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PAPER

Self-assembled fibrillar networks of a multifaceted chiral squaramide: Supramolecular multistimuli-responsive alcogels†

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Chiral *N,N'*-disubstituted squaramide **1** has been found to undergo self-assembly in a variety of alcoholic solvents at low concentrations leading to the formation of novel nanostructured supramolecular alcogels. The gels responded to thermal, mechanical, optical and chemical stimuli. Solubility studies, gelation ability tests and computer modeling of a series of structurally related squaramides proved the existence of a unique combination of non-covalent molecular interactions and favorable hydrophobic/hydrophilic balance in **1** that drive the anisotropic growth of alcogel networks. The results have also revealed a remarkable effect of ultrasound on both the gelation kinetics and the properties of the alcogels. Overall, this work expands the classical applications of squaramides in organocatalysis and biomedicine towards the synthesis of soft functional materials.

Introduction

Squaramides are four-membered vinylogously conjugated diamides derived from squaric acid and possess a very high synthetic versatility.[1] Overall, the field of squaramides has experienced an extraordinary growth since the pioneering study of Rawal and co-workers[2] using these compounds as organocatalysts. Moreover, squaramides have been recognized as bioisosteres of ureas[3] exhibiting appealing properties for diverse research areas beyond organocatalysis,[4,5,6] such as biomedicine,[1] synthesis[7] and crystal engineering[8,9,10,11,12] (Figure 1). One of the most important features of these scaffolds is their capacity for selectively binding to different hydrogen bond acceptors through their acidic NH groups. Remarkably, squaramides play a dual role as they are also able to act as good hydrogen bond acceptors, making them suitable as receptors for cation recognition. This property has been explored to find promising candidates for the development of novel drugs[1,13,14] and in the field of organocatalysis as chiral hydrogen bond donor catalysts.[4] However, despite the increasing number of squaramide-based compounds in the literature, the study of their self-assembly properties in solution for the synthesis of soft functional materials has remained virtually unexplored.[15]

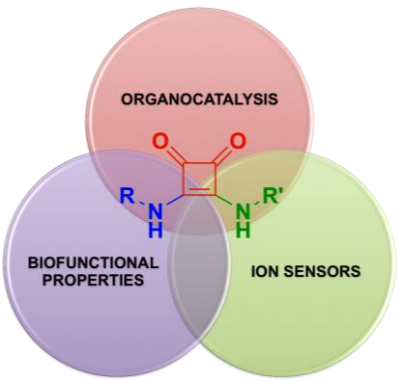

Fig. 1 Most common areas of research involving squaramide derivatives.

Within this context, hierarchical gel-based materials have received increasing attention over the last decades[16,17,18,19,20,21,22,23,24,25,26,27] due to their unique architectures and potential for high-tech applications in numerous fields including, among others,[28,29,30,31,32] the fabrication of sensors,[33] liquid crystals,[34] electrically conductive scaffolds,[35,36] templates for the growth of cells and inorganic structures,[37,38] chemical catalysis,[39] as well as in cosmetic and food industries.[16] In contrast to chemical gels[40,41,42] that are based on covalent bonds, (e.g., cross-linked polymers), physical gels[1,43,44,45,46,47,48,49,50] are typically made of low molecular weight compounds self-assembled through non-covalent interactions (e.g., hydrogen-

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bonding, van der Waals, charge-transfer, dipole-dipole, π-π stacking and coordination interactions), which usually provides reversible *gel*-to-*sol* phase transitions as response to environmental stimuli.[51,52] Systems based on both types of connections are also known.[53,54] The solid-like appearance and rheological properties of the gels result from the immobilization of the liquid (major component) into the interstices of a solid matrix (minor component) through capillary forces.[51,55] The formation of the 3D-network with numerous junction zones[56,57] is a consequence of the entanglement of 1D-polymeric strands of gelator molecules[16] typically of nm diameters and μm lengths.[58,59]

Herein, we report the unprecedented self-assembly properties of a chiral squaramide in numerous alcoholic solvents leading to the formation of multistimuli-responsive supramolecular alcogels. The remarkable effect of ultrasound during the preparation of the gels as well as the plausible gelation mechanism supported by quantum mechanical calculations are also discussed. This work expands the applications of squaramides towards materials synthesis.

Experimental

A) Synthesis and characterization of compounds

Materials

Unless otherwise noted, all solvents and reagents were purchased from commercial suppliers and used as received.

Characterization methods: Purification of reaction products was carried out by filtration. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI ionization method and mass analyzer type MicroTof-Q were used for the MS measurements. ^{1}H-NMR spectra were recorded at 400 MHz and ^{13}C-NMR-APT spectra were recorded at 100 MHz, using DMSO-d_6 as deuterated solvent. Chemical shifts were reported in the δ scale relative to residual DMSO (2.50 ppm for ^{1}H-NMR and 39.43 ppm for ^{13}C-NMR-APT). The ^{1}H-NMR and ^{13}C-NMR spectra of compounds **1**,[60] **2**,[61] **3**,[62] **4**,[60] **7**,[60] **8**,[60] and **9**[60] were consistent with those previously reported in the literature.

General procedure for the synthesis of compounds 5, 6 and 10: To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (**11**) (1.2 or 3 mmol) in MeOH (3-3.75 mL), amine **12** (1.2 or 3 mmol) was added at room temperature. After the corresponding reaction time (t_1), amine **13** (1.2 or 3 mmol) was then added dissolved in MeOH (9 or 11.25 mL). After the corresponding reaction time (t_2), the reaction flask was placed in the freezer (-20 ºC) for 30 minutes and the obtained product was purified by filtration. See ESI (Scheme S1) for exact solvent volumes and reaction times in each case.

3-(((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione (5): Following the above general procedure using 3 mmol of **11**, compound **5** was obtained after 9 h of reaction at room temperature as a white solid in 86% yield. $[\alpha]_D^{30}$ = +39.6 (*c* 0.61, DMSO). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.90 (br s, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.42-7.21 (m, 6H), 7.07-6.96 (m, 1H), 5.54 (br s, 1H), 5.54 (dd, *J* = 8.8, 5.0 Hz, 1H), 4.58 (dt, *J* = 4.9, 1.6 Hz, 1H), 3.14 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.88 (dd, *J* = 16.3, 1.4 Hz, 1H). ^{13}C-NMR-APT (75 MHz, DMSO-d_6) δ 183.9 (1C), 180.3 (1C), 169.0 (1C), 163.7 (1C), 141.3 (1C), 140.5 (1C), 139.1 (1C), 129.2 (2C), 127.9 (1C), 126.6 (1C), 125.0 (1C), 124.2 (1C), 122.4 (1C), 117.8 (2C), 72.3 (1C), 61.1 (1C), 39.3 (1C). IR (KBr film) (cm^{-1}) ν 3426, 3283, 2923, 2853, 1797, 1661, 1606, 1567, 1543, 1455, 1423, 1377, 1092, 760, 751, 744, 430. MS (ESI+) 343.1 [M+Na].

3-(((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-4-((4-methoxyphenyl)ami-no)cyclobut-3-ene-1,2-dione (6): Following the above general procedure using 3 mmol of **11**, compound **6** was obtained after 10 h of reaction at room temperature as a white solid in 88% yield. $[\alpha]_D^{29}$ = +41.8 (*c* 0.60, DMSO). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.07 (br d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.46-7.19 (m, 4H), 6.93 (d, *J* = 9.0 Hz, 2H), 5.55 (br s, 1H), 5.53 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.57 (dt, *J* = 4.8, 1.6 Hz, 1H), 3.73 (s, 3H), 3.14 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.87 (dd, *J* = 16.5, 1.3 Hz, 1H). ^{13}C-NMR-APT (75 MHz, DMSO-d_6) δ 183.3 (1C), 180.4 (1C), 168.6 (1C), 163.7 (1C), 155.1 (1C), 141.4 (1C), 140.5 (1C), 132.3 (1C), 127.9 (1C), 126.5 (1C), 125.0 (1C), 124.2 (1C), 119.3 (2C), 114.5 (2C), 72.3 (1C), 61.1 (1C), 55.2 (1C), 39.3 (1C). IR (KBr film) (cm^{-1}) ν 3413, 3278, 2923, 2853, 1795, 1656, 1605, 1565, 1541, 1517, 1496, 1459, 1426, 1419, 1377, 1351, 1321, 1257, 1209, 1183, 1157, 1140, 1116, 1099, 1032, 1001, 872, 861, 801, 773, 747, 637, 599, 439. MS (ESI+) 373.2 [M+Na].

***N*-((1*R*,2*R*)-2-((2-(Hexylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)cyclohexyl)-4-methylbenzenesulfonamide (10):** Following the above general procedure using 1.2 mmol of **11**, compound **10** was obtained after 5 h of reaction at room temperature as a white solid in 74% yield. $[\alpha]_D^{30}$ = +18.2 (*c* 0.64, DMSO). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.32 (br s, 1H), 7.29 (d, *J* = 8.1, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 3.60-3.36 (m, 3H), 3.12-2.96 (m, 1H), 2.36 (s, 3H), 1.92-1.78 (m, 1H), 1.66-1.00 (m, 14H), 0.96-0.77 (m, 4H). ^{13}C-NMR-APT (75 MHz, DMSO-d_6) δ 182.0 (1C), 181.8 (1C), 167.7 (1C), 167.2 (1C), 142.0 (1C), 139.3 (1C), 129.2 (2C), 125.9 (2C), 56.8 (1C), 56.4 (1C), 43.1 (1C), 33.0 (1C), 32.5 (1C), 30.7 (1C), 30.5 (1C), 25.4 (1C), 24.0 (2C), 21.9 (1C), 20.8 (1C), 13.8 (1C). IR (KBr film) (cm^{-1}) ν 3197, 2956, 2923, 28569, 1798, 1656, 1650, 1572, 1521, 1465, 1342, 1162, 1094, 814, 665, 575, 549, 419. MS (ESI+) 470.3 [M+Na].

B) Preparation and characterization of gel materials

Characterization methods: Oscillatory rheological measurements were performed at 25 ºC with an AR 2000 Advanced rheometer (TA Instruments) equipped with a Julabo C cooling system (Universität Regensburg). A 40 mm plain plate geometry (stainless steel) was used. Typically, the following experiments were carried out using 2 mL total gel volume: a) Dynamic strain sweep (DSS) was performed between 0.01% and 100% strain and a frequency of 1 Hz in order to estimate the strain value at which reasonable torque values were given; b) dynamic frequency sweep (DFS) experiments were performed between 0.1 to 10 Hz and a strain of 0.1%; and c) dynamic time sweep (DTS) measurements were performed with constant values of frequency and strain within the linear viscoelastic regime as

determined with DSS and DFS (0.1% strain, 1 Hz frequency). Additionally, the thixotropic nature of the gels was confirmed with a three-step loop test: (1) application of a low shear strain (0.1%) at 0.1 Hz frequency for 10 min (i.e., material is in gel state: $G' > G''$), (2) increase of the strain until the gel fractures (1000%) at 0.1 Hz frequency for 5 min (material turns into a viscous fluid: $G' < G''$), and (3) application of the initial strain value (0.1%) at 1 Hz frequency for 30 min (gel is recovered: $G' > G''$).

FTIR spectra were recorded using an Agilent Carry 630 spectrophotometer (Universität Regensburg) spectrophotometer.

Morphological characterization of the samples was carried out by field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). a) FESEM: Images were obtained with a Carl Zeiss Merlin field emission scanning electron microscope (0.8 mm resolution) equipped with a digital camera (SAI, Universidad de Zaragoza) and operating at 3 kV and 158 pA. Sample preparation: Specimens were prepared by freeze-drying. Prior to imaging, a 5 nm sized Pt film was sputtered (40 mA, 30 seconds) on the samples placed on carbon tape. b) TEM: Images were recorded using a JEOL-2000 FXII transmission electron microscope (0.28 nm resolution) equipped with a CCD Gatan 694 digital camera (SAI, Universidad de Zaragoza) and operating at 10 kV (accelerating voltage). Sample preparation: 10 μL of the gel suspension was allowed to adsorb for 30 s onto carbon-coated grids (300 mesh, from Aname). The grid was placed over a piece of filter paper in order to absorb the excess of solvent. c) AFM: Imaging was performed on a Multimode 8 (Bruker) instrument (LMA-INA, Zaragoza) in tapping mode at 0.5 Hz scanning rate using freshly cleaved mica surface as substrate and a single crystal silicon tip (TAP150A, 0.01-0.025 Ω-cm, Antimony doped Si) at 128-152 kHz drive frequency. Drive amplitude ranged from 300 to 400 mV. Sample preparation: 10 μL of the alcogel suspension (ca. 5-fold dilution in MeOH) was placed on the substrate and homogeneously dispersed to form a thin layer that was allowed to dry in air for overnight before measurement.

The growth of crystals in the gel phase was monitored using a Wild Makroskop M420 optical microscope equipped with a Canon Power shot A640 digital camera (Universität Regensburg). A polarization filter was used to observe the birefringence of the gels under polarized light.

Temperature-dependent ^{1}H-NMR studies were carried out on a 400 MHz Bruker Avance instrument (Universität Regensburg) equipped with a BVT 2000 heating system (Bruker BioSpin GmbH).

Powder X-ray diffraction (PXRD) patterns were collected on a STOE STADI P powder diffractometer (Universität Regensburg) (StartFragment Transmission mode, flat samples, Dectris MYTHEN 1k microstrip solid-state detector) with CuKα1 radiation operated at 40 kV and 40 mA. Conditions: a) 0.015°, time 1200 s/step, 2 theta range 10–55° (short measurement); b) StartFragment 0.015°, time 320 s/step, 2 theta range 10–90° (long measurement).

Critical gelation concentrations (CGC) were determined by adding solvent in several portions (0.1 mL each) into the vial until everything remained dissolved, precipitation and/or gelation took place upon heating-cooling (and/or ultrasound) treatment as described above. The initial concentration for gelation tests was 100 g L^{-1}.

Gel-to-*sol* transition temperatures (T_{gel}) were determined by the inverse-flow method by placing the sealed vials containing the organogels into a thermoblock (Figure S1), which was heated up at the rate of 2 ºC min^{-1}. In this work, the temperature at which the gel started to break was defined as T_{gel}. The average values of at least two random experiments were given. These values were correlated with the first differential scanning calorimetry (DSC) endothermic transition of model using a DSC7 (Perkin Elmer) instrument (Universität Regensburg) at a scan rate of 2 ºC min^{-1} under nitrogen atmosphere (gas flow rate = 20 mL min^{-1}). For the measurements, an appropriate amount of gel was placed into a pre-weighted Al pan (Perkin-Elmer), which was sealed and weight on a six-decimal plate balance. The pans were weighted again after each measurement to check for possible leakage.

General procedure for the preparation of organogels: Solvents (p.a. grade) used for gelation tests were purchased from commercial suppliers. In general, a certain amount of triturated squaramide was weighted and placed into a screw-cap vial (4.5 cm length × 1.2 cm diameter) and 1 mL of the corresponding solvent was added. Standard protocols for gel formation: (1) The heating-cooling protocol for the gel formation involved gently heating of the closed vial with a heat gun until the solid compound was completely dissolved, followed by spontaneous cooling of the isotropic solution to room temperature. (2) Alternatively, the heating-ultrasound protocol involved the application of ultrasound (ultrasound bath USC200TH, VWR™) directly after the heating. In each case, the material was classified as gel if no flow was observed upon turning the vial upside-down at room temperature. This phase was further confirmed by rheological measurements of model systems. Note: In some cases (see Table 1) the samples had to be pretreated in order to facilitate the dissolution of the compound during the standard protocols (i.e., heating-cooling or heating-ultrasound). The pretreatment consisted of gently heating followed by ca. 30 s sonication.

Phase-selective gelation experiments: Distilled water (1 mL) and 1-hexanol (1 mL) were added to compound **1** (7 mg, 0.014 mmol) placed into a screw-capped vial (4.5 cm length × 1.2 cm diameter). The vial was sealed and gently heated with a heat gun until the compound was completely dissolved. The mixture was sonicated for 1 min and kept undisturbed for 30 min, resulting in the gelation of the organic phase. The state of the material was established by turning the vial upside-down.

Responsiveness to external ions: Comparative experiments were made using the following metal salts: $FeCl_3$, $Ni(OAc)_2{\cdot}3H_2O$, $NiCl_2{\cdot}6H_2O$ and $CuCl_2$. A) Gels in methanol (1 mL) were prepared by heating-cooling using squaramide **1** at c = 10 g L^{-1}. After equilibration of the gels for 4 h, the desired metal salt solution (1 M in methanol) was added to each gel in 1μL portions and left to rest for at least 18 h until the cation reached a concentration of 60 mM in the gel. The integrity of the gel phase was evaluated by visual inspection. B) In order to crosscheck the values obtained in A), 10 mg of compound **1** was added to 1 mL of the corresponding metal salt solution in methanol prepared at the critical concentration defined by experiment A) (i.e.,

concentration where a response of the gel was evident to the naked eye). The mixture was heated for complete dissolution of the materials and subsequently cooled down to room temperature. The state of the bulk gel was monitored over time.

C) Quantum mechanical calculations

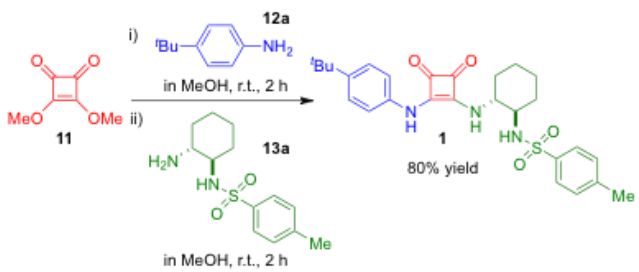
XXXX.

Results and discussion

Design and synthesis of squaramides

In the frame of our interdisciplinary research program focused on the development of new hydrogen bond based functional molecules, some of us have recently focused on the synthesis of new squaramide structures,[60,63] due to their important ability for selectively binding through cooperative hydrogen bonds to different acceptors.[4,5,6,1,7] During the synthesis of squaramide **1** (Scheme 1) we observed a clear tendency to increase the viscosity of the solvent (i.e., MeOH). Hence, we decided to investigate in detail the formation of supramolecular aggregates in solution, after taking also into consideration a) the facile and scalable synthesis of this family of compounds, b) the intrinsic potential as highly substituted scaffolds and c) the isosteric relationship with ureas, which represent ubiquitous synthons in supramolecular chemistry[64] including the formation of softgels.[65]

In this context, unsymmetrical substituted squaramide **1** was easily accessible following our own developed procedure in a one-pot synthesis using equimolar amounts of commercially available 3,4-dimethoxycyclobut-3-ene-1,2-dione (**11**), 4-*tert*-butylaniline (**12a**) and *N*-((1*R*,2*R*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide (**13a**) in methanol at room temperature (Scheme 1). After 4 hours of reaction, squaramide **1** was obtained in very good yield (80%) after simple filtration as an amorphous powder (i.e., the lack of crystallinity was confirmed by PXRD analysis. See ESI, Figure S16).



Scheme 1 One-pot synthesis of squaramide **1** in MeOH.

To correlate the structural functionalities of **1** with its gelation properties, we designed and synthesized the library of squaramides outlined in Figure 2. Specifically, different analogous squaramides **7-10** were designed by incorporating substituents with different steric and electronic properties, following the same synthetic procedure.[60,63] For this purpose, squaramides **7** and **9**, with electron-withdrawing groups, or squaramide **8** with an electron-donating substituent in the aromatic ring, or **10** in the absence of the aromatic ring, were synthesized with the aim of modifying the basicity and/or conferring distinctive solvation properties to these organic compounds, which is believed to play a key role on the gelation phenomena.[16-27] In all these cases (**1**, **7-10**), the stereochemical configuration and the structural core were maintained. On the other hand, squaramides **2** and **3** were included for comparison with **1**, since we also observed that the viscosity of MeOH increased during their preparation. Additionally, and encouraged by our last work with urea-based compounds as efficient gelators,[66] we also carried out the preparation of squaramide **4**, which is the equivalent squaramide to the best urea compound used in our previous work.[66] Related with compound **4**, squaramide **5**, lacking the substituent in the aromatic ring, or **6**, bearing a methoxy group, were also explored.

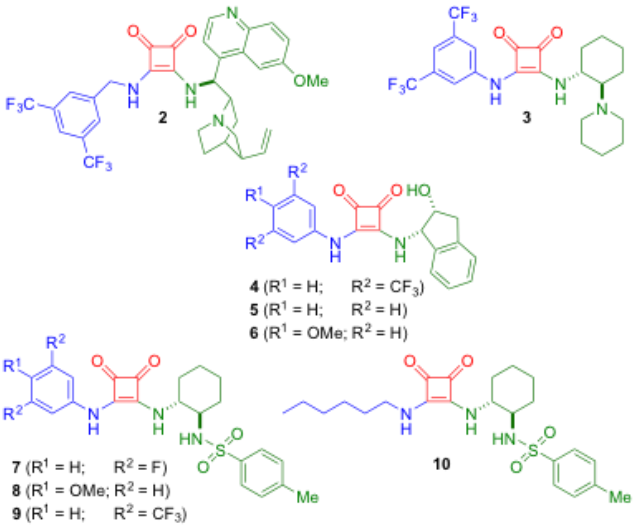


Fig. 2 Library of additional squaramides **2-10** synthesized for this work.

All synthesized squaramides **1-10** were appropriately characterized after purification by a simple and straight filtration (see Experimental Section).

Solubility and gelation properties

The gelation ability of compound **1** was initially screened for 34 different solvents using the heating-cooling protocol within a broad concentration range (Table 1; ESI, Table S1). For instance, squaramide **1** was found to be insoluble in dichloromethane, chloroform, ethyl acetate, diethyl ether, dibutyl ether, toluene, glycerol, 1,3-dichlorobenzene and water upon heating and/or sonication. Unexpectedly, **1** showed an unusual selectivity to form stable gels in a number of alcoholic solvents (alcogels), including primary, secondary, tertiary, lineal and branched alcohols. The only exception to this rule was the gel obtained in acetone. However, it should be considered that although acetone is present at >99% keto form at equilibrium, the formation of hydrogen bonding gel networks could stabilize to some extend the enol form of the acetone (2-propenol). In sharp contrast, no gelation tendency was detected for squaramides **2-10**. These results suggested the existence of unique molecular interactions and a hydrophilic/hydrophobic balance that favor the self-assembly of **1** in alcohols. This was later confirmed by computational studies (*vide infra*).

The gel nature of the samples was initially confirmed by the absence of flow upon turning the vial upside-down and further

confirmed by oscillatory rheological measurements in model solvents (*vide infra*). The critical gelation concentration (CGC) values estimated for the gels obtained with **1** ranged between 3 and 21 g L^{-1} (see the Experimental Section for the procedure). These values indicate that hundreds or thousands of solvent molecules are immobilized per gelator molecule (e.g., the highest solvent/gelator ratio ~ 1750:1 was obtained in methanol). As far as we are aware, the only precedent in the literature describing the formation of an organogel with squaramides corresponds to a recent report from Ohsedo and co-workers[15] describing a series of squarylium monoalkylamides and dialkylamides. Therein, gelation was only observed in DMF (forming opaque gels) and in some cases only after cooling down the mixture to -15 ºC.

Table 1 Gelation capacity of **1**, optical appearance of the gel phase, critical gelation concentration (CGC), gelation time, *gel*-to-*sol* transition temperature (T_{gel}), procedure for gel formation and temporal stability of the gels.

entry	solvent[a]	phase[b]	optical appearance	CGC (g L^{-1})[e]	gelation time[f]	T_{gel} (ºC)[g]	procedure[h]	temporal stability[k]
1	methanol	G	transparent	7	24 ± 2 h	45	heating-cooling	> 6 months
2	2-methylpentan-1-ol	G + U	nd	nd	nd	nd	heating-cooling	nd
3	butan-2-ol	G	transparent	20	24 ± 6 h	nd	heating-cooling[i]	> 4 months
4	ethanol	G	translucent	5.8	10 min	46	heating-ultrasound	cryst. after 18 h
5	2-methylpropan-2-ol	G	translucent	3	5 min	57	heating-ultrasound	> 1 month
6	butane-1,4-diol	G	translucent	5.5	10 min	47	heating-ultrasound[j]	> 1 week
7	2-methylpropan-1-ol	G	translucent	4	1 min	67	heating-ultrasound[j]	> 1 week
8	phenylmethanol	G	opaque	21	8 min	42	heating-ultrasound	> 2 months
9	acetone	G	translucent	7.1	1 min	54	heating-ultrasound[j]	> 1 week
10	2-methylbutan-2-ol	G	translucent	3.3	5 min	70	heating-ultrasound[j]	> 2 weeks
11	propan-1-ol	G + C	opaque[d]	5.2	2 h	64	heating-cooling	> 6 months
12	propan-1-ol	G	translucent	5.2	5 min	56	heating-ultrasound	> 4 months
13	pentane-1,5-diol	G	opaque	10	15 min	47	heating-cooling	> 2 months
14	pentane-1,5-diol	G	translucent	6.1	12 min	36	heating-ultrasound	> 1 week
15	butan-1-ol	G	transparent	8.4	3.5 ± 0.25 h	39	heating-cooling	> 1 month
16	butan-1-ol	G	transparent	8.4	6 min	36	heating-ultrasound	> 1 month
17	hexan-1-ol	G + C	transparent	9.1	9 min	35	heating-cooling[j]	> 1 week
18	hexan-1-ol	G	transparent	7	1 min	75	heating-ultrasound[j]	> 2 months
19	3-methylbutan-2-ol	G[c]	transparent	5	20 ± 4 h	nd	heating-cooling[j]	> 1 month
20	3-methylbutan-2-ol	G	translucent	3.7	2 min	54	heating-ultrasound[j]	> 2 months
21	pentan-2-ol	G	transparent	5.5	11 ± 1 d	81	heating-cooling	> 1 month
22	pentan-2-ol	G	transparent	5.0	1 min	65	heating-ultrasound	> 2 months
23	2-methylbutan-1-ol	G + C	transparent	4.7	2.3 ± 0.15 h	65	heating-cooling	cryst. during gelation
24	2-methylbutan-1-ol	G	translucent	3.9	2 min	53	heating-ultrasound	> 1.5 months

[a] Solvent volume = 1 mL. Systematic IUPAC name is provided for each case. [b] Abbreviations: G = gel; U = undissolved gelator; C = crystals, nd = not determined due to unreliable variables. [c] Approximately 10% of the total volume remained ungelled. [d] Cluster of white needles are visible within the fresh gel sample, which turned into a transparent gel after 12 days (*vide infra*). [e] Values calculated by the inverse-flow method. Estimated error ± 0.5-1 g L^{-1}. [f] Abbreviations: h = hour; min = minute; d = day. Unless otherwise noted, estimated error ± 1 min (for gelation times > 1 min). [g] Estimated error ± 2 ºC. [h] Rows of gels prepared by heating-ultrasound treatment are shaded in blue. [i] To form this gel it was necessary to predissolve **1** in 20 μL of DMSO. [j] The sample was pretreated by heating-ultrasound as explain in the experimental section. [k] The gels were stable *at least* for the indicated period. Symbol " > " indicates that the stability could possibly be much longer although it was not monitored. Abbreviation: cryst = cyrstallization.

Stable gels were classified in 3 different groups depending on the experimental protocol that was used for their preparation. The first group could only be formed by the classical heating-cooling protocol (entries 1-3), the second group could only be formed by applying heating and subsequent ultrasound treatment (entries 4-10) and the third group could be formed by any of these two methods (entries 11-24). Thus, ca. 47% of the obtained gels could be formed by heating-cooling, whereas ca. 82% could be prepared by a heating-ultrasound protocol (blue shaded rows). Although there is not an apparent correlation between the type of alcohol and the gel preparation method, heating followed by ultrasound was found to be a very convenient technique for the gelation of branched alcohols within minutes regardless the degree of substitution at the α-carbon. Based on these groups, we selected one model solvent of each group (i.e., methanol, phenyl methanol and hexan-1-ol) for further characterization and comparisons. So obtained alcogels displayed different degree of translucency (Figure 3). Such optical differences indicate the formation of aggregates of different sizes.

Ultrasound-induced gelation (sonogelation), mainly by solvent cavitation, has attracted much attention over the last few years.[67,68,69,70] During our work we found that the application of ultrasound after heating not only allowed the fabrication of stable gels that could otherwise (i.e., via heating-cooling) not be formed, but also decreased the gelation time drastically (e.g., entries 11, 15, 19, 21, 23 *vs* entries 12, 16, 20, 22, 24, respectively). The most impressive case was pentan-2-ol that needed more than 10 days to be gelled by heating-cooling and only 1 min by heating-ultrasound even at lower concentration (entry 21 *vs* entry 22). This is very appealing since the application of ultrasound to an already isotropic solution seems counterintuitive. However, sonication of the hot clear solution prior gelation may hinder the self-assembled system (non-entangled nanofibers) to fall into its lowest energy level making

possible the formation of new gel networks. In addition, both the CGC was reduced in practically all cases in which the heating-ultrasound protocol was used instead of heating-cooling. This was also accompanied by certain reduction of the T_{gel} values. The case of hexan-1-ol should not be considered prematurely as an exception because the heating-cooling protocol gave a combination of gel and crystals (entry 17 *vs* entry 18). Remarkably, the dynamic nature of the gels was evidenced by a gradual increase over time of the T_{gel} for the gel prepared by heating-ultrasound reaching eventually the same value obtained by heating-cooling (i.e., T_{gel} (fresh gel made in propan-1-ol) = 56 ºC; T_{gel} (3-month old gel made in propan-1-ol) = 63 ºC).

Fig. 3 Representative photographs of upside-down vials containing organogels made of **1** in different alcohols prepared at the CGC (see Table 1) via heating-cooling (H-C) or heating-ultrasound (H-U).

Phase-selective gelation capacity: Very interestingly, squaramide **1** was also able to gel selectively the organic phase of alcohol/water mixtures. In principle, such phase-selective gelation is always challenging due to the expected alteration of the hydrogen bonding network.[71] As a proof-of-concept, **1** (c = 7 g L^{-1}) was dissolved in 1:1 v/v water/hexan-1-ol by heating and subsequently submitted to sonication for 1 min. After 30 min of resting, only the organic phase was completely gelled, which was stiff enough to hold the liquid water phase upon inversion of the vial. Due to the partial solubility of hexan-1-ol in water (i.e., 5.9 g L^{-1} at 20 ºC), the aqueous phase was not completely clear after gelation of the alcohol. However, after 24 h the water phase got clearer and the organic phase more turbid (Figure 4). This was presumably due to the disruption of the microemulsion and diffusion of the tiny fraction of gelator molecules that could be trapped into the aqueous phase. Phase-selective gelation using water-soluble alcohols such as methanol was not successful. The addition of 10-20% water either before or after gel formation resulted in the collapse of the gel after several days caused by a thick precipitation (ESI, Figure S14).

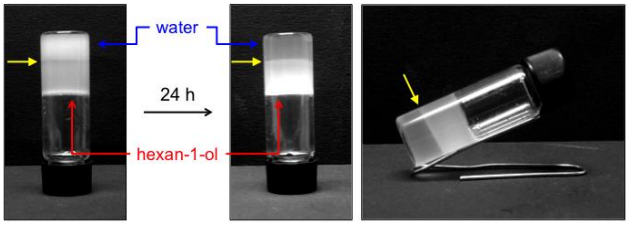


Fig. 4 Phase-selective gelation and change in opacity of hexan-1-ol /water mixture after 24 h (c = 7 g L^{-1}). Total volume = 2 mL. Yellow arrow indicates the boundary between phases.

Thermal and temporal stability of alcogels

In general, the supramolecular gels were thermoreversible and stable to multiple heating-cooling cycles. The *gel*-to-*sol* transition temperatures (T_{gel}) were estimated by the inverse flow method (IFM). Due to the dependence of this method with the cooling rate and thermal history of the sample, we confirmed the good agreement of the T_{gel} with the first endothermic transition observed by differential scanning calorimetry (DSC) of a model gel (ESI, Figure S5).

As usually observed in physical gels, T_{gel} values increased as the gelator concentration increased until reaching a plateau before visible crystal nucleation. For example, T_{gel} of the gel made in methanol increased ca. 23 ºC upon increasing ca. 3-fold the concentration of **1** with respect to the CGC (7 g L^{-1}). Crystal formation was observed over 22 g L^{-1} within 10 min (Figure 5). These results are in agreement with the formation of more entangled networks at higher gelator concentrations.

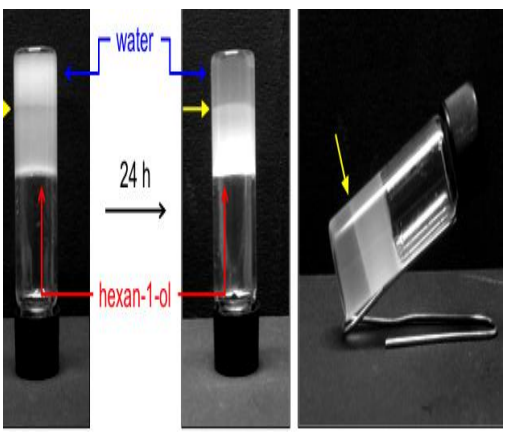


Fig. 5 Phase diagram and variation of T_{gel} as a function of the concentration of gelator **1** in methanol.

Very interestingly, in several cases we have observed an enhancement of both the gelation kinetics and the gel stability when the gels were reformed after being thermally destroyed for the first time. We believe that the *gel*-to-*sol* thermal transition could be controlled to avoid the complete dissociation of the supramolecular network (even when behaving as a fluid from the rheological standpoint). This could preserve the thermodynamically more stable aggregates through a self-sorting mechanism, thus providing a more robust starting platform for rebuilding the gel structure. We believe that such "preformation hypothesis" could be more general and become an important contribution to the gelation theory. We are currently studying this

in detail and we will publish our results at due course.

On the other hand, *gel*-to-*crystal* transitions have been previously related to Ostwald rule of stages.[72,73] The subtle equilibrium between the metastable gel phase and the thermodynamically stable crystalline phase[74,75,76,77] could also be monitored in several of our alcogels. For instance, crystallization in the form of long needles was observed first at the interface between air and the developing gel phase made of **1** in 2-methylbutan-1-ol, hexan-1-ol or propan-1-ol via heating-cooling (Figure 6). Nevertheless, the robustness of the gel phase allowed in most of the cases the coexistence of crystalline and gel phases for at least one month supporting the inversion of the test tube. In general, the alcogels prepared via heating-ultrasound remained stable for several months without visible crystallization when stored in dark at room temperature.

Fig. 6 A) Digital photograph showing crystal growth in the gel made of **1** in 2-methylbutan-1-ol. B) Optical microscope picture of the crystals observed in A). C) Crystal growth observed during the gelation of hexan-1-ol using **1**. Both gels were prepared at the CGC (Table 1) using the heating-cooling protocol.

Although *gel*-to-*gel* transitions have already been reported,[78,79,80,81] it is still a rare phenomenon. The gels made in phenylmethanol showed an optical transition from transparent to opaque within 30 min at the CGC (Figure 7A). This behavior is typically observed during the growth of fibrilar aggregates over time. Intriguingly, the uncommon opposite phenomenon was observed with the alcogel prepared in propan-1-ol by heating-cooling. In this case, initial crystallization was observed during the gelation process leading to a transient opaque gel, which turned into a thermodynamically stable transparent gel within 12 days (Figure 7B).

Fig. 7 A) Transparent-to-opaque transition recorded for the gel made in phenylmethanol within 30 min after gel formation via heating-ultrasound. B) Opaque-to-transparent transition observed in the gel made in propan-1-ol within 12 days after gel formation via heating-cooling. Gels were prepared at the CGC as shown in Table 1.

Influence of gelator enantiopurity on gel formation

Chirality plays a fundamental role in the formation of supramolecular gel networks.[82] Therefore, we also examined the influence of the enantiomeric purity of **1** on its gelation ability. Samples with different enantiomeric excesses (ee) were prepared by combining (*R*,*R*)-**1** with the appropriate amount of the racemic compound, which was prepared following the general synthetic procedure using the corresponding racemic diamine (see Experimental Section). Stable-to-inversion gels could only be formed with the enantiomerically pure (*R*,*R*)-**1**. The squaramide with 80% ee yielded a weak partial gel after 88 h. Crystallization of the gelator was observed after 9 days. The use of **1** with ee < 80% led to snow flake-like precipitation of **1** without any gel formation (Figure 8).

Fig. 8 Influence of enantiomeric purity of gelator **1** on its gelation ability in methanol (c = 7 g L^{-1}) monitored over time. Enantiomeric excesses are given in percentages.

Driving forces for molecular aggregation

The comparison of FTIR spectrum of solid squaramide **1** with those of the xerogel (prepared by freeze-drying the corresponding alcogel) and **1** in solution revealed only slight alteration with small frequency shifts to lower wavelengths ($\Delta\lambda$ < 4 cm^{-1}) for characteristic peaks (e.g, stretching absorptions bands for C=O ~1658-1794 cm^{-1}; secondary amines ~3210-3345 cm^{-1}; aromatic C-H ~2910-3005 cm^{-1}; aromatic C-N ~1265-1370 cm^{-1}) (Figure S4). This suggests that **1** may also be aggregated in the solid state involving intuitive hydrogen bonding and π-stacking interactions similarly to its analogue urea-based organogelator.[66]

On the other hand, temperature-dependent ^{1}H-NMR experiments could provide additional information regarding phase interconversions. However, it should be noted that NMR signals of gelator molecules are unlikely to be observed in the gel phase due to long correlation times. Therefore, the observed signals are typically ascribed to small amounts of gelator molecules dissolved in the immobilized solvent.[83,84] Preliminary NMR measurements of the alcogel made of **1** in d_4-methanol with increasing temperature from 25 ºC to 60 ºC showed gradual chemical shifts (δ) of almost all protons of **1** suggesting at least conformational changes and/or expected modification in the aggregation pattern (e.g., through hydrogen bonding, π-stacking

and/or electrostatic interactions) (ESI, Figure S6).

In order to gain a clearer insight into the potential aggregation mode of **1** and its unique gelation ability, we carried out comparative quantum mechanical calculations. XXXX.

Morphological properties of alcogels

Field emission scanning electron microscopy (FESEM) of the corresponding xerogels showed a remarkable influence of the solvent on the morphologies. For instance, straight laths of ca. 0.2-1.4 μm in width were observed for gel made in phenylmethanol (Figure X), whereas dense fibrilar networks with entangled fibers of ca. 10-20 nm in diameter were characteristic of the gels made in hexan-1-ol and methanol (Figure X). The exact molecular mechanism associated with each morphology remains unclear. No major differences were observed for the gel phase obtained either by heating-cooling or heating-ultrasound for the gel made in hexan-1-ol (Figure X; ESI, Figure S8). However, transmission electron microscopy (TEM) revealed a less dense fibrilar network for the gel prepared by heating-ultrasound (Figure X; ESI, Figure S9).

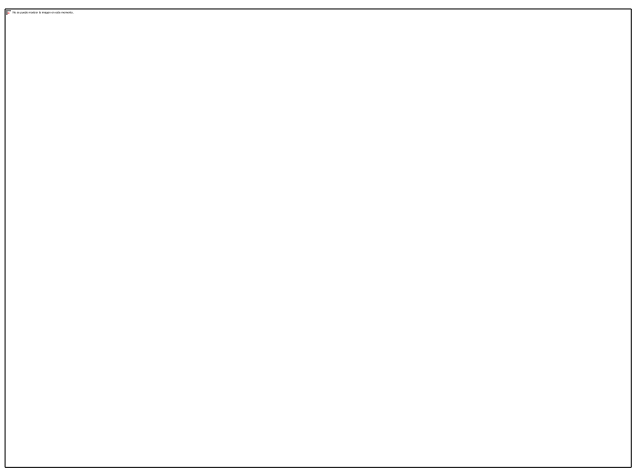


Fig. X Representative FESEM images of the xerogels prepared by freeze-drying of the corresponding organogels in different solvents at CGC. A) methanol (heating-cooling), B) phenylmethanol (heating-ultrasound), C) hexan-1-ol (heating-ultrasound) and D) hexan-1-ol (heating-cooling).

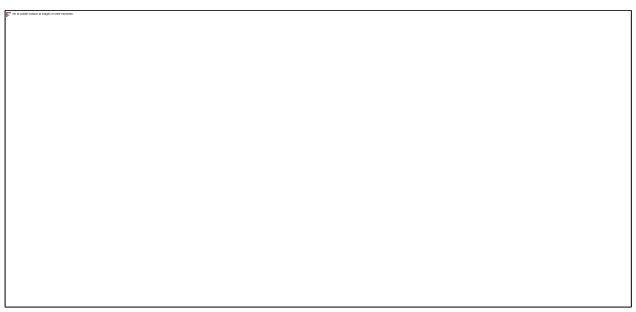


Fig. X Representative TEM images of xerogels of the corresponding organogels prepared in different solvents at CGC: A) Methanol (heating-cooling), B) hexan-1-ol (heating-ultrasound).

As expected, complementary fibril structures with average heights between ca. 4 nm and 10 nm were also observed by atomic force microscopy (AFM) (Figure X). Certain fiber helicity was detected by FESEM and AFM imaging (ESI, Figure S10).

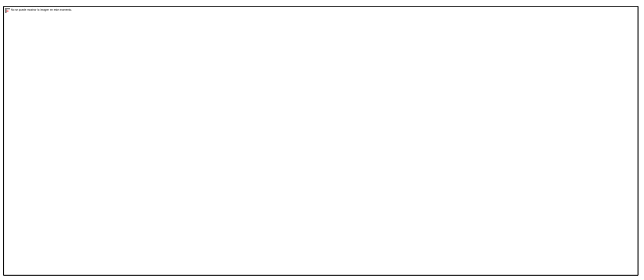


Fig. X Representative AFM images of the gel made of **1** in methanol (heating-cooling) at CGC.

In addition, the anisotropic and thermoreversible features of the alcogels allowed turning on/off their birefringence under polarized light (Figure X). The ability to control the refractive index of soft materials constitutes an important property for applications in optical devices.[85]

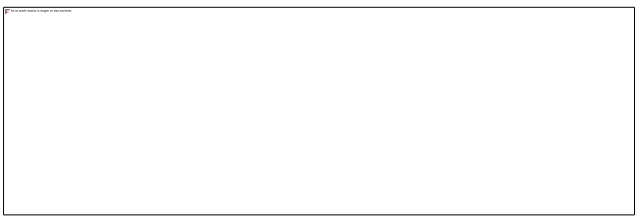


Fig. X Polarized light (90º) microscope images of A) alcogel made of **1** in methanol at CGC and B) solution upon *gel*-to-*sol* thermal transition.

Rheological properties of alcogels

The viscoelastic properties of the model gels were confirmed by oscillatory rheological measurements (ESI, Figure S7). The storage (G') and loss modulus (G'') were measured at room temperature as a function of the shear strain (dynamic strain sweep, DSS) and the frequency (dynamic frequency sweep, DFS) to define the linear viscoelastic regime of the material (Figure X; ESI, Figure S7). Reasonably constant value of tan δ (G''/G') during the measurements indicates a relative good tolerance of the materials towards external forces. Moreover, the value of the storage modulus was always ca. one order of magnitude higher than the loss modulus. The aging stability of the gels at room temperature was confirmed by dynamic time sweep (DTS) measurements within the predetermined linear limits (i.e., 0.1% strain, 1 Hz frequency).

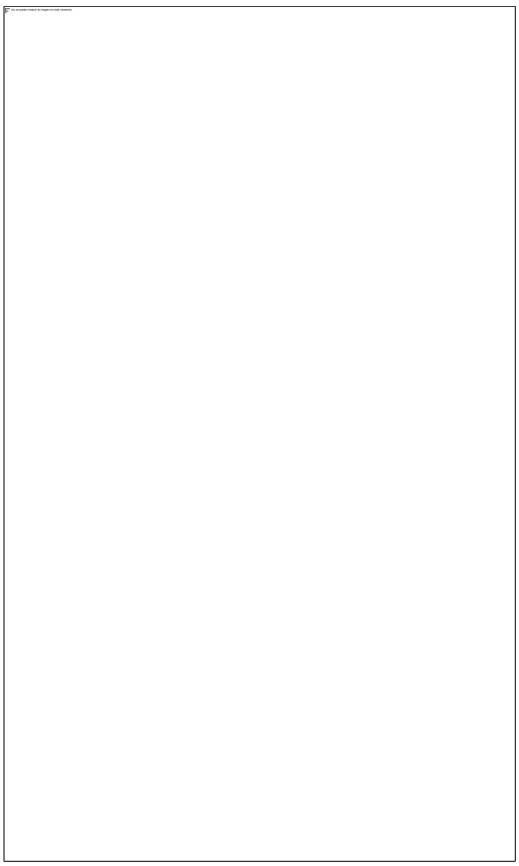


Fig. X Representative oscillatory rheological plots of the model gel made of **1** in methanol at CGC. *Top*: DFS experiment. *Bottom*: DSS experiment.

Furthermore, these gels were also found to be thixotropic,[86] a key property for real-life applications of many gel-based materials.[87] This behavior was confirmed by a three-steep rheological loop test consisting of (1) application of shear strain as defined by DTS experiments ($G' > G''$), (2) subsequent increase of the strain until the gel collapses ($G' < G''$) and (3) return to the starting strain value ($G' > G''$). Full recovery of the gel strength was observed within seconds after each cycle (Figure X). This self-healing behavior was also macroscopically observed upon vigorous shaking of the vial containing the bulk gel followed by a resting period (Figure S17G).

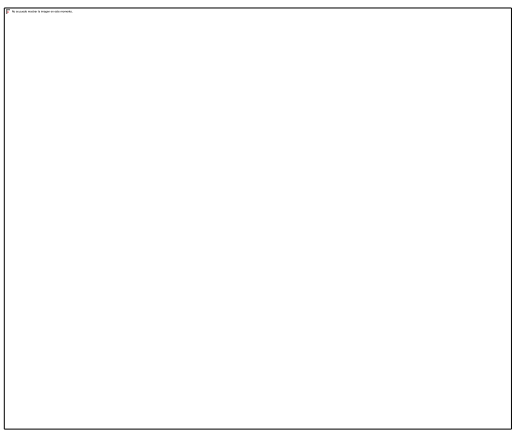


Fig. X Rheological loop test of the gel made of **1** in butan-1-ol at CGC. Steps: 1) 1 Hz, 0.1 % strain, 10 min; 2) 0.1 Hz, 1000 % strain, 5 min; 3) 1 Hz, 0.1 % strain, 30 min. Steps 2 and 3 were repeated for a second cycle.

Responsiveness to external ions

Since squaramide derivatives are known to coordinate to cations at the N-H groups and to anions at the carbonyl moiety, we expected a response of the alcogels to the presence of external ions. In order to confirm this, a small amount of different metal salt solutions in methanol (i.e., $FeCl_3$, $Ni(OAc)_2{\cdot}3H_2O$, $NiCl_2{\cdot}6H_2O$, $Cu(NO_3)_2$ and $CuCl_2$) were layered over 1 mL of the model gel made of **1** in methanol (c = 10 g L^{-1}). Potential complexation of the ions with the gelator molecule may disrupt the nanofibers causing the gradual collapse of the gel network. As a matter of fact, this was observed in preliminary experiments upon addition of either 30 mM $FeCl_3$ or 60 mM $NiCl_2{\cdot}6H_2O$ stock solutions within 3.5 h and 6 h, respectively (Figures XC-D). Interestingly, the addition of 60 mM $CuCl_2$ or $Ni(OAc)_2{\cdot}3H_2O$ did not cause visible decomposition of the gel network within 72 h (Figures XA-B), suggesting different effects of metal ions and counterions on the gel stability. The response of the gel was independent on the procedure used for the preparation of the hybrid material (Figure XE). Future research is still necessary to elucidate the exact nature of the metal complexes and the dominant mechanism for the gel destruction.

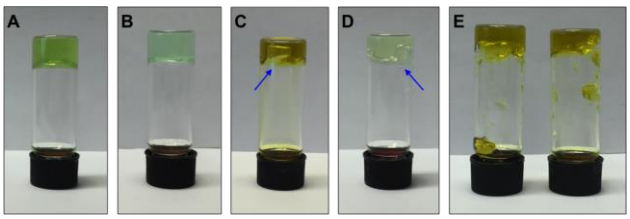


Fig. X Effect of external ions on the stability of the gel made of **1** in methanol (c = 10 g L^{-1}). A) 60 mM $CuCl_2$: stable gel. B) 60 mM $Ni(OAc)_2{\cdot}3H_2O$: stable gel. C) 30 mM $FeCl_3$: gel decomposition in 3.5 h. D) 60 mM $NiCl_2{\cdot}6H_2O$: gel decomposition within 6 h. E) *Left*: addition of **1** to metal solution (30 mM $FeCl_3$) followed by heating-cooling. *Right*: addition of metal solution (30 mM $FeCl_3$) to preformed gel via heating-cooling. Gel colours correspond to the colours of the metal salt solutions.

Conclusions

The foregoing results demonstrate that chiral *N*,*N'*-disubstituted squaramide **1** self-assembles selectively in a large variety of alcohols at concentrations ranging from 3 to 21 g L^{-1}. This phenomenon leads to the formation of nanostructured supramolecular alcogels with the ability to response to thermal, mechanical, optical and chemical stimuli. Experimental gelation tests and computer modeling of a series of structurally related squaramides (**2-10**) demonstrated the existence of a unique combination of non-covalent molecular interactions and favorable hydrophobic/hydrophilic balance in **1** that drive the growth of stable gel networks. The application of a heating ultrasound protocol instead of the classical heating-cooling cycle allows not only the formation of alcogels that could otherwise not be formed, but it also decreases both CGC and gelation times in comparison to the heating-cooling treatment. Moreover, the nature of the solvent has a remarkable effect on the morphology of the aggregates (e.g., straight laths, entangled fibers) and some

gels also exemplify the strong competition between gelation and crystallization typically observed in physical gels. Thixotropic behavior and phase selective gelation of non-miscible alcohol/water mixtures are other interesting features of these alcogels.

This work opens a Pandora's box of possibilities for the use of squaramides in materials synthesis beyond their classical applications in catalysis, sensors and medicine. Investigations related to the described "preformation hypothesis" within the overall gelation theory for similar systems, as well as the study of the observed *gel*-to-*gel* transitions are currently underway in our laboratories and the results will be published at due course.

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