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# Development of furan-2,5-dicarboxylic acid (FDCA)-based organogelators

Dorian Rabaud,<sup>a</sup> Paul Dussart,<sup>a</sup> Guylaine Ducouret,<sup>b</sup> Pierre-Antoine Albouy,<sup>c</sup> Jérémy Forté,<sup>a</sup> Benjamin Isare,<sup>\*a</sup> and Laurent Bouteiller,<sup>\*a</sup>

Organogels are used in a wide range of applications for which the development of new bio-based organogelators is highly desirable. While furan-2,5-dicarboxylic acid (FDCA) is a promising molecule for the synthesis of bio-based polyesters, it has never been used in the context of organogels. This study explores the possibility to design FDCA-based organogelators that self-assemble into fibrillar networks stabilized by hydrogen bonding. Gelation tests show the versatility of this gelator family with a wide variety of gelled liquids, especially apolar liquids. The structure of the gels was investigated by FTIR and CD spectroscopies, cristallography, powder X-ray diffraction and rheology.

## Introduction

With the increasing demand over the last decades to replace products from the petrochemical industry, the use of more sustainable processes as well as the production of new molecules from biomass has become one of the most important topics in chemical research worldwide. In 2004, the US Department of Energy (DOE) listed 12 molecules having the potential to replace petrochemical building blocks.<sup>[1]</sup> Amongst them, furan-2,5-dicarboxylic acid (FDCA) has been identified as a key bio-based platform because of its potential as a source of a wide variety of chemicals and materials. For the past decade, the studies involving FDCA have mainly been concentrated on two topics: the improvement of its production<sup>[2]</sup> and its use in the synthesis of bio-based polymers<sup>[3–7]</sup>, notably the replacement of terephthalic acid (TPA). FDCA is composed of a furan ring with two carboxylic acid groups, which can be chemically modified to form numerous materials. Furanic–aliphatic polyesters are one of the most studied furan polymer families,<sup>[3]</sup> with poly(ethylene 2,5-furandicarboxylate) (PEF) being a possible substitute for poly(ethylene terephthalate) (PET).<sup>[8]</sup> Some FDCA-based molecules such as 2,5-diamidofurans have also been exploited in the context of supramolecular chemistry for their ability to form hydrogen bonds.<sup>[9–11]</sup> In particular, Camiolo et al. have demonstrated the possibility to form extended chains of hydrogen bonds in the crystal state (Figure 1).<sup>[9]</sup> Such linear chains of hydrogen bonds are particularly useful in the context of Low Molecular Weight Gelators (LMWGs). These gelators are small organic molecules that self-assemble into anisotropic structures, mostly fibers which entangle and form a network, thus turning a liquid into a gel.<sup>[12–16]</sup> The presence of such strong directional interaction is a desirable feature to design an organogelator because it favors the formation of highly anisotropic fibers.<sup>[17]</sup>

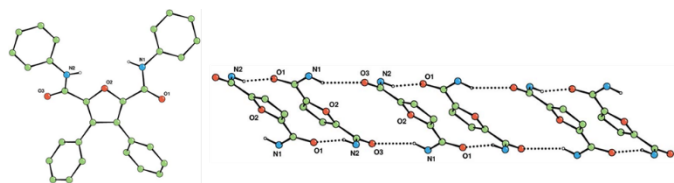


Figure 1. Left) X-ray crystal structure of 3,4-diphenylfuran-2,5-dicarboxylic acid bis-*N*-phenylamide (acetonitrile and certain hydrogen atoms omitted for clarity); Right) Hydrogen bond chains formed along *a*-axis (certain atoms have been omitted for clarity). Reproduced with permission from Ref. [9]

Only few bio-sourced organogelators are on the market, the best-known being (1,3:2,4) dibenzylidene sorbitol (DBS) and 12-

hydroxystearic acid (12-HSA).<sup>[18,19]</sup> Therefore, in this study, we decided to investigate FDCA as platform to synthesize new bio-based organogelators. Their gelling properties were tested in a range of liquids with different polarities.

## Experimental

### Materials

All chemicals, reagents and solvents were of analytical grade, purchased from Sigma-Aldrich, Fluorochem, Alfa Aesar or Acros Organics and unless stated otherwise used without further purification. Deionized water was used for preparing aqueous solutions.

### Characterization

**<sup>1</sup>H and <sup>13</sup>C NMR.** <sup>1</sup>H and <sup>13</sup>C spectra were recorded on a Bruker Avance 400 or 300 spectrometer. DMSO-*D*<sub>6</sub> (99.80% D, Eurisotop) and CD<sub>2</sub>Cl<sub>2</sub> (99.80% D, Eurisotop) were used as solvents. Calibration was done using the chemical shift of the solvent residual resonance.

**FTIR spectroscopy.** Fourier-Transform Infrared (FTIR) measurements of solutions were performed on a Nicolet iS10 spectrometer. Spectra were measured in a CaF<sub>2</sub> cell of various pathlength (0.5, 1 or 2 mm according to the concentration) and were corrected for air, solvent and cell absorption. The Attenuated Total Reflectance (ATR) FTIR spectra of the bulk samples were recorded on a Perkin Elmer Spectrum Two spectrometer equipped with a single bounce diamond crystal and a LiTaO<sub>3</sub> detector. The FTIR spectra of samples were acquired in the MIR range of 400–4000 cm<sup>-1</sup> with a resolution of 4 cm<sup>-1</sup>. Each spectrum was collected from 50 scans in the absorbance mode.

**Gelation tests.** Gelation was tested by introducing the desired amount of gelator and 1 mL of liquid in a screw-cap vial, heating until dissolution (if possible) and leaving the vial to cool on the bench. If the gelator solubilized at high temperature and reprecipitated at room temperature, it was reported as precipitate. If the gelator remained insoluble at high temperature, it was reported as insoluble.

**Circular Dichroism spectroscopy.** Circular dichroism (CD) measurements were performed on a Jasco J-1500 spectrometer equipped with a Peltier thermostated cell holder and Xe laser. Data were recorded with the following parameters: 50 nm.min<sup>-1</sup> sweep rate, 0.05 nm data pitch, 2 nm bandwidth, and between 400 and 200 nm. Spectra were corrected for air, solvent, and cell contribution at the same temperature. Molar CD values are reported in L.mol<sup>-1</sup>.cm<sup>-1</sup> and expressed as follows:  $\Delta\epsilon = \theta / (32980 \times l \times c)$  where  $\theta$  is the

measured ellipticity in mdeg,  $l$  is the optical pathlength in cm, and  $c$  is the concentration in mol.L<sup>-1</sup>.

**Viscometry.** An automated micro viscosimeter AMVn Anton Paar equipped with a capillary tube of diameter 1.6mm with a 1.5mm diameter steel ball was used for viscometry measurements. The falling time of the ball inside the capillary tube filled with the studied solution was measured at a 50° angle of inclination of the tube. The ratio between the falling time of the ball in the solution versus falling time of the ball in the solvent (i.e., relative viscosity) was plotted versus temperature (every 5°C between 25 and 80°C).

**Rheology. Preparation of the sample:** In order to erase its thermo-mechanical history, the solution was stirred on a heating plate at 110°C for 15 minutes to make it fluid. Then the solution was poured on the rheometer plate at 25°C. The cone was gently lowered down to a distance from the plate equal to 100 microns, then the sample that flowed out of the geometry was pulled out. The gap was then fixed at 54 microns (corresponding to the measurement distance between the cone and plate). The sample was then kept at 25°C for 2 hours to allow the gel to stabilize before performing the measurements. The rheological measurements were carried out at 25°C. Viscoelastic moduli  $G'$  and  $G''$  and yield stress were measured on a stress-controlled rheometer TA Instruments DHR 3 equipped with a sanded stainless-steel cone-plane geometry (diameter: 40 mm, gap: 54  $\mu$ m,  $\alpha$ : 2°). First, an oscillating strain sweep was performed at 1 Hz to determine the viscoelastic linear plateau. The measurement was stopped before reaching the maximum strain corresponding to the end of the linear regime, in order to preserve the sample. Then, a frequency sweep was performed covering a pulsation ( $\omega$ ) range from 0.1 to 100 rad/s in the linear viscoelastic regime, the set strain value depended on the concentration of the sample. Finally, the sample was subjected to a total oscillating strain sweep over the linear and non-linear domain until 1000% strain to evaluate the yield stress. Measurements were repeated on several samples to check the reproducibility.

**X-Ray crystal structure determination.** A suitable crystal was selected, mounted onto a cryoloop and transferred into a cold nitrogen gas stream. Intensity data were collected with a Bruker Kappa APEX-II CCD diffractometer using a micro-focused Cu-K $\alpha$  radiation ( $\lambda$  = 1.54178 Å). Data collection was performed at 200K with the Bruker APEXIII suite. Unit-cell parameters determination, integration and data reduction were carried out with SAINT program. SADABS was used for scaling and absorption corrections. The structure was solved with SHELXT<sup>[20]</sup> and refined by full-matrix least-squares methods with SHELXL<sup>[21]</sup> using Olex2 software package<sup>[22]</sup>. All non-hydrogen atoms were refined anisotropically. This structure was deposited at the Cambridge Crystallographic Data Centre with number CCDC 2221526 and can be obtained free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).

**Wide Angle X-Ray Scattering (WAXS).** Gel samples were first formed, then the solvent was evaporated in order to obtain dry fibers. The two-dimensional wide-angle X-ray scattering (WAXS) patterns were collected on a MAR345 detector using Cu-K  $\alpha$  radiation (wavelength: 1.542 Å) of a rotating anode X-ray source (40 kV, 40 mA; multilayer graded monochromator). Exposure time was 1200s.

**High Resolution Mass Spectrometry (HRMS).** Exact mass measurements (HRMS) were obtained on TQ R30-10 HRMS spectrometer by ESI+ ionization and are reported in  $m/z$  for the major signal.

**Differential Scanning Calorimetry (DSC).** The analyses were carried out using a Q2000 instrument (TA Instruments). The samples (about 5-10 mg) were introduced in sealed aluminum capsules. Two heating and cooling cycles were performed at a rate of 10°C.min<sup>-1</sup>. The first cycle was performed to remove the thermal history of the material. An isotherm of 2 min was maintained at the end of each heating and cooling step. The crystallization and melting temperatures were measured during the second cycle.

#### Synthetic procedures

##### Synthesis of diethyl furan-2,5-dicarboxylate (1)

Diethyl furan-2,5-dicarboxylate was synthesized according to Ravasco et al.<sup>[23]</sup>

##### Synthesis of alkyl and aromatic diamides (2)

To a 1M solution of **1** (50 mg, 236  $\mu$ mol) in anhydrous THF (236  $\mu$ L) was added the amine (46  $\mu$ L, 468  $\mu$ mol, 2 equiv.) followed by CAL B (10 mg) and the mixture was stirred under reflux for 24h. The solvent was evaporated and the crude product was purified by column chromatography on silica gel, eluting with hexane/EtOAc 90:10 – 50:50 gradient. For **2e**, the concentration of the reaction was 0.5M instead of 1M.

##### Synthesis of ester ammonium salts (3-6)

Procedure for compounds **3a**, **4a**, **5a** and **6a**: To a solution of amino acid (1 eq) in ethanol (20 mL), 1.2 eq of thionyl chloride was added under stirring. The reaction was put under argon atmosphere and refluxed overnight. The solvent was removed under reduced pressure and the white solid was dried under vacuum. Procedure for compound **3c**: In a Dean-Stark apparatus-mounted flask, 1 eq of amino acid, 1.1 eq of alcohol and 1.1 eq of PTSA.H<sub>2</sub>O were added to toluene (0.1M) and the mixture was stirred under reflux overnight. The solvent was evaporated under vacuum, the crude solid was redissolved in DCM and washed with NaOH 5% (3x30 mL) and HCl 5% (30 mL). The organic phase was evaporated under reduced pressure and the crude product was purified by sublimation to obtain white crystals. Procedure for **all other compounds**: In a Dean-Stark apparatus-mounted flask, 1 eq of amino acid, 1.1 eq of alcohol and 1.1 eq of PTSA.H<sub>2</sub>O were added to toluene (0.1M) and the mixture was stirred under reflux overnight. The mixture was then concentrated under reduced pressure and diluted in Et<sub>2</sub>O. The solution was gently heated to 35°C, and let cool in an ice bath to precipitate for a couple of hours. Then, the precipitate was filtered, washed with cold Et<sub>2</sub>O and dried under vacuum.

##### Synthesis of furan-2,5-dicarbonyl dichloride (FDCCI) (7)

To a solution of FDCA (500 mg) in thionyl chloride (10 mL), 3 drops of DMF was added under stirring. The reaction was put under argon atmosphere and refluxed for 3h. The excess thionyl chloride was removed under reduced pressure and the white solid was dried under vacuum (99%).

##### Synthesis of di(amido-esters) (8-11)

In a flame-dried round-bottom flask under argon atmosphere, FDCCI (100 mg, 0.52 mmol, 1 eq) was dissolved in dry DCM (20 mL)

at room temperature. The ammonium salt (1.56 mmol, 3 eq) was then added in one portion, and the resulting mixture was cooled to 0°C with an ice/water bath. NEt<sub>3</sub> (0.52 mL, 3.64 mmol, 7 eq) was then added dropwise, the reaction was let warm to room temperature and stirred for 48h. Brine was then added to the flask, and the crude mixture was extracted twice with DCM. The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The resulting solid was then purified by column chromatography on silica gel, eluting with hexane/EtOAc 90:10 – 50:50 gradient.

#### Synthesis of amino-amides (12-15)

**First step:** Synthesis of *N*-(tert-butoxycarbonyl)-*L*-amino acid: An *L*-amino acid (23 mmol, 1 eq) was dissolved in dioxane/water (2:1, 50 mL), which was made alkaline with NaOH (1 M, 23 mL) and cooled in an ice-bath. Then, (Boc)<sub>2</sub>O (1.3 eq) and NaHCO<sub>3</sub> (1 eq) were added. The reaction mixture was stirred overnight at room temperature and was then evaporated to half of the original volume. The residue was diluted with EtOAc (40 mL), cooled in an ice-bath and acidified to pH = 2.5-3 with HCl (1 M). The layers were separated and the aqueous fraction was extracted with EtOAc (2x30 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. **Second step:** Amidation of *N*-(tert-butoxycarbonyl)-*L*-amino acid: The alkyl amine (7.53 mmol) was added to the boc-protected amino acid (7.53 mmol) predissolved in dried DCM (20 mL). The mixture was cooled in an ice-bath followed by successive addition of EDC.HCl (1.44 g, 7.53 mmol), HOBT (1.98 g, 7.53 mmol) and DMAP (0.092 g, 0.75 mmol). After the solution was stirred at room temperature overnight, it was washed with acetic acid (10%, 10 mL), water, aq. NaHCO<sub>3</sub> and again with water, dried over MgSO<sub>4</sub> and evaporated, leaving a product as a colorless oil that was further purified by column chromatography on silica gel (CHCl<sub>3</sub>/MeOH = 99:1). **Third step:** Deprotection of *N*-(tert-butoxycarbonyl)-*L*-amino amide: In a 100 mL round-bottom flask, a boc-protected amino amide (3.37 mmol, 1 eq) was solubilized with a mixture of TFA and DCM (1:1, 20 mL). The mixture was stirred for 30 minutes at room temperature. The solvent was then evaporated under reduced pressure and the crude liquid was diluted with 6M NaOH (10 mL) and extracted with DCM (15 mL). The organic layer was washed with water (2x20 mL), brine (20 mL), dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure.

#### Synthesis of di(amido-amides) (16-19)

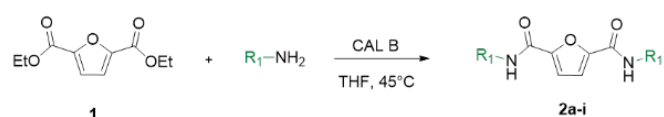
In a flame-dried round-bottom flask under argon atmosphere, FDCDCI (100 mg, 0.52 mmol, 1 eq) was dissolved in dry dichloromethane (10 mL) at room temperature. The amino-amide (1.14 mmol, 2.2 eq) was then added in one portion, and the resulting mixture was cooled to 0°C with an ice/water bath. NEt<sub>3</sub> (0.37 mL, 2.6 mmol, 5 eq) was then added dropwise, the reaction was let warm to For the latter molecule, the low yield is probably due to steric hindrance. Gelation tests were performed in a range of liquids with different polarities, even if the main goal was to gel apolar liquids such as vegetable oils or *n*-hexadecane. As displayed in Table S1, no gel was obtained and most diamides remained insoluble or precipitated in apolar liquids. In order to increase the solubility of the molecules while retaining the amide functions for self-assembly,

room temperature and stirred for 48h. Brine (30 mL) was then added to the flask, and the crude mixture was extracted twice with DCM (30 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure to give a yellow mixture. Acetonitrile was then added to the crude product and a white precipitate appeared. The solid was filtered, washed three times with acetonitrile and dried under vacuum.

## Results

### Diamides and di(amido-esters)

First, a range of diamide molecules have been synthesized from FDCA ester **1** and alkyl or aromatic amines (Scheme 1). The method used in this section has been adapted from Ravasco et al.<sup>[23]</sup>, and the resulting molecules are shown on Chart 1. The yields obtained range from good to very good, except for **2e** and **2g**. The former was synthesized with a more dilute concentration which led to the synthesis of both the monoamide and the diamide.



Scheme 1. Synthesis of alkyl and aromatic diamide

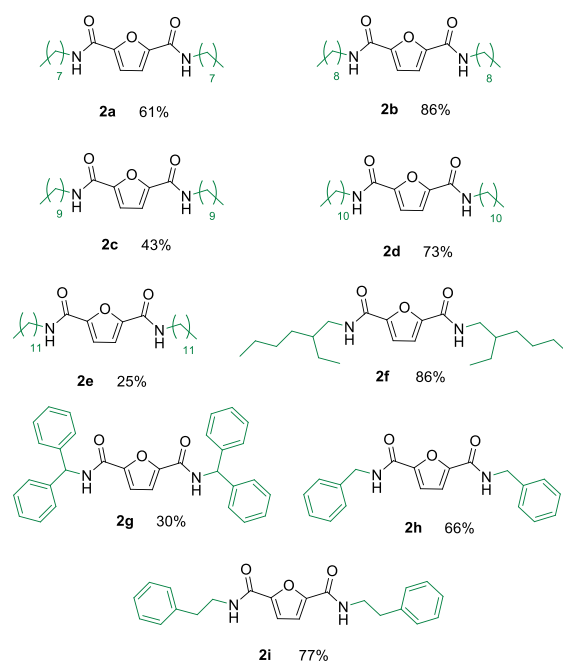
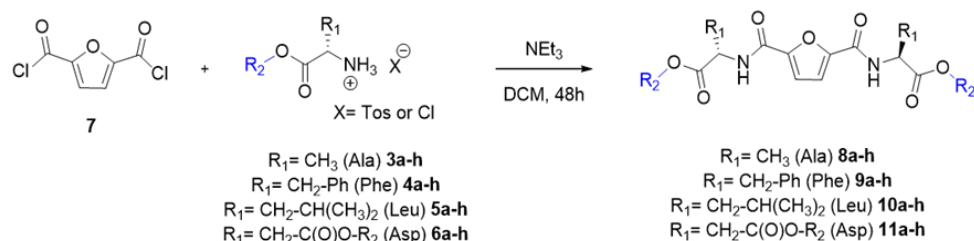


Chart 1. Alkyl and aromatic diamides synthesized

amines were replaced by esterified amino acids (Scheme 2). Amino-acids are widely used in the design of organogelators.<sup>[24,25]</sup> The synthesis of these di(amido-esters) has been performed in two-steps. The first consisted in the esterification of the carboxylic acid group of an amino acid by an alcohol. The corresponding ammonium salt (chloride or tosylate salt) was reacted in a second step with furan-2,5-dicarbonyl dichloride (FDCDCI) to obtain a di(amido-ester) with

the desired alkyl chain. Four amino acids have been selected: alanine (Ala), phenylalanine (Phe), leucine (Leu) and aspartic acid (Asp) to tune weak intermolecular interactions and solubility. The yields are quite good going from 47% to 90% (Table 1). All of the molecules have been characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR (chemical shifts in the supporting information) and gelation tests have been carried out (Table S2). The results show that the insertion of amino ester units indeed improve the solubility of the molecules in apolar liquids.



Scheme 2. Synthesis of di(amido-esters)

Table 1. Yields of the reaction between compound 7 and ester ammonium salts

R <sub>2</sub>	(S)-Ala		(S)-Phe		(S)-Leu		(S)-Asp	
	Entry	Yield	Entry	Yield	Entry	Yield	Entry	Yield
Ethyl (C2)	<b>8a</b>	84%	<b>9a</b>	62%	<b>10a</b>	85%	<b>11a</b>	82%
Hexyl (C6)	ns		<b>9b</b>	81%	ns		<b>11b</b>	86%
Octyl (C8)	<b>8c</b>	84%	<b>9c</b>	80%	<b>10c</b>	89%	ns	
Dodecyl (C12)	<b>8d</b>	75%	<b>9d</b>	77%	<b>10d</b>	88%	<b>11d</b>	75%
Tridecyl (C13)	<b>8e</b>	80%	<b>9e</b>	78%	<b>10e</b>	73%	<b>11e</b>	74%
Pentadecyl (C15)	<b>8f</b>	63%	<b>9f</b>	65%	<b>10f</b>	65%	ns	
Hexadecyl (C16)	<b>8g</b>	71%	<b>9g</b>	70%	<b>10g</b>	88%	<b>11g</b>	47%
Octadecyl (C18)	<b>8h</b>	88%	<b>9h</b>	90%	<b>10h</b>	77%	<b>11h</b>	64%

ns: not synthesized

Unfortunately, none of the synthesized molecules have formed a gel or even a viscous solution in any liquid. In almost all cases, solutions have been obtained which indicates that intermolecular interactions are not strong enough to trigger self-assembly and form a gel. In order to promote the assembly, the number of hydrogen bonding groups has been increased by replacing the ester functions by amide functions.

### Di(amido-amides)

The synthesis of the di(amido-amides) involved a longer synthesis than for the di(amido-esters) because of the necessity for the protection and deprotection of the amine function of the amino acid. First step is the protection of the amine, followed by the reaction between an alkyl amine and the carboxylic acid of the protected amino acid. The third step is the deprotection of the boc-protected amino-amide. Finally, the last step is similar to that of the di(amido-esters), i.e., reacting FDCDCI with the synthesized amino-amide to

obtain the di(amido-amides) (Scheme 3). Yields at this stage have been highly variable (Table 2). These results can be explained by the small quantities involved and the possible hydrolysis of FDCDCI during the reaction. For the aspartic acid-based molecules, the fact that hexaamides instead of tetraamides have been synthesized increased the difficulty to purify them. The products have been characterized by NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) in order to ensure their purity, and to verify that epimers have not been formed.



Scheme 3. Synthesis of di(amido-amides)

Table 2. Results of the reaction between compound 7 and amino-amides

R <sub>2</sub>	(S)-Ala		(S)-Phe		(S)-Leu		(S)-Asp	
	Entry	Yield	Entry	Yield	Entry	Yield	Entry	Yield
Hexyl (C6)	<b>16a</b>	80%	<b>17a</b>	37%	<b>18a</b>	52%	<b>19a</b>	27%
2-ethylhexyl (2-EH)	ns		<b>17b</b>	21%	<b>18b</b>	46%	<b>19b</b>	18%
Decyl (C10)	ns		ns		<b>18c</b>	36%	ns	
Dodecyl (C12)	<b>16d</b>	17%	<b>17d</b>	39%	<b>18d</b>	57%	ns	
Tetradecyl (C14)	ns		ns		<b>18e</b>	46%	ns	
Octadecyl (C18)	ns		<b>17f</b>	61%	<b>18f</b>	67%	ns	

ns: not synthesized

Then, gelation tests have been carried out (Table 3). In contrast to diamides and di(amido-esters), di(amido-amides) displayed an interesting gelling behavior. Indeed, several molecules based on phenylalanine, leucine or aspartic acid form gels or viscous solutions in apolar liquids. In general, the C6 alkyl chain is too short, which means that the molecules remain insoluble in apolar solvents. Except for alanine, increasing the length of the chain improved the solubility of the compound when heated, which led to the formation of gels (2-EH for Asp, C10 for Leu and C18 for Phe). On the other hand, too long alkyl chains unbalance the polarity of the molecules and reduce their ability to self-assemble. This chain length effect reveals the required balance between strong inter-gelator interactions (hydrogen bonds

from the amide functions) and solubilization from the alkyl chains.<sup>[17]</sup> Besides the influence of the length of the alkyl chain which is a key factor in tuning the solubility of the molecules in organic solvents, the lateral chain of the amino acids also has to be taken into account. When comparing the molecules with dodecyl chain, **16d** (alanine) does not show results indicating supramolecular assembly, **17d** (phenylalanine) increases the viscosity of some liquids and **18d** (leucine) displays promising gelling properties. The compound **18d** seems to be the most promising as it formed gels in all the apolar liquids of the list. It should also be noted that with the range of molecules synthesized, any liquid of the list can be gelled, which shows the versatility of this gelator family.

Table 3. Gelation tests of di(amido-amides) at 1wt%<sup>a</sup>

Compounds	propylene carbonate	diacetone alcohol	benzyl acetate	1,4-dioxane	m-xylene	R(+)-limonene	rapeseed oil	cyclohexane	n-hexadecane	methyl-cyclohexane	petroleum ether
<b>16a</b>	I	I	I	I	I	I	I	/	I	I	/
<b>16d</b>	I	I	I	I	I	I	I	/	I	I	/
<b>17a</b>	I	I	I	I	I	I	I	/	I	I	/
<b>17b</b>	I	I	I	I	I	I	I	/	I	I	/
<b>17d</b>	I	P	I	P	V	V	I	/	I	V	/
<b>17f</b>	I	S	V	S	S	S	I	G	I	V	I
<b>18a</b>	P	S	S	S	P	I	I	I	I	I	I
<b>18b</b>	P	S	S	S	P	S	I	/	I	/	/
<b>18c</b>	G	S	V	S	V	S	G	G	V	G	I
<b>18d</b>	V	S	G	S	V	S	G	G	G	G	G
<b>18e</b>	OG	P	G	P	V	S	V	P	G	P	I
<b>18f</b>	P	P	V	P	V	S	V	P	G	P	I
<b>19a</b>	OG	G	OG	G	S	S	I	I	I	I	I
<b>19b</b>	I	S	P	S	G	G	G	G	I	PG	I

<sup>a</sup> G: gel; OG: opaque gel; PG: partial gel; V: viscous; P: precipitate; S: soluble; I: insoluble; /: not tested

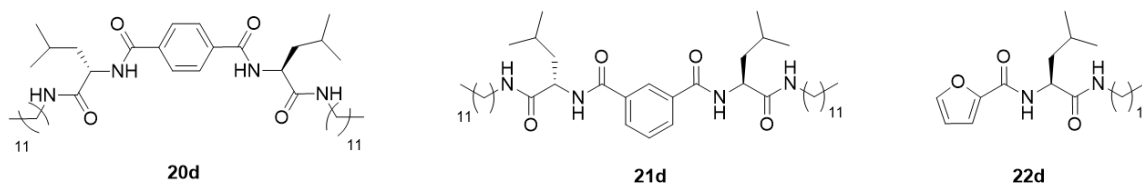


Chart 2. Synthesized analogues of di(amido-amide) **18d**

Table 4. Gelation properties of di(amido-amide) **18d** and the synthesized analogues at 1wt%<sup>a</sup>

Compounds	propylene carbonate	diacetone alcohol	benzyl acetate	1,4-dioxane	<i>m</i> -xylene	<i>R</i> (+)-limonene	rapeseed oil	cyclohexane	<i>n</i> -hexadecane	methyl-cyclohexane	petroleum ether
<b>20d</b>	I	G	S	P	S	S	I	I	I	I	I
<b>21d</b>	I	S	S	S	S	S	I	V	I	S	V
<b>22d</b>	S	S	S	S	S	S	S	S	S	S	S
<b>18d</b>	V	S	G	S	V	S	G	G	G	G	G

<sup>a</sup> G: gel; V: viscous; P: precipitate; S: soluble; I: insoluble

### Specificity of the furan group in the gel formation

After understanding the effect of the amino acid and alkyl chain length, we investigated the impact of the furanic cycle on the supramolecular self-assembly. Therefore, three analogues of compound **18d** have been synthesized by varying the core of the molecule (Chart 2). Terephthalic and isophthalic acids were selected as the closest possible analogues to reveal if any particular behavior can be attributed to the furanic cycle. Furoic acid was chosen as the final analogue to determine whether disubstitution of the furanic cycle is necessary to obtain gelation. The synthesis as well as the gelation tests were carried out according to the same procedures as for the di(amido-amides). On Table 4, the results of the gelation tests of the analogues have been compared. First of all, compound **22d** did not display any gelling properties. This could be explained by the number of hydrogen bond donor/acceptor groups which is twice lower than for gelator **18d**. In apolar solvents, compound **20d** based on terephthalic acid remained mostly insoluble probably because its straight conformation stabilizes too much the crystal state. With compound **21d** based on isophthalic acid, the solubility is improved, possibly due to its bent chemical structure. For example, poly(butylene isophthalate) (PBI) is known to exhibit less stable crystals than poly(butylene terephthalate).<sup>[26]</sup> However, in contrast to furan-based **18d**, this improved solubility results only in the formation of a few viscous solutions, but no gels. Therefore, among these analogues, the furanic core brings the best balance between solubility and supramolecular interactions.

### Supramolecular assembly characterization

Among the range of gelators described above, **18d** was selected to probe the gel properties and the self-assembly mechanism by complementary techniques and over a large range of concentrations, going from the gel state to the monomeric state.

### Rheology

The viscoelastic properties of the gels have been quantified by rheology, at different concentrations (0.8 to 2wt%) in a vegetable oil (rapeseed oil). The storage ( $G'$ ) and loss ( $G''$ ) moduli in the linear domain at each concentration are shown on Figure 2 left. At concentrations above 1wt% an elastic behavior is observed with  $G' > G''$  over the whole frequency range, while at 0.8wt%, a viscoelastic solution is obtained ( $G'' > G'$  at high frequency). The critical gel concentration is therefore close to 1wt%. As expected, both moduli increase with the concentration of the solutions. Then, a total oscillating strain sweep has been performed (Figure 2 right) in order to evaluate the yield stress which slightly increased from 1.2 Pa at 1wt% to 4.5 Pa at 2wt% (Figure S34-S36).

### FTIR spectroscopy

Then, the involvement of hydrogen bonding in the supramolecular assembly has been characterized by FTIR spectroscopy. For this study, methylcyclohexane has been used as liquid because of its suitable transparency. First, a gel of **18d** at 1wt% (14.8mM) in methylcyclohexane has been studied. The spectrum in the NH stretching region is displayed in Figure 3 (see Figure S29 for C=O region). Two bands are observed in the NH stretching region: they correspond to the NH from the amide closest to the furan ring (3370  $\text{cm}^{-1}$ ) and to the NH from the aliphatic amide (3250  $\text{cm}^{-1}$ ) (see Figure S32 for the assignment). Interestingly, both NH groups are hydrogen bonded but the larger shift of the latter indicates a much stronger hydrogen bond. Increasing the temperature reveals a broadening of the hydrogen bonded NH bands and the appearance at 90°C of a very small band at 3450  $\text{cm}^{-1}$  which corresponds to free NH groups. Therefore, at 100°C, although the solution is fluid, most molecules are still hydrogen bonded, but the broadness of the band indicates that these hydrogen bonds are poorly ordered.



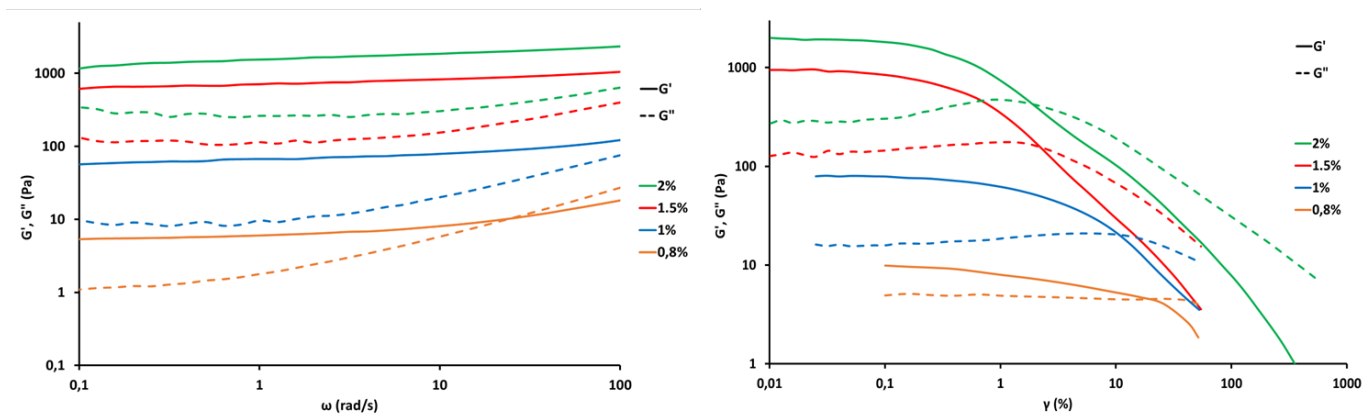


Figure 2. Left) Storage ( $G'$ ) and loss ( $G''$ ) moduli as a function of oscillation frequency ( $\omega$ ) for solutions of gelator **18d** in rapeseed oil at different mass percentages ( $\gamma = 0.08\%$ ,  $25^\circ\text{C}$ ); Right) Evolution of the storage ( $G'$ ) and loss ( $G''$ ) moduli as a function of strain ( $\gamma$ ) ( $\omega = 1\text{Hz}$ )

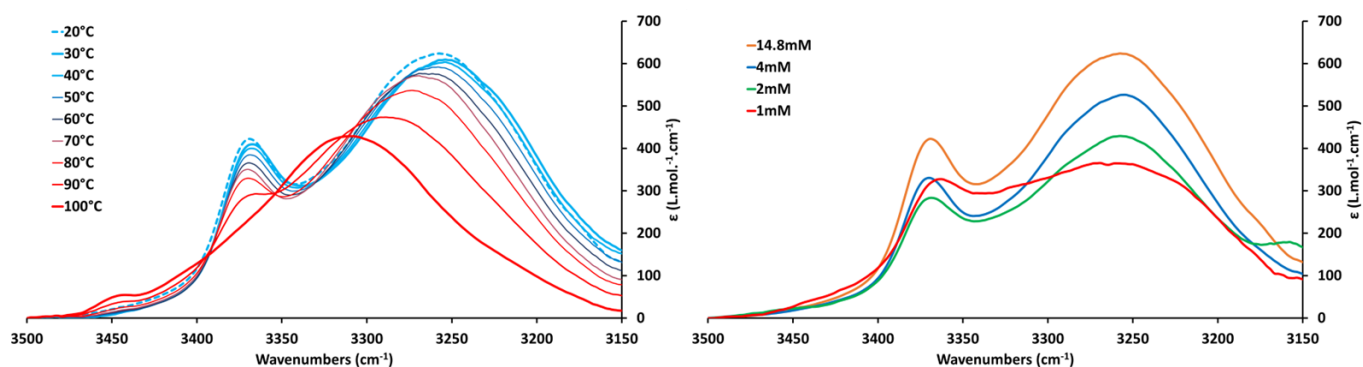


Figure 3. Left) VT-FTIR spectra of gelator **18d** in methylcyclohexane; 1wt% (14.8mM), heating process,  $1^\circ\text{C}/\text{min}$  ramp; NH bands; Right) FTIR spectra of gelator **18d** solutions at  $20^\circ\text{C}$  in methylcyclohexane at various concentrations: 14.8mM (orange line), 4mM (blue line), 2mM (red line) and 1mM (green line)

It can be seen that the intensity of the peak at  $3250\text{ cm}^{-1}$  decreases significantly above  $70^\circ\text{C}$  (Figure S30). This change corresponds to a reorganization in the assembly, from ordered to disordered hydrogen bonds. The influence of concentration is shown on Figure 3. The same evolution is observed when the concentration is decreased as when the temperature is increased: even at 1mM (i.e. much lower than the gelation concentration) no free NH band is observed but a broad hydrogen bonded NH band is present. Therefore, the gelator is not in the monomeric state at this concentration but is hydrogen bonded into ill-defined aggregates.

#### Circular dichroism spectroscopy

It was not possible to measure FTIR spectra at concentrations below 1mM, therefore CD spectroscopy was used to extend the concentration range (Figure 4 left). At 1mM in methylcyclohexane and at  $20^\circ\text{C}$ , an intense signature was observed which decreases when the temperature increases. This signal therefore corresponds to the supramolecular chirality of the assembly. This indicates that the molecules are still self-assembled and not in a monomeric state at 1mM and  $20^\circ\text{C}$ , in agreement with the FTIR spectroscopy results. Then, the supramolecular assembly has been investigated at lower concentration. A strong decrease in intensity is observed at 0.5mM (Figure 4 left). Moreover, at 0.5mM, the CD spectrum is not affected significantly by heating to  $100^\circ\text{C}$  or by the nature of the solvent

(dichloromethane and ethanol are good solvents for **18d**). This proves that **18d** is no longer self-assembled but in the monomeric state at 0.5mM in methylcyclohexane.

#### Viscometry

In order to corroborate the spectroscopy data, the temperature evolution of the relative viscosity of **18d** solutions in methylcyclohexane has been measured (Figure 4 right). At 0.5mM the solution is not more viscous than the solvent. At 1mM, the relative viscosity is slightly higher than at 0.5mM and it increases further at higher concentrations. These results are in perfect agreement with the spectroscopy data: at  $20^\circ\text{C}$ , self-assembly starts at a concentration between 0.5 and 1mM. Moreover, the viscosity of the solutions decreases at high temperatures indicating the breakdown of the assemblies.

#### Wide Angle X-Ray Scattering (WAXS)

In an attempt to determine the characteristic intermolecular distances of the assembly, WAXS has been carried out. In order to perform this analysis, a gel was first formed and then the solvent was removed by filtration to obtain the dry fibers, which were then analyzed. Few well-defined isotropic diffraction rings could be observed that were not sufficient to propose any molecular packing. The gel was then evaporated on a thin beryllium plate so as to tentatively induce preferential orientation.



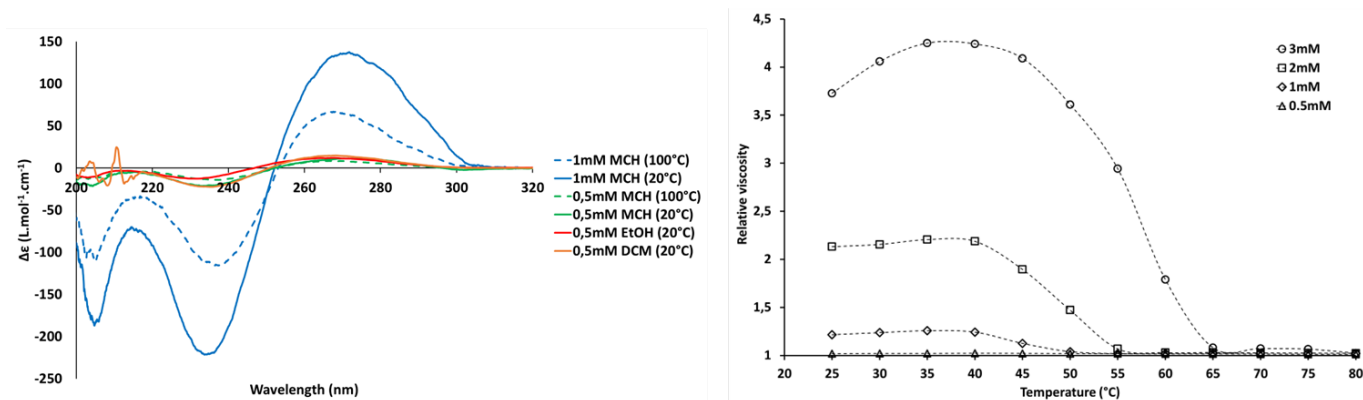


Figure 4. Left) CD spectra of gelator **18d** solutions at 0.5mM in methylcyclohexane, ethanol and dichloromethane and 1mM in methylcyclohexane; the spectra at 20°C are in bold lines and the spectra at 100°C are in dotted lines; Right) Relative viscosity of gelator **18d** solutions at different concentrations in methylcyclohexane depending on the temperature, 3mM (○), 2mM (□), 1mM (◇) and 0.5mM (△)

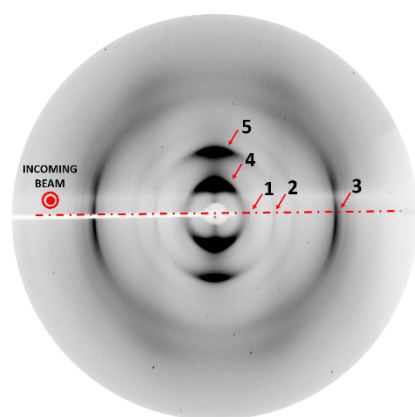


Figure 5. X-ray diffraction pattern obtained in grazing incidence geometry from a **18d** gel in methylcyclohexane evaporated on a beryllium platelet

A representative pattern obtained in grazing incidence geometry is displayed in Figure 5. The peaks 1, 2 and 3 located at: 1: 16.33 Å; 2: 9.38 Å; 3: 4.69 Å, are associated to in-plane distances; the intense peak 3 is probably a second harmonic of peak 2. The two in-plane distances that can be unambiguously attributed to in-plane distances are therefore: 16.33 Å and 9.38 Å. Two peaks are observed perpendicular to the substrate surface: 4: 16.98 Å; 5: 8.47 Å. Peak 5 is a second harmonic of peak 4, and there is thus only one out-of-the-plane distance: 16.98 Å. Generally speaking, reticular planes with higher density tend to align parallel to substrate and their spacing is therefore: 16.98 Å. If molecules tend to self-assemble into columns, it can be expected that the column axis is flat-lying. At this stage, it is however difficult to propose a precise packing therefore single crystal diffraction was considered.

**Crystal structure analysis.** Although crystallization of **18d** was not successful, colorless crystals of **18a** were obtained by slow vapor diffusion of cyclohexane into a solution of ethanol at room temperature. Its molecular packing was probed by X-ray diffraction (XRD) (Figure 6a). Thus, **18a** crystallized in P1 space group (triclinic system). Asymmetric unit and unit cell consist of two molecules and weak intermolecular interactions, including intermolecular H-bonds, contribute to the crystal cohesion. X-ray analysis confirms *S,S* enantiopurity in the crystal because P1 is a non-enantiogenic<sup>[27]</sup> space group and Flack parameter is close to zero (0.01(12)).<sup>[28]</sup> Crystal data and structure refinement parameters are available in Table S3. Crystal structure of **18a** (Figure 6b and Figure 6c) depicts the asymmetric unit wherein the two molecules are connected by three intermolecular H-bonds and the diamidofuran moieties are arranged in the same plane. Each molecule is also composed of two disordered C6-aliphatic chains. One of them is straight whereas the other one is bent above the furan of the second molecule. Crystal packing (Figure 6d) shows a H-bond network where each molecule is bounded to three neighbors by eight H-bonds. No furan is involved in H-bond, but a  $\pi$ - $\pi$  stacking interaction can be observed between the furan group of each molecule and one of a neighboring molecule (distance between each centroid = 3.42 Å).<sup>[29]</sup> A complete list of amide H-bond lengths can be found in Table S4. Although the hydrogen bond network is more complex than in the structure reported by Camiolo et al. (Figure 1),<sup>[9]</sup> it still reveals a possible preferential growth direction in the crystal, as indicated by the sequence of molecules held by 3 or 4 hydrogen bonds (pink, green and red molecules in Figure 6d) that grow along the *a* axis. Of course, there is no guaranty that this structure determined for the single crystal of the model compound **18a** is valid for **18d** in the gel fibers.

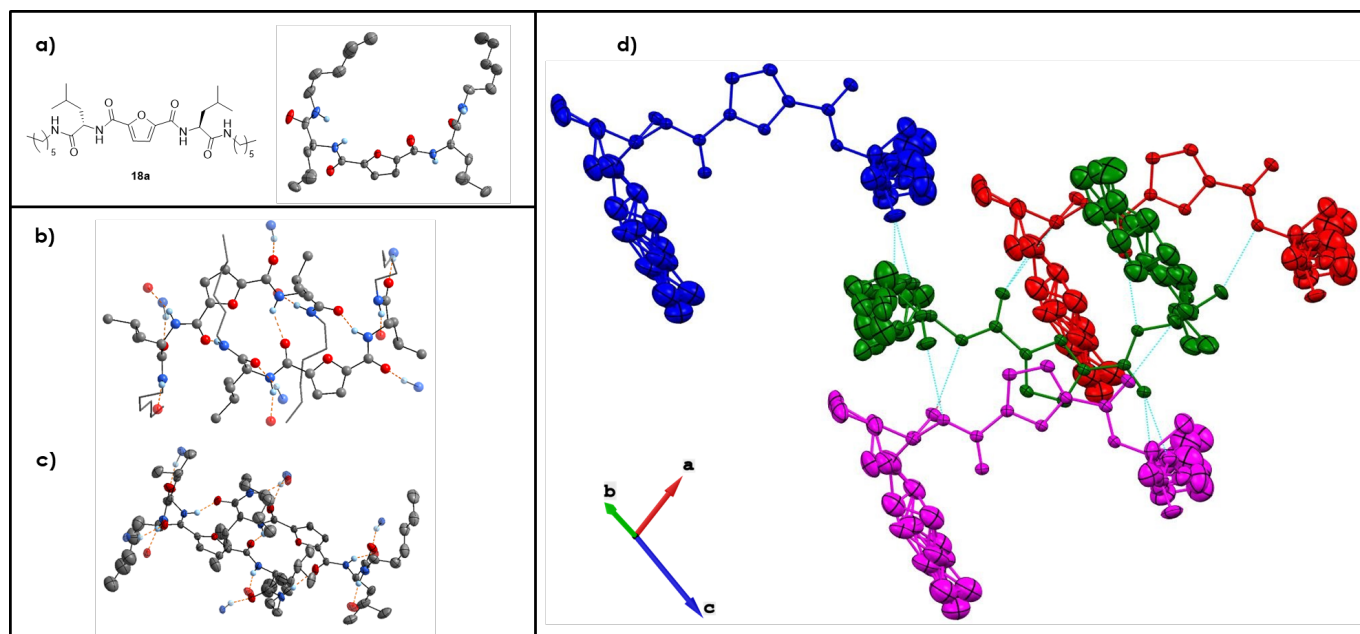


Figure 6. a) Left) Molecular representation; Right) Molecular structure of **18a** obtained by XRD; b) and c) Crystal structure of **18a** in the asymmetric unit. Two molecules are present; b) Ball-and-Stick representation, aliphatic C6 chains are depicted in wireframe mode for a best view because of the important disorder on this part; c) Ellipsoid representation. For b) and c), most of the hydrogen atoms are not shown for sake of clarity, only hydrogen atoms involved in hydrogen bonds are shown and intermolecular H-bonds are depicted as orange dotted lines. Nitrogen atoms are blue, oxygen atoms are red, carbon atoms are grey and hydrogen atoms are white. Regarding a), b), c), only major position of disordered groups is shown; d) Crystal packing of **18a**. Each neighboring molecule of **18a** is depicted in a different color. Green molecule is bounded to three neighboring molecules by eight H-bonds (3 with the red one, 4 with the pink one and 1 with the blue one). These H-bonds are shown in light blue; All hydrogen atoms and H-bonds connected to minor positions are not shown for sake of clarity. Concerning a), b), c) and d), only *S,S* enantiomers are present and for a), c) and d) ellipsoids are drawn with 30% probability.

However, Figure S33 shows that the FTIR spectra of crystallized **18a** and **18d** gel are similar, which supports this possibility. In particular, for both systems the hydrogen bonded NH band is composed of two contributions with a weak hydrogen bond (ca. 3370  $\text{cm}^{-1}$ ) and a stronger hydrogen bond (ca. 3250  $\text{cm}^{-1}$ ). Moreover, the crystal structure of **18a** is in agreement with the FTIR assignment proposed above, i.e. the NH closest to the furan ring forms weaker hydrogen bonds (ca. 2.9 Å) than the NH from the aliphatic amide (ca. 2.8 Å).<sup>[30]</sup>

## Conclusion

In this study, we used furan-2,5-dicarboxylic acid (FDCA) as bio-sourced platform to synthesize new organogelators. In order to provide hydrogen bond donor/acceptor functions, amide functions were chosen. Numerous molecules have been synthesized, and we discovered that molecules with amino acids functionalized with alkyl chains provide a good balance of solubility and self-association resulting in interesting gelling properties. The assembly of the supramolecular gels has been characterized. Through the various characterization techniques, we determined that microscale assembly starts at a concentration of 1mM in methylcyclohexane. On a macroscopic scale, rheology shows a supramolecular gel behavior from 14.8mM i.e., 1wt% in rapeseed oil. In conclusion, we have developed the first bio-sourced organogelators based on FDCA. These could be a green alternative to gelators derived from petrochemicals to increase the viscosity of polar or apolar media such as essential oils or mineral oils and perhaps use them in fields such as cosmetics, pharmaceuticals or food industry.

## Conflicts of interest

There are no conflicts to declare.

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