New *N*-acylamino acids and derivatives from renewable fatty acids: gelation of hydrocarbons and thermal properties

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ABSTRACT

This work reports the synthesis of new fatty *N*-acylamino acids and *N*-acylamino esters from the C16:0, C18:0, C18:1, and C18:1(OH) fatty acid families and demonstrates the activity of these compounds as organogel agents. Compounds were heated and dissolved in various solvents (*n*-hexane, toluene, and gasoline). Only saturated C16:0 and C18:0 derived from alanine were able to form gels in toluene, and saturated C16:0 derived from phenylalanine showed gelation in *n*-hexane. This is the first evidence that fatty *N*-acylamino esters and *N*-acylamino acid derivatives of L-serine and fatty acids C16:0, C18:0, and C18:1 are able to form gels with hexane. This observation confirms the importance of the hydroxyl group in the segment derivative of L-serine in forming good gels.

Introduction

Fatty *N*-acylamino acid, fatty acid amides, and fatty *N*-acylamino esters are noted for their ability to gelatinize organic solvents[1–3] and their role in important biological activities (Fig. 1).[4,5] Moreover, these gelators can selectively form gels in water,[6] and because they are biodegradable they are biocompatible with biological systems.[7] These compounds belong to a class of materials called low-molecular-weight gelators, which include derivatives of long-chain hydrocarbons, salts of organic compounds, steroids, metallic complexes, and derivatives of fatty ureas and amino acids.[8]

N-acylamino acids and their fatty derivatives harden organic solvents at the supramolecular level, resulting in a network of three-dimensional structures. The role of these compounds in the gelation of organic solvents originates from intermolecular interactions between gelator molecules such as dipole–dipole, Van der Waals, π–π-stacking, hydrogen bond interaction, and so on.[9] However, researchers still do not understand how and why an organogelator gelatinizes one particular solvent over another.

Low-molecular-weight gelators have attracted interest from technicians as well as academics because they are present in many commercial products (e.g., cosmetics, food, medicine) and are involved in tissue engineering and effluent treatment.[8,9] *N*-Acylamino acid derivatives and fatty derivatives are also used in the pharmacological field as carriers of drugs.[10–13] A subcutaneous implant form of the organogelator *N*-stearyl alanine methyl ester showed advantages over the known polymeric matrix for delivering drugs, as it was easy to prepare and non-toxic.[11]

There are a few reports of fatty *N*-acylamino acid synthesis and its various applications in the literature, but usually the main focus is on the physical characteristics and the mechanisms of forming gels from non-complex mixtures of hydrocarbons. However, there is little information in the literature on variation in the hydrophobic portion, because most of the studies report the use of saturated chains.

Here we describe the synthesis of new fatty *N*-acylamino ester derivatives **1–5a–d** and fatty *N*-acylamino acids **6–10a–d** from fatty acids with saturated and unsaturated chains derived from vegetable oils (common substrates in the chemical industry) and commercial amino acids. The gelation properties of 40 compounds were evaluated using *n*-hexane, toluene, and gasoline (a complex mixture of hydrocarbons) as organic solvents. We used the thermoanalytical technique of differential scanning calorimetry (DSC) and infrared (IR) spectroscopy to characterize the structural factors that affected the gels. Then we studied the structure–activity relationship of the new compounds in the gelation of organic solvents.

Results and discussion

The structural design of the new fatty amino acids and esters was based on the natural availability of the amino acids and fatty

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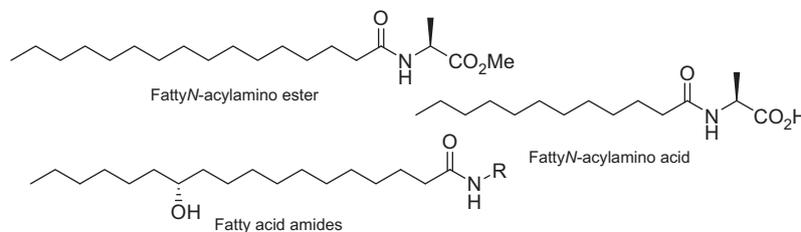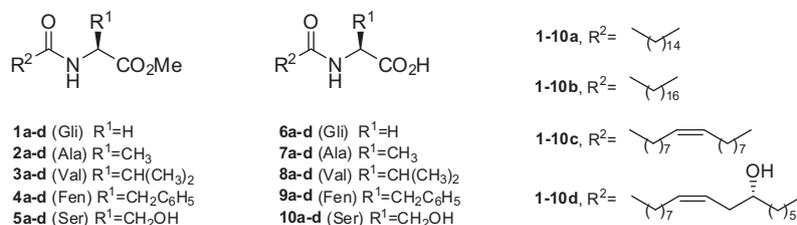 *E-mail address:* dqmdoca@furg.br (G. M. D'Oca).

Figure 1. Fatty acid organogels.

Figure 2. Fatty N-acylamino esters **1–5a–d** and N-acylamino acids **6–10a–d**.

acids, considering their biodegradability and their ability to solidify organic solvents. We considered a large number of derivatives to understand the mechanism of gelation as well as to determine the structural motifs required by these systems to exhibit efficient gelation behavior. In order to analyze the role of the lipophilic chain in determining gelation properties, we synthesized fatty N-acylamino acid and ester derivatives of the molecules with saturated, unsaturated, and hydroxylated chains. Structural variation was also considered for the amino acid moiety.

Fatty N-acylamino esters **1–5a–d** were synthesized by reacting fatty acids C16:0, 18:0, 18:1, and 18:1(OH) with amino esters, triethylamine, a catalytic amount of (dimethylamino)pyridine, and dicyclohexyl carbodiimide in CH_2Cl_2 and stirring at room temperature for 12 h (Fig. 2).[4] Compounds **1–5a–d** were purified using column chromatography on a silica gel (with 7:3 n-hexane:ethyl acetate as the eluent).

As shown in Figure 2, fatty N-acylamino acids **6–10a–d** were obtained by basic hydrolysis. For this reaction, the respective fatty N-acylamino esters **1–5a–d** were dissolved in a 1:1 mixture of methanol:THF.[8] Then an aqueous solution of sodium hydroxide was added. The mixture was stirred for 4 h at room temperature. Compounds **6–10a–d** were purified using column chromatography with ethyl acetate as the eluent.

All of the compounds were analyzed by ^{1}H NMR, ^{13}C NMR and IR spectral data and were consistent with their given structures.

Formation of physical gel

Compounds **1–10a–d** were tested for their ability to gelatinize organic solvents. A total of 10 mg of each compound was heated in 1 mL of a given solvent (n-hexane, toluene, or gasoline). Then the vial containing the mixture was cooled to 25 °C. After 10 min the vial was inverted to enable us to observe the gelation effect.[3,8] Tables 1–5 show the gelation ability of fatty N-acylamino esters **1–5a–d** and N-acylamino acids **6–10a–d** in various hydrocarbons at 25 °C.

Structure–activity relationship

Tables 1–5 show that the ability to gelatinize organic solvents was highly influenced by the nature of the long chain. In addition, the substituent present in the amino acid moiety of some of the derivatives was an important factor (Fig. 3).

Almost all unsaturated and saturated fatty N-acylamino esters obtained were soluble in the solvents studied.

The N-acylamino acids with unsaturated chains derived from oleic and ricinoleic acids, C18:1 and C18:1(OH), respectively, were soluble in all solvents, except for **6c, d** derived from glycine, which were insoluble in hexane (Table 1). In addition, unsaturated N-

Table 1
Gelation ability of fatty N-acylamino esters **1a–d** and N-acylamino acids **6a–d** derived from glycine in various hydrocarbons at 25 °C

Compound	Structure[a]	Physical characteristics[b]		
		Toluene	Hexane	Gasoline
1a		S	S	S
1b		S	S	S
1c		S	S	S
1d		S	S	S
6a		S	I	P
6b		S	I	P
6c		S	I	S
6d		S	I	S

[a] A gelator of 1 wt % was used for all tests.
[b] S: soluble, I: insoluble, P: immediate precipitation.

Table 2
Gelation ability of fatty N-acylamino esters 2a–d and N-acylamino acids 7a–d derived from alanine in various hydrocarbons at 25 °C

Compound	Structure[a]	Physical characteristics[b]		
		Toluene	Hexane	Gasoline
2a		S	S	S
2b[7,10]		S	S	S
2c		S	S	S
2d		S	S	S
7a[8]		G	P	S
7b[1,8]		G	P	S
7c		S	S	S
7d		S	S	S

[a] A gelator of 1 wt % was used for all tests.
[b] G: good gel, S: soluble, P: immediate precipitation.

Table 3
Gelation ability of fatty N-acylamino esters 3a–d and N-acylamino acids 8a–d derived from valine in various hydrocarbons at 25 °C

Compound	Structure[a]	Physical characteristics[b]		
		Toluene	Hexane	Gasoline
3a[8]		S	S	S
3b		S	S	S
3c		S	S	S
3d		S	S	S
8a[8]		S	A	P
8b		S	A	P
8c		S	S	S
8d		S	S	S

[a] A gelator of 1 wt % was used for all tests.
[b] S: soluble, P: immediate precipitation, A: aggregation leading to gradual precipitation.

acylamino acid **10c** derived from serine showed gelation in n-hexane, and **10d** was insoluble in hexane, toluene, and gasoline (Table 5).

Most of the saturated fatty N-acylamino acids were soluble in toluene, but only saturated **7a, b** derived from alanine were able to form gels in this aromatic hydrocarbon (Table 2).[1,8] In addition, saturated fatty N-acylamino acid **9a** derived from phenylalanine showed gelation in n-hexane, but its respective homologous **9b** formed precipitate, unlike previous reports in the literature (Table 4).[8]

The experiments also demonstrated that the presence of different substituents near the carboxyl group plays a crucial role in the formation of gel. The bulkier isopropyl group, as in derivatives of L-valine **3a–d** and **8a–d**, prevented the formation of the effective intermolecular hydrogen bonds that are crucial for the formation of bilayers that make up the framework of hydrocarbon gelation (Table 3). However, the presence of methyl and benzyl groups near the carboxyl group was important for forming good gels (e.g., see **7a, b** in Table 2 and **9a** in Table 4). This behavior has been observed among N-dodecanoyl derivatives of amino acids.[3]

These observations of gelation underscore the importance of the presence of a stereogenic center in the segment derivative of the amino acid. This is implied by the fact that derivatives of glycine **1a–d** and **6a–d** (Table 1) do not possess chirality, as none of these derivatives were able to gel in the solvents studied.

In addition, the results demonstrate that the presence of a polar stereogenic center is crucial for the gelation of hydrocarbons. This polar stereogenic center establishes strong intermolecular interactions during the self-assembling of the gelators in the segment

derivative of the amino acid. This is implied by the fact that fatty N-acylamino esters **5a, b**, derivatives of L-serine[14] (Table 5), were able to form gels with hexane. In this case, the formation of the gel can be attributed to the presence of a hydroxyl group in the amino ester; the lipophilic saturated chain of the palmitic and stearic acids, C16:0 and C18:0, respectively; and the polarity of the solvent.

Moreover, unsaturated fatty N-acylamino acid **10c**, a derivative of serine and oleic acid also formed gel in hexane.[13] This observation confirms the importance of the hydroxyl group in the segment derivative of the amino acid in forming good gels (Table 5).

However, saturated fatty N-acylamino acids **10a, b** derived from serine were insoluble in hexane, unlike reports in the literature indicating that **10b** forms partial gels in hexane.[13] According to literature the L-serine amphiphiles have also been used to produce solid gels in CHCl₃, CH₂Cl₂ and also in CCl₄.[15]

Therefore, the balance between gelator structure, intermolecular interaction, and gelation properties are very important for forming good gels.

Figure 4a and b show gels obtained from hexane with **5a** and from toluene with **7a**, respectively.

IR spectroscopy

IR spectroscopy was carried out to understand the role of amino acid residue and fatty chains of **5a**, **b**, and **7a** in gelating non-polar

Table 4
Gelation ability of fatty N-acylamino esters **4a–d** and N-acylamino acids **9a–d** derived from phenylalanine in various hydrocarbons at 25 °C

Compound	Structure[a]	Physical characteristics[b]		
		Toluene	Hexane	Gasoline
4a[8]		S	S	S
4b[8]		S	S	S
4c		S	S	S
4d		S	S	S
9a[8]		S	G	A
9b[8]		S	P	P
9c		S	S	S
9d		S	S	S

[a] A gelator of 1 wt % was used for all tests.
[b] G: good gel, S: soluble, P: immediate precipitation, A: aggregation leading to gradual precipitation.

Table 5
Gelation ability of fatty N-acylamino esters **5a–d** and N-acylamino acids **10a–d** derived from serine in various hydrocarbons at 25 °C

| Compound	Structure[a]	Physical characteristics[b]		
		Toluene	Hexane	Gasoline
5a[14]		S	G	A
5b[14]		S	G	S
5c		S	S	S
5d		S	S	S
10a[14]		S	I	P
10b[13,14]		S	I	P
10c[13]		S	G	S
10d		I	I	I

[a] A gelator of 1 wt % was used for all tests.
[b] G: good gel, S: soluble, I: insoluble, P: immediate precipitation, A: aggregation leading to gradual precipitation.

organic solvents. Samples of **5a, b** gel produced in hexane and **7a** gel produced in toluene were dried under a vacuum, and the resulting solids were examined by IR spectroscopy as KBr pellets. The same compounds had previously been dissolved in 1 mL chloroform (in conditions in which they were not able to form gel) to observe the changes in absorption bands related to intermolecular interactions (Figs. 5 and 6).

In IR spectra of gels derived from fatty N-acylamino esters **5a, b,** amide N–H asymmetric stretching appeared at 3518 and 3520 cm^{-1} and the O–H of amino acid residue of methyl serinate at 3338 and 3340 cm^{-1}, respectively, showing a strong molecular

interaction. The ester carbonyl band showed at 1730 and 1732 cm^{-1}, respectively, and the amide carbonyl band showed at 1656 cm^{-1} for two structures. The IR spectra of N-acylamino esters **5a, b** solubilized in CHCl$_3$ revealed that the profile underwent great changes. Characteristic amide N–H bands showed up weaker at 3622 cm^{-1}, a region of higher energy. The O–H band of the side group of methyl serinate also appeared weaker at 3433 cm^{-1}, showing the weakening of the intermolecular hydrogen bonds. This proves the importance of intermolecular interactions of hydrogen bonds in the amino acid residue for the auto-organization of three-dimensional structures of these molecules (Fig. 7).
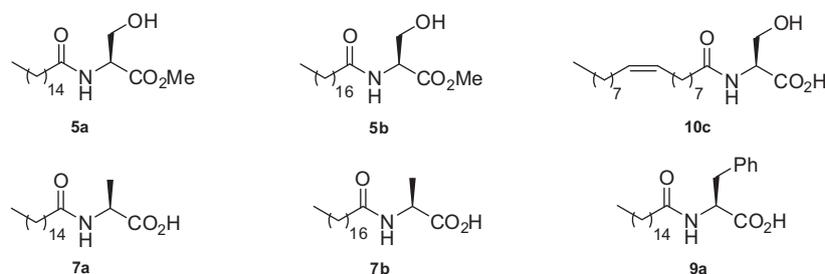
Figure 3. Molecular structures of fatty N-acyl organogels **5a, b, 9a, 7a, b,** and **10c**.
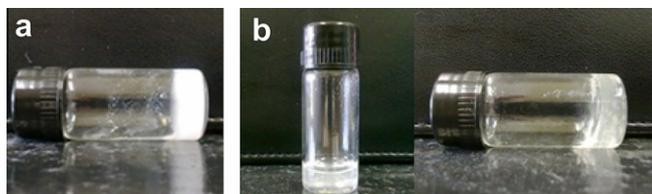
Figure 4. Gels obtained from various compositions: (a) hexane with 10 mg **5a**, (b) toluene with 10 mg **7a**.

IR spectra of the derivative gel of compound **7a** showed a strong interaction between the groups able to form hydrogen bonds, namely strong stretches of amide N–H at 3311 cm^{-1} and of car-

boxyl acid C=O at 1645 cm^{-1}. Moreover, an analysis of the IR spectra of compound **7a** in CHCl$_3$ showed different values of bands and signals: the amide N–H band showed a weak stretch at 3433 cm^{-1}, and the C=O stretch was absorbed at 1755 cm^{-1}. This behavior ensured the energy increase necessary for bond vibrations and could signal a decrease in intermolecular interactions due to the absence of carboxyl acid dimmers, as has been described for other fatty N-acylamino acid derivatives of L-alanine.[1,8]

Thermotropic behavior of the organogels

Properties of the gels were investigated using DSC. The transition temperatures and enthalpics of compounds **5a**, **b**, **9a**, **7a**, **b**, and **10c** are summarized in Table 6 and Figure 8. The gel-to-sol
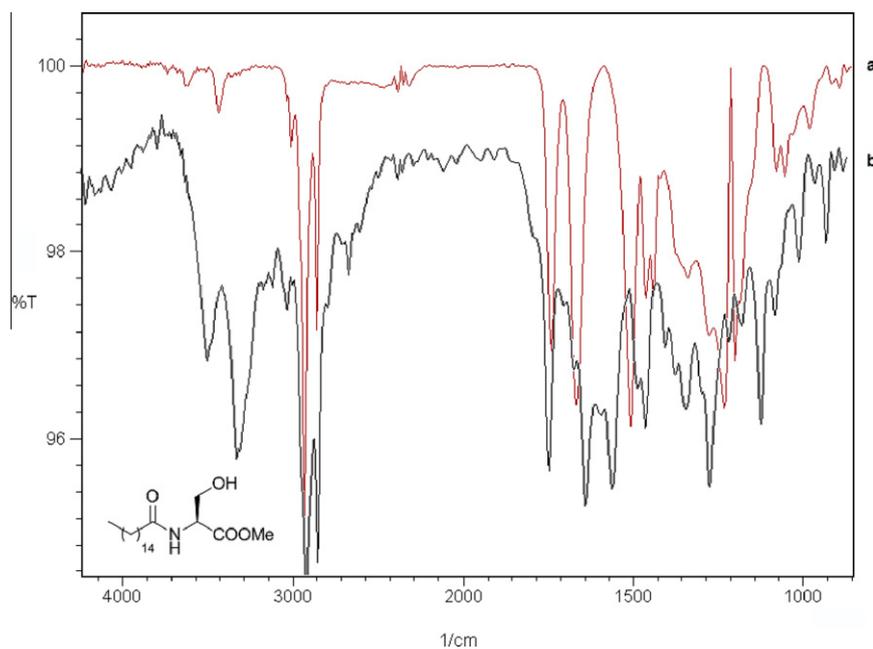
Figure 5. Infrared spectra I: (a) compound **5a** in CHCl$_3$, (b) compound **5a** in gel form.
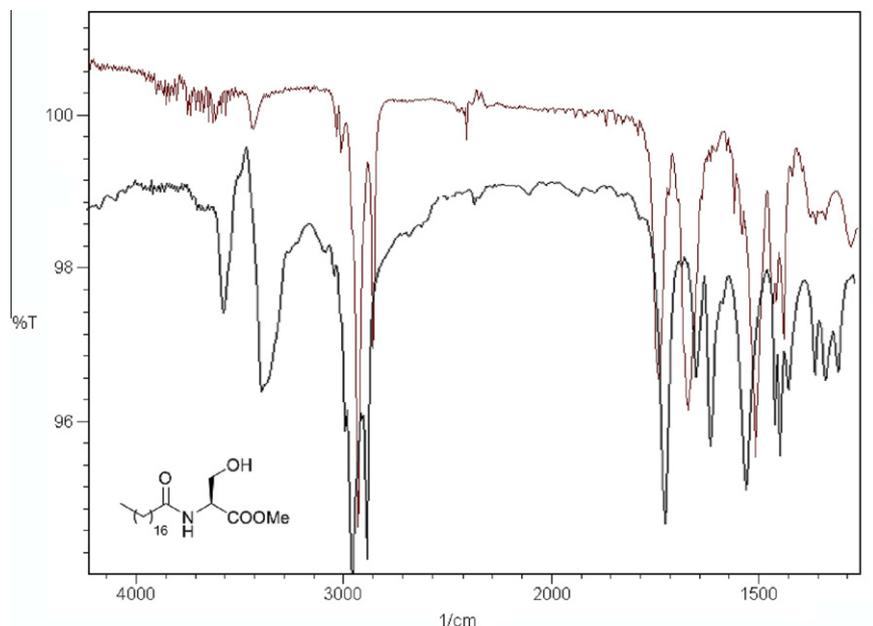
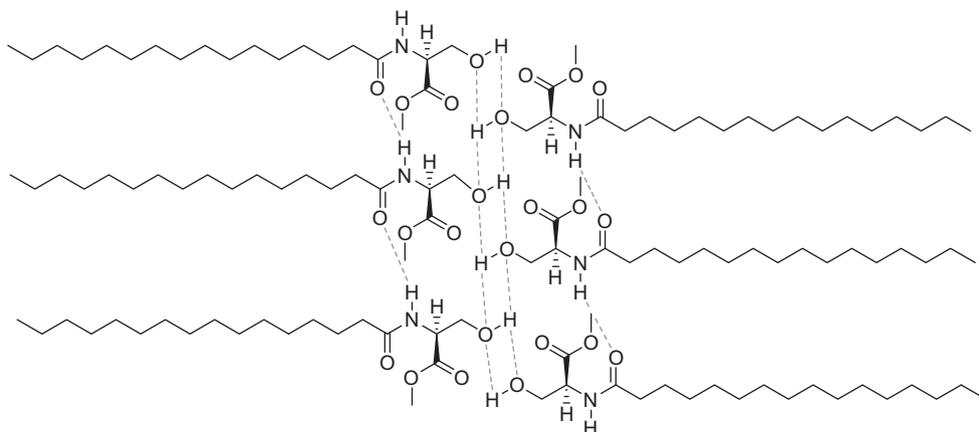**Figure 6.** Infrared spectra II: (c) compound **5b** in CHCl$_3$, (d) compound **5b** in gel form.

Figure 7. Physical gelation of hexane by fatty *N*-acylamino ester **5a** derivatives of L-serine.

Table 6
Thermotropic behavior of the organogels as measured by differential scanning calorimetry

Entry	Solvent	Compound	Heating T_{g-s} (°C)[a]	Freezing T_{s-g} (°C)[b]	ΔH^{g-s} (mcal)[c]	ΔH^{s-g} (mcal)[d]
1	Hexane	**5a**	59.82	53.86	8.37	7.35
2		**5b**	65.49	58.37	18.46	20.79
3	Toluene	**9a**	54.37	36.30	1.83	0.36
4		**7a**	57.10	40.52	8.66	9.35

[a] T_{g-s}: gel-to-sol temperature.
[b] T_{s-g}: sol-to-gel temperature.
[c] ΔH^{g-s}: gel-to-sol enthalpy variation.
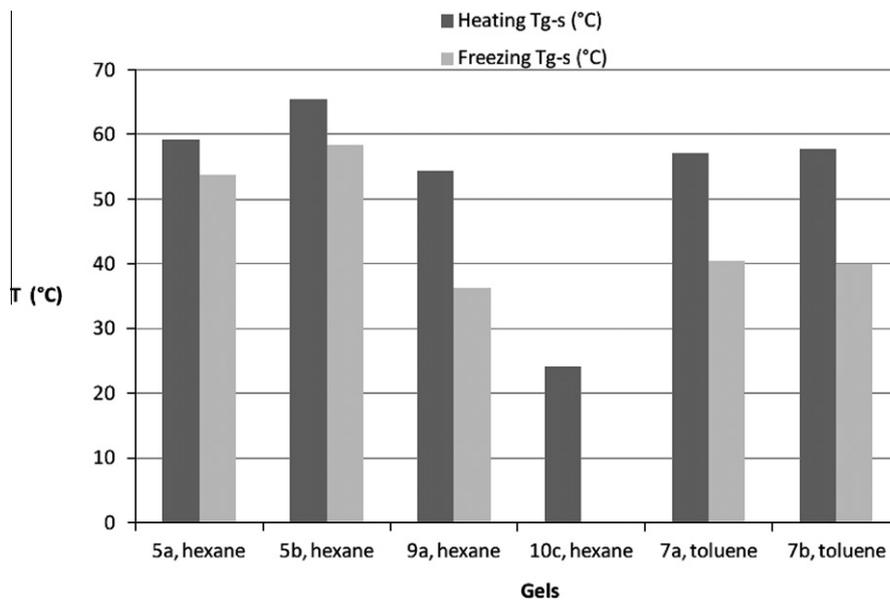[d] ΔH^{s-g}: sol-to-gel enthalpy variation.

Figure 8. Gel-to-sol (T_{g-s}) and sol-to-gel (T_{s-g}) variation for gels of compounds **5a**, **b**, **9a**, **7a**, **b**, and **10c**.

(T_{g-s}) melting temperatures of compounds **5a**, **b**, **9a**, **7a**, **b**, and **10c** were higher than the freezing temperatures for the sol-to-gel (T_{s-g}) transition (Fig. 8, Table 6). Furthermore, in the DSC thermograms the peaks for T_{g-s} transitions were less pronounced than those for T_{s-g}. Figure 9 shows the DSC thermogram for compound **5b**.

For organogels **5a**, **b**, the T_{g-s} and T_{s-g} temperatures increased with an increase in the fatty chain, and the same characteristics were observed for the gel-to-sol enthalpy variation (ΔH^{g-s}) and sol-to-gel enthalpy variation (ΔH^{s-g}; Table 6, entries 1 and 2).

The large peaks of T_{g-s} transition observed in the DSC curves for heating for compounds **5a** (Fig. 9) and **5b** may be associated with the higher energy required to phase change, according to values obtained for ΔH^{g-s}. For gelator **5b** the enthalpy in hexane was greater than for **5a** because of an increase in carbon atoms in the lipophilic chain. The increase in carbon atoms favored the self-assembling of the gelator and the apolar solvent hexane. This result confirms that lipophilic characteristics play an important function in the stabilization of the gel.
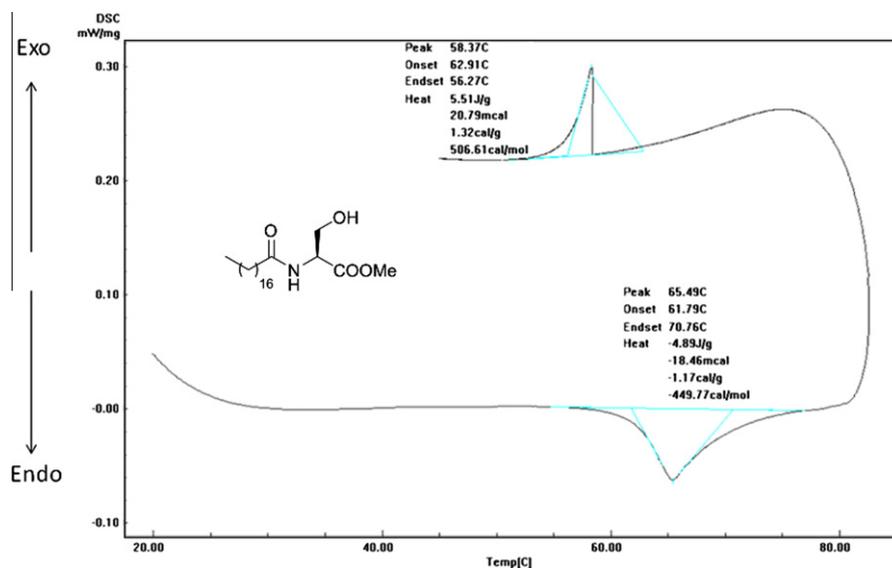
Figure 9. Thermogram for the gel-derived hexane of *N*-octadecenoyl methyl serinate (**5b**). DSC, differential scanning calorimetry.

The transition temperatures of organogels of hexane and *N*-acylamino acid derivatives of serine **10c** were not detected because of the lower thermal stability of the material formed (due to the *cis* configuration of the double bond) and the nature of the head polar group, which was not appropriate for the gelation of apolar solvents.

Conclusion

This study reports the synthesis of new fatty *N*-acylamino acids and *N*-acylamino esters from renewable fatty acids with saturated and unsaturated chains and amino acids. The gelation properties of 40 compounds were evaluated using *n*-hexane, toluene, and gasoline (a complex mixture of hydrocarbons) as organic solvents. The formation of gel was attributed to the presence of a hydroxyl group in the amino acid serine, and the lipophilic saturated chain of the palmitic and stearic acids, C16:0 and C18:0, respectively. In addition, the fatty *N*-acylamino acid derivative of serine and oleic acid, although it had an unsaturated side chain, formed gel in hexane. These observations confirm the importance of the hydroxyl group in the segment derivative of the amino acid in forming good gels. Finally, the results reveal that these derived gels can be synthesized very easily from naturally occurring sources (e.g., fatty acids and amino acid—common substrates in the chemical industry), making these low-molecular-weight gelators excellent materials for use in various applications.

Acknowledgments

Supplementary data

Supplementary data (detailed experimental procedures, characterization data, ^{1}H NMR spectra, and DSC thermograms of compounds **5a**, **b**, **7a**, **b**, and **9a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.015.

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