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Thermal properties of 2-(aminomethyl)dicarboxylic acids

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Abstract

The melting point of an organic compound is commonly used for its characterization. In studies of 2-(aminomethyl)butanedioic acid, we found an apparent melting point that differed significantly from the literature values. Differential scanning calorimetry (DSC) revealed endothermic events prior to melting, and gravimetric analysis showed a concomitant mass loss. On heating, it appears that one water molecule is lost via dehydration of the monohydrate (the samples were recrystallized from aqueous solutions) and a second water molecule is lost from the cyclization reaction to form the corresponding lactam. The latter was confirmed by IR, NMR, and MS analysis of the product obtained by heating 2-(aminomethyl)butanedioic acid. Further studies of 2-(aminomethyl)pentanedioic acid gave similar results: loss of water and cyclization to form the lactam. However, the longer-chain amino acids, 2-(aminomethyl)hexanedioic acid and 2-(aminomethyl)heptanedioic acid, decompose on heating without cyclization.

Keywords: Melting point; Differential scanning calorimetry; Amino acids

1. Introduction

Melting point is one of the most important properties used to characterize organic compounds. The information contained in the melting point is more than just the temperature of the phase change; its value also can be related to molecular symmetry, as compounds of a high molecular symmetry generally will have high melting points [1]. Melting thermodynamics, such as enthalpy of fusion ($\Delta_{\text{fus}}H$) and especially entropy of fusion ($\Delta_{\text{fus}}S$), can be related to disorder in the solid state [2,3].

In the present investigation, the thermal behaviour near the melting point was determined by differential scanning calorimetry (DSC) for a series of 2-(aminomethyl)dicarboxylic acids that are examples of β^2-amino acids [4]. The β^2-amino acids were synthesized as homologues and isomers of common α-amino acids (or α-aminodicarboxylic acids; refer to Fig. 1 for structures). The α-amino acids are involved in a large number of metabolic processes, and the motivation for synthesis of these β^2-amino acids [5] was based on their biological effects and intrinsic potential as enzyme inhibitors [6–9].

In our initial investigations, however, we found some apparent contradictions with reported melting points. There are various potential reasons for melting point differences in organic compounds, including incorrect compounds, impurities, enantiomer *vs.* racemate, closed *vs.* open containers, calibration of thermometers, presence of hydrate, decomposition, and reaction before melting. Indeed, some amino acids are known to decompose [10] and to cyclize on heating [11].

DSC can offer more information than is obtained from traditional melting point methods. For example, in compounds that undergo multiple heat-induced transformations, each individual event can be distinguished from the DSC results. Also the thermodynamics parameters of the thermal events, especially $\Delta_{\text{fus}}H$ and $\Delta_{\text{fus}}S$, can be determined and this information can lead to better understanding of the processes involved.

2. Experimental

2.1. Materials and characterization

The synthesis and characterization of the 2-(aminomethyl) dicarboxylic acids studied in this work (Fig. 1; $n = 1$–4) are

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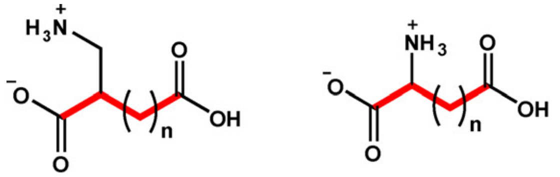


Fig. 1. Structures of 2-(aminomethyl)dicarboxylic acids (left) and α-amino acids (right). The common dicarboxylic acid backbone is highlighted.

described in detail elsewhere [5]. All compounds were prepared as racemates, and recrystallized from water or water/acetone.

The lactam products obtained by heating solid samples of 2-(aminomethyl)butanedioic acid and 2-(aminomethyl) pentanedioic acid at 130 °C were characterized by IR spectroscopy (Bomem MB-Series), electrospray ionization tandem mass spectrometry (ESI-MS/MS; Finnigan LCQ Duo Ion Trap) in negative ion mode [12] and NMR spectroscopy (Bruker Avance 500). The assignment of NMR resonances was based on 2-D NMR experiments (COSY, HSQC and HMBC).

5-Oxo-3-pyrrolidinecarboxylic acid: IR (Nujol) cm^{-1}: 3600–2600, 1698; ^1H NMR (CD_3OD) δ 3.54–3.46 (2H, AB system coupled to H-3, $J_{AB} = 10$ Hz, H-2), 3.18–3.12 (1H, m, H-3), 2.57–2.40 (2H, AB system coupled to H-3, $J_{AB} = 17$ Hz, H-4); ^{13}C NMR (CD_3OD) δ 180.1 (C-5), 178.8 (C-3′), 46.9 (C-2), 42.3 (C-3), 35.4 (C-4); ESI-MS m/z 128 (100), CID (22%) of m/z 128 ($[M-H]^-$): m/z 98 (100), 84 (5).

6-Oxo-3-piperidinecarboxylic acid: IR (Nujol) cm^{-1}: 3600–2600, 3201, 1640; ^1H NMR (D_2O) δ 3.54–3.44 (2H, AB system coupled to H-3, $J_{AB} = 13$ Hz, H-2), 2.85–2.79 (1H, m, H-3), 2.45–2.42 (2H, m, H-5), 2.16–2.11 and 2.02–1.95 (2H, m, H-4); ^{13}C NMR (D_2O) δ 179.0 (C-3′), 175.1 (C-6), 43.1 (C-2), 39.0 (C-3), 29.0 (C-5), 23.0 (C-4); ESI-MS m/z 142 ($[M-H]^-$), CID (23%) of m/z 142: m/z 112 (25), 98 (100).

2.2. *Differential scanning calorimetry*

Thermal analyses of the compounds were performed using a PerkinElmer Pyris-1 DSC. A scan rate of 5 K min^{-1} was used on heating and cooling. The samples were sealed in non-volatile aluminium pans (unless specified otherwise below) and were measured in a nitrogen atmosphere. Where sufficient quantities were available, typical sample masses were 5–10 mg. High-purity indium standards were used to calibrate onset temperatures and enthalpy changes on fusion (T_{fus} and $\Delta_{fus}H$, respectively). Sample masses were determined before and after DSC experiments to check for mass loss.

3. Results and discussion

3.1. *2-(Aminomethyl)butanedioic acid (Fig. 1; n = 1)*

3.1.1. *Melting behaviour*

The melting behaviour of this compound was measured first by open capillary and also by open cover slip. A “melting point” of 123–124 °C was obtained with the open capillary method. The sample changed from transparent to translucent at 124 °C in the open cover slip method and subsequently melted at 180–184 °C.

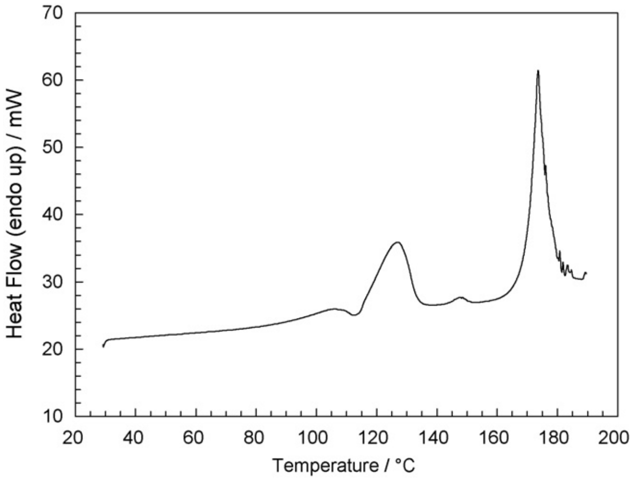


Fig. 2. DSC of 2-(aminomethyl)butanedioic acid, heated from room temperature to 190 °C. This sample experienced a 26% mass loss.

There is reasonable agreement among the melting points recorded in the literature: 180–181 °C by Zilkha et al. [13]; 179–180 °C by Harada and Matsuyama [14]; and 178–180 °C by Bauce and Goren [15]. In each case, the racemate was prepared from a water–ethanol mixture, and was most likely hydrated. The *S*-enantiomer of the monohydrate was isolated by Arvanitis et al. [16] and its melting point was 161 °C. No previous reports mentioned melting features in the temperature range of 123–124 °C.

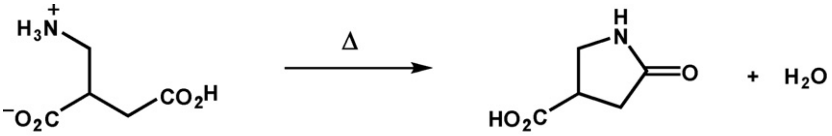
3.1.2. *DSC*

DSC of this compound showed four thermal features upon heating the sample from room temperature to 190 °C with some possible decomposition above 185 °C (Fig. 2). This sample experienced a mass loss of 26%.

A second sample was measured, but only heated to 150 °C on the first cycle. Again, the first three features were present. On heating to 180 °C on the second cycle, the fourth feature was apparent. This high-temperature feature degraded on the three subsequent heating cycles. Fig. 3 shows all five heating scans. The overall mass loss was 25% for this second sample. The onset temperatures, T_{onset}, of the main features from each heating cycle are given in Table 1 along with changes of enthalpy and entropy associated with the transition. The values of $\Delta_{trs}H$ and $\Delta_{trs}S$ were calculated using the molecular mass of the anhydrous compound for this and in all subsequent calculations.

Table 1
T_{onset}, $\Delta_{trs}H$, and $\Delta_{trs}S$ of the main features (denoted by arrows in Fig. 3) in each of the five heat scans for 2-(aminomethyl)butanedioic acid sealed in a non-volatile pan

Heating	T_{onset} (°C)	$\Delta_{trs}H$ (kJ mol^{-1})	$\Delta_{trs}S$ (J K^{-1} mol^{-1})
1st	115.4	43.4	112
2nd	165.5	47.2	108
3rd	137.5	10.7	26.2
4th	137.6	9.5	23.2
5th	141.4	1.9	4.7



Scheme 1. Conversion of 2-(aminomethyl)butanedioic acid to the corresponding lactam (5-oxo-3-pyrrolidinecarboxylic acid).

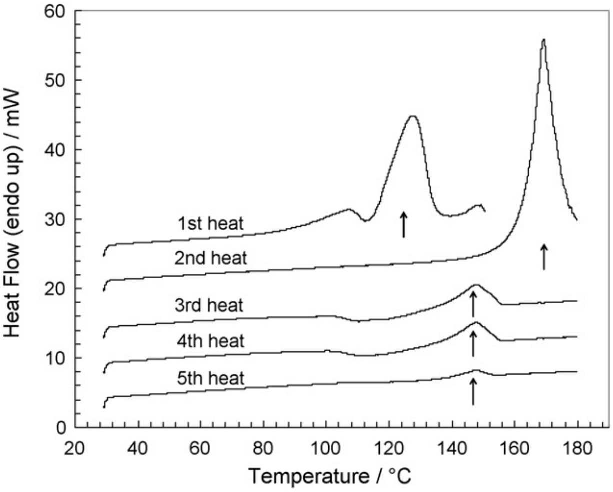


Fig. 3. DSC of 2-(aminomethyl)butanedioic acid. This sample experienced a 25% mass loss. The values of T_{onset}, $\Delta_{\text{trs}}H$, and $\Delta_{\text{trs}}S$ of the main features (as indicated by the arrows) are given in Table 1.

A sample sealed in an aluminium volatile pan was also run in the DSC. There were two thermal events for this sample in the first heat scan. The pan burst due to pressure build up so an accurate mass loss could not be determined. The thermograph is shown in Fig. 4 and Table 2 gives the T_{onset}, $\Delta_{\text{trs}}H$, and $\Delta_{\text{trs}}S$.

3.1.3. Heating experiments and analytical characterization

A sample of 2-(aminomethyl)butanedioic acid was heated in open air at 130 °C until it reached constant mass (8 h). It had a mass loss of 21%. The resulting product was a colourless, hygroscopic solid, and due to its hygroscopic nature, a melting point could not be determined. Negative ion ESI-MS of the heated product yielded a spectrum containing a predominant peak at m/z 128, indicating the formation of an anion that is 18 u less than the anion formed by deprotonation of the amino acid (m/z 146 not detected). The IR spectrum of the heated product showed a carbonyl stretch at 1698 cm^{-1}, characteristic of a 5-membered lactam ring (refer to Scheme 1 for details), and the structure of the lactam was confirmed by ^1H and ^{13}C NMR spectroscopy. The heating experiments and analytical characterization indicate that the original sample of 2-(aminomethyl)butanedioic was synthesized as a monohydrate and, when heated, it lost two H_2O molecules to form the lactam. Removing two H_2O molecules from the monohydrate would result in 22% mass loss, which is consistent with the heating experiments (21% mass loss) and the DSC experiments (25% and 26% mass loss).

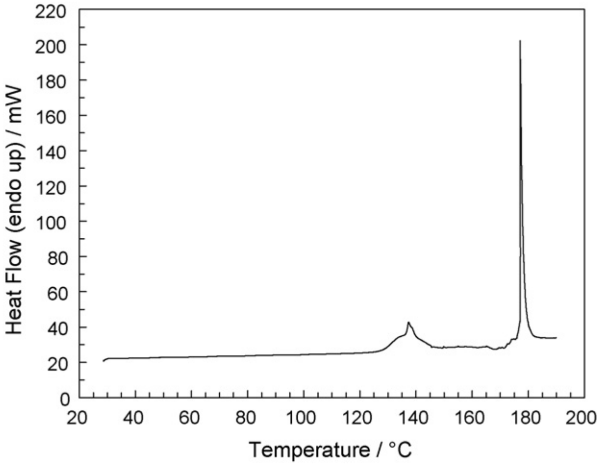


Fig. 4. DSC of 2-(aminomethyl)butanedioic acid sealed in a volatile pan, heated from room temperature to 190 °C. This sample pan burst due to pressure build up and therefore a mass loss calculation was not possible.

3.1.4. Conclusions for 2-(aminomethyl)butanedioic acid

It is apparent from the characterization performed on 2-(aminomethyl)butanedioic acid that the monohydrate is formed from aqueous solution. When it is heated above about 120–130 °C, it loses a water of hydration and another water to form the corresponding lactam. Clearly, the sealed pan burst because of pressure build up due to water vapour. The lactam formed is hygroscopic and does not have a well-defined melting point, but it likely gives rise to the thermal event in the DSC experiment with the T_{onset} of 165 °C in Fig. 2 and cycle 2 of Fig. 3. In cycles 3–5 in Fig. 3, the endothermic peak shifts to lower temperature and decreases in magnitude below that expected to correspond to $\Delta_{\text{fus}}S$ for an organic compound [2], likely due to decomposition of the lactam.

Considering the literature melting points, the reported values of 180–181 °C [13], 179–180 °C [14] and 178–180 °C [15] most likely correspond to the melting point of the lactam. Independent preparations of the lactam by Klein and Reimschuessel [17] and Bauce and Goren [15] yielded samples that melted at 159–160 °C and 153–155 °C, respectively. The 161 °C melting point reported for the S-enantiomer of the monohydrate [16] is probably indicative of a different melting point for the pure enantiomer compared to the racemate.

Table 2
T_{onset}, $\Delta_{\text{trs}}H$, and $\Delta_{\text{trs}}S$ for 2-(aminomethyl)butanedioic acid sealed in a volatile pan

T_{onset} (°C)	$\Delta_{\text{trs}}H$ (kJ mol^{-1})	$\Delta_{\text{trs}}S$ (J K^{-1} mol^{-1})
135.9	28.5	69.7
177.1	48.2	107.0

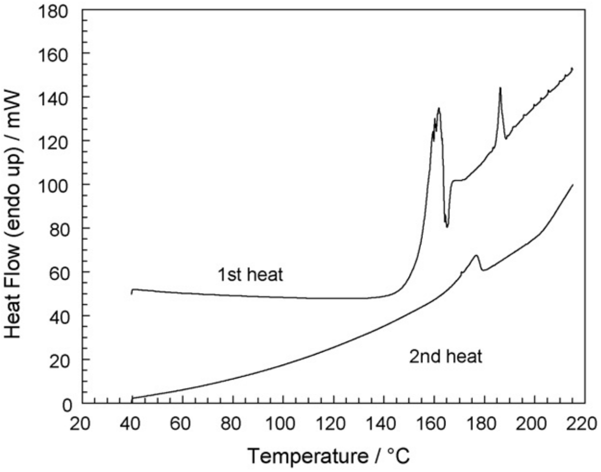


Fig. 5. DSC of 2-(aminomethyl)pentanedioic acid heated from room temperature to 215 °C and then repeated. The sample lost 23% of its mass.

3.2. 2-(Aminomethyl)pentanedioic acid (*Fig. 1*; *n* = 2)

3.2.1. Melting behaviour

The melting behaviour of this compound was measured by open capillary and also by open cover slip, and the results were similar: melting points of 164–165 °C and 166–168 °C, respectively. Again the results differ from previous reports. Scott [18] reported that the sample darkened and decomposed above 200 °C, but Sekura et al. [8] reported a melting point of 171–173 °C with cyclization.

3.2.2. DSC

DSC of this compound showed two main thermal features on the first heat, one with an onset of 158 °C and the second at 176 °C (Fig. 5). Only one thermal event was present in the second heat. This sample lost 23% of its mass on heating.

A new sample from the same batch was measured again several months later in the DSC, but was heated to only 195 °C. The results, shown in Fig. 6, revealed similar thermal events on the first and second scan as the previous sample, but a smaller mass loss (11%). Table 3 gives the values for T_{onset}, $\Delta_{\mathrm{trs}}H$, and $\Delta_{\mathrm{trs}}S$ for this sample. The high-temperature feature at ∼176 °C degraded with each heating cycle.

Table 3

T_{onset}, $\Delta_{\mathrm{trs}}H$, and $\Delta_{\mathrm{trs}}S$ for each thermal feature in the three heating cycles for 2-(aminomethyl)pentanedioic acid shown in Fig. 6

Heat step	T_{onset} (°C)	$\Delta_{\mathrm{trs}}H$ (kJ mol^{-1})	$\Delta_{\mathrm{trs}}S$ (J K^{-1} mol^{-1})
1st	157.7	65.7	153
1st	176.3	19.1	42.4
2nd	176.4	14.8	32.9
3rd	174.2	13.2	29.4

3.2.3. Heating experiments and analytical characterization

Duplicate samples of 2-(aminomethyl)pentanedioic acid were heated in air at 135 °C for 13 h. The mass loss for both was 11%, and the new material had a melting point of 178–180 °C. Another sample was heated at 130 °C until constant mass (5 h) and gave a loss of 20%. The products of these two experiments gave identical ^{1}H NMR spectra, indicating that the original samples were in different states of hydration.

Heating a 0.201 g sample for 16 h at 130 °C gave a product that, when dissolved in 20 mL of water, treated with activated charcoal for 11 h, filtered through Celite and freeze dried to remove the water, gave 0.126 g of white powder (70% yield) with a melting point of 169–171 °C. DSC of the heated product measured several months after the heating experiment gave a lot of features, starting at 60 °C, with a mass loss of 8% (Fig. 7). This indicates that the 2-(aminomethyl)pentanedioic acid heating product, likely the corresponding lactam (see below), takes on water over time.

The negative ion ESI mass spectrum of the heated product showed a predominant signal at *m*/*z* 142, 18 u less than the *m*/*z* 160 expected for the deprotonated parent amino acid (not detected) and confirming the loss of water upon heating the amino acid. The IR spectrum showed an N–H stretch at 3200 cm^{-1} and a carbonyl stretch at 1640 cm^{-1}, characteristic of

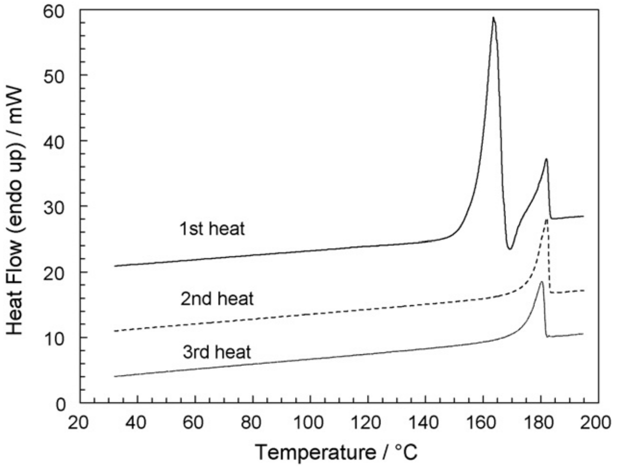


Fig. 6. DSC of 2-(aminomethyl)pentanedioic acid heated from room temperature to 195 °C. The sample lost 11% of its mass.

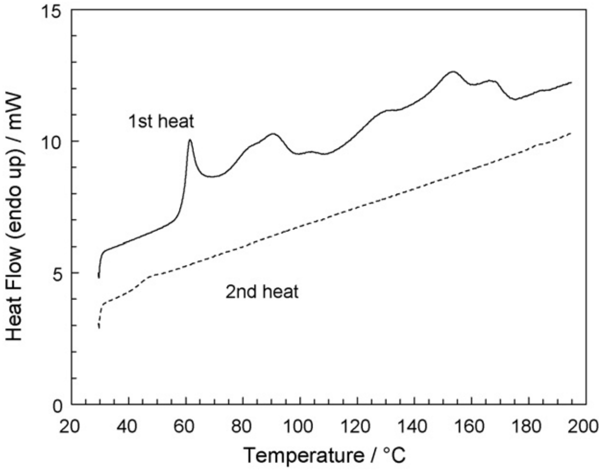
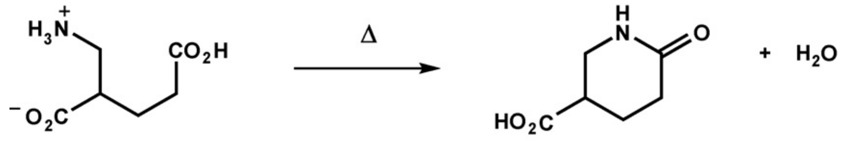


Fig. 7. DSC of the product obtained by heating 2-(aminomethyl)pentanedioic acid at 130 °C for 16 h, measured some months later. The sample lost 8% of its mass in the DSC run.



Scheme 2. Conversion of 2-(aminomethyl)pentanedioic acid to the corresponding lactam (6-oxo-3-piperidinecarboxylic acid).

Table 4
T_{onset}, $\Delta_{trs}H$, and $\Delta_{trs}S$ of each thermal feature for 2-(aminomethyl)hexanedioic acid

Heat step	T_{onset} (°C)	$\Delta_{trs}H$ (kJ mol^{-1})	$\Delta_{trs}S$ (J K^{-1} mol^{-1})
1st	206.7	0.9	1.8
1st	221.0	1.8	3.5
2nd	239.4	3.0	5.9
3rd	237.9	4.2	8.2

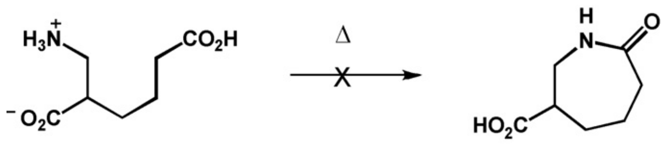
a 6-membered lactam ring and not observed for the amino acid. The structure of the lactam, shown in Scheme 2, was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

3.2.4. Conclusions for 2-(aminomethyl)pentanedioic acid

The heating experiments and analytical characterization show that 2-(aminomethyl)pentanedioic acid was synthesized as a hydrate from aqueous solution, but the degree of hydration can be variable. When heated, it loses water of hydration (if present) and additional water to form the corresponding lactam. (Loss of one H_2O molecule from the anhydrous amino acid would correspond to 11% mass loss, while loss of two H_2O molecules from the monohydrate would decrease the mass by 20%.)

The melting point reported in the literature, *i.e.* 171–173 °C with cyclization [8], corresponds to loss of water (if present) and cyclization followed by melting of the lactam. The report of decomposition at about 200 °C could have been due to heating the sample too quickly to observe melting [18].

DSC of 2-(aminomethyl)pentanedioic acid shows broad melting with an onset of ∼175 °C on the second and subsequent heating cycles (Fig. 6), corresponding to the melting point reported by Sekura et al. after thermal cyclization of the acid [8].



Scheme 3. Unlike shorter-chain analogues, 2-(aminomethyl)hexanedioic acid does not convert thermally to the corresponding lactam.

The temperature of the feature is stable on several heating and cooling cycles in the DSC and corresponds to the melting of the lactam, recorded as 182–185 °C [8]. However, the enthalpy and entropy changes decrease with subsequent cycles, indicating thermal degradation of the lactam. The lactam also degrades while sitting in air over time, as evidenced by DSC (Fig. 7).

3.3. 2-(Aminomethyl)hexanedioic acid (Fig. 1; n = 3)

We found that 2-(aminomethyl)hexanedioic acid had a open capillary melting point of 235–240 °C with decomposition. The DSC on a very small (<3 mg) sample showed subtle thermal events at 207 °C and 221 °C in the first cycle (Fig. 8). In the second and third cycles, only one peak was present at ∼238–239 °C. This sample underwent a mass loss of 10%. The T_{onset}, $\Delta_{trs}H$, and $\Delta_{trs}S$ of the thermal features are given in Table 4.

Loss of one H_2O molecule from the anhydrous amino acid would correspond to a mass loss of 10%. Loss of two H_2O molecules from the monohydrate would be 20%. The mass loss of this compound corresponds to only one water molecule, and the peak at 207 °C likely is the corresponding thermal event because it is not present in subsequent cycles. The thermal event at higher temperature has too small a $\Delta_{trs}S$ to be melting [2].

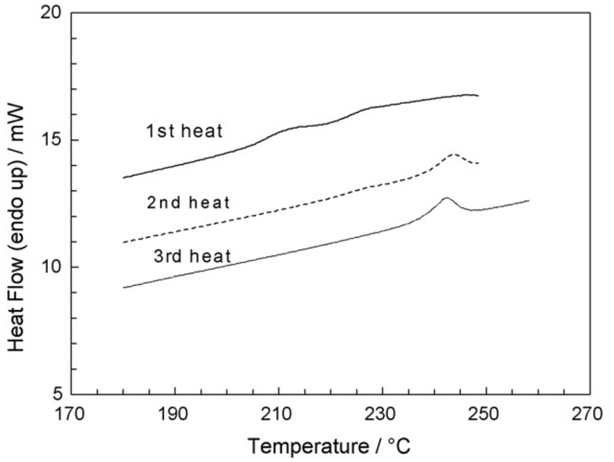


Fig. 8. DSC of 2-(aminomethyl)hexanedioic acid. The mass loss from the sample was 10%.

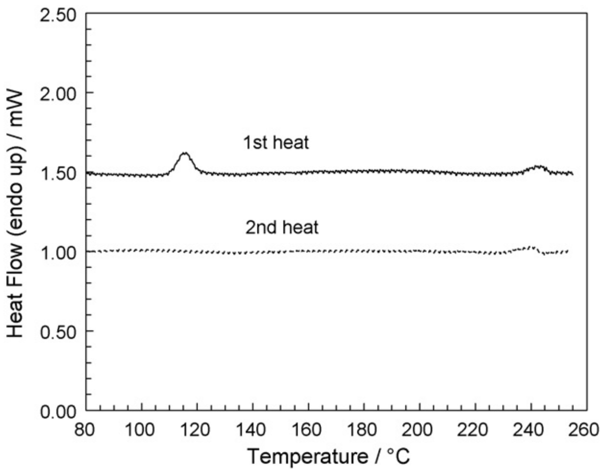


Fig. 9. DSC of 2-(aminomethyl)heptanedioic acid. The mass loss from the sample was 5% after the first peak in the first cycle, and 8% total.

Table 5
T_{onset}, $\Delta_{\mathrm{trs}}H$, and $\Delta_{\mathrm{trs}}S$ of each thermal feature for 2-(aminomethyl)heptanedioic acid

Heat step	T_{onset} (°C)	$\Delta_{\mathrm{trs}}H$ (kJ mol^{-1})	$\Delta_{\mathrm{trs}}S$ (J K^{-1} mol^{-1})
1st	112	3	8
1st	230	1	2
2nd	230	1	2

Negative ion ESI-MS of the DSC sample after heating showed no evidence of lactam formation (Scheme 3).

From the mass loss, we conclude that 2-(aminomethyl) hexanedioic acid was synthesized as a monohydrate. Unlike the shorter chain β^2-amino acids, there is no evidence for thermally induced lactam formation.

3.4. *2-(Aminomethyl)heptanedioic acid (Fig. 1; $n = 4$)*

In an open capillary, 2-(aminomethyl)heptanedioic acid had a melting point of 265–270 °C with decomposition. The DSC experiment (very small sample, 0.8 mg) showed small thermal events at 112 °C and 230 °C in the first cycle (Fig. 9). In the second cycle, only one peak was present at 230 °C. This sample experienced a mass loss of 5% at the first peak, 8% total. The values of T_{onset}, $\Delta_{\mathrm{trs}}H$, and $\Delta_{\mathrm{trs}}S$ of each feature are given in Table 5.

The loss of one H_2O molecule from the anhydrous amino acid would correspond to a mass loss of 9.5%. Loss of two H_2O molecules from the monohydrate would give 17%. The peak at 112 °C appears to be due to the loss of water from a partially hydrated amino acid, in other words containing less than one water molecule per amino acid. The thermal event at higher temperature has too a small value of $\Delta_{\mathrm{trs}}S$ to be melting, so likely some decomposition is occurring. Negative ion ESI-MS analysis of the heated DSC sample showed no evidence of lactam formation.

4. Concluding comments

Our results show that the formation of the 5-membered and 6-membered rings from the cyclization of β^2-amino acids is thermally favoured, but the β^2-amino acids that would form 7-membered and 8-membered rings appear to decompose thermally before the ring-closing reaction takes place. Although the 7-membered ring is considered to be a favoured ring-closing reaction according to Baldwin's rules [19], as are the 5- and 6-membered rings, studies of α-aminoheptanedioic acid also show resistance of cyclization to form the 7-membered ring [11].

In general, none of the β^2-amino acids investigated shows a reproducible melting point. Indeed, with the complications of kinetic effects of dehydration and/or cyclization, melting point is not a reasonable characterization property for these β^2-amino acids. However, their thermal properties do reveal interesting chemistry that can, in some instances, be used for synthetic purposes, such as the preparation of lactams. Furthermore, knowledge of cyclization of amino acids can be important in understanding other characterization results. For example, on heating to induce volatility for mass spectrometric characterization studies, glutamic acid, creatine and dipeptides have been reported to dehydrate with concurrent cyclization [20–22].

Acknowledgements

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