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Enthalpimetric measurements in solid–solid interactions: The reactions of dicarboxylic acids with α-amino acids. Part 2. Isophthalic acid + DL-α-alanine

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Abstract

Reaction in the solid state between isophthalic acid and DL-α-alanine was attempted by heating the reactants directly in a DSC and TG apparatus. By reacting equivalent amounts of starting materials, the results suggest that isophthalic acid interacts with DL-α-alanine in a 2:1 molar ratio mixture, yielding an immino derivative which, during formation, melts and evaporates. The DSC, TG, IR and NMR data confirm the proposed mechanism.

Keywords: Alanine; Amino acid; DSC; DTG; Dicarboxylic acid; Enthalpy; IRS; NMR; TG

1. Introduction

The ability of the dicarboxylic groups of phthalic acid to interact in the solid state with DL-α-alanine in a 1:1 molar ratio mixture, has been previously investigated [1,2] and it was found that the product of the reaction condenses as phthalimmide following the simultaneous release of two water molecules, without formation of intermediate products.

The aim of the present research was to study the solid-state interaction between isophthalic acid and DL-α-alanine in a 1:1 molar ratio, in order to understand the role of the meta position of the two carboxylic groups with respect to the ortho position, and also because it is known that the presence in the main backbone of phenylene rings linked at the meta position results in more kinked polymers [3,4].

Furthermore, we wanted to study the solid-state interaction between the carboxylic groups of isophthalic acid and the amino and/or carboxylic groups of

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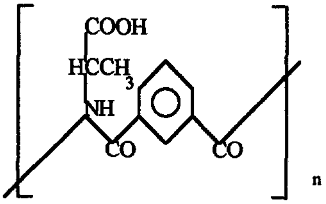
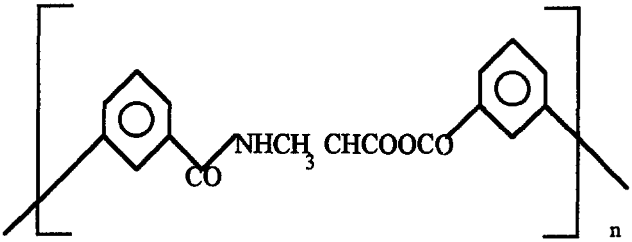
DL-α-alanine in order to observe possible competition between its $-NH_2$ and $-COOH$ groups, considering also the role of peptide chemistry in the field of immuno suppressors that fight rejection of transplanted organs [5].

Assuming 1:1 interaction, owing to the energetically favoured formation of a hepta ring, the expected result is a copolymer having the structure **1** if the amino group is responsible for condensation, or if the amino and carboxylic groups of the amino acid are both involved in the formation of the polymeric structure **2**.



Structure **1**.



Structure **2**.

Nevertheless we cannot exclude a priori the possibility that the mixture can interact in molar ratios different from 1:1, thus yielding different products and structures.

2. Experimental

2.1. Materials

The following reagent grade materials were used: isophthalic acid (Aldrich) and DL-α-alanine (Carlo Erba).

2.2. DSC measurements

The DSC measurements were performed using a Mettler 20 S DSC calorimeter, in covered aluminium pans, in a dynamic nitrogen atmosphere ($5\ l\ h^{-1}$) at different heating rates or under isothermal conditions.

The reference was an empty closed aluminium pan. The reaction was performed by placing finely powdered stoichiometric mixtures of the reactants in the pan.

The ΔH for the reaction was evaluated by using the $\Delta_{\mathrm{melt}}H$ value of indium 28.43 J g^{-1} as standard.

The reaction was also followed using a Kofler apparatus to observe melting or decomposition during the reaction.

2.3. TG measurements

All measurements were made using a Mettler TA model 50 thermoanalyser, in a dynamic nitrogen atmosphere (3.6 l h^{-1}) using open alumina crucibles and

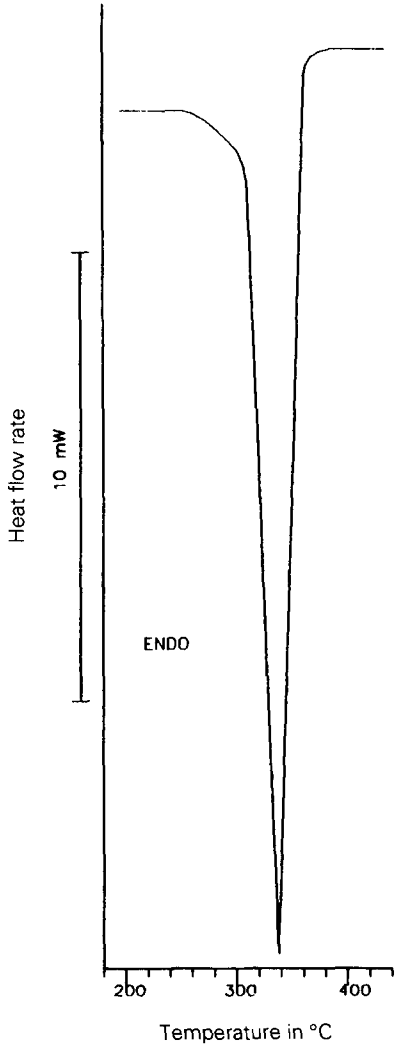


Fig. 1. Thermal behaviour of isophthalic acid. DSC curve (neat flow rate vs. temperature) under dynamic conditions.

different heating rates or under isothermal conditions at appropriate temperature values.

The solid–solid interactions were performed as previously described for DSC measurement.

2.4. *IR measurements*

The IR spectra were obtained from KBr pellets, using a Perkin-Elmer 1725X FT-IR spectrophotometer (4000–400 cm^{-1}).

2.5. *^{1}H NMR spectra*

The NMR spectra were taken on a Bruker W.P. 80 instrument using tetramethylsilane (TMS) as internal reference.

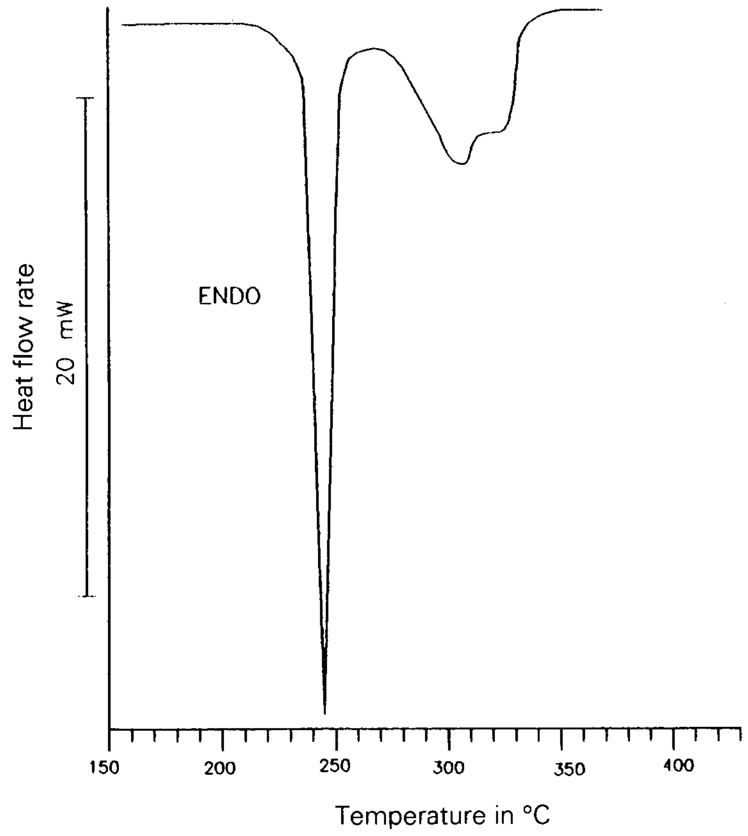


Fig. 2. Thermal behaviour of 1:1 mixture. DSC curve (neat flow rate vs. temperature) under dynamic conditions.

3. Results and discussion

The reactions were performed using solid reactants and the curves obtained were compared with those of the reactants.

3.1. DSC measurements

The DSC curve of isophthalic acid (11.93 mg) shows an endothermic effect in the temperature range 259–370°C with a T_{max} of 339°C, due to the complete solid–vapour tansition (Fig. 1). The relative ΔH sublimation value is 764 J g^{-1}.

The DSC curve of DL-α-alanine (11.41 mg), as previously reported [2], shows a continuous endothermic effect in the temperature range 215–309°C with $T_{max} = 389$°C, due to the solid–vapour transition; $\Delta H = 1074$ J g^{-1}.

The DSC curve of the 1:1 mixture (7.622 mg) of the reactants recorded at a heating rate of 4 K min^{-1} shows three endothemic processes: the first is present in

Table 1
Thermoanalytical data

Component	T start in °C	T peak in °C	ΔH in J g^{-1}		Mass in mg	Reaction [a]
Isophthalic acid						
DSC dyn.	259	339	370	764	11.93	S/V
TG dyn.	234		335		23.413	S/V
DTG dyn.	–	320	–		23.413	S/V
DL-α-alanine						
DSC dyn.	215	289	309	1074	11.41	S/V
TG dyn.	221		373		10.390	S/V
1:1 Mixture						
DSC dyn.						
First process	200	245	259	337	7.622	S/V + 0.5DL-α-al.
Second and third processes	259	309 325	340	295		Dehydr. 5(s) → 5(v) 5(s) → decomp.
TG dyn.						
First process	212		261		16.310	S/V + 0.5DL-α-al
Second process	261		289			Dehydr.
Third and fourth processes	289		342			5(s) → 5(v) 5(s) → decomp.
DTG dyn.		245 269 319 329				
TG iso (80 min)	220					Dehydr. Decarb.

[a] S/V, solid–vapour transition.

the temperature range 200–259°C ($T_{\max} = 245$°C) with a ΔH_1 value of 337 J g^{-1}, while the second and third, which are unresolved, occur in the temperature range 259–340°C with $T_{\max}$ values of respectively 309 and 325°C ($\Delta H_{\text{tot}} = \Delta H_2 + \Delta H_3 =$ 295 J g^{-1}) (Fig. 2).

Table 1 reports the enthalpic values for these processes.

3.2. *TG and DTG measurements*

The thermogravimetric analysis of the reactants performed at 4 K min^{-1} confirmed the sublimation, without decomposition, of both the dicarboxylic acid (Fig. 3) and amino acid [2]. The temperature ranges of sublimation are respectively 234–335°C and 221–373°C for isophthalic acid (23.413 mg) and DL-α-alanine (10.390 mg).

The TG and DTG curves of the 1 : 1 mixture recorded at 4 K min^{-1} show a different behaviour from that of the DSC curve: four consecutive processes are observed (Fig. 4). The first occurs in the temperature range 212–261°C with

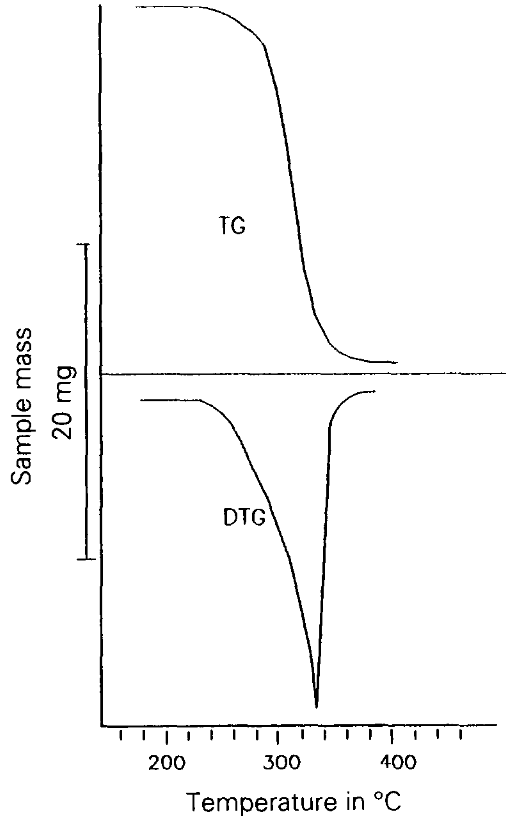


Fig. 3. Thermal behaviour of isophthalic acid. TG and DTG curves under dynamic conditions.

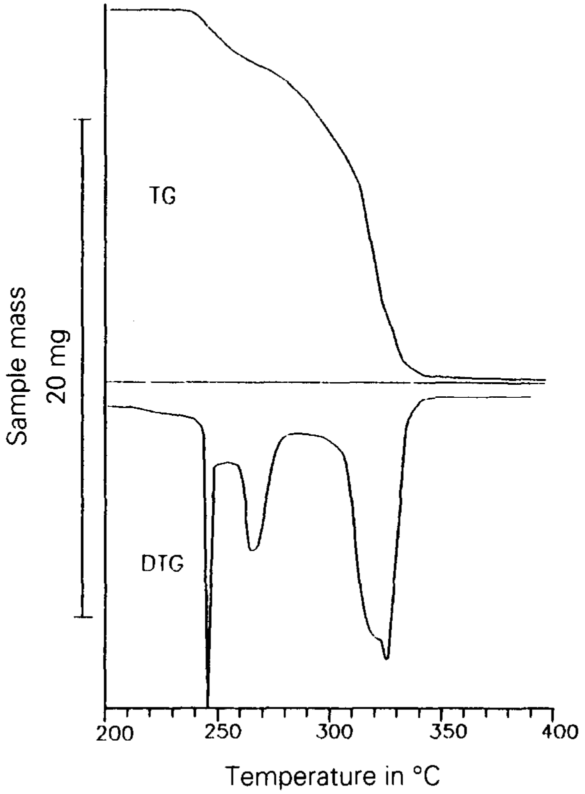


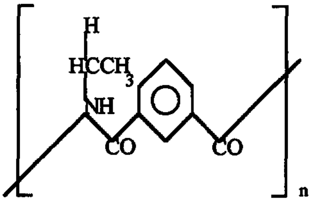
Fig. 4. Thermal behaviour of 1 : 1 mixture. TG and DTG curves under dynamic conditions.

T_{max} = 243°C, showing a relative mass loss of about 16%. The second, which begins at T_{start} = 261°C and concludes at T_{end} = 289°C, shows a 17% mass loss. The third and fourth processes take place in the temperature range 289–342°C and correspond to a mass loss of 56%.

According to structures **1** or **2**, the first process (TG and DSC) might be due to a condensation step that releases two water molecules. In fact the mass loss of about 16% agrees with a M.W. of about 38. The mass loss of about 17% in the second thermal process suggests a subsequent decarboxylation of compound **1** only, with formation of a new product with structure **3**.

In an attempt to isolate the products corresponding to these two steps, we performed the thermogravimetric analysis under isothermal conditions.

To obtain **1** or **2**, we operated isothermally at 220°C for 80 min, observing a mass loss of about 35% (Fig. 5). The product was cooled and heated again under dynamic conditions (4 K min^{-1}) showing a single TG step in the 230–330°C temperature range with a total loss in mass, not the expected second, third and fourth step, as described above.



Structure 3.

The DSC analysis of the residual product performed under the same conditions showed a single endothermic process with a ΔH value of 750 J g^{-1}, i.e the same ΔH value previously found for solid–vapour transition of isophthalic acid.

IR and NMR analyses confirmed that the observed product was really isophthalic acid.

During the isothermal analysis, as described above, when a gaseous product was released, a solid was found sublimated in a cold part of the TG apparatus.

DSC, IR and NMR analyses of this sublimate indicated that it was DL-α-alanine. Therefore, under isothermal conditions, the 1:1 mixture separately releases both DL-α-alanine (as a gaseous product) and isophthalic acid as the residue.

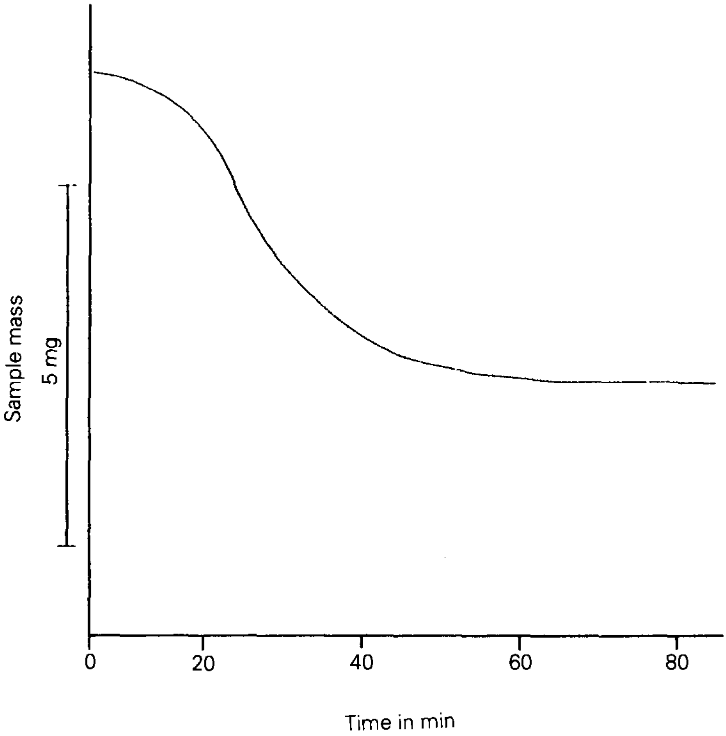
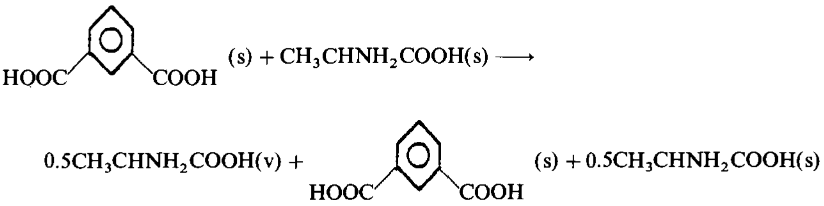


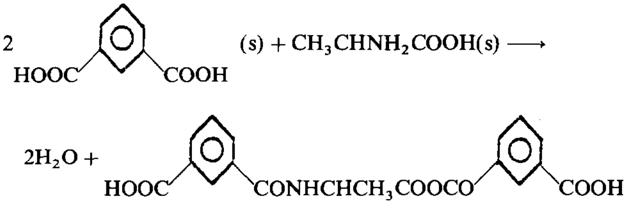
Fig. 5. Thermal behaviour of 1:1 mixture. TG curve under isothermal conditions.

As a consequence, the first registered process (Figs. 2 and 4) might be attributed to the sublimation of unreacted DL-α-alanine (about 0.5 mol from the 1 : 1 mixture), and evaluating again the enthalpic effect, the relative value was about 812 J g^{-1}, i.e. the same ΔH as previously found for the sublimation of the α-amino acid. Therefore the first step should be interpreted according to Scheme 1 where a new molar ratio (2 : 1) is achieved



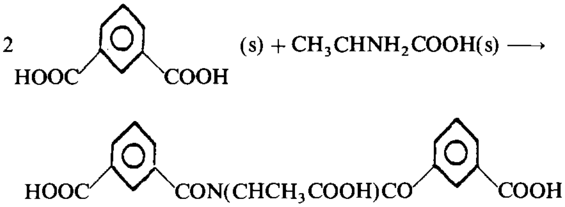
Scheme 1.

Consequently the second TG step, registered under dynamic conditions, can be attributed to the release of two water molecules forming structure **4** or **5** according to Scheme 2



Structure **4**.

or



Structure **5**.

Scheme 2.

Because the experiment carried out in the Kofler apparatus showed that a melting process occurred in the temperature range corresponding to the second TG step, we decided to run a thermal analysis (TG and DSC) under the following conditions.

(i) Heating the 1 : 1 mixture until the second TG or DSC process is complete.
(ii) Cooling at 2 K min^{-1} to room temperature.
(iii) Further heating of the remaining material until total mass loss.

After heating according to condition (i), on subsequent cooling, the DSC analysis showed only an exothermic process in the temperature range 273–163°C (Fig. 5).

On reheating, the TG and DSC curves showed no sign of the first and second processes, while the shape of the third and fourth process was the same.

It should be pointed out that the disappearance of the second DSC process confirms, according to Scheme 2, the dehydration and consequent formation of the condensation product **4** of **5** which melts when forming (which confirms the exothermic peak registered on cooling).

On reheating the cooled product according to condition (iii), no endothermic process due to melting was observed, but the product remains in the solid state until its sublimation at 319°C (third DTG thermal process), followed by decomposition at 329°C (fourth DTG thermal process).

However, significant differences were found for the enthalpy values of these last two processes (Table 1) on performing the interaction in a continuous dynamic heating process or applying a thermal cycle as described above.

To determine if the product of the condensation is Structure **4** or **5**, it was analysed by IR spectrography. On comparing the IR data of the compound with respect to the IR data of the reactants, we observe the disappearance of the $-NH_2$ band and an intensification of the $-CO$ band. Moreover, the absence of any $-NH$ band frequency suggests the formation of structure **5**.

Therefore, overall, the observed reaction for the 1:1 mixture acording to the above conditions can be summarised as follows.

(i) On heating for the first time:
First TG and DSC process: see Scheme 1;
Second TG and DSC process: see Scheme 2, with formation of **5**.

(ii) On cooling:
DSC exothermic process: $\mathbf{5}(l) \rightarrow \mathbf{5}(s)$.

(iii) On reheating:
Third TG and DSC process: $\mathbf{5}(s) \rightarrow \mathbf{5}(v)$;
Fourth process: $\mathbf{5}(s) \rightarrow$ decomposition.

If we do not cool **5** and continue to heat dynamically, we observe an incomplete liquid–vapour transition followed by decomposition.

On conclusion, comparing these results with the previously investigated phthalic acid–DL-α-alanine 1:1 system, we observe that the interaction is strongly dependent on the thermal behaviour of the dicarboxylic acid: the interaction only occurs when the observed energy of the carboxylic group of the aromatic acid makes the bonds unstable, and the amino acid is less reactive.

When phthalic acid was used, it became unstable at 218°C and its product with amino acid was obtained [2]; in contrast, on using isophthalic acid, its instability occurred at 234°C, higher than the thermal instability of DL-α-alanine, so that the amino acid sublimed as the pure component before it reacted.

Only when, in the dynamic heating process, the dicarboxylic acid became unstable could the remaining mixture react, but obviously not using a 1:1 stoichiometric ratio. Therefore, the product obtained was the unexpected structure **5** rather than the expected **1** or **2** copolymers.

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