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Theoretical study of the gas-phase decomposition of neutral α-amino acid ethyl esters. Part 1—The elimination of *N,N*-dimethylglycine ethyl ester and ethyl 1-piperidineacetate

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ABSTRACT: Theoretical studies of the thermolysis of two α-amino acid ethyl esters in the gas phase were carried out using *ab initio* theoretical methods, at the HF/6–31G(d) and the MP2/6–311 + G(2d,p)//MP2/6–31G(d) levels of theory. The reactions studied have two steps: the first one corresponds to the formation of ethylene and 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 © 2002 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

Recent studies[1–7] on both experimental determinations and *ab initio* theoretical calculations on the gas-phase pyrolyses of 2-substituted chloro-, hydroxy-, alkoxy-, phenoxy- and acetoxycarboxylic acids suggested a mechanism in which the acidic H of the COOH group assists the leaving group for elimination, as shown in Fig. 1.

An interesting substituent at the 2-position of carboxylic acids is the amino group, as in the known amino acid molecules. However, the amino or a nitrogen derivative, as a leaving group in organic molecules, has been found to be very difficult to displace in gas-phase elimination reactions. Because of this, the gas-phase pyrolysis of some types of amino acids may probably undergo a different mechanistic process from that described in Fig. 1.

In view of the scarce information available on the gas-phase pyrolysis of amino acids at sub-atmospheric pressure, we recently carried out[8] an experimental study of the gas-phase elimination kinetics of the ethyl esters of two α-amino acid *N,N*-dialkylated glycine derivatives, *N,N*-dimethylglycine ethyl ester (**I**) and ethyl 1-piperidineacetate (**II**) (Fig. 2).

The results proved 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 derivative and the ethylene compound as expected for a single *cis*-elimination reaction.[9] However, it was shown that under the experimental conditions [26–86 Torr (1 Torr = 133.3 Pa), 360–430 °C], the neutral amino acid intermediate under-

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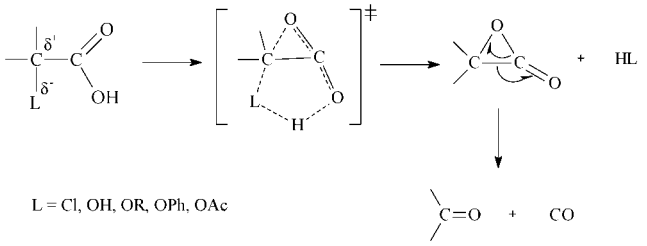

Figure 1. General mechanism of the elimination of α-L-carboxylic acids

goes a fast decarboxylation process.[8] The experimental results under the pyrolysis conditions indicate a 3:1 stoichiometry. There is no evidence for anything but a transient existence of the neutral amino acid.

The suggested mechanism for the decomposition process for these types of compounds is described in Fig. 2. The temperature dependence of the rate constants for the formation of these products from their corresponding Arrhenius equation is given in Table 1. The experimental results suggest that the process should proceed via a six-membered cyclic transition state for the first step and via a five- or four-membered cyclic transition state for the second step (a and b in Fig. 2, respectively).

In the absence of other types of theoretical studies and with the aim of further examining and characterizing in detail both pathways of the above-suggested mechanism, we report in this paper a theoretical study of the thermal elimination of compounds **I** and **II** (Fig. 3). Our results were examined in the light of the available experimental data.

COMPUTATIONAL DETAILS

All calculations were performed with the Gaussian 98 computational package.[10] The geometric parameters for all the reactants, the transition states (TS) and the products for both reactions [(I) and (II)] were fully optimized at the HF/6–31G(d) level[11] in order to draw the energy profiles corresponding to both reactions studied. Each stationary structure was characterized as a minimum or a saddle point of first order by frequency calculations. A scaling factor[12] of 0.9135 for the zero-point vibrational energies was used.

With the aim of characterizing the first step of the studied reactions better and to obtain more reliable kinetic parameters comparable to the experimental values, the reactants **I** and **II**, the transition states, **TS1-I** and **TS1-II** and the products of the first step of the reactions were also fully reoptimized at the MP2/6–31G(d) level,[13] with single-point energy calculations using the 6–311 + G(2d,p) basis set.[14] A scaling factor[12] of 0.9670 for the zero-point vibrational energies evaluated at the MP2/6–31G(d) level was used. Thermal corrections to enthalpy and entropy values were evaluated at the experimental conditions of 673.15 K and 0.04 atm. To calculate enthalpy and entropy values at a temperature *T*, the difference between the values at that temperature and 0 K can be evaluated according to standard thermodynamics.[15] Intrinsic reaction coordinate (IRC) calculations[16] were performed in all cases to verify that the localized transition state structures connect with the corresponding minima stationary points associated with reactants and products.

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.[17,18] The NBO formalism provides values for the atomic natural total charges and also provides the Wiberg bond indices[19] which can be used to follow the progress of the reactions. The NBO analysis was performed using the NBO program,[20] implemented in the Gaussian 98 package,[10] and was carried out using the MP2 charge densities in

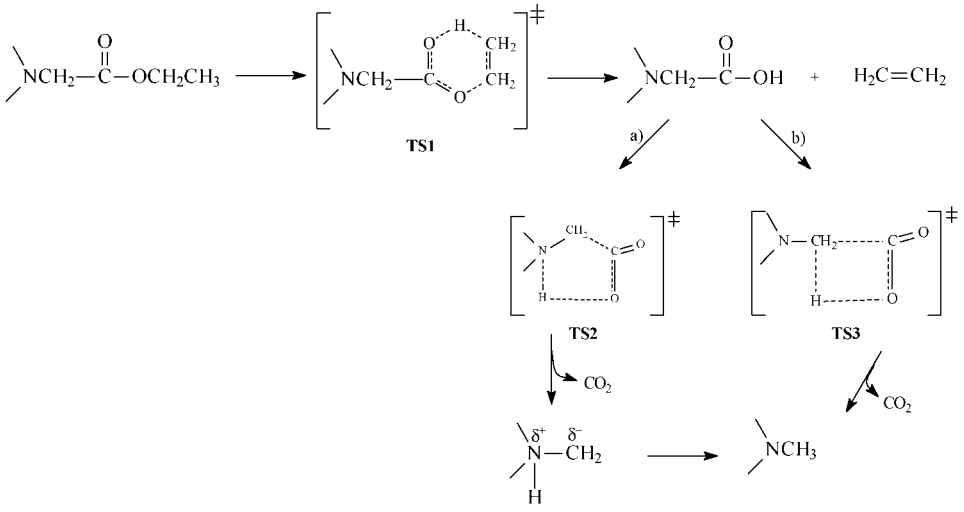

Figure 2. Suggested mechanism for the decomposition of ethyl α-amino esters

Table 1. Temperature dependence of experimental rate coefficients[a]

Compound	Arrhenius equation
N,N-Dimethylglycine ethyl ester	Log k (s^{-1}) = (13.01 ± 3.7) −(202.3 ± 0.3) kJ mol^{-1} (2.303 RT)$^{-1}$
Ethyl 1-piperidineacetate	Log k (s^{-1}) = (12.91 ± 0.31) −(204.4 ± 0.1) kJ mol^{-1} (2.303 RT)$^{-1}$

[a] Taken from Ref. 1.

order to include explicitly some degree of electron correlation effects.

We selected the classical transition state theory (TST)[21,22] to calculate the kinetic parameters. The rate constant, $k(T)$, for each elementary step of the kinetic scheme (see Fig. 2) was computed using this theory assuming that the transmission coefficient is equal to unity, as expressed by the following relation:

$$k(T) = (k_B T/h) \exp[-\Delta G^{\neq}(T)/RT] \quad (1)$$

where k_B, h and R are the Boltzman constant, the Planck constant and the universal gas constant, respectively, and $\Delta G^{\neq}(T)$ is the standard-state free energy of activation, at the absolute temperature T. The activation energies, E_a, and the Arrhenius factors A, were calculated using Eqns (2) and (3), respectively, derived from the TST theory:

$$E_a = \Delta H^{\neq}(T) + RT \quad (2)$$

$$A = e k_B T/h \exp[\Delta S^{\neq}(T)/R] \quad (3)$$

RESULTS AND DISCUSSION

As pointed out above, theoretical calculations at the HF/6–31G(d) level of theory were carried out in order to start the exploration of the nature of the reaction mechanism for the unimolecular decomposition of the two studied neutral α-amino acid ethyl esters in the gas phase. The pathway (see Fig. 2) involves 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.

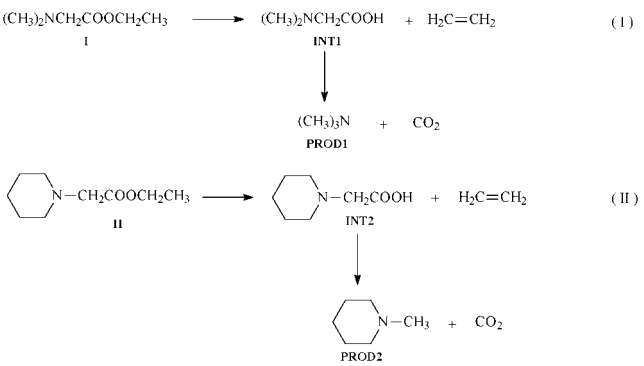

Figure 3. The reactions investigated in this work

Free energy profiles for the decomposition processes of the two studied α-amino acid ethyl esters, *N,N*-dimethylglicine ethyl ester (**I**) and ethyl 1-piperidineacetate (**II**), are presented in of Fig. 4(a) and (b), respectively.

At first sight, it appears clearly that the decarboxylation process is kinetically more favorable via a five-membered cyclic transition state, **TS2**, than via a four-membered cyclic transition state, **TS3**, and that the first step of the reaction is slower than the second and hence is the rate-limiting step of the global process. The overall process is exergonic, with reaction free energies of −170.2 and −167.0 kJ mol^{-1}, for reactions (I) and (II), respectively.

In order to carry out a more detailed study of the first step of the studied reactions, all the reactants, transition states and products corresponding to this step were fully reoptimized at the MP2/6–31G(d) level of theory. The theoretical mechanism for the first step of the principal reactions is presented in Fig. 5. The reactions occur via a six-membered cyclic transition state.

There is one and only one imaginary vibrational frequency in the transition states for the first step of the studied thermal decomposition reactions [1664i and 1726i 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, when the reactant (ethyl ester) is being transformed into its transition state, the O_1—C_2, O_3—C_4 and C_5—H_6 distances are increasing, whereas the C_2—O_3, C_4—C_5 and H_6—O_1 distances are decreasing. The geometries which were found for the transition states are shown in Fig. 6 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 reaction was followed by means of the Wiberg bond indices,[19] B_i. 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

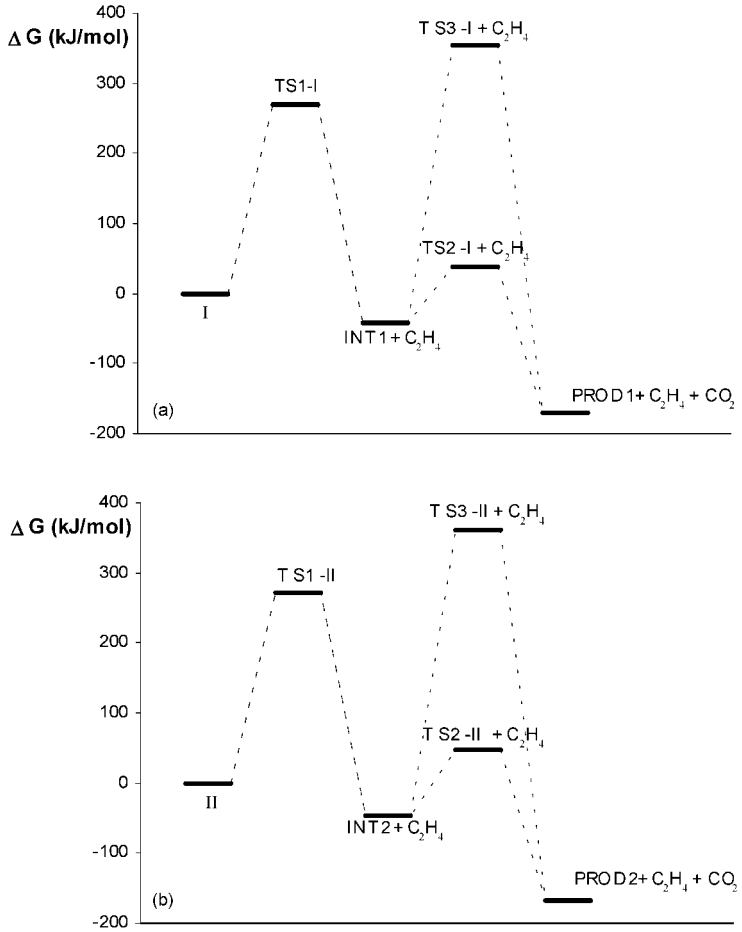

Figure 4. Free energy profiles at 673.15 K, evaluated at the HF/6–31G(d) level, for the decomposition processes (a) (I) and (b) (II). (a) Relative free energy values (to reactant **I**, in kJ mol^{-1}) of the stationary points found are as follows: **TS1-I**, 269.9; **INT1** + C_2H_4, −41.0; **TS2-I** + C_2H_4, 39.0; **TS3-I** + C_2H_4, 355.0; **PROD1** + C_2H_4 + CO_2, −170.2. (b) Relative free energy values (with respect to reactant **II**, in kJ mol^{-1}) of the stationary points found are as follows: **TS1-II**, 271.0; **INT2** + C_2H_4, −46.4; **TS2-II** + C_2H_4, 47.3; **TS3-II** + C_2H_4, 361.5; **PROD2** + C_2H_4 + CO_2, −167.0

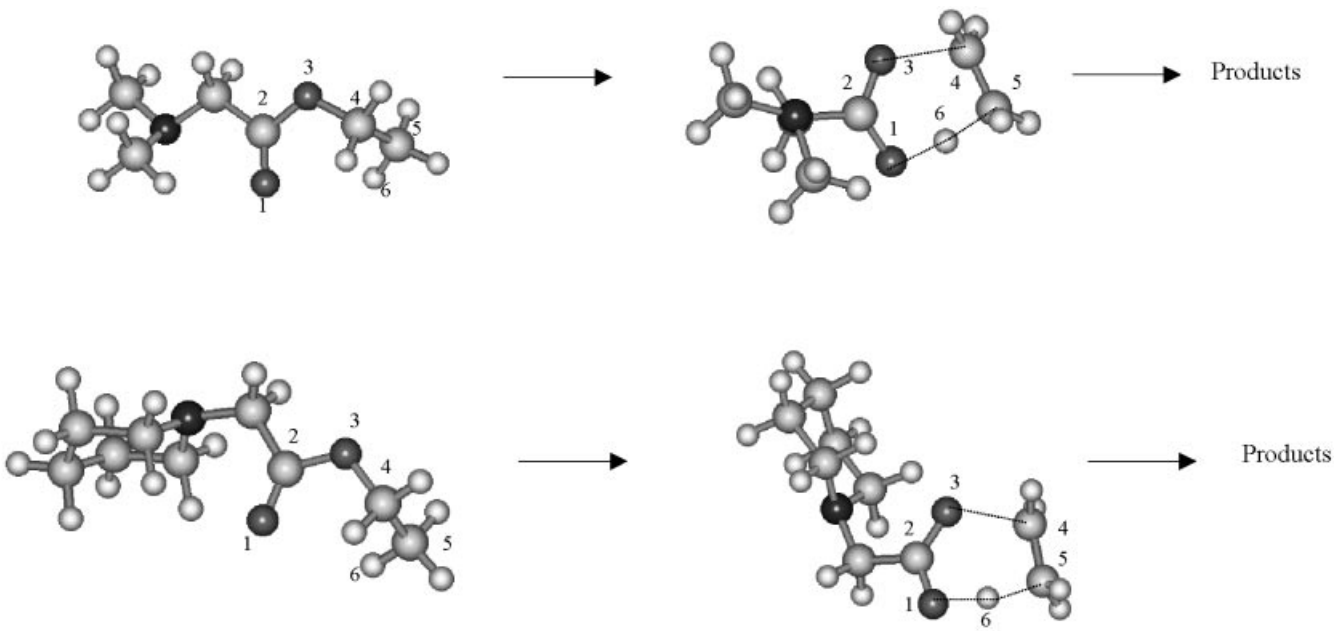

Figure 5. Theoretical mechanism of the first step of the studied reactions, calculated at the MP2/6–31G(d) level

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

Species	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	1.218	1.358	1.451	1.516	1.091	2.699
TS1-I	1.290	1.270	1.972	1.397	1.342	1.278
II	1.221	1.358	1.452	1.516	1.091	2.701
TS1-II	1.286	1.273	1.962	1.397	1.342	1.279
	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	−34.9		13.7		6.0	−34.7
TS1-II	25.7		−7.2		−6.7	−24.9

timing and extent of the bond-breaking and bond-making processes at every point can be achieved.[23] The Wiberg bond indices corresponding to the bonds being made or broken in the studied reactions, for the reactants, transition states and products, are collected in Table 3. In order to perform the bond index analysis, it is convenient to define[23] a relative variation of the bond index at the transition state, δB_i, for every bond, i, involved in a chemical reaction as

$$\delta B_i = (B_i^{TS} - B_i^{R})/(B_i^{P} - B_i^{R}) \quad (4)$$

where the superscripts R, TS and P refer to reactants, transition states and products, respectively. The percentage (EV) evolution of the bond order through the chemical step was therefore calculated through the equation[4]

$$EV(\%) = 100\delta B_i \quad (5)$$

and the values are given Table 3.

For **TS1-I**, it can be seen that the H_6 displacement from C_5 to O_1 is not very advanced. The C_5—H_6 bond is only broken to 53.1% whereas the H_6—O_1 bond is only formed to 42%. The breaking of the O_3—C_4 bond is the most advanced process (63.1%), and the least advanced is the C_4—C_5 double bond formation (only 33.4%). The other two processes, O_1—C_2 double bond breaking and C_2—O_3 double bond formation, show evolutions of 58.6 and 52.6%, respectively. The enlargement of the O_3—C_4 bond with the migration of the H_6 atom from C_5 to O_1 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 H_6 atom being slightly less advanced (see Table 3).

The average value, δB_{av}, calculated as[23]

$$\delta B_{av} = 1/n\Sigma\delta B_i \quad (6)$$

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 shown 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.

Furthermore, we can also obtain information on the absolute asynchronicity, A, of a chemical reaction, using the expression proposed by Moyano *et al.*:[23]

$$A = 1/(2n-2)\ \Sigma\ |\delta B_i - \delta B_{av}|/\delta B_{av} \quad (7)$$

The opposite to the asynchronicity, the synchronicity, Sy, defined as

$$Sy = 1 - A \quad (8)$$

changes from zero, when one of the n bonds has completely broken at the TS whereas the other $(n-1)$

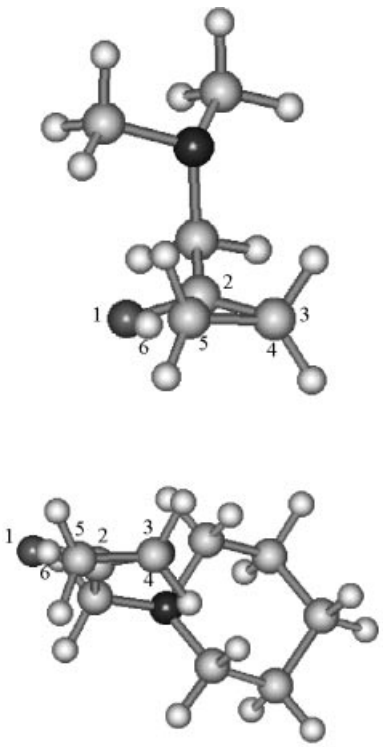

Figure 6. The two six-membered cyclic transition states corresponding to the first step of the studied reactions, calculated at the MP2/6–31G(d) level

Table 3. Wiberg bond indices, B_i, of reactants, transition states and products of the first step of the reactions, and percentage evolution, *EV*, through the chemical process of the bond indices at the transition states, together with the degree of advancement of the transition states, δB_{av}, and the absolute synchronicities, *Sy* [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 (I)	B_i^R	1.708	0.985	0.833	1.029	0.929	0.001
	B_i^{TS}	1.303	1.376	0.307	1.365	0.436	0.279
	B_i^P	1.017	1.728	0.000	2.034	0.000	0.663
	EV (%)	58.6	52.6	63.1	33.4	53.1	42.0
			$\delta B_{av} = 0.51$		$Sy = 0.90$		
Reaction (II)	B_i^R	1.692	0.988	0.832	1.029	0.930	0.001
	B_i^{TS}	1.311	1.352	0.314	1.356	0.435	0.278
	B_i^P	0.986	1.709	0.000	2.034	0.000	0.711
	EV (%)	54.0	50.5	62.3	32.5	53.2	39.0
			$\delta B_{av} = 0.49$		$Sy = 0.89$		

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

Species	O_1	C_2	O_3	C_4	C_5	H_6
I	−0.703	0.989	−0.668	−0.046	−0.672	0.237
TS1-I	−0.818	1.020	−0.767	0.023	−0.872	0.468
II	−0.719	0.976	−0.667	−0.046	−0.671	0.235
TS1-II	−0.819	1.009	−0.781	0.031	−0.880	0.471

bonds remain completely unchanged, to one, when all the *n* bonds have broken or formed to exactly the same extent in the TS. The *Sy* values obtained in this way are, in principle, independent of the degree of advancement of the transition state. The *Sy* values calculated for the studied reactions are shown in Table 3. As can be seen, the synchronicities are close to 0.9 in both cases, indicating that the mechanisms correspond to concerted and slightly asynchronous processes.

A final aspect to be taken into account is the relative asynchronicity of the bond-breaking and bond-forming processes that would be a measure of 'bond deficiency' along the reaction path. In the studied reactions, the bond-breaking processes are clearly more advanced (an average of 58.3 and 56.5% in **TS1-I** and **TS1-II**, respectively) than the bond-forming processes (an average of 42.7 and 40.7% in **TS1-I** and **TS1-II**, respectively), indicating a bond deficiency in the transition states.

The charge distribution in reactants and transition states was analyzed by means of the natural bond orbital (NBO) analysis of Reed and co-workers.[17,18] Table 4 gives the natural atomic charges (the nuclear charges minus summed natural populations of the natural atomic orbitals on the atoms) at the centers involved in the reaction. Charges at **TS1-I** show an important positive charge developed on H_6 (0.468 at the TS and 0.237 at the reactant), while the electronic excess is supported by the two oxygens (−0.818 at the TS and −0.703 at the reactant, for O_1; and −0.767 at the TS and −0.668 at the reactant, for O_3) and by C_5 (−0.872 at the TS and −0.672 at the reactant). The negative character of O_1 allows it to attract the H_6 in the TS. The same hydrogen atom has a more positive character in the TS and O_1 thus increases its negative character, while C_5 has a more negative character, as would be expected from the postulated cyclic transition state. A very similar analysis can be made for **TS1-II**.

In order to obtain more reliable kinetic parameters for the two studied reactions, single-point energy calcula-

Table 5. Calculated[a] and experimental[b] kinetic and activation parameters for the pyrolysis of α-amino acid ethyl esters in the gas phase, at 673.15 K

	10^3 *k* (s^{-1})		E_a (kJ mol^{-1})		Log *A*		$\Delta H^{\neq}$ (kJ mol^{-1})		$\Delta G^{\neq}$, kJ mol^{-1}	
Reaction	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
(I)	1.48	2.04	213.2	202.3 ± 0.3	13.7	13.01 ± 3.7	207.6	196.7	206.0	204.1
(II)	1.31	1.1	212.9	204.4 ± 0.1	13.6	12.91 ± 0.3	207.3	198.7	206.7	207.4

[a] At the MP2/6–311 + G(2d,p)//MP2/6–31G(d) level.
[b] Taken from Ref. 1.

tions at the MP2/6–311 + G(2d,p) level were carried out on the structures optimized at the MP2/6–31G(d) level. The kinetics and activation parameters were calculated at the same temperature and pressure as used in the experiments, 673.15 K and 0.04 atm. These data are compared with the available experimental results in Table 5. As can be seen, the results obtained agree very well with the available experimental data.

In the second step of the reactions, the neutral α-amino acid intermediate formed undergoes a decarboxylation process, via a five-membered cyclic transition state. This second step is an extremely rapid process, with activation energies of only 81.0 and 87.8 kJ mol^{-1} and with calculated rate constants of 8.76×10^6 and 7.59×10^5 s^{-1} for reactions (I) and (II), respectively, evaluated as was pointed out only at the HF/6–31G(d) level of theory. Therefore, this step being uninteresting for our present kinetic comparisons, further studies at higher levels of theory were not undertaken in the present work.

CONCLUSIONS

A theoretical study on the gas-phase thermal decomposition of two α-amino acid ethyl esters was carried out. The free energy profiles, evaluated at the HF/6–31G(d) level of theory, show that the reactions present 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. This is followed by a faster decarboxylation process of the neutral α-amino acid 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 enlargement of the O_3—C_4 bond with the migration of the H_6 atom from C_5 to O_1 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 studied reactions, evaluated at the MP2/6–311 + G(2d,p)//MP2/6–31G(d) level of theory, agree very well with the available experimental data, confirming the reliability of the proposed mechanism.

Acknowledgments

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