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Decarboxylation Mechanism of Amino Acids by Density Functional Theory

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The decarboxylation mechanisms of amino acids with and without water were studied by density functional theory at the B3LYP/6-31G level. Without water, two decarboxylation channels exist for the low molecular weight amino acids glycine (Gly) and alanine (Ala), whereas only one exists for the other amino acids. Channel one for Gly and Ala takes place from a neutral conformer in which the carboxylic hydrogen is intramolecularly hydrogen bonded to the nitrogen atom of the amino group. During the development of the transition-state structure, the carboxylic hydrogen atom first shifts to the amino group forming the zwitterion and then from the $-NH_3^+$ group to the α-carbon forming the product amine. Accompanying proton transfer, the $C-CO_2$ bond elongates. Channel two starts from the higher-energy anti carboxylic hydrogen conformer and involves the direct heterolytic loss of CO_2 accompanied by simultaneous proton transfer. The calculated energy barriers range from 288 to 307 kJ/mol with an average of 299 kJ/mol. The decarboxylation channels and side-chain structures have a negligible effect on the energy barriers. The water-catalyzed transition-state structures start from the zwitterion in which a water molecule is hydrogen bonded between the carboxylate group and $-NH_3^+$ group and have imaginary frequencies that correspond to "swinging" of the water molecule from the carboxylate oxygen to the α-carbon. The calculated energy barriers range from 177 to 195 kJ/mol with an average of 186 kJ/mol. An intrinsic reaction coordinate analysis indicates that crossing the energy barrier does not take the activated complex forward in the direction of the products. However, geometry optimization of the carbanion−water activated complex after the loss of CO_2 leads to the formation of the product amine and the water molecule. Consequently, solvent dynamics and steric effects in the solvated transition state are responsible for the difference in the relative decarboxylation rates of amino acids. The transition-state structures are less polar than the reactants, which confirms experimental findings about the salt effect.

Introduction

The discovery of thermophilic organisms in submarine hydrothermal systems has led to the conjecture that life on the earth may have originated, at least in part, from these systems. To support this conjecture, amino acids must be proven to persist at hydrothermal conditions, at least long enough to be trapped in the cooler mixing layer. It is well known that amino acids undergo irreversible destruction through decarboxylation,[1] deamination,[2] dehydration,[3] hydrolysis,[4] and racemization[5] if left at static hydrothermal conditions. However, high hydrogen fugacity,[1d] a controlled redox state by mineral assemblies,[1e] and high ionic strength[1c] significantly retard the decarboxylation rate of amino acids.

Intimately tied to the hypothesis that submarine hydrothermal vents are in some way responsible for the origin of life are the flexible properties of high-temperature water.[6,7] Water can act simultaneously as the medium, catalyst, reactant, and product. Computational studies of the catalytic involvement of water molecules in the transition-state structures include the tautomerization of DNA bases,[8] formamidine,[9] and protonated peptides,[10] hydrolysis of the peptide bond,[11] decarboxylation of carboxylic acids,[12] hydration and hydrolysis of α-oxo carboxylic acid derivatives,[13] proton transfer in methoxyl and benzyloxyl radicals,[14] and proton transfer from the neutral form to the zwitterionic form of amino acids.[15] In these transition-state structures, water acts as a proton acceptor and donor at the same time, and the transferring proton may be in a symmetric or asymmetric position.

Theoretical[16−19] and experimental[20] research on the zwitterionic form of amino acids has shown that at least two water molecules are needed to lower the potential energy of the water−zwitterion complex below that of the water−neutral complex. The direct pathway,[21] in which the carboxylic hydrogen atom shifts to the amino group, and the indirect pathway,[15] in which it shifts via a water molecule bridge, are energetically comparable.

The general mechanism of decarboxylation of the carboxylic acid and carboxylate groups appears[22] to be S_N2, in which three transition-state structures have been recognized: (1) an intramolecular cyclic structure in which the anti carboxylic hydrogen bridges to an electronegative atom or a multiply bonded carbon atom. Decarboxylation and proton transfer occur concomitantly;[23] (2) direct thermal decarboxylation of the zwitterion;[23a−c,24] and (3) a cyclic structure in which a water molecule(s) acts as a bridge linking the anti carboxylic hydrogen and α-position carbon atom, where proton transfer and decarboxylation are symmetric or asymmetric concerted processes.[12]

In this paper, a study of the thermal decarboxylation mechanism of amino acids in aqueous solution was undertaken by density functional theory. The calculated energy barriers are compared to those experimentally determined to test the influence of the side chains on the energy barrier of decarboxylation. It has been shown[1b] that a strong kinetic compensation effect exists between the experimental activation energy and the preexponential factor, which suggests that the decarboxy-

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lation of amino acids occurs via the same mechanism or at least the same rate-determining step. A new picture of catalysis by a water molecule in the transition-state structure was found. This mechanism differs from that in which the water molecule acts simply as a proton relay.

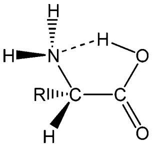
Computational Methods

Calculations were performed with Gaussian 98 software[25] using B3LYP[26] density functional theory with the 6-31G basis set. A comparison by Bach et al.[23a−c] has shown that the activation barriers for decarboxylation are overestimated at the MP2 level and underestimated at the B3LYP level, but the difference is small. The greatest inaccuracies occur at the Hartree−Fock level. The activation-energy comparisons in this paper are intended to be relative rather than absolute, so the choice of the computational method is not an issue.

Optimizations of the geometries of the reactants and transition states were carried out, followed by vibrational frequency analyses to confirm that the optimized geometry was a local minimum or a transition state. The frequency analyses also provided thermal-energy corrections to the total energy. Details can be found in Table S of the Supporting Information. All calculations were made at 298.15 K and 1 bar. The effect of temperature and pressure differences was found to be negligible.[12h]

Results and Discussion

Low-Energy Conformers of Amino Acids. There are many conformers for amino acids, especially if the side chain is aliphatic. Both theoretical calculations and experiment show that three conformers (structures 1−3) are lower in energy regardless of the side chains.[27,28]



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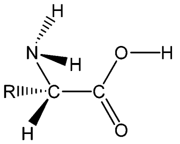

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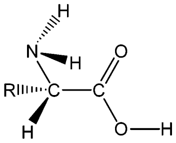

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On the basis of this result, structure 1 with anti carboxylic hydrogen bonded to the amino nitrogen atom was selected as the starting conformer because this conformation decarboxylates most readily as a result of the transfer of the carboxylic hydrogen atom in the anti orientation.

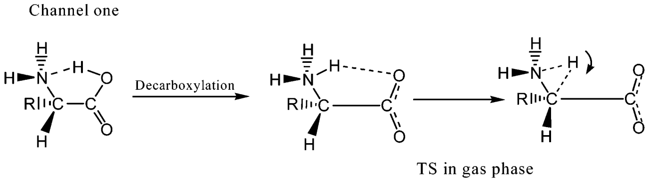
Zwitterion Stabilized by a Single Water Molecule. Zwitterionic forms of amino acids are not stable without the electrostatic field provided by ions and/or the polar solvent unless constraints are introduced during the geometry optimization. To enable the zwitterion stabilized by water molecules to be energetically lower than the corresponding neutral supermolecular form in the potential energy surface, at least two water molecules are required to bridge the $-NH_3^+$ and $-CO_2^-$ sites.[11a] Molecular simulation[15,21a] of the amino acid in aqueous solution has shown that at least one water molecule is hydrogen bonded between the carboxylate group and the amino group in the zwitterion or at least is in the vicinity of this site. Therefore, neutral and zwitterionic forms with a single water molecule hydrogen bonded between the carboxylate and amino groups were optimized. The results indicated that both optimized structures were energy minima and that the zwitterion was energetically higher than the neutral form. We did not include additional water molecules in the zwitterion, in part because the orientations of the water molecules in the first solvation shell of amino acids depend on the side chain. It was found that the geometry optimization of the supermolecule consisting of one reactant molecule surrounded by several water molecules had difficulty reaching convergence.

TABLE 1: Experimental Arrhenius Parameters, Relative Decarboxylation Rates at 320 °C, and Calculated Activation Energies with and without Water Molecules Involved in Transition-State Structures for Amino Acids

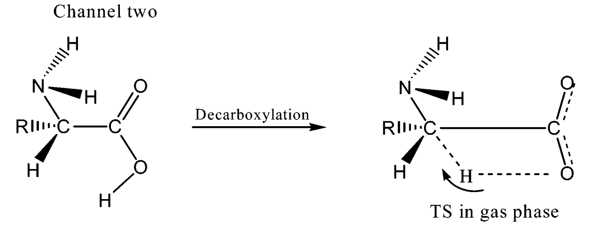
	exptl			calcd E_a (kJ·mol^{-1})	
amino acids	E_a (kJ·mol^{-1})[a]	ln(A, s^{-1}) [a]	rel rate at 320 °C	without H_2O	with H_2O
Ala	190.55 ± 7.36	34.01 ± 1.49	1	301.76[e]	181.72
	175.50 ± 8.25	30.09 ± 1.99		303.16[f]	
Gly	138.38 ± 3.89	25.25 ± 0.79	6.06	305.64[e]	182.46
	165.70[b]	28.40[b]		307.01[f]	
α-Aib	207.22 ± 7.40	36.81 ± 1.49	0.56	303.64	195.39
Val	185.89 ± 4.01	33.58 ± 0.81	1.57	300.28	194.33
Leu	141.99 ± 4.41	24.84 ± 0.89	1.91	304.88	190.27
	189.12[c]	32.77[c]			
Ile	180.77 ± 12.31	32.51 ± 2.47	1.65	299.33	195.16
Ser	110.93 ± 4.65	21.07 ± 1.00	23.72	288.77	183.98
	122.80[d]	28.32[d]			
Thr	142.11 ± 3.41	27.44 ± 0.74	24.79	288.88	177.12
	141.25[d]	28.22[d]			
Met	125.04 ± 1.61	23.15 ± 0.35	10.69	296.27	181.61
Phe	171.03 ± 7.88	30.57 ± 1.6	1.73	296.90	179.96
	128.87[d]	18.95[d]			
Tyr				297.28	180.89
His	151.76 ± 7.97	27.20 ± 1.62	2.98	295.03	186.47
Pro	189.40 ± 3.52	32.22 ± 0.70	0.20	291.72	177.22
	177.40[c]	28.04[c]			
Trp				301.07	195.16

[a] Reference 1b. [b] Snider, M. J. College of Wooster, personal communication, 2002. [c] Reference 1l. [d] Reference 1n. [e] Channel 1. [f] Channel 2.

SCHEME 1



SCHEME 2



Decarboxylation of Amino Acids without Water. For the purpose of comparison with experiment,[1] the 13 protein amino acids and 1 nonprotein amino acid shown in Table 1 were selected for calculation. The side chain of the other amino acids either deaminates or hydrolyzes. Two amino acids [tryptophan (Trp) and tyrosine (Tyr)] were also selected for calculation because the most probable hydrothermolysis route of these two amino acids is decarboxylation. No experimental kinetic data were available because of their very low solubility and high thermal stability. In the gas phase, two decarboxylation channels were found for the low molecular weight amino acids Gly and Ala, and one decarboxylation channel was found for the higher molecular weight amino acids because of their bulkier side chains. Schemes1 and 2 show the two channels. For a better understanding, the reactants, transition-state structures, and

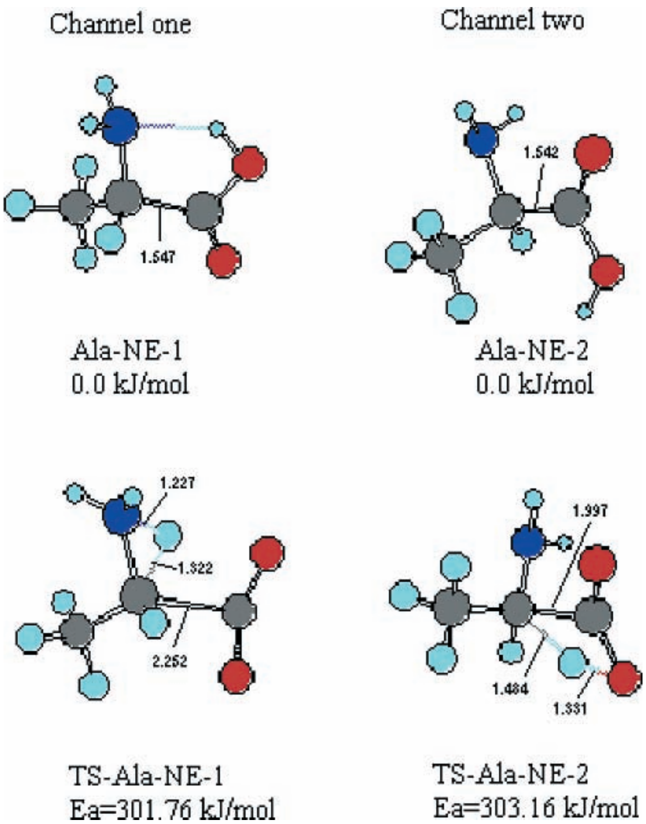
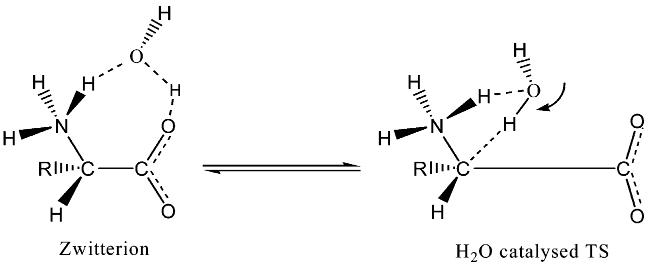


Figure 1. Transition-state structures and starting structures for Ala in the gas phase. Bond distances are given in angstroms.

SCHEME 3



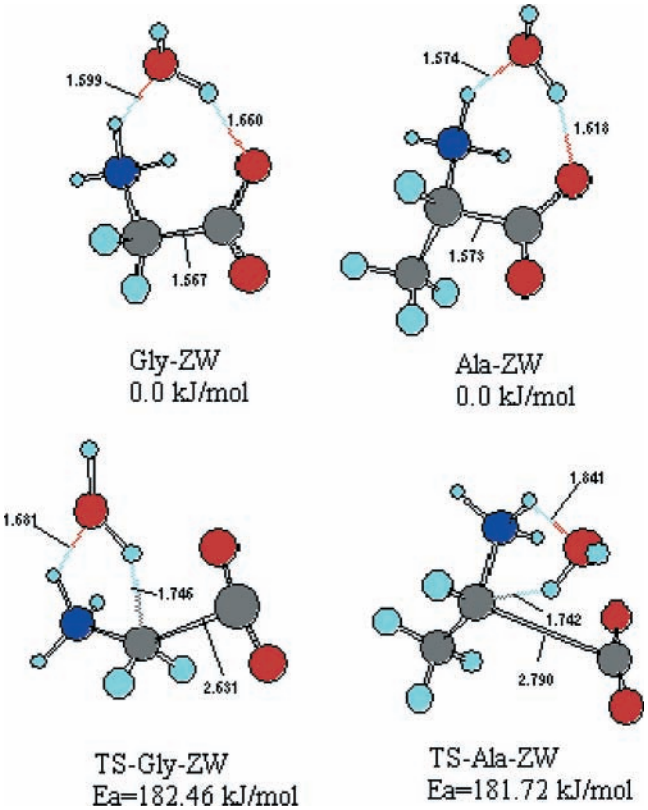


Figure 2. Water molecule-catalyzed transition-state structures and one water molecule-stabilized zwitterionic form for Gly and Ala. Bond distances are given in angstroms.

corresponding energy barriers for Ala are displayed in Figure 1. The imaginary frequencies are about i1650 cm^{-1}, which correspond to proton transfer. The intrinsic reaction coordinate (IRC) analysis for Scheme 1 indicated that the carboxylic hydrogen first shifts to the amino group to form the zwitterion and then shifts to the α-carbon atom to form the product amine during the development of the transition-state structure. Accompanying this proton-transfer step is an elongation of the $C-CO_2$ bond.

The energy barriers (Table 1) toward decarboxylation for all selected amino acids in the gas phase are seen to be about 300 kJ/mol and are independent of the side-chain structure. It is interesting to compare the energy barriers for amino acids with those of other carboxylic acids. The energy barriers via Scheme 2 for carboxylic acids with a single, double, or triple bond attached at the α-carbon are 290, 260, and 228 kJ/mol, respectively.[12g] Therefore, the energy barrier via the anti carboxylic hydrogen conformation is mainly controlled by the bond type at the α-carbon.

Water Molecule-Catalyzed Transition-State Structures. Single water molecule-catalyzed transition-state structures were found and are represented by Scheme 3. Examples for Gly and Ala are given in Figure 2. The imaginary frequencies are in the range of i55−i165 cm^{-1}. Animation of the vibration shows that these frequencies correspond to “swinging” of the water molecule with the hydrogen atom of water shifting from the carboxylate oxygen toward the α-carbon. The calculated activation energies are listed in Table 1 and lie in the range of 177 to 195 kJ/mol with an average of 186 kJ/mol. The IRC analysis of both the forward and reverse directions shows that the transition-state structure equilibrated with the reactant rather than crossing the energy barrier to form products. Therefore, it is highly probable that solvent dynamics are responsible for separating the CO_2 leaving group from the resultant carbanion in aqueous solution. A geometry optimization of the carbanion, which is hydrogen bonded to a water molecule, shows the formation of the product amine and the regeneration of the water molecule. Without the interaction of the water molecule, the zwitterionic carbanion is stable in the gas phase and will not transfer a proton from the amino group to the α-carbon atom. This result indicates that the zwitterionic carbanion with H_2O as a hydrogen-bonding bridge is not stable in the potential energy surface. As an intermediate, its lifetime[29] can be as short as 10^{-11} s.

It is not possible to compare the experimental and calculated activation energies because a strong kinetic compensation effect exists in the experimental Arrhenius parameters. However, the kinetic compensation effect supports the rationality of transition-state structures presented in this paper. It suggests that the same mechanism is involved in decarboxylation. The differences in the relative decarboxylation rates can be attributed to the steric and solvation effects of the side chains. The fact that increasing the ionic strength decreases the decarboxylation rate[1c] means that the transition-state structures are less polar than the reactants. This is confirmed by comparing the dipole moments of transition-state structures and reactants, which shows that the dipole moments of the transition-state structures are smaller than those of the reactants. For example, the dipole moments of the transition-state structure and reactant for Ala are 3.83 D and 8.11 D, respectively.

The effect of solvation on the calculated energy barriers was not included because the dielectric continuum and discrete models are not able to represent the true solvation effect at the present time.[30] The hybrid dielectric continuum/discrete model, in which the discrete model describes the first solvation shell of the solute, is an option, but one difficulty in its use for amino acids lies in the fact that the first solvation shell varies with the side chains. The anticipated result is a slight increase in the calculated energy barriers due to desolvation of the transition-state structure.[24c,d] It is also possible to involve more than 1 water molecule in the transition-state structure and form an 8- or 10-membered cyclic structure,[12f] but the extent by which more water molecules in the transition-state structure can reduce the energy barrier is limited because of compensation by the entropy factor.

In the end, the catalytic participation of water in the transition-state structure provides a good model for the study of how solvent dynamics in the condensed phase determine the reaction rate when the energy barriers are the same. When the transition-state structure equilibrates with the reactant, crossing the energy barrier does not necessarily move the activated complex forward to the product. The solvent dynamics, because of solvent molecule motion and reorientation in response to the charge redistribution, also play a role in the rate.

Conclusions

Density functional theory at the B3LYP/6-31G level leads to the following conclusions about the decarboxylation mechanism of amino acids in the gas phase and in aqueous solution.

Without the presence of water, there are two transition-state structures for Gly and Ala and one transition-state structure for the other protein amino acids. In channel one for Gly and Ala, two proton-transfer steps take place in which the carboxylic hydrogen atom first shifts to the amino group and then to the α-carbon atom. Channel two proceeds via direct proton transfer to the α-carbon atom from the anti carboxylic hydrogen conformation without intramolecular hydrogen bonding. The calculated activation energies are in range of 288 to 307 kJ/mol regardless of the decarboxylation channels and side-chain structures.

A single water molecule can stabilize the zwitterionic form of amino acids by linking the carboxylate and amino groups via hydrogen bonding, although the zwitterion−water complex is energetically higher than the corresponding neutral form−water complex.

A new view about the catalytic role of the water molecule participating in the transition-state structure is that the hydrogen-bonded water molecule acts as a stimulus when it “swings”, as opposed to acting as a proton relay. That is, catalysis develops when the H atom of the water molecule in the transition-state swings into the vicinity of the α-carbon atom and away from hydrogen bonding to the carboxylate group. However, the transition-state structures equilibrate with the reactants after crossing the energy barrier. Therefore, solvent dynamics are probably responsible for achieving the observed products. In particular, after the CO_2 fragment leaves, the resultant zwitterionic carbanion−water complex is unstable and transforms to the amine product using the hydrogen-bonded water molecule as a proton pipeline. The resulting calculated activation energies for decarboxylation fall into a narrow range of 177 to 195 kJ/mol with an average of 186 kJ/mol. This mechanism helps to explain why the side-chain structures have only a minor effect on the activation energies.

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Supporting Information Available: **Z** matrices for the optimized geometries of reactants and transition-state structures using B3LYP/6-31G (Gaussian 98). This material is available free of charge via the Internet at http://pubs.acs.org.

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