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MP2 study of the gas phase elimination mechanism of some neutral amino acids and their ethyl esters†

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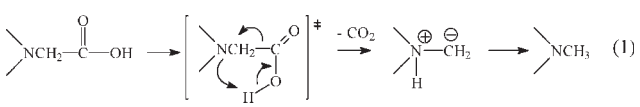
The mechanisms of the gas phase elimination of *N*,*N*-dimethylglycine, picolinic acid, and *N*-phenylglycine and their ethyl esters have been examined at Möller–Plesset MP2/6-31G (d, p) level of theory. The ethyl esters of these 2-amino carboxylic acids produce the corresponding amino carboxylic acid and ethylene in a rate-determining step. However, the unstable intermediate amino carboxylic acid rapidly decarboxylate to give the corresponding amino compound. These calculations imply a concerted, semi-polar six-membered cyclic transition state type of mechanism for the ethyl esters, and a non-synchronous five-membered cyclic transition state for the amino acids decarboxylation. The present results support previous mechanistic consideration of the elimination of the above-mentioned compounds in the gas phase. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: *N*,*N*-dimethylglycine; picolinic acid; *N*-phenylglycine and their ethyl esters; gas phase elimination; MP2/6-31G (d, p) calculations; kinetics; mechanism

INTRODUCTION

The experimental work of the gas phase thermal decomposition of α-amino acids as neutral molecules has been found to be very difficult to perform. To account this fact, most simple amino acids are solids that on heating sinter or decompose into amorphous materials. Also, their insolubility in organic solvents and high solubility in water forming zwitterion species make difficult their study as neutral molecules in the gas phase. However, in recent years, it was possible to determine the elimination kinetics of some two-substituted amino carboxylic acids and their ethyl esters. In this respect, the homogeneous, unimolecular gas phase pyrolysis of *N*,*N*-dimethylglycine,[1] picolinic acid,[2] and *N*-phenylglycine[3] were found to decarboxylate to give the corresponding amino compound (reaction (1)). These substrates were found to be very reactive molecules in the gas phase, when compared to their corresponding ethyl ester pyrolysis.[1–3] The theoretical study of the gas phase pyrolysis of the ethyl esters of *N*,*N*-dimethylglycine[4] and of picolinic acid[5] were recently described at the MP2/6-311 + G(2d, p)//MP2/6-31G(p) level with reasonable results. However, it is interesting to mention that calculation of the zwitterionic form of glycine, $NH_3^+CH_2COO^-$, using the *ab initio* molecular orbital technique, at the Hartree–Fock level,[6] reached the conclusion that glycine zwitterion does not exist in the gas phase.



The above information and results[1–3] led to the present work at examining the potential energy surface (PES) of the gas phase elimination of *N*,*N*-dimethylglycine, picolinic acid, and *N*-phenylglycine and their ethyl esters at the "*ab initio*" MP2/6-31G (d) level of theory. Consequently, the purpose is to consider or support a reasonable transition state type mechanism, especially, the gas phase elimination of α-amino acids as neutral molecules.

COMPUTATIONAL METHODS AND MODELS

Møller–Plesset perturbation calculations were carried out at MP2/6-31G (d) level as implemented in Gaussian 98W.[7] The Berny analytical gradient optimization routines were used. The requested convergence on the density matrix was 10^{-9} atomic units, the threshold value for maximum displacement was 0.0018 Å, and that for the maximum force was 0.00045 Hartree–Bohr. The nature of stationary points was established by

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† *Dedicated to Nouria Al-Awadi on her 55th Birthday and her appointment as Vice-President at the University of Kuwait.*

calculating and diagonalizing the Hessian matrix (force constant matrix). TS structures were characterized by means of normal-mode analysis. The transition vector (TV) associated with the unique imaginary frequency, i.e., the eigenvector associated with the unique negative eigenvalue of the force constant matrix, has been characterized.

Frequency calculations were carried out to obtain thermodynamic quantities such as zero point vibrational energy (ZPVE), temperature corrections $E(T)$, and absolute entropies $S(T)$. Temperature corrections and absolute entropies were obtained assuming ideal gas behavior from the harmonic frequencies and moments of inertia by standard methods.[8] Scaling factors for frequencies and zero point energies were taken from the literature.[9]

Method	f_{VIB}	f_{ZPE}
MP2/6-31G (d)	0.9427	0.9646

RESULTS AND DISCUSSION

The elimination reaction of these ethyl esters of amino acids: *N,N*-dimethylglycine, picolinic acid, and *N*-phenylglycine to produce the parent amino acid and ethylene was studied using perturbation method MP2. The amino acids further decomposes giving the corresponding amine and CO_2. This reaction was also studied.

Kinetic and thermodynamic parameters

Geometries for reactants, TS, and products for both reactions, were optimized using Møller–Plesset MP2/6-31G (d) level of theory. Frequency calculations carried out at standard conditions are the same to those at the average experimental conditions ($P = 0.4$ atm, Temp = 360 °C).

Results from MP2/6-31G (d) frequency calculations for ethyl esters elimination reaction are shown in Table 1 and for the corresponding amino acids in Table 2. Thermodynamic quantities such as ZPVE, temperature corrections ($E(T)$), energy, enthalpy, and free energies were obtained from vibrational analysis.

For all substrates, the activation parameters reveal that the elimination of ethyl esters to give ethylene have a greater barrier than that of the parent amino acids to give CO_2 and the corresponding amine, by roughly 46–21 kJ/mol. Picolinic acid has the smallest barrier for decarboxylation. Calculated activation parameters $\Delta H^{\neq}$, E_a, are in reasonable agreement with experimental values at MP2/6-31G (d).

Table 1. Activation parameters for the thermal decomposition of ethyl esters of the 2-amino acids at MP2/6-31G (d) level. Experimental values are shown in parentheses

Substrate	$\Delta H^{\neq}$ (kJ/mol)	E_a (kJ/mol)
Ethyl picolinate	177.8 (175.6)	183.1 (180.9)
Ethyl *N,N*-dimethylglycidate	194.0 (196.7)	199.6 (202.3)
Ethyl *N*-phenylglycidate	198.2 (188.3)	203.5 (193.6)

Table 2. Activation parameters for thermal decomposition of 2-amino acids at MP2/6-31G (d) level experimental values are shown in parentheses

Substrate	$\Delta H^{\neq}$ (kJ/mol)	E_a (kJ/mol)
Picolinic acid	132.1 (130.9)	137.4 (135.7)
N,N-dimethylglycine	172.9 (171.0)	177.7 (176.6)
N-phenylglycine	174.4 (172.1)	179.2 (177.4)

The rotational changes from reactant to TS producing entropies of activation deviated from experimental signifying that anharmonicity plays a significant role, particularly in the low frequency motion of the esters (data not shown). The smaller contribution in amino acids compared to the parent ester also imply the anharmonicity role in these reactions. The low frequency vibrations, particularly torsional modes need to be treated as hindered internal rotations.

Entropies of activation for amino acid ethyl esters are between −11 (ethyl *N,N*-dimetyl glycidate) and −43 J/mol K (ethyl picolinate) suggesting a concerted cyclic transition state structure. The most negative entropy of activation corresponds to the ester of picolinic acid implying a more constrained TS structure, with greater loss of degrees of freedom. Comparatively, the entropies of activation for the amino acid decarboxylation step lie between −7 (picolinic acid) and −12 J/mol K (*N*-phenylglycine), i.e., less negative, suggesting a looser structure.

Ethyl esters elimination: Transition state and mechanism

The atoms involved are: the carbon and the two oxygen atoms in the carbonyl moiety, the acid proton on oxygen, and carbons α and β on the ethyl group. The structure of all TS for ethylene elimination is a semi-chair, and the imaginary frequency is associated with the migration of the acidic proton. Atom distances in TS show bond breaking in O_3—C_4, C_5—H_6, bond formation in O_1—H_5, and bond order changes O_1—C_2, O_3—C_2, C_4—C_5. Geometrical parameters are shown in Table 3.

Ethyl esters elimination: Bond order and NBO charges analysis

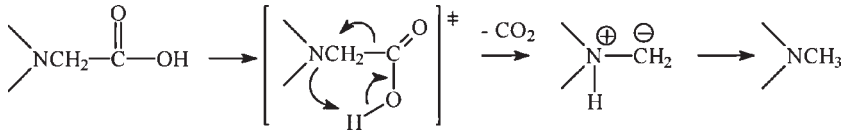
To further investigate the nature of the TS along the reaction pathway, bond order calculations NBO were performed.[10–12] Wiberg bond indexes[13] were computed using the natural bond orbital NBO program[14] as implemented in Gaussian 98W. Bond breaking and making process involved in the reaction mechanism can be monitored by means of the Synchronicity (Sy) concept proposed by Moyano *et al.*[15] defined by the expression:

$$\mathrm{Sy} = 1 - \frac{\left[\sum_{i=1}^{n} |\delta B_i - \delta B_{av}| / \delta B_{av}\right]}{2n - 2}$$

n is the number of bonds directly involved in the reaction and the relative variation of the bond index is obtained from

$$\delta B_i = \frac{[B_i^{TS} - B_i^{R}]}{[B_i^{P} - B_i^{R}]}$$

where the superscripts R, TS, and P, represent reactant, transition state, and product, respectively.



Scheme 1.

The evolution in bond change is calculated as:

$$\%E_v = \delta B_i \times 100$$

The average value is calculated from

$$\delta B_{av} = \frac{1}{n}\sum_{i=1}^{n} \delta B_i$$

Bonds indexes were calculated for those bonds involved in the reaction changes, shown in Scheme 1, Fig. 1. Other bonds remain practically unaltered during the process.

NBO calculations were carried out for the optimized structures ethyl picolinate, ethyl *N*,*N*-dimethylglycine, ethyl *N*-phenylglycine, and the TS associated with ethylene elimination, to follow the changes that occur in the reaction path.

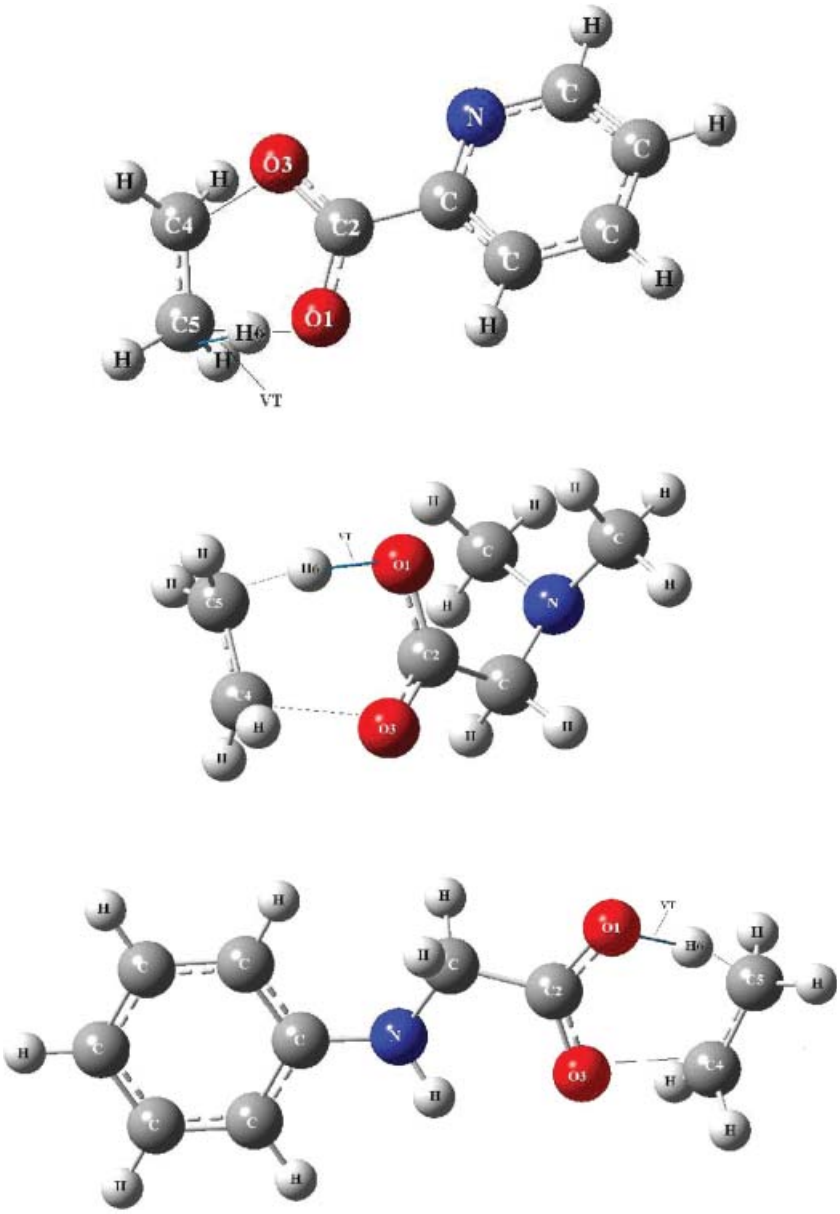


Figure 1. Transition state structures for amino acids ethyl esters elimination reaction: for ethyl picolinate (top), ethyl *N*,*N*-dimethylglycidate (center), and ethyl *N*-phenylglycidate (bottom) calculated at MP2/6-31G (d) level of theory. Vectors associated with the imaginary frequency of the TS are shown

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Table 3. Structural Parameters of reactants (R) and TS for ethyl esters elimination reaction calculated at MP2/6-31G (d) level

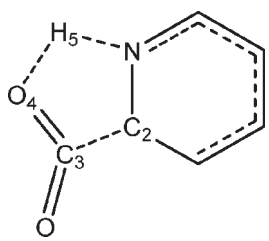
Compound	Ethyl picolinate		Ethyl *N,N*-dimethylglycidate		Ethyl *N*-phenylglycidate	
Distances (Å)	R	ET	R	ET	R	ET
O_3–C_2	1.40	1.30	1.39	1.31	1.40	1.31
O_3–C_4	1.50	2.06	1.50	2.05	1.50	2.07
C_4–C_5	1.53	1.41	1.53	1.41	1.53	1.41
C_5–H_6	1.09	1.33	1.09	1.34	1.09	1.32
H_6–O_1	2.66	1.32	2.83	1.32	2.82	1.34
O_1–C_2	1.24	1.33	1.25	1.32	1.25	1.32
Dihedral angles		TS		TS		TS
O_1–C_2–O_3–C_4		−42.09		34.59		−36.66
C_2–O_3–C_4–C_5		18.47		−14.16		15.43
O_3–C_4–C_5–H_6		4.79		−5.19		4.77
C_4–C_5–H_6–O_1		−28.64		26.45		−26.28
C_5–H_6–O_1–C_2		10.02		−9.79		9.34
H_6–O_1–C_2–O_3		35.33		−29.41		31.12

Table 4. NBO charges for reactants (R) and transition states (TS) for the ethyl ester elimination reaction at MP2/631G (d) level. Atom numbering is shown in Scheme 1

	Ethyl picolinate		Ethyl *N,N*-dimethylglycidate		Ethyl *N*-phenylglycidate	
Atom	R	TS	R	TS	R	TS
O_1	−0.645	−0.815	−0.699	−0.818	−0.680	−0.805
C_2	0.918	0.935	0.925	0.947	0.946	0.962
O_3	−0.679	−0.731	−0.673	−0.779	−0.683	−0.788
C_4	−0.082	0.007	−0.086	0.014	−0.082	0.028
C_5	−0.707	−0.894	−0.718	−0.901	−0.719	−0.898
H_6	0.239	0.469	0.241	0.473	0.242	0.467

Figure 2. Transition state structures for amino acid decarboxylation reaction in gas phase. TS for picolinic acid (left), *N,N*-dimethylglycine (center), *N*-phenylglycine (right) obtained at MP2/6-31G (d) level of theory

The most advanced reaction coordinate is the breaking of ester bond O_3—C_4 (64–69% evolution) with important charge separation increasing from 0.6 in the reactants to 0.7 in the TS (Tables 4 and 5). This bond breaking is more advanced for ethyl picolinate which eliminates ethylene faster. The changing in bond order from single bond to double in C_2—O_1 is also important. An increase in positive charge in H_6 occurs together with an increase in negative charge in O_1 as the acid hydrogen is transferred to carbon C_5. In general de TS geometry, charges and bond order is



Scheme 2. TS for decarboxylation of picolinic acid

similar for the three ethyl esters. The elimination reaction proceeds in semi-polar concerted fashion, the reaction having more progress in the O_3—C_4, and O_1—C_2 bond breaking and bond order, respectively than in other coordinates of reaction.

Amino acid decarboxylation: Transition state and mechanism

Decarboxylation of the amino acids reaction was examined performing frequency calculations under the reaction conditions on the optimized structures. TS structures for this reaction are shown in Fig. 2 and Scheme 2. These structures suggest that decarboxylation occurs with transference of the acidic hydrogen to the nitrogen, while C_2—C_3 bond is breaking, leading to an unstable intermediate as verified by IRC calculations. This intermediate rearranges by migration of the hydrogen to carbon C_2 to give the corresponding amine.

Geometrical parameters are shown in Table 6. Atom numbering is shown in Scheme 2 for clarity.

Amino acid decarboxylation: Bond order and NBO charges analysis

Bond indexes were calculated for the bonds involved in the reaction changes, shown in Scheme 2, Fig. 2.

As the reaction progress from reactants to TS, there is an increase in C_2—C_3 distance (bond breaking), an increase in O_4—H_5 distances (bond breaking), and a decrease in C_3—O_4 bond distance according to change from single to double bond. The hydrogen H_5 is close to the nitrogen in the TS (1.02 Å). The TS geometry is almost planar as seen in dihedral angles (Table 6).

Table 5. Wiberg bond order index from NBO calculations for reactant (R), transition state (TS), and products calculated at MP2/6-31G (d) level of theory for amino acid ethyl esters elimination. Atom numbering is shown in Scheme 1

Compound		O_1–C_2	C_2–O_3	O_3–C_4	C_4–C_5	C_5–H_6	H_6–O_1	δB_{av}	Sy
Ethyl picolinate	∂B_i^R	1.7242	0.9650	0.8160	1.0307	0.9269	0.0001		
	∂B_i^{TS}	1.2757	1.3994	0.2756	1.3619	0.4585	0.2565	0.528	0.873
	∂B_i^P	1.0293	1.6566	0.0009	2.0147	0.0131	0.6702		
	$\%E_V$	64.5	62.8	66.3	33.7	51.3	38.3		
Ethyl *N*,*N*-dimethylglycidate	∂B_i^R	1.6985	0.9846	0.8166	1.0297	0.9283	0.0000		
	∂B_i^{TS}	1.2984	1.3711	0.2748	1.3615	0.4505	0.2623	0.503	0.890
	∂B_i^P	0.9900	1.7058	0.0010	2.0143	0.0134	0.6631		
	$\%E_V$	56.5	53.6	64.4	33.7	52.2	39.3		
Ethyl *N*-phenyglycidate	∂B_i^R	1.7190	0.9808	0.8070	1.0306	0.9278	0.0000		
	∂B_i^{TS}	1.3257	1.3628	0.2524	1.3562	0.4713	0.2459	0.497	0.883
	∂B_i^P	1.0100	1.6950	0.0008	2.0125	0.0148	0.6617		
	$\%E_V$	55.5	53.5	68.8	33.2	50.0	37.2		

Table 6. Structural Parameters for reactants (R) and TS for amino acids decarboxylation reaction calculated at MP2/6-31G (d) level

Compound	Picolinic acid		*N*,*N*-dimethylglycine		*N*-phenylglycine	
Distances (Å)	R	TS	R	TS	R	TS
N_1–C_2	1.37	1.40	1.49	1.53	1.49	1.54
C_2–C_3	1.51	2.58	1.54	2.77	1.54	2.74
C_3–O_4	1.38	1.22	1.39	1.22	1.39	1.22
O_4–H_5	0.99	1.96	1.00	1.99	1.00	1.95
H_5–N_1	2.06	1.02	1.97	1.04	1.99	1.04
Dihedral angles		TS		TS		TS
N_1–C_2–C_3–O_4		−0.51		0.07		2.09
C_2–C_3–O_4–H_5		0.41		−0.09		−0.65
C_3–O_4–H_5–N_1		−0.54		0.22		−1.98
Imaginary frequency (cm^{-1})		TS picolinic acid		*N*,*N*-dimethylglycine		*N*-phenylglycine
		−73.63		−241.9		−289.65

Table 7. NBO charges for reactants (R) and TS for amino acid decarboxylation reaction at MP2/631G (d) level

	Picolinic acid		*N*,*N*-dimethylglycine		*N*-phenylglycine	
Atom	R	TS	R	TS	R	TS
N_1	−0.515	−0.650	−0.543	−0.544	−0.800	−0.701
C_2	0.073	0.014	−0.372	−0.752	−0.360	−0.758
C_3	0.910	1.223	0.925	1.187	0.917	1.185
O_4	−0.786	−0.688	−0.794	−0.672	−0.798	−0.676
H_5	0.547	0.483	0.506	0.466	0.541	0.466

Table 8. Wiberg bond order index from NBO calculations for reactant (R), transition state (TS), and products calculated at MP2/6-31G (d) level of theory for amino acid decarboxylation

Compound		N_1–C_2	C_2–C_3	C_3–O_4	O_4–H_5	H_5–N_1	δB_{av}	Sy
Picolinic acid	∂B_i^R	1.3698	0.9965	1.0105	0.6679	0.0203		
	∂B_i^{TS}	1.2159	0.1147	1.7060	0.0186	0.7198	0.900	0.9694
	∂B_i^P	1.1907	0.0000	1.8332	0.0000	0.7661		
	$\%E_V$	85.93	88.49	84.54	97.22	93.79		
N,*N*-dimethylglycine	∂B_i^R	0.9917	0.9890	0.9446	0.7313	0.0005		
	∂B_i^{TS}	0.8131	0.1147	1.7202	0.0213	0.7075	0.866	0.9438
	∂B_i^P	0.7456	0.0000	1.8329	0.0000	0.7614		
	$\%E_V$	67.12	88.40	87.31	97.09	92.92		
N-phenylglycine	∂B_i^R	0.9729	0.9759	1.0082	0.6624	0.0317		
	∂B_i^{TS}	0.8154	0.1245	1.7106	0.0251	0.7131	0.854	0.9376
	∂B_i^P	0.7279	0.0000	1.8329	0.0000	0.7565		
	$\%E_V$	64.29	87.24	85.17	96.21	94.01		

Charges from NBO calculations and Wiberg index (Tables 7 and 8) indicate that the most advanced reaction coordinate is the breaking of O_4—H_5 bond and H_4—N_1 bond formation, however C_3—O_4 bond order changing from single to double bond is also very advanced. The TS is similar for the three amino acids studied and is late in the reaction coordinate according to the Wiberg indexes indicating that the TS structure is close to that of the proposed intermediate in which the acidic hydrogen is transferred to the nitrogen and then rearranged to form the corresponding amine.

CONCLUSIONS

The thermal decomposition ethyl picolinate, ethyl *N*,*N*-dimethylglycidate, *N*-phenylglycidate, and the parent amino acids was studied using MP2/6-31G (d) method. We found a reasonable agreement with the experimental data for activation parameters at this level of theory. The TS structure for ethylene elimination is a six-member ring similar in all substrates with the breaking of *O*-alkyl bond being the determining factor. At the experimental conditions the subsequent amino acid decarboxylation occurs with somewhat smaller barriers compared to the ethylene elimination. The TS found for this reaction suggest that the nitrogen plays a role in abstracting the hydrogen followed by a rearrangement to yield the parent amine. The ease of decarboxylation of aminoacids compared to the ester decomposition can be observed in the smaller activation energies.

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