Decarboxylation of 2-Lactylthiazolium Cation. AM1 and ab Initio MO/MP2 Studies

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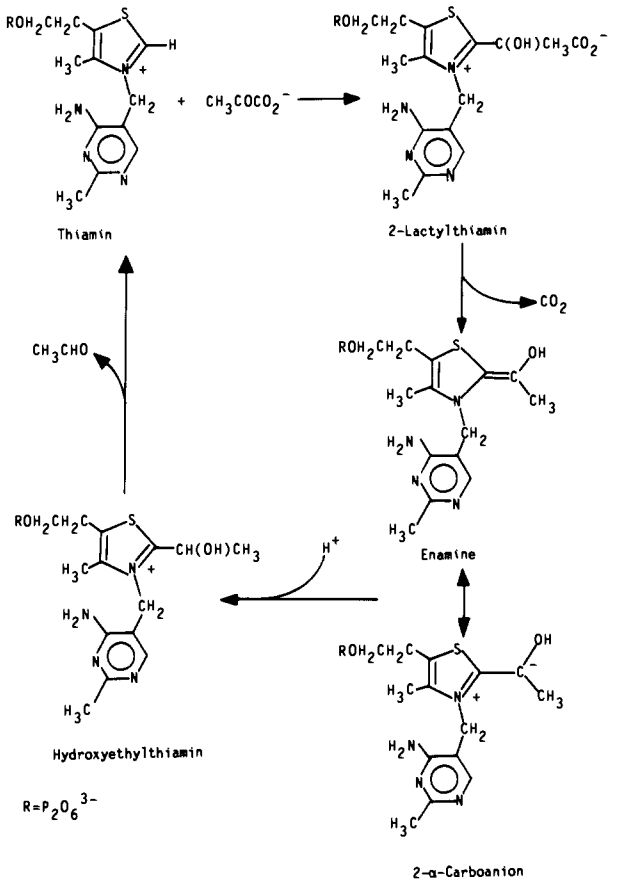
Abstract: The decarboxylation reaction of 2-lactylthiazolium is investigated with AM1 and ab initio MO/MP2 methods. The calculated activation barrier E_a is extremely small, while the calculated exothermicity E_{exo} is considerably large: E_a = 1.5 (AM1), 3.9 (MP2/MIDI-4), and 4.4 kcal/mol (MP2/6-31G) and E_{exc} = 23.8 kcal/mol (AM1). Water molecules interacting with 2-lactylthiazolium increase the activation barrier and decrease the exothermicity, which agrees well with the experimental report of Lienhard et al. The product optimized here is characteristic of the enamine. This theoretical result, as well as experimental results of Jordan et al., clearly indicates that an enamine compound exists as an intermediate in the decarboxylation of 2-lactylthiazolium. For decarboxylation reactions of 2-lactyloxazolium and 2-lactylimidazolium, the calculated activation energy is higher but the calculated exothermicity is lower than those of the 2-lactylthiazolium decarboxylation: E_a = 2.8 and E_{exo} = 18.1 kcal/mol (AM1) for 2-lactyloxazolium, and E_a = 6.4 and E_{exo} = 3.9 kcal/mol (AM1) for 2-lactylimidazolium. The difference in reactivity between 2-lactylthiazolium, 2-lactyloxazolium, and 2-lactylimidazolium is interpreted in terms of the electron-withdrawing ability of the azolium ring.

Introduction

Thiamin diphosphate (TDP) is a coenzyme that participates in the enzymatic decarboxylation of pyruvate.[1] The reaction mechanism of the pyruvate decarboxylation proposed by Breslow is shown in Scheme I.[2] In this mechanism, lactylTDP (LTDP), an enamine (or 2α-carbanion) species, and 2-(hydroxyethyl)TDP (HETDP) are involved as key intermediates. So far, there have been reported several experimental results supporting this reaction mechanism. For instance, HETDP was isolated from yeast pyruvate decarboxylase.[3] In addition, Krampitz et al. succeeded in the chemical synthesis of HETDP and reported that HETDP was converted to acetaldehyde and thiamin diphosphate by wheat germ pyruvate decarboxylase.[4] Also, LTDP and lactylthiamin (a model of LTDP) were chemically synthesized, and their reaction behaviors have been investigated.[5,6] In particular, experimental results of Lienhard et al.[7] are worthy of note; here, the decarboxylation of the 2-lactyl-3,4-dimethylthiazolium cation proceeds with the high activation barrier of 31.2 kcal/mol in water but with a very small activation barrier in ethanol. From these results, the authors proposed that the desolvation action of the enzyme might be a major cause of catalysis in thiamin pyrophosphate-dependent enzymatic reactions.

Although several convincing results have been reported on LTDP and HETDP as described above, the enamine intermediate has not been chemically synthesized and its existence has not been directly confirmed yet, probably owing to its high reactivity. Recently, Kluger et al. provided us with experimental support for the enamine intermediate.[8] In addition, Jordan's interesting result has been reported indicating that the enamine intermediate is, indeed, on the reaction pathway.[9] Molecular orbital calculations

Scheme I



are also expected to offer valid information on the enamine species.

In this work, AM1 and ab initio MO/MP2 calculations are carried out on the decarboxylation reaction of 2-lactylthiazolium, a model of LTDP. Also, decarboxylation reactions of 2-lactyloxazolium and 2-lactylimidazolium are investigated in an attempt

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(8) (a) Kluger, R.; Karimian, K.; Gish, G.; Pangborn, W. A.; DeTitta, G. *J. Am. Chem. Soc.* **1987**, *109*, 618. (b) Kluger, R.; Karimian, K.; Kitamura, K. *J. Am. Chem. Soc.* **1987**, *109*, 6368.

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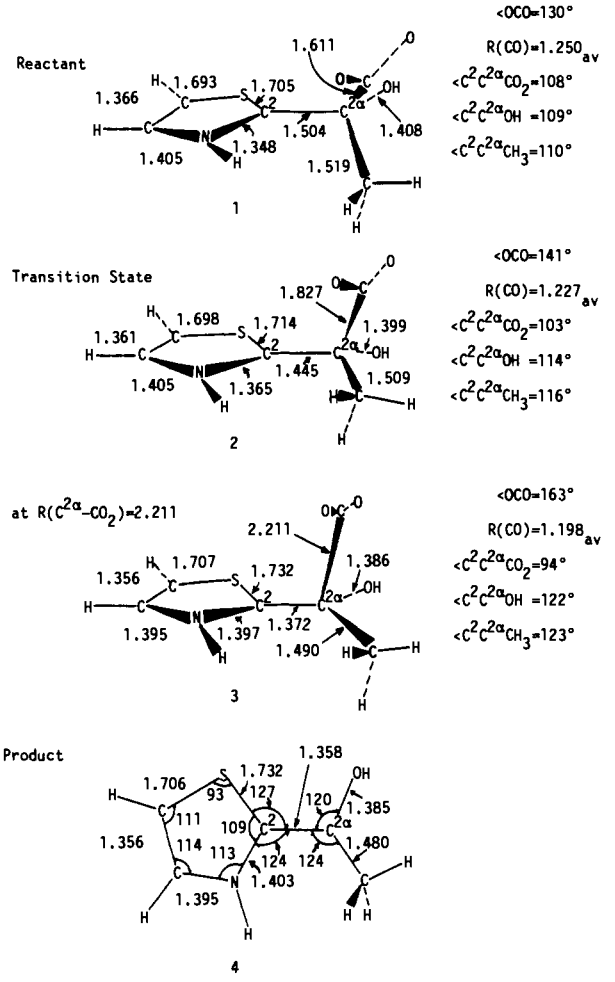

Figure 1. Geometry changes caused by the decarboxylation reaction of 2-lactylthiazolium (bond distances in angstroms and bond angles in degrees).

to compare their reactivities with the 2-lactylthiazolium reactivity. It is our intention with this work to present (1) good understanding of the decarboxylation reaction of 2-lactylthiazolium, (2) theoretical evidence of the enamine intermediate, and (3) a clear comparison of the decarboxylation reactivity between thiazolium, oxazolium, and imidazolium cations.

Computational Details

AM1 calculations were carried out with the MOPAC program (version 3.0),[10] where AM1 standard parameters[11] were employed, except for MNDO parameters used for the S atom.[12] Ab initio closed-shell Hartree–Fock (HF) and MP2 calculations were performed with Gaussian 82 and 86 programs.[13] The MINI-1 basis set[14a,b] was used for geometry optimization at the HF level. The 6-31G[15] and MIDI-4[14a,c] basis sets were employed for MP2 calculations.

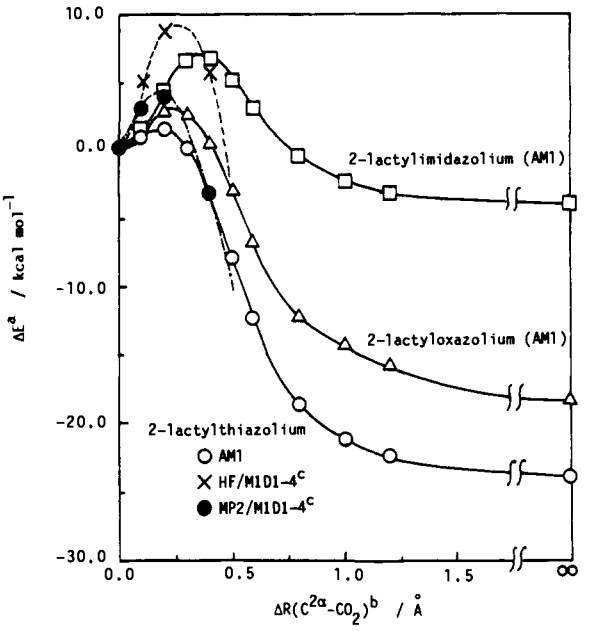

Figure 2. Energy changes caused by decarboxylation reactions of 2-lactylthiazolium, 2-lactyloxazolium, and 2-lactylimidazolium. (a) ΔE represents the change in total energy, where a standard (energy = 0) is taken for 2-lactylazoliums. (b) $\Delta R(C^{2\alpha}–CO_2)$ means the lengthening of the $C^{2\alpha}–CO_2$ distance from 2-lactylazoliums. (c) Results of HF/6-31G and MP2/6-31G are very close to results of HF/MIDI-4 and MP2/MIDI-4, respectively.

In AM1 calculations, geometries of reactants, transition states, and products were optimized with the Davidon–Fletcher–Powell method,[16] where the azolium ring was assumed to be planar. This assumption seems reasonable, because 2-lactylthiazolium is destabilized in energy by the out-of-plane distortion of its N–H bond. Geometry changes caused by the decarboxylation were investigated, taking the $C^{2\alpha}–CO_2$ distance as a reaction coordinate (see Figure 1 for C^2, $C^{2\alpha}$, etc.).

In ab initio MO calculations, geometries were optimized with the energy gradient method at the HF level, where the geometry of the thiazolium ring was taken to be the same as that in the AM1-optimized structure of 2-lactylthiazolium.[17a,c] This assumption is reasonable when the early stage of the decarboxylation is investigated, because AM1 calculations showed that geometry changes of the thiazolium ring were very small upon going to the TS from 2-lactylthiazolium. MP2 calculations were performed with all the core orbitals excluded from the active space.

Results and Discussion

Decarboxylation Reaction of 2-Lactylthiazolium. The geometry of 2-lactylthiazolium (**1**) optimized by the AM1 method is shown in Figure 1. This optimized geometry agrees well with the experimental structure of phosphalactylthiamin (methyl 2-hydroxy-2-(2-thiamin)ethylphosphonate).[17b] The energy change caused by the 2-lactylthiazolium decarboxylation is given as a function of the $C^{2\alpha}–CO_2$ distance (see Figure 2). AM1 calculations, like ab initio MO/MP2 calculations, indicate that the $C^{2\alpha}–CO_2$ distance lengthens at the TS by ca. 0.2 Å. Thus, we can consider that the AM1 method presents reliable results on this decarboxylation reaction. Geometries of the TS **2** and the product **4** of this decarboxylation are also shown in Figure 1. Going to **4** from **1**, the $C^2–N$ distance is getting longer, the $C^2–C^{2\alpha}$

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(17) (a) The optimized geometry of the thiazolium ring by the AM1 method agrees well with the experimental structure.[17b] The ab initio MO method overestimated bond lengths of the thiazolium ring by ~0.06–0.2 Å when MINI-1, STO-3G, or 3-21G was employed. When a d-polarization function is added on the S atom, the optimized geometry agrees well with the experimental structure.[17b] (b) Turano, A.; Furey, W.; Pletcher, J.; Sax, M.; Pike, D.; Kluger, R. *J. Am. Chem. Soc.* **1982**, *104*, 3089. (b) In ab initio MO calculations, the reaction coordinate, $C^{2\alpha}–CO_2$ distance, is increased with an increment of 0.2 Å, and the geometry was optimized at each $C^{2\alpha}–CO_2$ distance. The TS was located by a least-squares fitting of total energies.

Table I. Activation Barrier (E_a) and Exothermicity (E_{exo}) of Decarboxylations of 2-Lactylazoliums (kcal/mol)

	method	$\Delta R_{C^{2\alpha}-CO_2}$[a]	E_a	E_{exo}
2-lactylthiazolium	AM1	0.22	1.5	23.8
	HF/MIDI-4	0.25	8.9	*b*
	HF/6-31G	0.25	9.0	*b*
	MP2/MIDI-4	0.17	3.9	*b*
	MP2/6-31G	0.18	4.4	*b*
2-lactylthiazolium[c] with 2 H_2O	AM1	0.30	5.6	14.7
2-lactylthiazolium[d] with 3 H_2O	AM1	0.32	19.0	−2.1[e]
2-lactyloxazolium	AM1	0.18	2.8	18.1
2-lactylimidazolium	AM1	0.42	6.4	3.9

[a] Bond lengthening at TS. [b] Reference 18. [c] Reference 19a. [d] Reference 19b. [e] Endothermic.

distance is getting shorter, and the OCO, $C^2C^{2\alpha}CH_3$ and $C^2C^{2\alpha}$–OH angles are gradually opening. These results mean that the C^2—$C^{2\alpha}$ single bond is changing to its double bond, the C^2=N double bond is changing to its single bond, and the CH_3 and OH groups are going into the plane of the C^2=$C^{2\alpha}$ double bond. Lengthening the $C^{2\alpha}$–CO_2 distance to 2.211 Å (i.e., going to the late stage of the reaction), the C^2–$C^{2\alpha}$ distance shortens to 1.363 Å and the C^2–N distance lengthens to 1.397 Å, as shown by **3** in Figure 1. These distances of the C^2—$C^{2\alpha}$ and C^2—N bonds are similar in magnitude to those of the C=C double and C—N single bonds, respectively, indicating that **3** is characteristic of the enamine compound. Also, the product **4** apparently takes the enamine structure (Figure 1). Thus, these results provide us with the theoretical evidence that the enamine intermediate is, indeed, on the reaction pathway.

AM1 calculations show that the activation barrier of this decarboxylation is considerably small (E_a = 1.5 kcal/mol). Although somewhat large activation barriers (8.9 and 9.0 kcal/mol) are evaluated by HF/MIDI-4 and HF/6-31G calculations, respectively, inclusion of electron correlation by the MP2 method substantially decreases the activation barrier to 3.9 (MP2/MIDI-4) and 4.4 kcal/mol (MP2/6-31G), as shown in Table I. Corresponding to this small activation barrier, the exothermicity E_{exo} calculated for this decarboxylation is extremely large: E_{exo} = 23.8 kcal/mol (AM1 calculation).[18] All these results suggest that the decarboxylation of 2-lactylthiazolium proceeds very easily in nonpolar solvents.

In such a polar solvent as water, the situation would change. 2-Lactylthiazolium is considered to be a zwitterion because the CO_2 part is negatively charged and the thiamin ring is positively charged. On the other hand, the products (enamine and CO_2) are neutral. Thus, a polar solvent stabilizes 2-lactylthiazolium more than it does the products, which would increase the activation barrier and decrease the exothermicity. In order to examine how water molecules influence this decarboxylation, we carried out AM1 calculations on this decarboxylation reaction in the presence of several water molecules. First, let us investigate the case in which two water molecules interact with the CO_2 part of 2-lactylthiazolium. Positions of water molecules are roughly optimized.[19a] These two water molecules increase the activation barrier to 5.6 kcal/mol and decrease the exothermicity to 14.7 kcal/mol. Next, let us investigate the case in which one additional water molecule is placed so as to interact with the N atom of the thiazolium ring. Again, the position of this water molecule is roughly optimized,[19b] whereas the positions of the other two water molecules are not reoptimized. This new water molecule further increases the activation barrier to 19.0 kcal/mol and significantly decreases the exothermicity to −2.1 kcal/mol (i.e., the reaction becomes endothermic). These results are consistent with Lienhard's experiment, which showed that the decarboxylation reaction of a lactylthiazolium derivative (2-(1-carboxy-1-hydroxyethyl)-3,4-dimethylthiazolium chloride) proceeds very rapidly in ethanol but very slowly in water.[7]

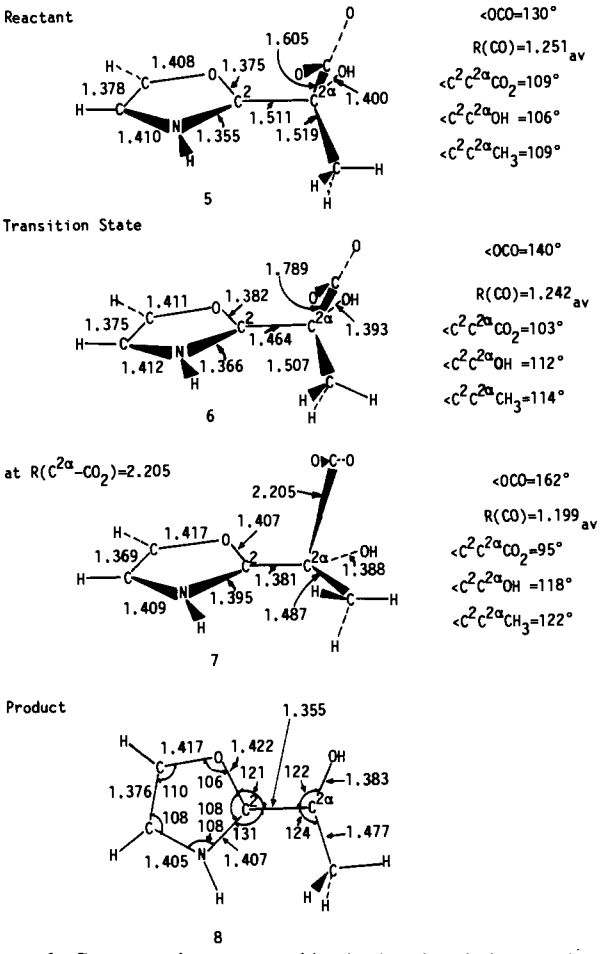

Figure 3. Geometry changes caused by the decarboxylation reaction of 2-lactyloxazolium (bond distances in angstroms and bond angles in degrees).

Decarboxylation Reactions of 2-Lactyloxazolium and 2-Lactylimidazolium. These decarboxylation reactions are investigated with the AM1 method, in which the $C^{2\alpha}$–CO_2 distance is taken as a reaction coordinate as it is in the decarboxylation of 2-lactylthiazolium. Geometry changes caused by these decarboxylations are given in Figures 3 and 4. As these decarboxylations proceed (i.e., as the $C^{2\alpha}$–CO_2 distance lengthens), the C^2–N distance is getting longer, the C^2–$C^{2\alpha}$ distance is getting shorter, and the OCO, $C^2C^{2\alpha}$–CH_3, and $C^2C^{2\alpha}$ OH angles are gradually opening, as they do in the decarboxylation of 2-lactylthiazolium. Consequently, 2-lactyloxazolium and 2-lactylimidazolium change to **7** (Figure 3) and **11** (Figure 4), respectively, at the late stage of the reaction. Both **7** and **11** are typical enamine compounds. Furthermore, the products **8** and **12** of these reactions take the enamine structure, as does the product **4** of the 2-lactylthiazolium decarboxylation.

The activation barrier calculated with the AM1 method increases in the order 2-lactylthiazolium (1.5 kcal/mol) < 2-lactyloxazolium (2.8 kcal/mol) < 2-lactylimidazolium (6.4 kcal/mol), and the exothermicity decreases in the order 2-lactylthiazolium (23.8 kcal/mol) > 2-lactyloxazolium (18.1 kcal/mol) > 2-lactylimidazolium (3.9 kcal/mol). Thus, the decarboxylation of 2-lactylthiazolium proceeds the most easily, but that of 2-lac-

(18) Since the structure of the thiazolium's five-membered ring is considerably different between **1** and the enamine product, the thiazolium ring in the product should be reoptimized for calculation of the exothermicity. However, such optimization is time-consuming in ab initio MO calculations, because use of a d-polarization function is indispensable for obtaining a good geometry of the five-membered ring.[17a] Thus, the exothermicity was not calculated by the ab initio MO/MP2 method.

(19) (a) Water molecules are placed in the CO_2 plane, where waters approach the O atom of CO_2 with the H atom in the lead. The approaching angle of H_2O (∠COH) and the distance between O of CO_2 and H of H_2O are optimized. (b) A water molecule is placed above the thiazolium ring, perpendicular to the ring, where the O atom of the water molecule approaches the N atom of thiazolium. The N–O distance and the approaching angle of H_2O are optimized.

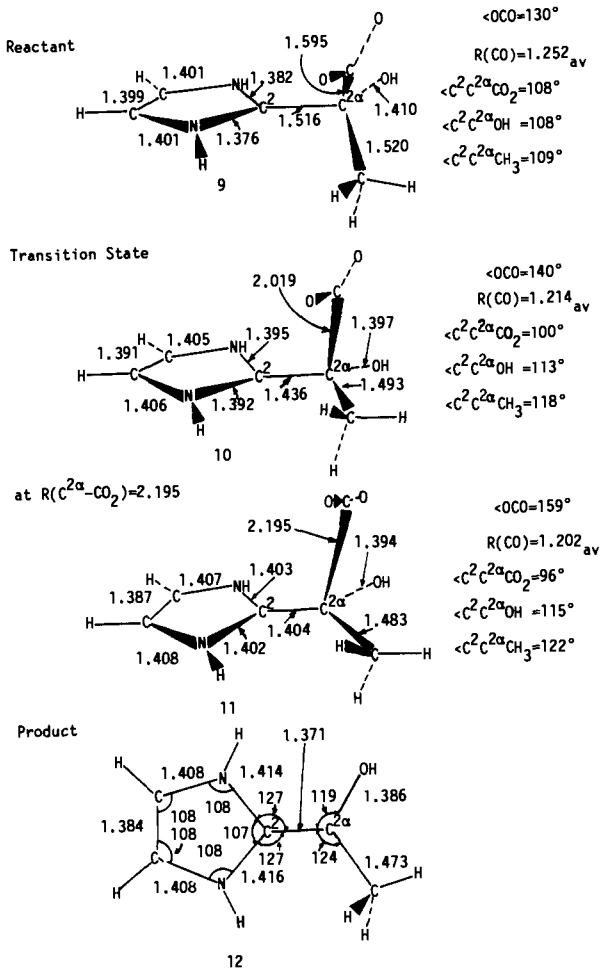

Figure 4. Geometry changes caused by the decarboxylation reaction of 2-lactylimidazolium (bond distances in angstroms and bond angles in degrees).

tylimidazolium proceeds with the most difficulty of these three decarboxylations.

It is interesting to compare geometries of the TS in these decarboxylations. As described above, the C^2—$C^{2\alpha}$ bond changes to its double bond but the C^2—N bond changes to its single bond upon going to the product from the reactant. To indicate how much the C^2—$C^{2\alpha}$ single bond changes to its double bond at the TS, the factor f is defined as follows:

$$f_1 = [R(C{-}C)_P - R(C{-}C)_{TS}]/[R(C{-}C)_R - R(C{=}C)_P]$$

where the subscripts P, R, and TS represent product, reactant, and transition state, respectively. Apparently, f_1 is 0% for the C^2—$C^{2\alpha}$ single bond and 100% for the C^2=$C^{2\alpha}$ double bond. Also, the factor f_2 is defined on the C^2—N bond to illustrate how much the C^2=N double bond changes to its single bond at the TS

$$f_2 = [R(C{=}N)_R - R(C{-}N)_{TS}]/[R(C{=}N)_R - R(C{-}N)_P]$$

Apparently, f_2 is 0% for the C^2=N double bond and 100% for the C^2—N single bond. These factors f_1 and f_2 are considered to be measures indicating the character of the TS. As listed in Table II, f_1 and f_2 exhibit interesting differences between 2-lactylimidazolium and the other two: f_1 = 38% and f_2 = 31% in the decarboxylation of 2-lactylthiazolium; f_1 = 30% and f_2 = 21% in the decarboxylation of 2-lactyloxazolium; f_1 = 58% and f_2 = 40% in the decarboxylation of 2-lactylimidazolium. These results suggest that the decarboxylation of 2-lactylimidazolium reaches the TS later than in the other decarboxylations.

Pauling's bond order is also useful in discussing the character of TS. As shown in Table II, the decarboxylation of 2-lactylimidazolium exhibits the greater value of the C^2–$C^{2\alpha}$ bond order and the smaller value of the C^2–N one at the TS than those for the other decarboxylations, indicating that in the 2-lactyl-

Table II. Measures of C^2–$C^{2\alpha}$ Bond Lengthening (f_1), and C^2–N^3 Bond Shortening (f_2), and Pauling's Bond Order (n) of the C^2–$C^{2\alpha}$ and C^2–N^3 Bonds at the Transition State of the Decarboxylation of 2-Lactylazoliums

	measure of change in bond distance (%)		Pauling's bond order	
	f_1[a]	f_2[b]	$n_{C^2-C^{2\alpha}}$[c]	$n_{C^2-N^3}$[c]
2-lactylthiazolium	38	31	1.323	1.615
2-lactyloxazolium	30	21	1.232	1.727
2-lactylimidazolium	58	40	1.466	1.516

[a] f_1 is the measure indicating how much the C^2–$C^{2\alpha}$ bond changes to the double bond from the single bond (see text). [b] f_2 is the measure indicating how much the C^2–N bond changes to the single bond from the double bond (see text). [c] Pauling's bond order; $n = \exp[(R_1 - R_n)/C]$, where R_1 and R_n are bond lengths for bonds of order 1 and n, respectively. C is estimated so that n = 1 for the single bond and n = 2 for the double bond.

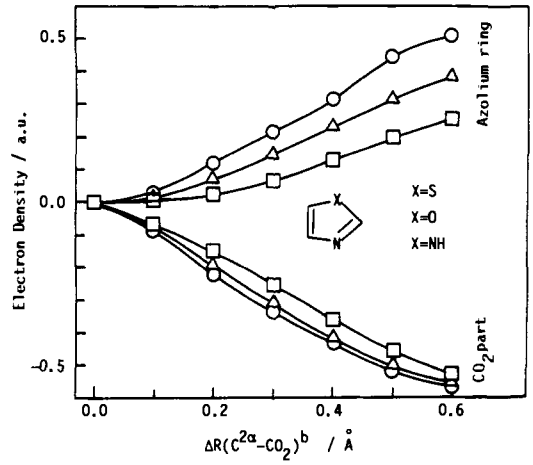

Figure 5. Changes in the electron density of the CO_2 part and the azolium ring caused by decarboxylation reactions of 2-lactylthiazolium, 2-lactyloxazolium, and 2-lactylimidazolium. (a) The definition of ΔR-($C^{2\alpha}$–CO_2) is given in b of Figure 2.

imidazolium decarboxylation the C^2—$C^{2\alpha}$ single bond changes to its double bond and the C^2=N double bond changes to its single bond at the TS to a greater extent than in the other decarboxylations. These results again suggest that the decarboxylation of 2-lactylimidazolium reaches the TS later than the other decarboxylations.

Electron Redistribution Caused by These Decarboxylations and Factors Determining the Reactivity of Azoliums. The decarboxylation decreases the electron density of the CO_2 part but increases that of the azolium ring, as is clearly shown in Figure 5. The greatest change is caused by the decarboxylation of 2-lactylthiazolium. This means that the thiazolium ring is the most electron-withdrawing (i.e., the least electron-donating) in these three azoliums.

It is worthwhile to investigate whether or not the decarboxylation reactivity is related to the electron-withdrawing character of the azolium ring. The more the azolium ring is electron-withdrawing, the more its π^* orbital lies low in energy. Thus, let us inspect the relation between the π^* orbital of the azolium ring and the decarboxylation reactivity of 2-lactylazolium. Since a neutral CO_2 molecule eliminates from 2-lactylazolium, 2-lactylazolium is considered to consist of CO_2 and such a remaining fragment as 2-(hydroxyethyl)thiazolium (**10**), 2-(hydroxyethyl)oxazolium (**11**), and 2-(hydroxyethyl)imidazolium (**12**). These fragments **10**, **11**, and **12** are calculated with the AM1 method, where their geometries are taken to be the same as in the TS. Here we should notice the HOMO of 2-(hydroxyethyl)azolium, because the charge transfer from Lewis base to CO_2 is considered important to the CO_2 binding with the base.[20]

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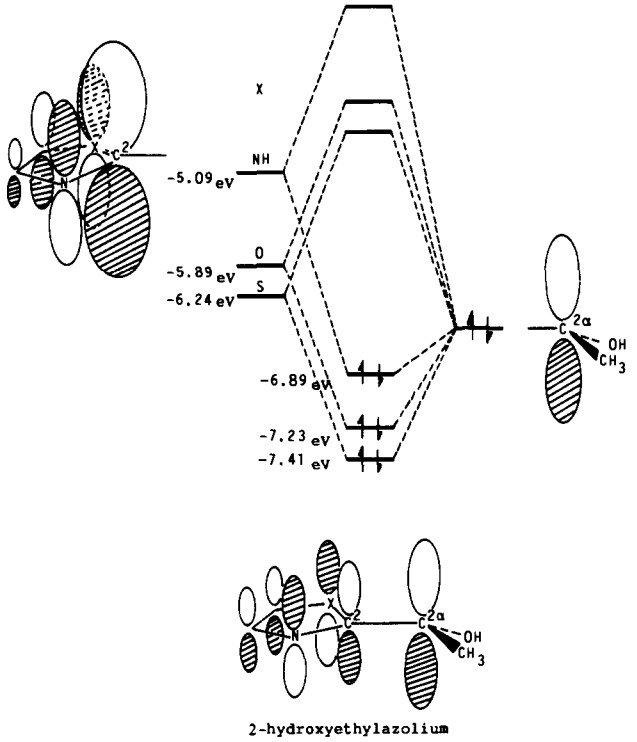

Figure 6. Schematic representation of the CO_2 interaction with the $C^{2\alpha}$ atom at the transition state.

As is schematically shown in Figure 6, their HOMOs mainly consist of the $C^{2\alpha}$ p_π orbital, into which the π^* orbital of the azolium ring mixes in a bonding way. Because the π^* orbital of the azolium ring rises in energy in the order thiazolium < oxazolium < imidazolium, the bond mixing between the π^* orbital of the azolium ring and the $C^{2\alpha}$ p_π orbital weakens in the order **10 > 11 > 12**, and therefore, the HOMO of 2-(hydroxyethyl)-azolium rises in energy in the order **10 < 11 < 12**, as shown in Figure 6. Thus, the charge transfer from 2-(hydroxyethyl)azolium to CO_2 strengthens in the order **10 < 11 < 12**, which leads to the weakest $C^{2\alpha}$–CO_2 binding in 2-lactylthiazolium and the strongest $C^{2\alpha}$–CO_2 binding in 2-lactylimidazolium. Consequently, the decarboxylation of 2-lactylthiazolium proceeds the most easily, but that of 2-lactylimidazolium occurs with the most difficulty of the 2-lactylazoliums examined.

In summary, the decarboxylation reactivity of 2-lactylazolium can be related to the electron-withdrawing ability of the azolium ring as follows. Since the π^* orbital of the thiazolium ring lies at the lowest energy level in these azoliums examined, thiazolium is the most electron-withdrawing, and at the same time, the HOMO of 2-(hydroxyethyl)thiazolium lies at the lowest energy level in these 2-(hydroxyethyl)azoliums. In 2-lactylthiazolium, therefore, the CO_2 binding with the $C^{2\alpha}$ atom is the weakest in these 2-lactylazoliums, which results in the easiest decarboxylation of 2-lactylthiazolium. In other words, the greatest decarboxylation reactivity of 2-lactylthiazolium comes from the most electron-withdrawing ability of the thiazolium ring. These results are consistent with Breslow's proposal that the thiazolium ring serves as an electron sink for the decarboxylation process.[2]

Finally, let us discuss briefly the reason that the π^* orbital of the thiazolium ring lies at the lowest energy level in these azoliums. Compared to the O atom of oxazolium and the NH group of imidazolium, the S atom of thiazolium possesses highly polarizable and diffuse orbitals, which would stabilize the π^* orbital of the thiazolium ring in energy and would enhance the electron-withdrawing ability of the thiazolium ring.

Concluding Remarks

AM1 and ab initio MO/MP2 calculations are carried out on the decarboxylation reaction of 2-lactylthiazolium, a model of thiamin diphosphate. For the decarboxylation, the calculated activation barrier E_a is very small and the calculated exothermicity E_{exo} is considerably large: E_a = 1.5 (AM1), 3.9 (MP2/MIDI-4), and 4.4 kcal/mol (MP2/6-31G) and E_{exo} = 23.8 kcal/mol (AM1). Two water molecules interacting with the CO_2 part of 2-lactylthiazolium increase the activation barrier to 5.6 kcal/mol and decrease the exothermicity to 14.7 kcal/mol. An additional water molecule interacting with the thiazolium ring further increases the activation barrier to 19.0 kcal/mol and significantly decreases the exothermicity to −2.1 kcal/mol (i.e., the reaction is endothermic). This result agrees well with Lienhard's experiment.

As the decarboxylation proceeds, the C^2—$C^{2\alpha}$ and C^2=N bonds are changing to the corresponding double and single bonds, respectively, and the product takes the typical enamine structure. This theoretical result, as well as Jordan's experiments, clearly indicates that the enamine is, indeed, on the reaction pathway.

Decarboxylation reactions of 2-lactyloxazolium and 2-lactylimidazolium are investigated to compare their reactivities with that of 2-lactylthiazolium. Products of their decarboxylations also take the enamine structure. In their decarboxylations, the activation barrier is slightly higher than that of 2-lactylthiazolium: 2.8 for 2-lactyloxazolium and 6.4 kcal/mol for 2-lactylimidazolium (AM1 calculation). The exothermicity is somewhat smaller in 2-lactyloxazolium (18.1 kcal/mol) and significantly smaller in 2-lactylimidazolium (3.9 kcal/mol) than in 2-lactylthiazolium. Thus, the decarboxylation reactivity decreases in the order thiazolium > oxazolium > imidazolium. This decreasing order is interpreted in terms of the π^* orbital of the azolium ring. Since the energy level of its π^* orbital lowers in the order imidazolium > oxazolium > thiazolium, the HOMO of 2-(hydroxyethyl)-azolium lowers in the same order, which results in the weakest $C^{2\alpha}$–CO_2 binding of 2-lactylthiazolium. Accordingly, the decarboxylation of 2-lactylthiazolium proceeds the most easily. The π^* orbital of the azolium ring would be stabilized in energy by highly polarizable and diffuse orbitals of the S atom.

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