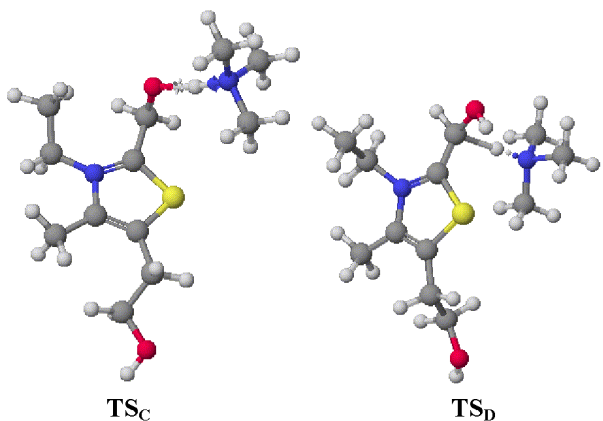


Figure 6. Geometries of transition state in Steps C (\mathbf{TS}_C) and D (\mathbf{TS}_D)

Table 2. Calculation results of \mathbf{TS}_C and \mathbf{TS}_D

Transition State		\mathbf{TS}_C	\mathbf{TS}_D
bond length	S1-C2	1.727	1.763
	C2-N3	1.355	1.411
	N3-C4	1.440	1.442
	C4-C5	1.375	1.362
	C5-S1	1.735	1.759
	C2-C1'	1.560	1.398
	C1'-O	1.337	1.377
	C1'-Ha	1.106	1.711
	C1'-Hb	1.113	1.104
	O-H	1.512	0.950
H-N(base)	1.200	1.195	
dihedral angle	C2-C1'-O-H	75.578	25.801
	C1'-O-H-N(base)	136.995	—
	N3-C2-C1'-H	-151.939	-105.403
	C2-C1'-Ha-N(base)	—	-81.030
bond angle	O-H-N(base)	169.906	—
	C1'-Ha-N(base)	—	172.770

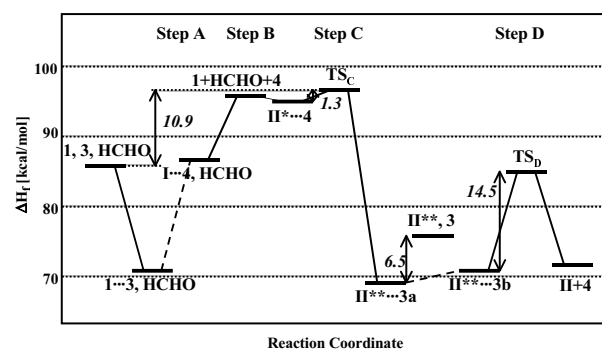


Figure 7. Energy diagram of formaldehyde addition process

Based on the optimized geometries of the intermediates, an attempt was made to search the transition states in the steps C and D. Only one transition state was found for each step as shown in Figure 6 and summarized in Table 2 (transition state in Step C: \mathbf{TS}_C , in Step D: \mathbf{TS}_D). Vibrational analysis confirmed that \mathbf{TS}_C and \mathbf{TS}_D were actually the transition state in each step. For the geometries of \mathbf{TS}_C and \mathbf{TS}_D , the H-N bond length was about 1.2 Å, which was close to the H-N bond length of **4** (1.00-1.04 Å). The C2-C1' bond length was 1.398 Å for \mathbf{TS}_D , which was close to the C-C double bond as shown in Scheme 3. The ΔH_f s of \mathbf{TS}_C and \mathbf{TS}_D were estimated to be 96.8 and 85.6 kcal/mol, respectively.

Based on the above results, the apparent activation energy for the steps A to D is estimated by subtracting the ΔH_f of the starting geometry from that of the transition state in the rate-determining step. The above results were summarized in the energy diagram of the reaction coordinate (Figure 7). As shown in Figure 7, it was found that the transition state \mathbf{TS}_C had the largest ΔH_f in the

steps toward **II**+4 formation. Thus, the apparent activation energy for the overall reaction was estimated to be 10.9 kcal/mol.

In the case of Step C, the activation energy was estimated to be 1.3 kcal/mol. Step C would proceed very smoothly since the activation energy is very low. In addition, when the geometry optimization was executed for **II***...4 by setting the initial length of the H-N bond to 2.0 Å instead of 1.2 Å (the original length in **II***...4), the optimized geometry was similar to **II****...3a. This clearly indicates that Step C proceeds very smoothly. On the other hand, in Step D, the activation energy is significantly large (14.5 kcal/mol) in comparison with those in other steps.

The complex **II****...3a would quickly be equilibrated with **II****...3b. This is because the energy required for dissociation of the complex **II****...3a into its components **II**** and **3** is calculated to be as low as 6.5 kcal/mol (Figure 7).

3.5 Proposal of a more plausible mechanism for the reaction

According to the above discussion on the basis of the MOPAC-PM3 calculation results, the mechanism shown in Scheme 4 is plausible for the initial stage of the formose reaction. The ammonium ion plays an important role in the reaction processes, in particular, in stabilization of the intermediates having a negative charge on the oxygen atom and in the proton transfer process. Formation of the ion pair stabilizes the zwitterion intermediates (Step B). The ammonium ion donates its proton to the zwitterion intermediate (Step C), and then the amine removes the C-H proton from the cationic intermediate (Step D). Another point to be noted is that the reaction would proceed through 2-hydroxy-methyl-3-ethyl-5-(2-hydroxyethyl)-4-methyl-thiazolium (**II*****) as a possible intermediate. Since the analogue of **II**** (2-C-hydroxymethyl-5-(2-hydroxyethyl)-4-methylthiazole) has been isolated as a reaction intermediate [5], the presence of **II**** is plausible in the reaction medium.

The apparent activation energy of the formose reaction has been estimated experimentally to be 19 kcal/mol in the presence of thiamine as the catalyst and an excessive amount of 2-dimethylamino-ethanol as the base [8]. The computationally estimated activation energy of the initial stage of the formose reaction, in which the intermediate **II** is formed from **I** and **HCHO**, is 10.9 kcal/mol. The difference between experimental and calculated results may be attributed either to the differences in structure, such as the N-substituted group, of the thiazolium or the neglecting of the Coulomb stabilization by the counter-anion and/or the effect of solvation, or the pK_b of the base. The initial stage is suggested to be the rate-determining step in the formose reaction since the energy of **TS**_C is the largest in the mechanism, although

no experimental evidence is available yet to distinguish the rate-determining step in the reaction.

4 Conclusion

The mechanism of the formose reaction catalyzed by thiazolium salt was discussed based on the MOPAC-PM3 calculation results. The generally accepted intermediates with a negative charge on the oxygen atom (**II***, **III***, **IV***, and **IV**) in the reaction have proved to be very unstable. The intermediates are stable only in the presence of the ammonium ion to form ion pairs. The ammonium ion also plays an important role in the proton transfer steps. In the process including the proton transfer steps, the structures of the transition states were successfully estimated by theoretical calculation. The estimated activation energy was 10.9 kcal/mol. Based on the results presented here, it is reasonable to consider that the mechanism including the contribution of ammonium ion is more plausible in the initial stage of the formose reaction.

In this paper, the computational study was executed for the process in which the first molecule of formaldehyde reacts with the thiazolium catalyst in the formose reaction. The similar addition process is repeated twice in the reaction until 1,3-dihydroxyacetone (**2**) is formed. To elucidate the overall mechanism of the formose reaction, further experimental and theoretical investigation is necessary.

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チアゾリウム塩を用いたホルモース反応の 反応機構についての理論的研究

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チアゾリウム塩を用いたホルモース反応の反応機構中の中間体の安定性を議論するために、MOPAC-PM3 プログラムを用いて理論的な検証を行った。一般に知られている反応機構 (Scheme 2) 中の中間体のうち、C1' 位に負の電荷を持つ中間体 (II, III) はエナミン形を取ることで安定に存在できることが確かめられた (Scheme 3)。一方、酸素原子上に負の電荷を持つ中間体 (II*, III*, IV*, IV) は、そのままでは非常に不安定であることが認められた。この不安定性を解消する因子として、反応メディア中のアンモニウムイオンの存在に注目した。アンモニウムイオン存在下では、負の電荷を持つそれぞれの反応中間体はアンモニウムイオンとイオン対を形成して安定に存在できることが計算より確かめられた。そこで、このようなイオン対形成を考慮した反応機構 (Scheme 4) を提案し、特にプロトン転位過程における Step C と Step D についてその遷移状態計算を行った。どちらの場合もただ一つの遷移状態を見つけることができた (Figure 6)。この計算により、提案する反応機構の初期段階の見かけ上の活性化エネルギーは 10.9 kcal/mol に見積もられた。この値は実験的に求められた活性化エネルギー (19 kcal/mol) とは若干の開きがあるが、これはチアゾリウムの N 位置換基や塩基の pKb の違いによるものと考えられる。今のところ提案した反応機構は、よりもっともらしいスムーズなものであり、今後さらなる研究により明らかになるだろう。

キーワード: MOPAC-PM3, ホルモース反応, チアゾリウム塩, 反応機構, イオン対形成