

Theoretical study of the gas-phase decomposition of neutral α -amino acid ethyl esters. Part 2—Elimination of ethyl picolinate and ethyl 1-methylpipercolinate

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ABSTRACT: Theoretical studies of the thermolysis in the gas phase of two α -amino acid ethyl esters, ethyl picolinate and ethyl 1-methylpipercolinate, were carried out using *ab initio* theoretical methods, at the MP2/6–31G(d) and MP2/6–311+G(2d,p) levels of theory. The reactions studied have two steps: the first corresponds to the formation of a neutral amino acid intermediate via a six-membered cyclic transition state, and the second is the rapid decarboxylation of this intermediate via a five-membered cyclic transition state. The progress of the first step of the reactions was followed by means of the Wiberg bond indices. The results indicate that the transition states have an intermediate character between reactants and products, and the calculated synchronicities show that the reactions are concerted and slightly asynchronous. The bond-breaking processes are more advanced than the bond-forming processes, indicating a bond deficiency in the transition states. The kinetic parameters calculated for both reactions agree very well with the available experimental results. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: α -amino acid ethyl esters; thermal decomposition; *ab initio* computational methods; reaction mechanism; transition-state structure; Wiberg bond index

INTRODUCTION

Very recently, we carried out¹ a theoretical study on the pyrolysis of *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate in the gas phase. In this paper, we present a computational study of the thermal elimination of another two ethyl esters of α -amino acid type of molecules, ethyl picolinate (ethyl pyridine-2-carboxylate, **I**) and ethyl 1-methylpipercolinate (ethyl 1-methylpiperidine-2-carboxylate, **II**) (Fig. 1), the kinetics of which have recently been studied experimentally.² The

systems studied are of considerable interest owing to their relationship to amino acids.

Ethyl picolinate, and other esters, are used to obtain by electrochemical reduction alcohols derived from aromatic heterocycles that are intermediates for the synthesis of pharmaceutical and agrochemical products.³ It is also used for the detection or quantification of enzymes, in particular hydrolases, such as aminopeptidases and esterases.⁴ Several studies have been carried out^{5,6} on the effect of ethyl picolinate on the germination, growth and sporulation of *Bacillus* spores.

Ethyl 1-methylpipercolinate has been used as a precursor in the synthesis of deuterium-labeled piperidine-type phenothiazine antipsychotic agents.⁷

The experimental results proved² the reaction to be homogeneous, unimolecular and to obey a first-order rate law. The decomposition of these esters leads to the formation of the corresponding α -amino acid type of compound [picolinic acid (2-pyridinecarboxylic acid, **INT1**) and 1-methylpipercolinic acid (1-methylpiperidine-2-carboxylic acid, **INT2**), Fig. 1] and ethylene as been expected by a molecular *cis*-elimination.⁸ However, the neutral amino acid intermediates, under the experimental conditions [26–86 Torr (1 Torr = 133.3 Pa), 350–

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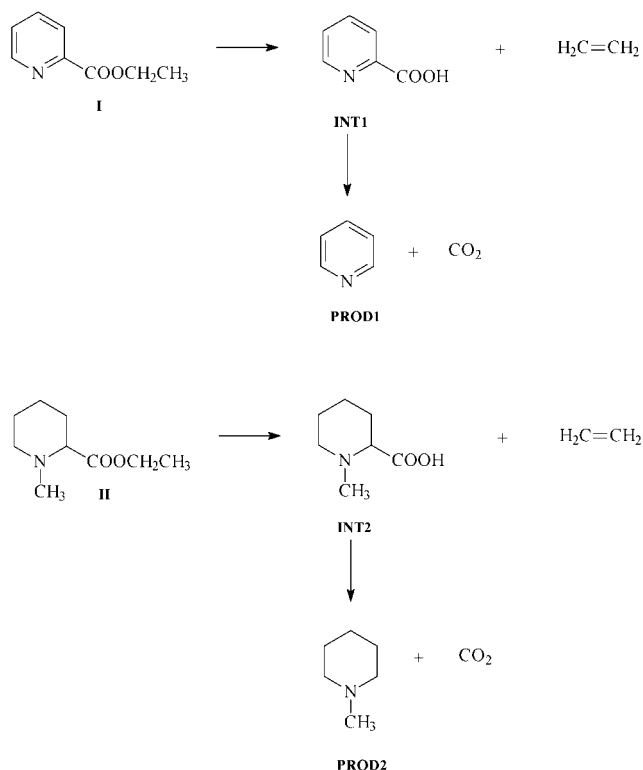


Figure 1. Thermal elimination reactions of ethyl picolinate (**I**) and ethyl 1-methylpipercolinate (**II**)

420 °C], undergo an extremely rapid decarboxylation process, leading to CO₂ and pyridine (**PROD1**) and 1-methylpiperidine (**PROD2**), respectively.²

Both experimental and theoretical studies^{9–18} on the gas-phase elimination kinetics of carboxylic acids containing different substituents at the 2-position suggest a mechanism where the acidic H of the COOH group assists the elimination of the leaving group and the participation of the oxygen carbonyl to give an unstable α -lactone, that decomposes into the corresponding carbonyl compound and CO. When considering the amino or a nitrogen derivative as a leaving group at the 2-position of carboxylic acids, these substituents are difficult to displace. This means that the gas-phase pyrolysis of this type of compound may well undergo a different type of mechanistic process.²

The mechanism suggested from the experiments² for the decomposition process for these types of compounds is described in Fig. 2. The results suggest that the process should be via a six-membered cyclic transition state for the first step and via a five- or four-membered cyclic transition state for the second one (a and b in Fig. 2, respectively).

The temperature dependence of the rate constants for the formation of these products in their corresponding Arrhenius equations, obtained previously,² is given by

$$\log k \text{ (s}^{-1}\text{)} = (11.30 \pm 0.24) - (180.9 \pm 3.0) \text{ kJ mol}^{-1} (2.303 RT)^{-1} \quad (1)$$

for **I** and

$$\log k \text{ (s}^{-1}\text{)} = (13.36 \pm 0.31) - (209.4 \pm 3.9) \text{ kJ mol}^{-1} (2.303 RT)^{-1} \quad (2)$$

for **II**.

In the case of ethyl picolinate (**I**) there has been another experimental study of its gas-phase pyrolytic reaction.¹⁹ In that work, the Arrhenius equation obtained was

$$\log k \text{ (s}^{-1}\text{)} = (12.12 \pm 0.10) - (195.4 \pm 1.1) \text{ kJ mol}^{-1} (2.303 RT)^{-1} \quad (3)$$

very different to Eqn. (1) obtained in Ref. 2.

This fact prompted us to recalculate the kinetic and activation parameters for the pyrolysis of ethyl picolinate through Arrhenius plots from the experimental rate coefficients at different temperatures measured in Ref. 2. The Arrhenius equation obtained now, not taking into account one of the experimental measurements which presented a larger deviation of the straight line, is

$$\log k \text{ (s}^{-1}\text{)} = (12.39 \pm 0.60) - (194.6 \pm 7.5) \text{ kJ mol}^{-1} (2.303 RT)^{-1} \quad (4)$$

in very good agreement with the Eqn. (3) obtained by Al-Awadi *et al.*¹⁹

The aim of this work was to carry out a computational study in order to explore the nature of the reaction mechanism for the unimolecular decomposition of the two studied neutral α -amino acid ethyl esters in the gas phase.

COMPUTATIONAL DETAILS

All calculations were carried out using the Gaussian 98 computational package.²⁰ The geometric parameters for all the reactants, the transition states (TS) and the products of the two reactions studied were fully optimized using *ab initio* analytical gradients at the MP2 level²¹ with the 6–31G(d) basis set.²² Each stationary structure was characterized as a minimum or a saddle point of first order by analytical frequency calculations. A scaling factor²³ of 0.9670 for the zero-point vibrational energies was used. Thermal corrections to enthalpy and entropy values were evaluated at the experimental temperature of 673.15 K. To calculate enthalpy and entropy values at a temperature T , the difference between the values at that temperature and 0 K was evaluated according to standard thermodynamics.²⁴

Intrinsic reaction coordinate (IRC) calculations²⁵ were performed in all cases to verify that the localized transition-state structures connect with the corresponding

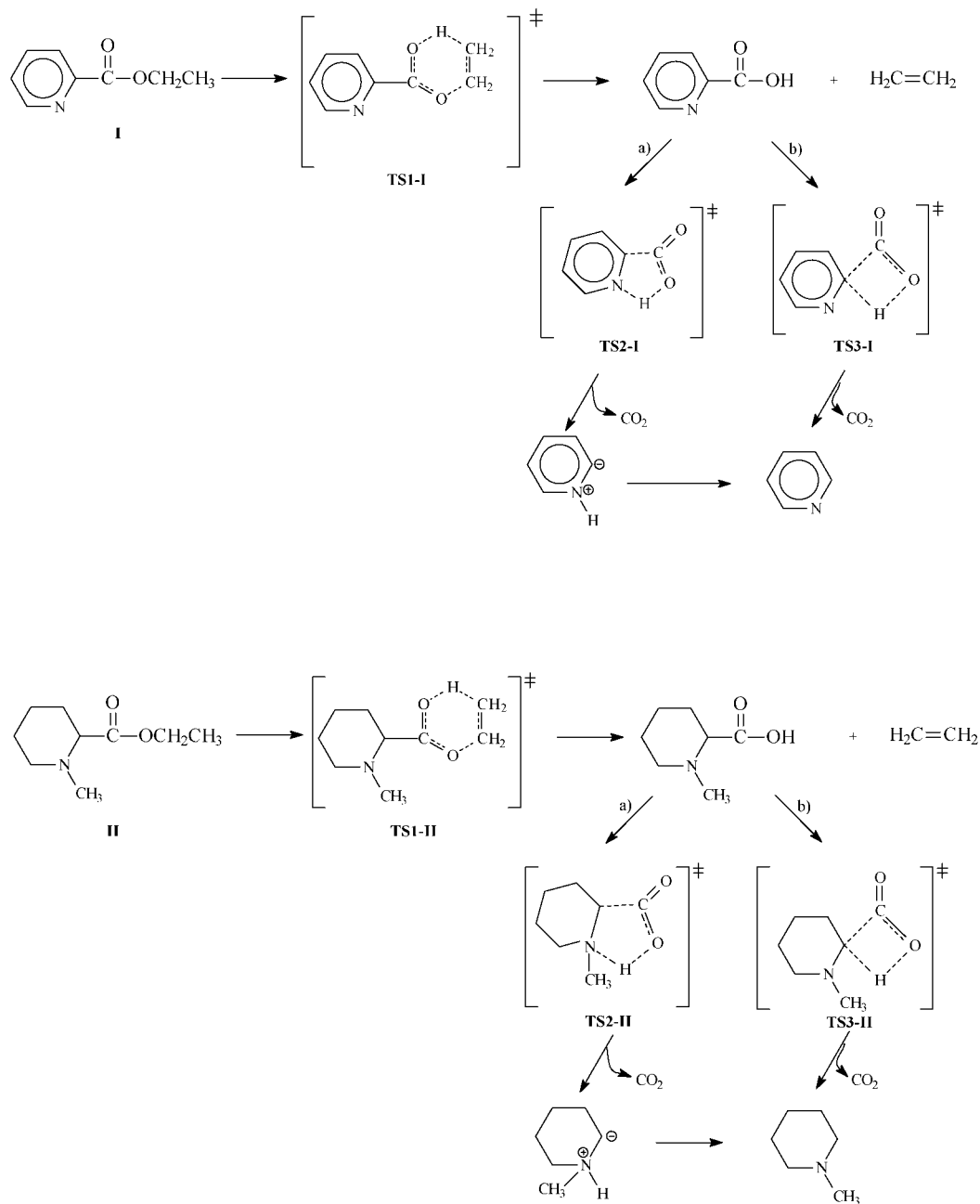


Figure 2. Mechanisms suggested from the experiments for the decomposition of the two α -amino acid ethyl esters studied

minimum stationary points associated with reactants and products.

Single-point energy calculations at the MP2/6-311+G(2d,p) level²⁶ were performed on the MP2/6-31G(d) optimized structures for all the reactants, transition states and products, to calculate reliable energy profiles and kinetic parameters.

The bonding characteristics of the different reactants, transition states and products were investigated using a population partition technique, the natural bond orbital (NBO) analysis of Reed and co-workers.^{27,28} The NBO

formalism provides values for the atomic natural total charges and also provides the Wiberg bond indices²⁹ used to follow the progress of the reactions. The NBO analysis was performed using the NBO program,³⁰ implemented in the Gaussian 98 package,²⁰ and was carried out on the MP2 charge densities in order to include explicitly electron correlation effects.

We selected the classical transition state theory (TST)^{31,32} to calculate the kinetic parameters. The rate constant, $k(T)$, for each elementary step of the kinetic scheme (see Fig. 1) was computed using this theory

assuming that the transmission coefficient is equal to unity, as expressed by the following relation:

$$k(T) = \frac{k_B T}{h} e^{-\frac{\Delta G^\ddagger(T)}{RT}} \quad (5)$$

where k_B , h and R are the Boltzmann constant, Planck's constant and the universal gas constant, respectively, and $\Delta G^\ddagger(T)$ is the standard-state free energy of activation at the absolute temperature T .

The activation energies, E_a , and the Arrhenius A factors were calculated using Eqns (6) and (7), respectively, derived from the TST theory:

$$E_a = \Delta H^\ddagger(T) + RT \quad (6)$$

$$A = \frac{ek_B T}{h} e^{\frac{\Delta S^\ddagger(T)}{R}} \quad (7)$$

RESULTS AND DISCUSSION

Electronic energies, evaluated at the MP2/6-31G(d) and MP2/6-311+G(2d,p)//6-31G(d) levels of theory, and zero-point vibrational energies, thermal correction to enthalpies and entropies, obtained at the MP2/6-31G(d) level, for all the reactants, transition states and products involved in the two reactions studied are given in Table 1.

The pathway (see Fig. 2) describes a two-step mechanism. The first step is a concerted process in which ethylene and an α -amino acid intermediate are formed via a six-membered cyclic transition state, **TS1**, where the hydrogen atom of the CH_3 of the ethoxy group migrates to the oxygen atom of the carbonyl group. The second step is the rapid decarboxylation process of the neutral α -

amino acid intermediate, via a five- or a four-membered cyclic transition state, **TS2** or **TS3**, respectively.

Free energy reaction profiles, obtained at the MP2/6-311+G(2d,p)//6-31G(d) level of theory, for the decomposition processes of ethyl picolinate (**I**) and ethyl 1-methylpipercolinate (**II**) are presented in Figure 3a and b, respectively. These profiles are similar to those obtained¹ for the decomposition processes of *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate.

Based on the results reported here, it is clear that the first step of the process is the rate-determining step, whereas the decarboxylation of the corresponding amino acid intermediate via a five-membered cyclic transition state (**TS2**) is a very rapid process with a small activation energy. The calculated activation free energies for the first reaction step are 204.4 and 206.3 kJ mol⁻¹ for the reactions of **I** and **II**, respectively, whereas the activation free energies for the second reaction step, via **TS2** transition states, are only 70.9 and 71.6 kJ mol⁻¹ for the reactions of **I** and **II**, respectively.

The overall process is exergonic, with reaction free energies of -136.9, and -126.7 kJ mol⁻¹ for reactions of **I** and **II**, respectively.

Our calculations for the reactions in Fig. 1 indicate that both reactions have very similar concerted processes with a hydrogen at the alkyl moiety of ester transferring and a C—O bond breaking via a six-membered cyclic transition state (molecular *cis*-elimination) for the first step. The theoretical mechanism of this process is shown in Fig. 4.

There is one and only one imaginary vibrational frequency in the transition states, for the first step of the elimination reactions studied [1667i and 1687i cm⁻¹ for **TS1-I**, and **TS1-II**, respectively, evaluated at the MP2/6-31G(d) level of theory].

The results in Table 2 show the main distances for each optimized structure. During the thermolysis process,

Table 1. Electronic energies, evaluated at the MP2/6-31G(d) and MP2/6-311 + G(2d,p)//6-31G(d) levels of theory, zero-point vibrational energies (ZPE) and thermal corrections to enthalpies (TCH) in hartree, and entropies (S) in J mol⁻¹ K⁻¹, for all the reactants, transition states and products involved in the reactions studied

Species	MP2/6-31G(d)	MP2/6-311 + G(2d,p)// MP2/6-31G(d)	ZPE	TCH	S
I	-513.902115	-514.285614	0.162535	0.207147	150.253
TS1-I	-513.808109	-514.200604	0.155076	0.199658	150.175
INT1	-435.581092	-435.897750	0.104526	0.137160	122.139
TS2-I	-435.548674	-435.868761	0.100724	0.132143	119.423
TS3-I	-435.455831	-435.776848	0.096615	0.129672	125.522
PROD1	-247.482533	-247.656840	0.089444	0.112062	97.833
II	-556.583164	-557.058545	0.264698	0.322190	174.079
TS1-II	-556.488818	-556.973294	0.257319	0.314732	173.572
INT2	-478.259866	-478.667986	0.207049	0.252386	145.299
TS2-II	-478.231134	-478.640385	0.204295	0.248261	141.838
TS3-II	-478.133484	-478.548687	0.197868	0.243955	148.850
PROD2	-290.167291	-290.432417	0.191763	0.227199	122.071
C ₂ H ₄	-78.285028	-78.361593	0.052042	0.064428	69.741
CO ₂	-188.107747	-188.245432	0.010062	0.020023	53.167

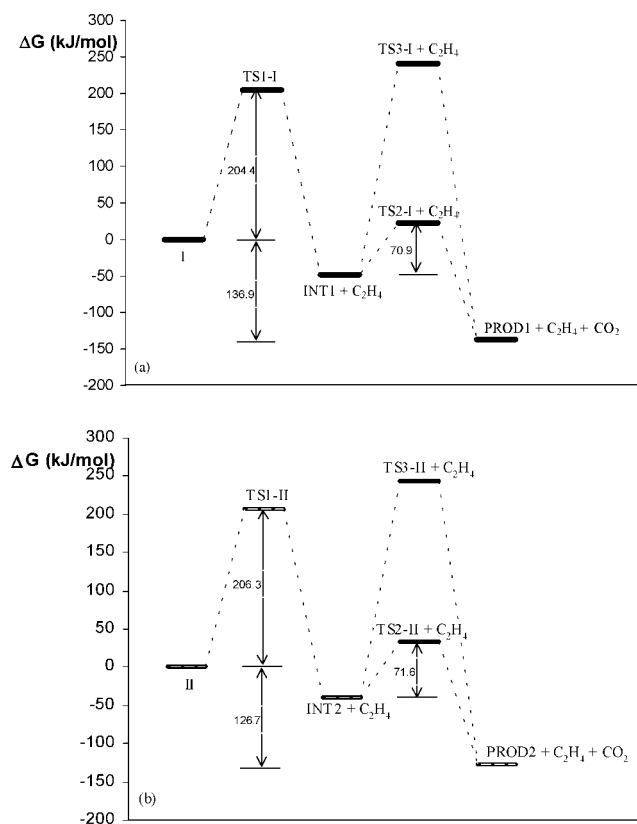


Figure 3. Free energy profiles at 673.15 K, evaluated at the MP2/6-311+G(2d,p)//6-31G(d) level, for the decomposition processes. (a) Relative free energy values (to reactant **I**, in kJ mol^{-1}) of the stationary points found are as follows: **TS1-I**, 204.4; **INT1 + C₂H₄**, -48.2; **TS2-I + C₂H₄**, 22.7; **TS3-I + C₂H₄**, 240.7; **PROD1 + C₂H₄ + CO₂**, -136.9. (b) Relative free energy values (to reactant **II**, in kJ mol^{-1}) of the stationary points found are as follows: **TS1-II**, 206.3; **INT2 + C₂H₄**, -38.8; **TS2-II + C₂H₄**, 32.8; **TS3-II + C₂H₄**, 243.1; **PROD2 + C₂H₄ + CO₂**, -126.7

when the reactant (ethyl ester) is being transformed into its TS, the $\text{O}_1\text{—C}_2$, $\text{O}_3\text{—C}_4$ and $\text{C}_5\text{—H}_6$ distances increase, whereas the $\text{C}_2\text{—O}_3$, $\text{C}_4\text{—C}_5$ and $\text{H}_6\text{—O}_1$ distances decrease.

The fundamental characteristics in this process are the $\text{O}_3\text{—C}_4$ (1.452 and 1.451 Å in **I** and **II**, respectively) and $\text{H}_6\text{—O}_1$ (2.689 Å in **I** and 2.691 Å in **II**) distances for each reactant. In the corresponding TSs, the $\text{O}_3\text{—C}_4$ distance increases significantly (1.973 and 1.961 Å in **TS1-I** and **TS1-II**, respectively), by the breaking of this bond, whereas the $\text{H}_6\text{—O}_1$ distance decreases significantly (1.277 Å in **TS1-I** and 1.272 Å in **TS1-II**), by the formation of this bond. These distances are very similar to those obtained in a previous theoretical study 1 on two different α -amino acid ethyl esters, *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate.

The geometries which were found for the transition states are shown in Fig. 5 and the dihedral angles are reported in Table 2.

To avoid the subjective aspects associated with the geometric analysis of the transition states, the progress of the first step of the reactions was followed by means of the Wiberg bond indices,²⁹ B_i , defined as the sum of squares of off-diagonal density matrix elements between atoms. The bond index between two atoms is a measure of the bond order and, hence, of the bond strength between these two atoms. Thus, if the evolution of the bond indices corresponding to the bonds being made or broken in a chemical reaction is analyzed along the reaction path, a very precise image of the timing and extent of the bond-breaking and the bond-making processes at every point can be achieved.³³

The Wiberg bond indices corresponding to the bonds being made or broken in the studied reactions, for the reactants, transition states and products, are given in Table 3.

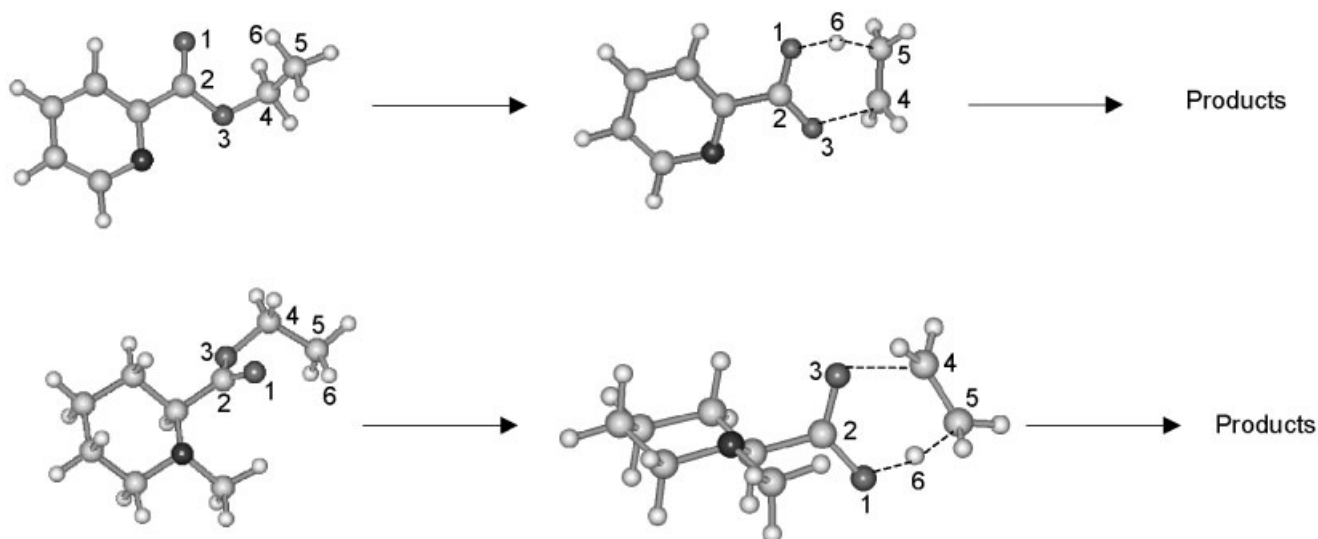


Figure 4. Theoretical mechanism of the first step of the studied reactions, optimized at the MP2/6-31G(d) level

Table 2. Main geometric parameters (distances in ångstroms and dihedral angles in degrees) for the reactants, transition states and products, corresponding to the first step of reactions, calculated at the MP2/6-31G(d) level

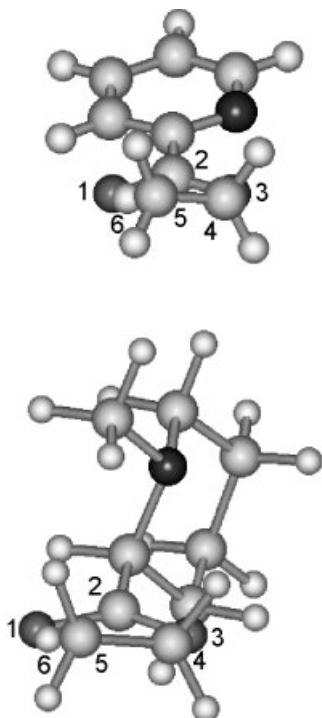
	O ₁ —C ₂	C ₂ —O ₃	O ₃ —C ₄	C ₄ —C ₅	C ₅ —H ₆	H ₆ —O ₁
I	1.226	1.344	1.452	1.515	1.091	2.689
TS1-I	1.292	1.267	1.973	1.397	1.341	1.277
INT1	1.346	1.218	—	—	—	0.987
C ₂ H ₄	—	—	—	1.317	—	—
II	1.219	1.359	1.451	1.515	1.091	2.691
TS1-II	1.288	1.271	1.961	1.398	1.348	1.272
INT2	1.355	1.215	—	—	—	0.991
	O ₁ —C ₂ —O ₃ —C ₄	C ₂ —O ₃ —C ₄ —C ₅	O ₃ —C ₄ —C ₅ —H ₆	C ₄ —C ₅ —H ₆ —O ₁		
TS1-I	—33.0	11.3	6.8	—31.2		
TS1-II	—32.0	11.4	6.9	—34.4		

In order to perform the bond index analysis, it is convenient to define³³ a relative variation of the bond index at the transition state, δB_i , for every bond, i , involved in a chemical reaction as:

$$\delta B_i = \frac{(B_i^{\text{TS}} - B_i^{\text{R}})}{(B_i^{\text{P}} - B_i^{\text{R}})} \quad (8)$$

where the superscripts R, TS and P refer to reactants, transition states and products, respectively.

The percentage of evolution of the bond order through

**Figure 5.** Geometries of the two six-membered cyclic transition states, **TS1-I** and **TS1-II**, corresponding to the first step of the studied reactions, optimized at the MP2/6-31G(d) level

the chemical step has been calculated by means of¹⁸

$$\%EV = 100\delta B_i \quad (9)$$

and the values are given in Table 3.

For **TS1-I**, it can be seen that the H₆ displacement from C₅ to O₁ is not very advanced. The C₅—H₆ bond is only broken to the extent of 53.1% whereas the H₆—O₁ bond is only formed to 41.3%. The breaking of the O₃—C₄ bond is the most advanced process (63.1%), and the least advanced one is the C₄—C₅ double bond formation (only 33.4%). The other two processes, O₁—C₂ double bond breaking and C₂—O₃ double bond formation, present a percentage of evolution of 59.5 and 53.8%, respectively.

The elongation of the O₃—C₄ bond with the migration of the H₆ atom from C₅ to O₁ can be seen as the driving force for the studied reaction.

For **TS1-II** the results are very similar to those obtained for **TS1-I**, the migration of the H₆ atom being slightly more advanced (see Table 3).

The average value, δB_{av} , calculated as³³

$$\delta B_{\text{av}} = \frac{1}{n} \sum \delta B_i \quad (10)$$

where n is the number of bonds involved in the reaction, affords a measure of the degree of advancement of the transition state along the reaction path.

Calculated δB_{av} values for the studied reactions are given in Table 3. As can be seen, the δB_{av} values show that the transition states have an intermediate character between the reactants and the products.

One can also obtain information on the absolute asynchronicity, A , of a chemical reaction, using the expression proposed by Moyano *et al.*³³

$$A = \frac{1}{(2N - 2)} \sum \frac{|\delta B_i - \delta B_{\text{av}}|}{\delta B_{\text{av}}} \quad (11)$$

The opposite of the asynchronicity, the synchronicity,

Table 3. Wiberg bond indices (B_i) of reactants, transition states and products of the first step of the reactions, percentage of evolution (% EV) through the chemical process of the bond indices at the transition states, degree of advancement of the transition states (δB_{av}) and absolute synchronicities, S_y [values calculated at the MP2/6–31G(d) level]

	Parameter	O ₁ —C ₂	C ₂ —O ₃	O ₃ —C ₄	C ₄ —C ₅	C ₅ —H ₆	H ₆ —O ₁
Reaction of I	B_i^R	1.662	1.021	0.832	1.029	0.930	0.001
	B_i^{TS}	1.284	1.388	0.307	1.365	0.436	0.278
	B_i^P	1.027	1.703	0.000	2.034	0.000	0.671
	% EV	59.5	53.8	63.1	33.4	53.1	41.3
		$\delta B_{av} = 0.51$			$S_y = 0.90$		
Reaction of II	B_i^R	1.708	0.988	0.833	1.029	0.930	0.001
	B_i^{TS}	1.315	1.369	0.315	1.362	0.430	0.283
	B_i^P	1.007	1.734	0.000	2.034	0.000	0.671
	% EV	56.1	51.1	62.2	33.1	53.8	42.1
		$\delta B_{av} = 0.50$			$S_y = 0.90$		

S_y , defined as

$$S_y = 1 - A \quad (12)$$

varies between zero, when one of the n bonds has completely broken at the TS while the other ($n - 1$) bonds remain completely unchanged, and unity, when all the n bonds have broken or formed to exactly the same extent in the TS.

The S_y values obtained in this way are, in principle, independent of the degree of advancement of the transition state. The S_y values calculated for the studied reactions are shown in Table 3. As it can be seen, the synchronicities are 0.90 in both cases, indicating that the mechanisms correspond to concerted and slightly asynchronous processes. Similar S_y values were obtained¹ for the decomposition reactions of *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate.

A final aspect to be taken into account is the relative asynchronicity of the bond-breaking and the bond-forming processes, which would be a measure of 'bond deficiency' along the reaction path. In the studied reactions, the bond-breaking processes are clearly more advanced (on average 58.6 and 57.4%, in **TS1-I** and **TS1-II**, respectively) than the bond-forming processes (on average 42.8 and 42.1% in **TS1-I** and **TS1-II**, respectively), indicating a bond deficiency in the transition states.

The charge distribution in the reactants and transition states was analyzed by means of the natural bond orbital (NBO) analysis of Reed and co-workers.^{27,28} Table 4

gives the natural atomic charges (the nuclear charges minus summed natural populations of the natural atomic orbitals on the atoms) at the atoms involved in the reaction.

The charges at **TS1-I** show an important positive charge developed on H₆ (0.470 at TS and 0.235 at reactant), while the electronic excess is supported by the two oxygens (−0.819 at TS and −0.718 at reactant for O₁ and −0.740 at TS and −0.632 at reactant for O₃) and by C₅ (−0.872 at TS and −0.672 at reactant). The negative character of O₁ allows it to attract the H₆ in the TS. The same hydrogen atom has a more positive character in the TS and thus O₁ increases its negative character, and C₅ has a more negative character, as would be expected from the postulated cyclic transition state. A similar analysis can be made for **TS1-II**.

The calculated kinetic and activation parameters for the reactions studied are shown in Table 5 and compared with the available experimental results. They were calculated at the same temperature and pressure as used in the experiments, 673.15 K and 0.04 atm. As it can be seen, the computed values, at the MP2/6–311+G(2d,p)//MP2/6–31G(d) level of theory, agree very well with the experimental data, the rate constants being very close to the experimental values.

Comparing the results of this work with those obtained in a previous study¹ on the gas-phase elimination reactions of *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate, we can observe that the calculated elimination rates follow the order ethyl picolinate > *N,N*-dimethylglycine ethyl ester > ethyl 1-methylpipercolinate

Table 4. NBO charges, calculated at the MP2/6–31G(d) level, at the atoms involved in the first step of the reactions

	O ₁	C ₂	O ₃	C ₄	C ₅	H ₆
I	−0.718	0.970	−0.632	−0.046	−0.672	0.235
TS1-I	−0.819	0.994	−0.740	0.024	−0.872	0.470
II	−0.705	0.994	−0.664	−0.046	−0.671	0.235
TS1-II	−0.808	1.022	−0.766	0.021	−0.876	0.470

Table 5. Calculated^a and experimental kinetic and activation parameters for the first step of the studied reactions

Reaction of	10^4k (s ⁻¹)		E_a (kJ mol ⁻¹)		Log A		ΔH^\ddagger (kJ mol ⁻¹)		ΔG^\ddagger (kJ mol ⁻¹)		ΔS^\ddagger (J mol ⁻¹ K ⁻¹)	
	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
I	19.7	19.88 ^b 9.14 ^c	209.8	194.6 ± 7.5 ^b 195.4 ± 1.1 ^c	13.6	12.39 ± 0.60 ^b 12.12 ± 0.10 ^c	204.2	189.0 ^b 189.8 ^c	204.4	204.3 ^b 208.7 ^c	-0.3	-22.8 ^b -28.0 ^c
II	14.1	12.31 ^d	210.5	209.4 ± 3.9 ^d	13.5	13.36 ± 0.31 ^d	204.9	203.8 ^d	206.3	207.0 ^d	-2.1	-3.98 ^d

^a At the MP2/6-311+G(2d,p)//MP2/6-31G(d) level. Values calculated at 673.15 K.

^b Values recalculated in this work from the experimental rate coefficients at different temperatures taken from Ref. 2.

^c Values taken from the results reported in Ref. 19.

^d Values taken from the results reported in Ref. 2.

>ethyl 1-piperidineacetate. The small but significant difference in rate seems to indicate that the aromaticity of the pyridine group in the first substrate must exert a greater electron-withdrawing effect, thus increasing the rate of elimination. In the last two compounds, the cyclic methylene chain containing the nitrogen atom decreases the electron-withdrawing effect, thus lowering the rate of elimination.

It appears clearly in Figure 3 that the second step of the decomposition process of both α -amino acid ethyl esters studied, corresponding to the decarboxylation of the amino acid intermediate, occurs via a five-membered cyclic transition state (**TS2s**) and not via a four-membered cyclic transition state (**TS3s**).

This second step is an extremely rapid process, with activation energies of only 68.9 and 67.5 kJ mol⁻¹, and with calculated rate constants of 4.45×10^7 and 3.93×10^7 s⁻¹ for the reactions of **I** and **II**, respectively, evaluated at the MP2/6-311+G(2d,p)//MP2/6-31G(d) level of theory.

CONCLUSIONS

A theoretical study on the thermal decomposition in the gas phase of two neutral α -amino acid ethyl esters was carried out in order to explore the nature of the reaction mechanism.

The decomposition process in the gas phase of the two α -amino esters, studied ethyl picolinate and ethyl 1-methylpipercolinate, occurs in two steps, a first one that it is the determining-rate step, that it is a concerted process in which ethylene and an α -amino acid intermediate are formed, via a six-membered cyclic transition state, and a second one, the rapid decarboxylation of the intermediate, via a five-membered cyclic transition state, as shown by the free energy profiles.

The progress of the first step of the reactions was followed by means of the Wiberg bond indices. The extension of the O₃—C₄ bond with the migration of the H₆ atom from C₅ to O₁ can be seen as the driving force for the studied reactions. The transition states have an intermediate character between reactants and products. The calculated synchronicities show that the reactions are

concerted and slightly asynchronous. The bond-breaking processes are more advanced than the bond-forming processes, indicating a bond deficiency in the transition states.

The kinetic parameters for the reactions studied, evaluated at the MP2/6-311+G(2d,p)//MP2/6-31G(d) level of theory, agree very well with the available experimental data.

The calculated rates for the gas-phase elimination of neutral α -amino acid ethyl esters follow the order ethyl picolinate > *N,N*-dimethylglycine ethyl ester > ethyl 1-methylpipercolinate > ethyl 1-piperidineacetate. The small but significant difference in rate seems to indicate that the aromaticity of the pyridine group in the former substrate must exert a greater electron-withdrawing effect, thus increasing the rate of elimination. However, the cyclic methylene chain containing the nitrogen atom decreases the electron-withdrawing effect, thus lowering the rate of elimination.

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REFERENCES

- Quijano J, Notario R, Chamorro E, León LA, Sánchez C, Alarcón G, Quijano JC, Chuchani G. *J. Phys. Org. Chem.* 2002; **15**: 413–419.
- Lafont J, Ensuncho A, Domínguez RM, Rotinov A, Herize A, Quijano J, Chuchani G. *Atual. Fis.-Quim. Org. (Brazil)* 1999; **12**: 179–186.
- Romulus AM, Savall A. *Electrochim. Acta* 1998; **43**: 1913–1919.
- Liwen D, Martin MT. *Anal. Biochem.* 1996; **236**: 344–347.

5. Pandey NK, Gollakota KG. *J. Appl. Bacteriol.* 1978; **45**: 365–372.
6. Pandey NK, Solanki S. *FEMS Microbiol. Lett.* 1980; **8**: 117–119.
7. Mohammad T, Midha KK, Hawes EM. *J. Labelled Compd. Radiopharm.* 1986; **23**: 749–760.
8. Chuchani G, Mishima M, Notario R, Abboud JLM. In *Advances in Quantitative Structure–Property Relationships*, vol. 2. Charton M, Charton BI (eds). JAI Press: Stanford, 1999; 35–126.
9. Chuchani G, Rotinov A, Martín I, Avila I, Domínguez RM. *J. Phys. Chem.* 1985; **89**: 4134–4137.
10. Domínguez RM, Rotinov A, Chuchani G. *J. Phys. Chem.* 1986; **90**: 6277–6281.
11. Chuchani G, Martín I, Rotinov A, Domínguez RM, Pérez IM. *J. Phys. Org. Chem.* 1995; **8**: 133–138.
12. Chuchani G, Rotinov A, Domínguez RM. *J. Phys. Org. Chem.* 1996; **9**: 787–794.
13. Chuchani G, Rotinov A, Domínguez RM, Martín I. *J. Phys. Org. Chem.* 1996; **9**: 348–354.
14. Safont VS, Moliner V, Andrés J, Domínguez LR. *J. Phys. Chem. A* 1997; **101**: 1859–1865.
15. Domingo LR, Andrés J, Moliner V, Safont VS. *J. Am. Chem. Soc.* 1997; **119**: 6415–6422.
16. Domingo LR, Picher MT, Andrés J, Safont VS, Chuchani G. *Chem. Phys. Lett.* 1997; **274**: 422–428.
17. Rotinov A, Chuchani G, Andrés J, Domingo LR, Safont VS. *Chem. Phys.* 1999; **246**: 1–12.
18. Domingo LR, Picher MT, Safont VS, Andrés J, Chuchani G. *J. Phys. Chem. A* 1999; **103**: 3935–3943.
19. Al-Awadi NA, El-Dusouqui OME, Matthew T. *Int. J. Chem. Kinet.* 1997; **29**: 289–293.
20. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin JL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Head-Gordon M, Replogle ES, Pople JA. Gaussian 98, Revision A.9. Gaussian: Pittsburgh, PA, 1998.
21. Møller C, Plesset M. *Phys. Rev.* 1934; **46**: 618–622.
22. Ditchfield R, Hehre WJ, Pople JA. *J. Chem. Phys.* 1971; **54**: 724–728.
23. Scott PA, Radom L. *J. Phys. Chem.* 1996; **100**: 16502–16513.
24. McQuarrie DA, Simon JD. *Molecular Thermodynamics*. University Science Books: Sausalito, CA, 1999.
25. Fukui K. *J. Phys. Chem.* 1970; **74**: 4161–4163.
26. Clark T, Chandrasekhar J, Spitznagel GW, Schleyer PvR. *J. Comput. Chem.* 1983; **4**: 294–301.
27. Reed AE, Weinhold F. *J. Chem. Phys.* 1983; **78**: 4066–4073.
28. Reed AE, Curtiss LA, Weinhold F. *Chem. Rev.* 1988; **88**: 899–926.
29. Wiberg KB. *Tetrahedron* 1968; **24**: 1083–1096.
30. Glendening ED, Reed AE, Carpenter JE, Weinhold F. NBO, Version 3.1.
31. Glasstone KJ, Laidler KJ, Eyring H. *The Theory of Rate Processes*. McGraw-Hill: New York, 1941; chapt. 4.
32. Benson SW. *The Foundations of Chemical Kinetics*. McGraw-Hill: New York, 1969.
33. Moyano A, Pericàs MA, Valentí E. *J. Org. Chem.* 1989; **54**: 573–582.