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PAPER

# Competition between gelation and crystallisation of a peculiar multicomponent liquid system based on ammonium salts†

Iti Kapoor,<sup>‡a</sup> Eva-Maria Schön,<sup>‡a</sup> Jürgen Bachl,<sup>ab</sup> Dennis Kühbeck,<sup>a</sup> Carlos Cativiela,<sup>b</sup> Subhadeep Saha,<sup>c</sup> Rahul Banerjee,<sup>c</sup> Stefano Roelens,<sup>d</sup> José Juan Marrero-Tellado<sup>\*e</sup> and David Díaz Díaz<sup>\*ab</sup>

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An exemplar competition between gelation and crystallisation phenomena was examined with an unusual synergistic multicomponent (organo)gelator solution (MGS), which consists of a well-defined methanolic solution of (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate containing 2.4 equiv. of concentrated hydrochloric acid. The optimal composition of the MGS was determined through meticulous solubility, gelation and structural studies, which support a transient gelation mechanism based on the kinetic self-assembly of the tartrate salt driven by hydrogen-bonding interactions, involving ammonium nitrogen donors and hydroxyl oxygen acceptors, and electrostatic interactions. The hydrochloric acid is involved in the solubilisation of the salt through an ionic dissociation-exchange process, which ends up with the formation-precipitation of (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride. As a consequence, an irreversible destruction of the gel takes place, which indicates the metastable nature of this phase that cannot be accessed from the thermodynamically equilibrated state. Gelation of a variety of oxygenated and nitrogenated solvents with moderate polarity occurred efficiently using extremely low MGS concentrations at low temperatures, and the gel phase was confirmed by dynamic rheological measurements. Several features make the described MGS unique: (1) it is a multicomponent solution where each component and its stoichiometry play a key role in the reproducible formation and stabilization of the gels; (2) it is formed by simple, small, and commercially available chiral building blocks (dissolved in a well-defined solvent system), which are easily amenable for further modifications; (3) the gelation phenomenon takes place efficiently at low temperature upon warming up the isotropic solution, conversely to the typical gel preparation protocol; and (4) the formed organogels are not thermoreversible despite the non-covalent interactions that characterize the 3D-network.

## Introduction

In a fascinating journey from serendipity to rational design, materials made by means of gelation of solvents (organogels or hydrogels in the case of organic solvents or water respectively)

have received increasing attention over the last two decades,<sup>1</sup> because of their unique supramolecular architectures and potential applications<sup>2</sup> as functional soft materials in the fabrication of sensors,<sup>3</sup> liquid crystallines,<sup>4</sup> electrophoretic and electrically conductive matrices,<sup>5</sup> templates for cell growth or the growth of sol-gel structures,<sup>6</sup> catalysis<sup>7</sup> and in many other industrial fields such as cosmetics, oils, and foods.<sup>1</sup> These hierarchical, self-assembled, and viscoelastic materials may be considered to be either hard or soft based on their rheological characteristics. Among the different classification criteria, their categorization according to the driving forces for molecular aggregation is probably the most common. Thus, the two major groups are constituted by chemical gels<sup>8,9</sup>—based on covalent bonds, usually cross-linked polymers—or physical gels<sup>1,10,11</sup>—made of either low-molecular-weight (LMW) compounds or polymers, and based on non-covalent bonds, predominantly hydrogen-bonding, van der Waals, charge-transfer, dipole-dipole,  $\pi$ - $\pi$  stacking, and coordination interactions, which usually lead to reversible *gel-to-sol* phase transitions.

<sup>a</sup>Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany. E-mail: David.Diaz@chemie.uni-regensburg.de; Fax: +49 941 9434121; Tel: +49 941 9434373

<sup>b</sup>Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza, Pedro Cerbuna 12, 50009 Zaragoza, Spain

<sup>c</sup>Physical/Materials Chemistry Division, National Chemical Laboratory, Dr Homi Bhabha Road, Pune 411008, India

<sup>d</sup>Istituto di Metodologie Chimiche (IMC), Consiglio Nazionale delle Ricerche (CNR), Dipartimento di Chimica, Università di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy

<sup>e</sup>Instituto Universitario de Bio-Organica "Antonio González", Universidad de La Laguna, Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain

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‡ Iti Kapoor and Eva-Maria Schön contributed equally to this work.

Furthermore, systems based on both types of connections are also known.<sup>12,13</sup> The solid-like appearance of gel materials is the result of the entrapment of the liquid (major component) into the compartments of a solid 3D-matrix of a large surface area (minor component), typically through surface tension and capillary forces.<sup>14,15</sup> The formation of the 3D-network through a number of “junction zones”<sup>16</sup> is a consequence of the entanglement of 1D-polymeric (or suprapolymeric) strands of macromolecules (or LMW molecules), the so-called gelators,<sup>1</sup> typically of micrometre scale lengths and nanometre scale diameters.<sup>17</sup> Hence, in many cases, gels may immobilize up to  $10^5$  liquid molecules per gelator and increase the viscosity of the medium by a factor of  $10^{10}$ , with the potential to respond to a variety of external stimuli.<sup>18,19</sup>

Despite the extensive and remarkable achievements of supramolecular chemistry in many controlled self-assembly processes,<sup>20</sup> most of the LMW gelators have been found by serendipity rather than rational design. Thus, the control of gelation phenomena and the design of new gelators are still challenging tasks,<sup>21</sup> in particular when multiple dynamic non-covalent interactions (*e.g.* gelator–gelator, gelator–solvent, solvent–solvent, gelator aggregates–solvent)<sup>22</sup> are taken into account. In this regard, gelators based on organic ammonium are interesting mainly due to their flexible and versatile hydrogen-bond pattern, which allows control of the dimensionality of the network.<sup>23</sup> On the other hand, organic ammonium salts have been recognized as structurally simple supramolecular synthons,<sup>24</sup> which could permit the fine-tuning of the non-covalent molecular aggregation mode by the incorporation of selected functional groups. In comparison with the conventional one-component gelators, the two-component ammonium-based systems provide additional interest because multicomponent systems allow a further complexity of the hierarchical self-assembling process to form higher aggregates, which are responsible for the microphase separation in the gel state.<sup>17,25</sup>

In this article, we report on the discovery and study of a new synergistic multicomponent organogelator liquid system (MGS), which shows intriguing gelation properties and exemplifies the tough competition existing between gelation and crystallisation phenomena. The MGS is formed by a methanolic solution of (1*R*,2*R*)-1,2-diaminocyclohexane *L*-tartrate and hydrochloric acid (Fig. 1).

Several features make this system unique in comparison with other organogelators, especially those based on ammonium carboxylates:<sup>23</sup> (1) it is a multicomponent solution, in which each component and its stoichiometry play a key role in the reproducible formation and stabilization of the organogels; (2) it is formed by simple, small, and commercially available chiral

building blocks (dissolved in a well-defined solvent system: MeOH/HCl/H<sub>2</sub>O), which are easily amenable for further modifications; (3) the gelation phenomenon takes place efficiently at low temperature upon warming up the isotropic solution, conversely to the typical gel preparation protocol (*i.e.*, heating–cooling process); and (4) the formed organogels are not thermoreversible despite the non-covalent interactions that characterize the 3D-network.

## Experimental<sup>26</sup>

### Materials

Unless otherwise noted, all organic compounds, mineral acids and anhydrous solvents were purchased from commercial suppliers and used without further purification. The manipulation of HCl-containing solutions must be carried out accurately by the use of precision glass syringes or pipettes, ensuring proper cleaning after each use.

### Preparation of optimal MGS

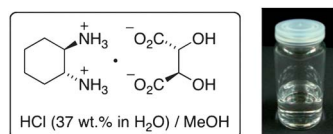
Typically, a 0.3 M HCl/MeOH stock solution was prepared using HCl 37 wt% in aqueous solution and dry MeOH. (1*R*,2*R*)-1,2-Diaminocyclohexane *L*-tartrate (254 mg, 0.96 mmol) was weighed in a glass vial and dissolved in 7.5 mL of the above HCl/MeOH stock solution (2.4 equivalents of HCl with respect to the tartrate salt). The organogelator solution prepared under these conditions is *ca.* 0.13 M (referred to tartrate salt), transparent, colourless and does not contain any visible solid particles. This guarantees the stoichiometry of each component, which is imperative for the formation of reproducible gel materials.

### Preparation of MGS-based gels

Typically, the appropriate solvent (1 mL) was placed in a glass screw-capped vial (10 cm length × 1 cm diameter, 1 mm wall thickness) and cooled down close to the freezing temperature of the solvent. Depending on this temperature, the proper cooling bath composition (*e.g.* liquid nitrogen–acetone) was prepared in a Dewar flask and the above glass vial immersed in the bath for at least 5 min prior to addition of the gelator system. The appropriate volume of MGS was subsequently added under gentle hand stirring of the vial, and the mixture kept at low temperature for 1 min. After this time, the cooling bath was removed and the resulting clear homogeneous solution was let to warm up to room temperature allowing the formation of the gels. Unless otherwise indicated, the degree of gel formation was quantified after 30 min by turning the vial upside-down and collecting the non-gelled solvent.

### Characterization

Nuclear magnetic resonance (NMR) spectra were recorded at 25 °C on a Bruker Avance-300 instrument. Fourier transform infrared (FT-IR) spectra were recorded at room temperature using an Excalibur FTS 3000 FT-IR spectrometer (Biorad) equipped with a single reflection ATR (attenuated total reflection) accessory (Golden Gate, Diamond). Differential scanning calorimetry (DSC) measurements were performed in



**Fig. 1** Left: components of the multicomponent organogelator liquid system (MGS). Right: digital photograph of a glass vial containing the transparent solution prepared under the optimal molar ratio (1*R*,2*R*)-1,2-diaminocyclohexane *L*-tartrate : MeOH : HCl : H<sub>2</sub>O ≈ 1 : 193 : 2.4 : 8.3.

a Perkin-Elmer DSC7. The DSC thermograms were obtained under dynamic nitrogen atmosphere (gas flow rate = 20 mL min<sup>-1</sup>) at a heating rate of 3 °C min<sup>-1</sup>. Samples were placed on open aluminium pans (Perkin-Elmer). An empty sample holder was used as the reference and the runs were performed by heating the samples from 25 up to 60–160 °C, depending on each sample. The values were reported as the average of two independent measurements. Field Emission Scanning Electron Microscopy (FESEM) images of xerogels (freeze-dried gel samples) were obtained with a Zeiss Merlin, Field Emission Scanning Electron Microscope operated at an accelerating voltage of 10 kV. The samples were sputtered (40 mA, 60 seconds) with Pt (film thickness ~10 nm) before imaging by a SCD500 Leica EM. Atomic force microscopy (AFM) was performed using Tapping Mode (Integra Probe Nano Laboratory, NT-MDT) at 1 Hz scanning rate with a TiN (NT-MDT Nanoprobe tip NSG01 series) tip at a drive frequency of 115–190 kHz (force constant 2.5–10 N m<sup>-1</sup>). Dynamic rheological measurements were carried out using an advanced rheometer AR 2000 (TA Instruments) equipped with a cooling system (Julabo C). A 20 mm plain plate (stainless steel) geometry was used for the measurements. Strain sweep measurements were initially performed to estimate the % at which reasonable torque values (*ca.* ×10 resolution limit of the transducer) could be obtained. Subsequently, frequency and time sweep measurements were performed in dynamic mode. To prevent solvent evaporation over the period of the experiment and the appearance of artefacts, a thin layer of low viscosity oil was added on the top of the sample. A Büchi GKR-50 Kugelrohr apparatus was used to estimate the gel destruction temperatures (*T<sub>d</sub>*) and compare them with the DSC thermograms. An optical microscope (Wild Makroskop M420 1.25×) equipped with a digital camera (Canon Power shot A640) was used at 15.6× magnification to photograph the crystals formed within the gel over time. XRD analyses were carried out with a SuperNova diffractometer (Agilent Technologies Inc.). A microfocus copper source was used together with an Atlas CCD camera. The cell parameters were determined in six different goniometer orientations by omega scans. Stock solutions were accurately prepared in volumetric flasks. Turbidity measurements were carried out at room temperature using a Camlab CW8100 Portable Turbidimeter calibrated with T-CAL standards and provided with an infrared LED as a light source ( $\lambda$  = 860 nm) and a photodiode scattered light detector at an angle of 90°. The samples were vigorously shaken for 1 min before measurement ensuring the absence of bubbles. The vials were rotated in the sample chamber about 45° after each measurement for each sample until the reading matches within ±0.01 nephelometric turbidity units (NTU). A VWR™ ultrasonic cleaner (USC200TH) was used during the solubility tests of the tartrate salt. The temperature of the ultrasonic water bath was 33 ± 2 °C after 30 min sonication. Statistical validation of results was performed by simple one-way analysis of variance yielding overall significance (*p* < 0.05). The values in the text, tables and figures are expressed as mean ± standard deviation.

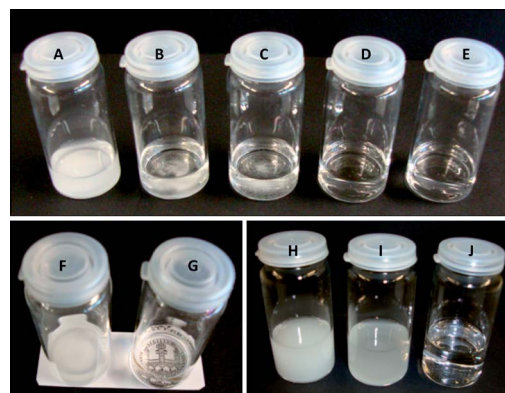
## Results and discussion

During the standard protocol of tartaric acid-mediated racemic resolution of (±)-*trans*-1,2-diaminocyclohexane,<sup>26,27</sup> we found

that one of the intermediate compositions, which contained (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate, MeOH and aqueous HCl, showed a remarkable ability to instantaneously form jellylike materials upon contact with a variety of other organic solvents at room temperature. A comprehensive study of this phenomenon (*vide infra*) led to a *ca.* 0.13 M methanolic solution of (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate and 2.4 equiv. of concentrated HCl (37 wt% in aqueous solution) as the optimal MGS, which corresponds to a molar ratio of (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate : MeOH : HCl : H<sub>2</sub>O ≈ 1 : 193 : 2.4 : 8.3. As it will be discussed later, the presence and stoichiometry of each component were found to play a key role in the gelation process.

### Determination of the optimal molar composition

In order to determine the optimal molar composition of the gelator solution, we first carried out an extensive two-variables screening defined by the tartrate salt concentration and the number of equivalents of HCl. This study provided a 2D-rectangular matrix of 132 elements.<sup>26</sup> In order to minimize the experimental error derived from multiple volume measurements, a 0.3075 M stock MeOH–HCl solution was prepared and used during the solubility screening of the salt. The results demonstrated that at least 2.1 equivalents of HCl (with respect to the (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate) were necessary to completely dissolve the salt and provide a transparent gelator solution without any visible residue (Fig. 2). The experimental turbidity values of these solutions were below 0.35 ± 0.05 NTU. All systems prepared using less than 2.1 equivalents of HCl afforded mixtures with visible remnants of undissolved material. From these samples, only the one containing 2.0 equivalents of HCl could be turned into a clear solution upon 1 min sonication.



**Fig. 2** Digital photographs showing the critical effect of the amount of HCl on the solubility of the tartrate salt in MeOH (*ca.* 0.13 M). The mixtures in vials A–D were sonicated for 10 min, and the pictures taken 30 min later: A = 1.7 equiv. HCl; B = 1.8 equiv. HCl; C = 1.9 equiv. HCl; D = 2.0 equiv. HCl; E = 2.4 equiv. HCl and without sonication. Vials F = A and G = E were placed over the logo of the University of Regensburg, which is only visible through the latter solution (2.4 equiv. HCl). Vials H (1.0 equiv. HCl), I (1.7 equiv. HCl) and J (2.4 equiv.) were photographed after 30 min sonication and vigorous hand-shaking of the closed vials. Herein, the equivalents of HCl are referred to the tartrate salt. Note that in the absence of HCl the tartrate salt remains insoluble in all tested solvents even after long periods of sonication and heat.<sup>26</sup>



Thus, the turbidity value of systems containing for example only 1.7 equivalents of HCl exceeded  $1040 \pm 50$  NTU even after 30 min sonication or gently heating with a heat-gun. These solubility properties were routinely observed within a salt concentration range of 0.06 to 1.0 M.<sup>26</sup>

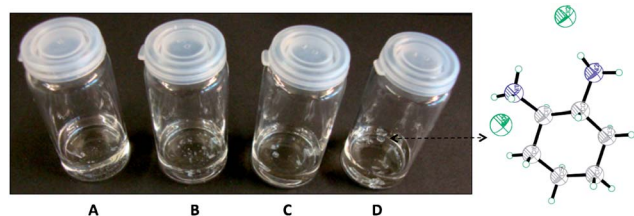
The use of concentrations higher than 0.3 M resulted in spontaneous slow growth of large monocrystals at room temperature in closed vials (Fig. 3). NMR and single crystal XRD studies confirmed that these crystals correspond to (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride.<sup>28</sup> This finding has significant mechanistic implications that are discussed later in this paper.

A comparative study of the stability of various gels prepared using the clear solutions of the 2D-matrix<sup>26</sup> allowed to establish *ca.* 0.13 M methanolic solution of tartrate salt containing 2.4 equivalents of HCl (with respect to the salt) as the optimal composition of the MGS. No major changes in the gel properties were observed when they were prepared using MGS aged for about 7 days in a sealed vial and in the dark. However, some detriment in the temporal stability of some gels could be observed when MGS aged for longer periods of time was used.

It is important to remark that the obtention of reproducible gel materials depends, among other factors described later, on the use of stable and clear gelator solutions. This ensures not only a well-defined gelator concentration in each experiment, but also the absence of any solid-particle nucleating agent that could favour the crystallisation of (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride, and consequently the destruction of the gel. Hence, the use of uncontaminated materials is also a major requirement during these experiments.

### Gel preparation

The formation of gel-like materials upon addition of small volumes of MGS to a variety of solvents took place extremely fast at room temperature.<sup>23</sup> However, such fast kinetics avoided the appropriate homogenization of the mixtures (MGS + solvent) before the gelation phenomenon, which caused no gelation of a significant amount of solvent. Under these conditions, the formation of fluid-filled cavities within the non-homogeneous gel phase could be observed and disrupted upon mechanical stress (*e.g.* shaking or manipulation of gel with a spatula). Among many experimental trials, homogeneous organogels were formed when the solvents were cooled down



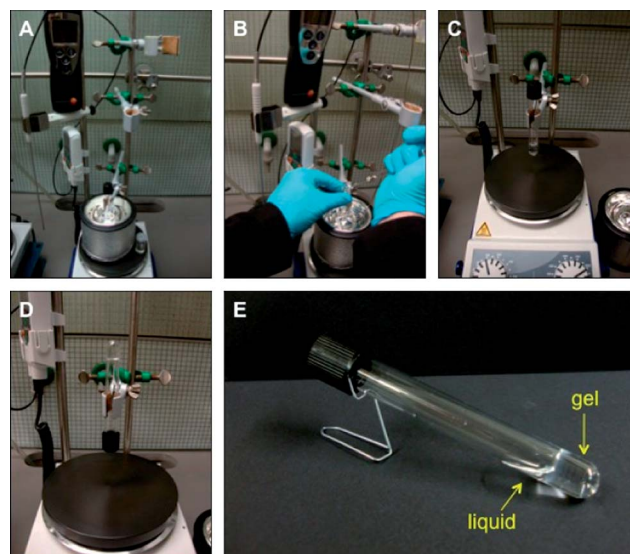
**Fig. 3** Digital photographs showing the formation of monocrystals of (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride from MGS solutions prepared with 2.4 equiv. HCl at different concentrations in MeOH: *A* = 0.25 M; *B* = 0.3 M; *C* = 0.5 M; *D* = 1.0 M. The appearance of the crystals was faster and more abundant at the higher concentrations. The ORTEP diagram on the right illustrates the crystal structure.

close to their freezing points<sup>26</sup> before addition of the MGS. By using this procedure the gelation kinetics could be dramatically slowed down, allowing the preparation of an isotropic solution containing MGS and the appropriate solvent, which further turned into homogeneous gel upon warming up to room temperature (Fig. 4). In general, we observed that a small portion of liquid remained non-gelled regardless of the concentration of species (Fig. 4, picture E). Thus, the degree of gel formation was quantified after gel formation by turning the vial upside-down and collecting the non-gelled liquid (Table 1).

Moreover, during this experimental procedure, we identified a series of factors that have a significant influence on the gel formation. In this regard, the control of the solvent temperature (close to its freezing point), as well as a good stirring of the mixture [MGS + solvent] at low temperature, could be used to regulate nucleation processes<sup>29</sup> and afford the formation of most stable and homogeneous gel materials. It is worth mentioning that the glass vial design features (*e.g.* wall thickness, diameter) have also an effect on the gelation concentration, gelation kinetics and gel stability, since they can affect the stirring efficiency as well as the promotion of heat transfer through the vial, which would directly influence the amount of energy transferred to the solvent mixtures.

### Solubility and gelation properties

The gelation ability of the optimal MGS was evaluated for 40 solvents<sup>26</sup> (Table 1). The state of the materials was examined by the “stable-to-inversion of a test tube” method.<sup>26</sup> As expected, the FT-IR spectra of both MGS and gel-based materials displayed the stretching vibration bands of both carboxylic



**Fig. 4** Gel preparation steps. (A) Cooling down the test tube containing the desired solvent close to its freezing temperature; (B) careful hand-shaking of the test tube and addition of the required amount of MGS at low temperature; (C) removal of the cooling bath; (D) gel state confirmed by the “stable-to-inversion of the test tube” method; and (E) photograph of the transparent gel made in 1,4-dioxane showing the amount of non-gelled solvent (the picture was taken 30 min after removing the cooling bath).

**Table 1** Gelation ability of the optimal MGS in different solvents<sup>a</sup>

Entry	Tested solvent	gv <sup>b</sup> /μL	T <sub>mix</sub> <sup>c</sup> /°C	Non-gelled liquid <sup>d</sup> /μL	T <sub>d</sub> <sup>e</sup> /°C	Aspect phase <sup>f</sup>	Temporal stability <sup>g</sup>
1	NM	100	−20	40 ± 20	95 <sup>h</sup>	TG	2–4 h
2	ACN	100	−40	40 ± 20	62	OG	1–3 d
3	BN	150	−10	240 ± 50	152	TG	1–2 h
4	ACT	250	−90	110 ± 20	43	OG	2–5 h
5	CHN	150	−10	115 ± 20	84 <sup>h</sup>	TG	2–3 h
6	MBN	100	−80	70 ± 10	68	OG	3–4 d <sup>i</sup>
7	DME	100	−50	40 ± 20	65	OG	1–4 h
8	MEE	100	−60	60 ± 10	128	OG	3–4 d
9	ETAC	250	−78	80 ± 15	44	OG	9–24 h
10	THF	150	−78	40 ± 20	54	TG	4–5 d
11	DEE	180	−100	90 ± 30	52	OG	3–4 d
12	DOX	80	13	50 ± 30	89	TG	2–3 d
13	Group I	—	—	—	—	M	—
14	Group II	—	—	—	—	I	—
15	Group III	—	—	—	—	P	—

<sup>a</sup> 1 mL of solvent was used in each experiment. Solvent abbreviations: ETAC = ethyl acetate; THF = tetrahydrofuran; DME = 1,2-dimethoxyethane; MEE = 2-methoxyethyl ether; DEE = diethyl ether; CHN = cyclohexanone; MBN = 3-methylbutan-2-one; ACN = acetonitrile; BN = benzonitrile; DOX = 1,4-dioxane; ACT = acetone; NM = nitromethane. Group I solvents = methylene chloride, 1,2-dichloroethane, carbon tetrachloride, dimethylformamide; dimethylacetamide, dimethyl sulfoxide, ethanol, *n*-hexane, benzene, toluene, ethylene glycol, dibutyl ether, *N*-methyl-2-pyrrolidone, water. Group II solvents = chloroform, 1,2-dichlorobenzene, nitrobenzene *n*-octane, glycerol, cyclohexane, tetrachloroethylene, carbon disulfide. Group III solvents = 1-butyl-3-methylimidazolium hexafluorophosphate (ionic liquid, [BMIM][PF<sub>6</sub>]), pyridine, methyl *tert*-butyl ether.

<sup>b</sup> Volume of MGS used. The minimum volume necessary to achieve gelation is around this value (see ESI†). <sup>c</sup> Temperature of mixing (cooling bath temperature during the addition of MGS). <sup>d</sup> Amount of non-gelled liquid collected 30 min after gel formation. The values represent the average of at least 6 randomized experiments. <sup>e</sup> Gel destruction temperature observed by DSC (error = ±2 °C). <sup>f</sup> Abbreviations: TG = transparent or slightly translucent gel; OG = opaque gel; M = miscible; I = immiscible; P = precipitate. In the case of methyl *tert*-butyl ether a turbid gel-like material was initially formed but broken into small pieces of gel-like material after inversion of the test tube. <sup>g</sup> Stability of the gels over time when stored undisturbed in a vertical position at 23 ± 2 °C. The lack of stability was defined when the gel was fragmented or partially liquefied without resistance to inversion of the test tube. Abbreviations: d = days; h = hours. <sup>h</sup> In this case the T<sub>d</sub> was determined by a Kugelrohr-based method (see ESI†) with an apparent error of ±5 °C for CHN and ±10 °C for NM. <sup>i</sup> The colour of this gel changes from white opaque to dark yellow-green opaque after 1–2 h. Stability was judged by the destruction of the coloured gel (see ESI†).

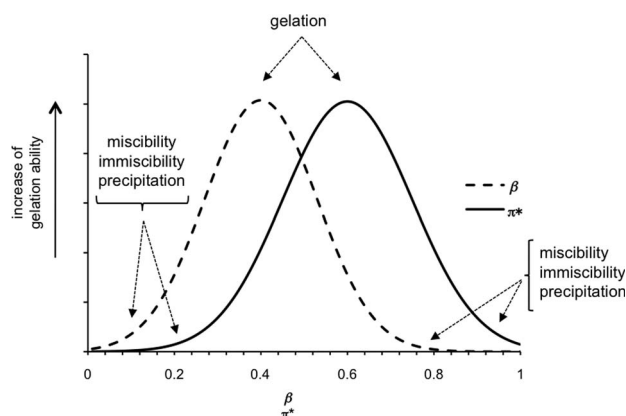
(1710–1749 cm<sup>−1</sup>) and ammonium (3250–2350 cm<sup>−1</sup>) groups. Hydrogen-bond association bands in the range 3600–3200 cm<sup>−1</sup> were also found for the gel material. However, for accurate interpretations of the spectra it should be considered that alkane, water and methanol O–H stretching bands are also overlapped in the above regions.<sup>26</sup> Thus, no further conclusive information could be obtained from these spectra. The introduction of a 2 mm diameter thermocouple into the solution (after removing the cooling bath) showed that in most cases the gelation process started well below 0 °C. The gel condition of model gels was further confirmed by dynamic rheological measurements (*vide infra*). As shown in Table 1, the MGS was able to gel a variety of oxygenated and nitrogenated organic solvents at very low concentrations (entries 1–12). In contrast, no gel formation was observed with, among others, halogenated, aromatic and hydrocarbon solvents (entries 13–15).<sup>26</sup> The volume of MGS that afforded reproducible gel samples (gelation volume, gv) was established in the range of 80–250 μL, which corresponds to a gelation concentration range of *ca.* 0.3–0.9 wt% referred to the tartrate salt.<sup>26</sup>

It has recently been established that Kamlet–Taft solvent parameters<sup>30</sup> account for specific interactions between solvent and gelator molecules.<sup>31</sup> The  $\alpha$  parameter defines the hydrogen-bond donor ability of the solvent, which is of special importance in 3D networks built by hydrogen-bonding. The  $\beta$  parameter represents the hydrogen-bond acceptor ability and can be associated with the thermal stability of the gel, whereas the  $\pi^*$  parameter accounts for the polarisability and plays a key role in solvation processes that occur during the gelation phenomenon.

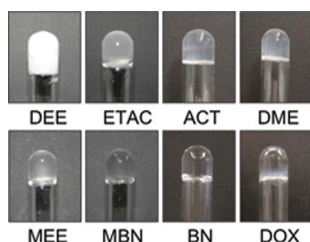
However, in contrast to most of the organogels reported in the literature so far, the systems described here represent one of the most remarkable examples of sol-to-gel-to-crystal phase evolution.<sup>32</sup> In this sense, the unique location of these transient gels right on the border between dissolution and crystallisation could contribute to explaining the lack of significant correlation between solvent parameters (*i.e.* relative permittivity and Kamlet–Taft parameters) and gel properties (*i.e.* thermal and temporal stability).<sup>26</sup> Nevertheless, it was still possible to clearly differentiate the ability of the solvent to be gelled by the MGS as a function of the Kamlet–Taft parameters fitted by a Gaussian function (Fig. 5). Typically, the solvents with higher tendency to form relatively stable gels were those presenting, simultaneously, no hydrogen-bond donor ability (*e.g.*  $\alpha \approx 0.0$ ), intermediate hydrogen-bond acceptor ability (*e.g.*  $\beta \approx 0.4$ ), and moderate polarisability (*e.g.*  $\pi^* \approx 0.6$ ). In contrast, solvents characterized by either lower or higher  $\beta$  and  $\pi^*$  values afforded precipitation or complete solubilisation of the mixture, usually regardless of the  $\alpha$  value.

Most of the formed organogels were off-white opaque with different degrees of translucence (Fig. 6), indicating the formation of aggregates smaller than  $\lambda = 400$ –700 nm (wavelength range of visible light). Only a few gels (*e.g.* THF, DOX, BN, and NM) were optically transparent or slightly turbid.<sup>26</sup>

During the evaluation of the temporal stability of the gels we were able to visualize a fascinating “arm wrestling” competition between gelation and crystallisation phenomena. The growth of (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride crystals (*vide infra*) inside the gel matrix was directly associated with the gel



**Fig. 5** Gaussian-like correlation between  $\beta$  and  $\pi^*$  solvent parameters and gelation ability of MGS. The model was built using 29 solvents.



**Fig. 6** Digital photographs of selected organogels made in various solvents showing different degrees of translucence.

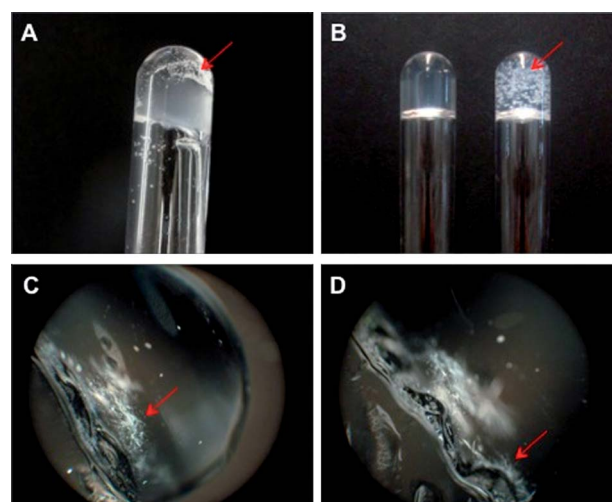
weakening over time (Fig. 7). Thus, the temporal stability of the gels, ranged from hours to several days (Table 1), represented an evident signature of the crystallisation kinetics. In many cases visible small crystals inside the gel matrix could be observed after the first day, even in those cases where the bulk material resisted the inversion of the test tube. It is important to mention that the non-gelled liquid presented in the samples should be removed as soon as possible, since it contributes to weaken the gels. The weak nature of the transient gels and the inherent crystallisation process make also possible to observe continued leaking of solvent over time in some of the samples, even when the initial non-gelled liquid is removed. Dynamic gel–crystal transitions have been previously related to the Ostwald rule of stages.<sup>33</sup>

Connecting to existing systems, the growth of superior inorganic, organic and protein crystals within supramolecular gels as media has been successfully used over decades<sup>34</sup> and has recently attracted also significant attention as a versatile new tool in pharmaceutical polymorph screening.<sup>35</sup>

Very interestingly, the use of MGS prepared from (1*R*,2*R*)-1,2-diaminocyclohexane and L-tartaric acid (ratio 1 : 1) instead of the preformed salt also afforded the formation of gels albeit with *ca.* 4-fold lower temporal stability.

### Thermal characterization

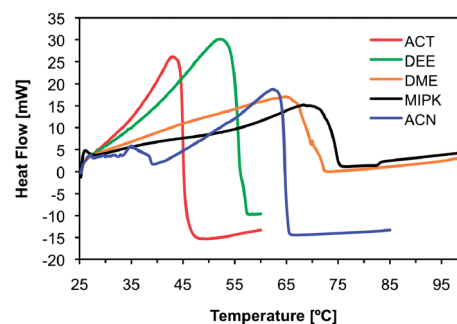
Despite the non-covalent nature of these supramolecular gels, they did not present thermoreversibility. As it happens when the samples are submitted to a mechanical stress, heating the gels caused their destruction by inducing the formation of (1*R*,2*R*)-



**Fig. 7** Formation of crystals (arrows) inside the gel matrix. (A) Partial destruction of the ACN-gel after crystallisation. (B) Comparison between initial translucent ACN-gel and crystal-containing gel prepared with 200  $\mu$ L of MGS. (C and D) Optical microscope images of early crystals formed close to the interface gel–air (solvent = ETAC). Note: the bottom border of the test tube is observable in (C).

1,2-diaminocyclohexane dihydrochloride as a white precipitate, which is fully insoluble in the solvent medium and unable to get back into the solution upon heating. This particular thermal behaviour made the “dropping ball method”<sup>36</sup> inappropriate for the thermal characterization of these materials due to the lack of a clear transition to a liquid phase. Moreover, heating the samples caused in many cases a violent ejection of the solid material due to the fast evaporation of the solvent trapped in the interstices. Although no reproducible values could be obtained using the “dropping ball method”, DSC measurements (Fig. 8) provided reliable information about the first endothermic transition, which was associated with the temperature at which the destruction of the gel network takes place ( $T_d$ ).<sup>26</sup>

In contrast to most supramolecular gels, in which the gel-to-sol transition temperature clearly increases with the concentration of the gelator, the  $T_d$  in our materials was only slightly enhanced with the amount of MGS used in the experiments.<sup>26</sup> However, DSC was sensitive enough not only to detect this enhancement but also the weakening of the material (decrease of the  $T_d$ ) when



**Fig. 8** DSC thermograms of different gels (for clarity, only a selection is shown here). Additional spectra can be found in the ESI†. Each DSC plot represents the average of two random measurements of gel samples prepared independently.



the amount of MGS induced the above-mentioned crystallisation process. For instance, the gel made in 1,4-dioxane showed the first endothermic transition at *ca.* 81, 84 and 88 °C using 40, 50 and 75  $\mu\text{L}$  of MGS respectively. However, the use of higher amounts of MGS, *i.e.* 100  $\mu\text{L}$ , destabilized the gel phase decreasing the  $T_d$  value until *ca.* 83 °C.<sup>26</sup>

### Influence of the components in the gelation ability of the MGS

Considering that chirality doubtless plays a central role in the functional property of gel-based materials,<sup>37</sup> and that our MGS is formed by chiral building blocks, we decided to investigate the effect that the enantiomeric purity of 1,2-diaminocyclohexane tartrate salt could have on the gel formation. All materials obtained using non-enantiomerically pure MGS solutions (*i.e.* 0%  $\leq$  salt ee  $\leq$  80%) were unable to resist without flowing the inversion of the test tube, despite the formation of small pieces of jelly-like matter that clearly gained consistence upon increasing the optical purity of the tartrate salt.<sup>26</sup> Stable-to-inversion of the test tube gels was only obtained when enantiomerically pure MGS was used. As expected, enantiomeric MGS showed identical gelation properties. Moreover, MGS based on (1*R*,2*R*)-1,2-diaminocyclohexane D-tartrate yielded gels with much lower temporal stability than its diastereomeric counterpart when prepared under identical experimental conditions, due to very fast crystal formation in the former.<sup>26</sup>

Moreover, we also studied the effect of the salt structure by replacing in the original MGS either the L-tartaric acid by different dicarboxylic acid derivatives or the (1*R*,2*R*)-1,2-diaminocyclohexane by alternative diamines. However, either turbid gelator solutions or non-stable gels were obtained with other diamines.<sup>26</sup> Nevertheless, the gelator system showed a higher tolerance towards the structure of the diacid counterpart. Thus, transient gels in different organic solvents could be obtained using MGS based on diethyl L-tartrate, succinic acid, adipic acid, dibenzoyl L-tartrate and L-(–)-malic acid. However, the temporal stability of these gels was at best half of that made with the MGS based on (1*R*,2*R*)-1,2-diaminocyclohexane and L-tartaric acid under the same conditions.<sup>26</sup> Among the different acids, the gels with higher stability (*ca.* 1 day) were obtained with dibenzoyl L-tartrate and L-(–)-malic acid, which pointed out the importance of both carboxylic acid groups (somewhat higher than the hydroxyl groups) and a chiral moiety for the formation of relatively self-standing gel networks.

In addition, a series of experiments demonstrated that each component presented in the optimal MGS was necessary for the formation of relatively stable gels. Thus, the use of a solution prepared in the absence of L-tartaric acid (*i.e.* (1*R*,2*R*)-1,2-diaminocyclohexane + MeOH (*ca.* 0.13 M in diamine) + HCl 37 wt.% in aqueous solution) resulted in the formation of either very weak partial gel-like materials or precipitates in less than 1 h.<sup>26</sup> On the other hand, the replacement of MeOH by other alcohols like EtOH, *i*-PrOH or *n*-BuOH did not allow the tartrate salt to be dissolved not even in the presence of 2.4 equiv. of HCl.

Concerning the role of the mineral acid, the use of 48% HBr instead of 37% HCl also allowed the formation of gels albeit with much lower temporal stability (*ca.* 80% lower than with the optimal MGS) due to the faster formation of crystals.<sup>26</sup> Remarkably, the amount of water in the MGS provided by the

use of 37 wt.% aqueous HCl was found to be necessary for the formation of gels with longer temporal stability. On the other hand, the presence of too much water (*e.g.* addition of 1 extra equivalent of water) induced the crystallisation of (1*R*,2*R*)-1,2-diaminocyclohexane dichloride in only 1 h.<sup>26</sup>

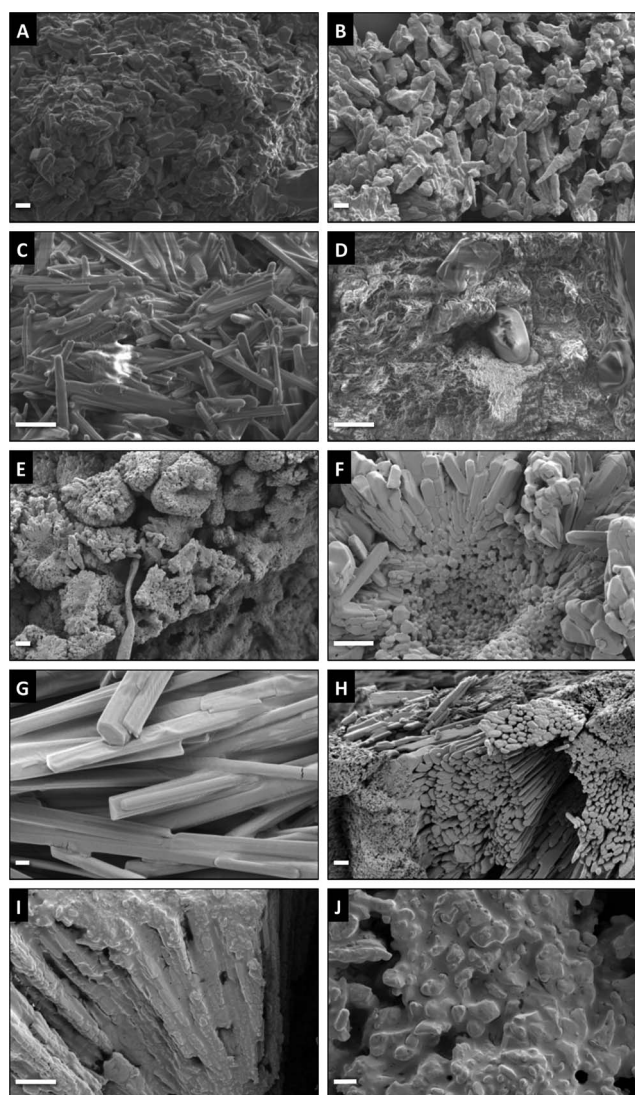
### Microscopy studies

Scanning electron microscopy (SEM) imaging was used to gain insight into the microstructure of the aggregates in different solvents. The existence of the metastable gel state very close to a crystalline phase was somehow also supported by the SEM images of high aspect ratios (Fig. 9). A highly entangled fibrillar-like morphology could be distinguished in the freeze-dried gel derived from the gel in 1,4-dioxane (Fig. 9D). However, most of the samples were characterized by the presence of aligned basalt-like (Fig. 9C, F–H) or cobbled paved-like densely packed structures (Fig. 9A, B and J), depending on the solvent used to prepare the gels. In general, the former structures presented uniform diameters of 2–3  $\mu\text{m}$ , whereas the latter ones were differentiated with large cluster aggregates of 20–40  $\mu\text{m}$  in diameter.

To be certain that the observed structures were not artefacts, we also took atomic force microscopy (AFM) 3D images of the surface topography, which were in agreement with the SEM images (Fig. 10). In general, the photographs showed aligned mountain-range-shaped surfaces with average heights in the range of 25–100 nm and apparent diameters of about 100–200 nm for the largest individual feature.<sup>26</sup> The lower limit was not considered significant as it is dictated by the size of the AFM tip.

### Dynamic rheological measurements of model gels

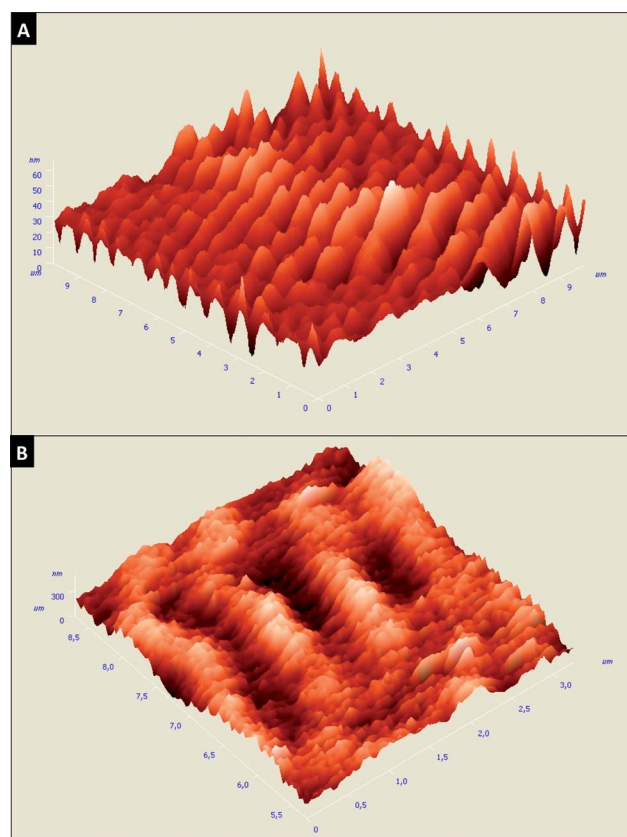
We used oscillatory rheological measurements to confirm the actual gel state of the short-lived materials (storage modulus  $G'$  > loss modulus  $G''$ ) and evaluate their mechanical response within a linear viscoelastic regime of strain and frequency. Dynamic frequency sweep (DFS) and dynamic strain sweep (DSS) experiments highlighted the viscoelastic and fragile nature of the gels, which were destroyed at low frequency in the range of 1–8% strain (Fig. 11, top). A considerable angular frequency dependence of the solid modulus was more evident for the gels that showed also lower temporal stability. Further dynamic time sweep (DTS) experiments (at 0.1% strain and  $\omega = 1$  Hz frequency) showed that  $G''$  was about one order of magnitude lower than  $G'$  indicating that the gels presented poor flexibility (Fig. 11, bottom). Moreover, the plot as a function of ageing time showed a fast decrease of the both  $G'$  and  $G''$  at almost the same rate. After only 10 min the solid modulus showed already a dramatic reduction (over 70% of the initial value!), pointing out the low tolerance of the gel matrix to the external shear force, which was in agreement with the easy disruption and liquid leakage of the transient gels observed for example during their manipulation with a spatula. As indicated by the rates of decrease in modulus, the mechanical damping properties of the materials did not suffer major changes during the first 10 min of the experiment (constant  $\tan \delta$  ( $G''/G'$ ) value  $\sim 0.2$  to 0.3). However, a rise in the  $\tan \delta$  value was evident as progressing the deterioration of the gel phase.<sup>26</sup>



**Fig. 9** SEM images of xerogels prepared from the gels made in different solvents as depicted in Table 1. (A) Gel made in ETAC, scale bar = 20  $\mu\text{m}$ ; (B) gel made in DME, scale bar = 20  $\mu\text{m}$ ; (C) gel made in THF, scale bar = 10  $\mu\text{m}$ ; (D) gel made in DOX, scale bar = 10  $\mu\text{m}$ ; (E) gel made in BN, scale bar = 20  $\mu\text{m}$ ; (F) gel made in BN, scale bar = 10  $\mu\text{m}$ ; (G) gel made in ACN, scale bar = 1  $\mu\text{m}$ ; (H) gel made in ACN, scale bar = 20  $\mu\text{m}$ ; (I) gel made in MBN, scale bar = 10  $\mu\text{m}$ ; and (J) gel made in DEE, scale bar = 30  $\mu\text{m}$ .

### Mechanistic considerations

The foregoing results have clearly demonstrated the formation of transient gels by using the described MGS based on (1*R*,2*R*)-1,2-diaminocyclohexane *L*-tartrate. Although the formed extended non-covalent network is stable, it is not the thermodynamic minimum. A previous detailed crystallographic study of this salt demonstrated that it exhibits a highly interconnected bidirectional hydrogen-bonding polymeric network. The constitutional element of the supramolecular aggregate is a tweezer-shaped pattern involving hydrogen-bonding interactions between ammonium nitrogen (donors) and hydroxyl oxygen (acceptors) (Fig. 12). In this assembly the ammonium groups are hydrogen-bonded to carboxylate groups in one

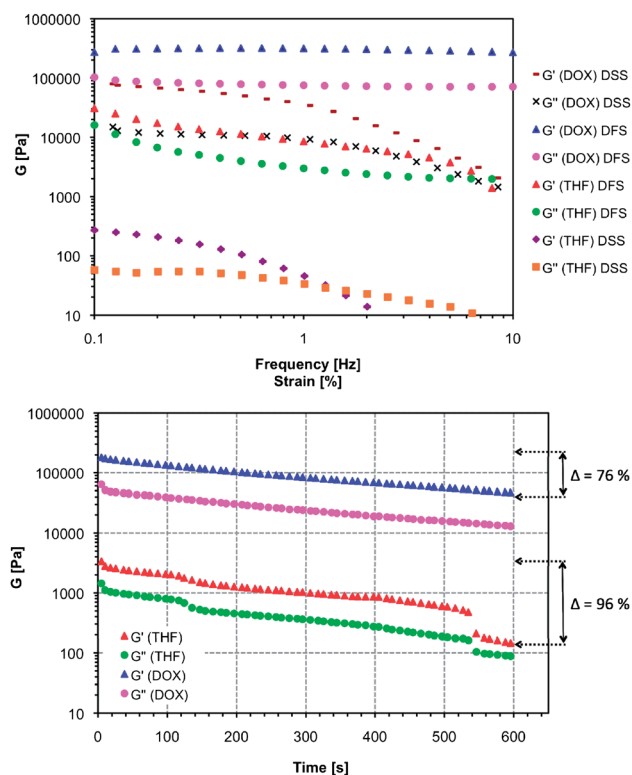


**Fig. 10** 3D-Surface topographic AFM images. (A) 10  $\times$  10 microns AFM image of the xerogel prepared from the gel in BN; (B) 8.5  $\times$  3 microns AFM image of the xerogel prepared from the gel in ETAC.

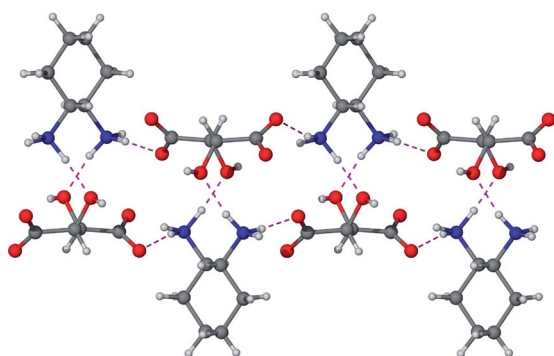
direction and to hydroxyl groups in the other. Such pattern of interactions needed for the development of an extended network is determined by the defined chiral centers in the tartrate salt. Canal-like cavities delimited by the carboxylate, ammonium and hydroxyl groups are easily envisaged from the top view of the assembly.<sup>38</sup>

A plausible mechanism to explain the formation of the short-lived gel is indeed based on the compact nature of the tartrate salt **1**. When **1** is suspended in MeOH, the strongly hydrogen-bonded polymeric system does not interact efficiently with the solvent because of its inaccessibility. However, in the presence of aqueous HCl, the ion-paired carboxylate-ammonium groups are initially surrounded by chloride ions (anion exchangers), water molecules and solvent molecules of the polar solvation shell.<sup>39</sup> This situation accommodates a complex hydrogen-bonded network, involving all these species, which now becomes soluble in MeOH and stable enough to survive within a metastable phase, which slowly tends to evolve to the thermodynamic equilibrium position. Such energetic minimum is defined by the crystallisation of the poorly soluble (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride (**4**)—upon completion of the ionic dissociation-exchange process—and the consequent release of soluble *L*-tartaric acid (**3**) (Fig. 13). Nevertheless, when a small amount of the above methanolic solution (MGS **2**) is mixed with another solvent that is a moderate hydrogen-bond acceptor, non-protic and less polar than MeOH, the solubility of the





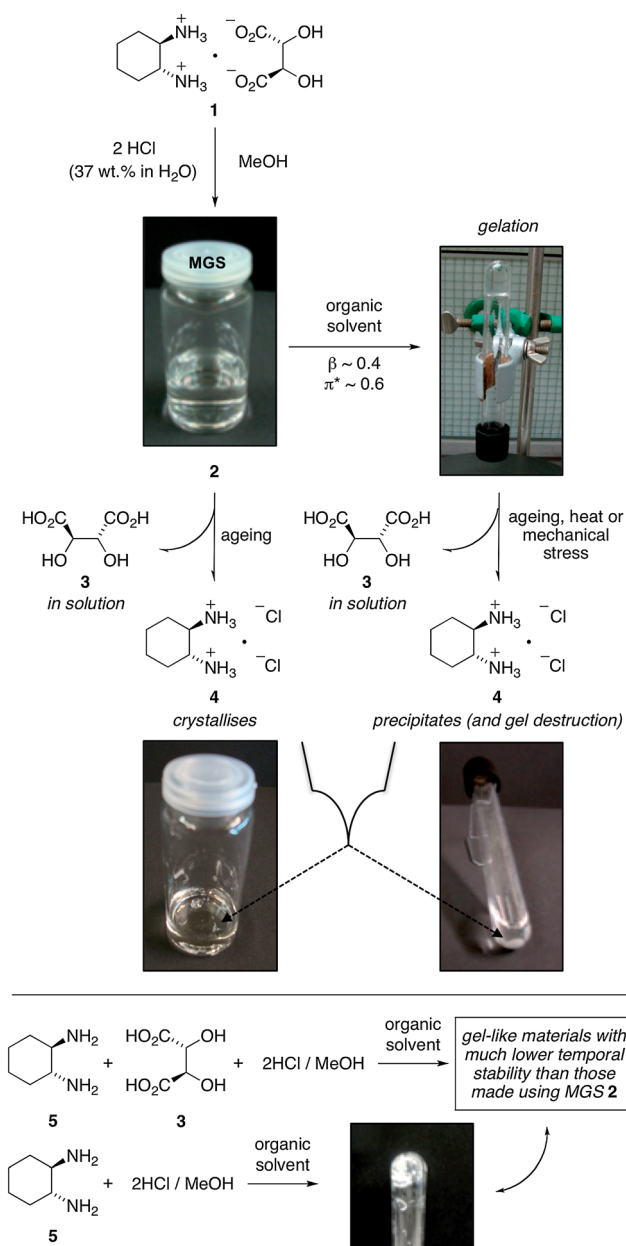
**Fig. 11** DFS, DSS (*top*) and DTS (*bottom*) rheological measurements of model transient gels prepared in THF and DOX.



**Fig. 12** Top view of the tweezer-shaped hydrogen-bonding between amino and hydroxy groups obtained from the crystallographic data of (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate.

multicomponent aggregates (which act as a supramolecular synthon<sup>40</sup>) decreases but it is still held within the dense hydrogen-bonded network.

In the above situation, an elusive balance of interactions between MeOH and H<sub>2</sub>O molecules and those of the organic non-protic solvent should take place. This allows the interfacial stabilization of the tartrate complex for enough time to permit its isotropic supramolecular assembly of limited solubility before the ionic exchange is completed (collapse of the gel and segregation of **4** as an amorphous precipitate—intergrown aggregates). The exhaustive study carried out with several multicomponent solutions designed within a 2D experimental matrix (salt concentration/equiv. HCl) has allowed us to



**Fig. 13** Overview of MGS-induced crystallisation and gelation processes, and further destructive-evolution of the latter by precipitation of amorphous solids (*top*). Influence of (1) the preformed ionic hydrogen-bonded polymeric structure of the salt **1** and (2) the presence of tartaric acid partner on the stability of the aggregates (*bottom*).

recognize this intriguing equilibrium state at both microscopic and macroscopic scales.

As we have shown earlier, the crystallisation rate of the dichloride salt can be fine-tuned by, among other factors, the concentration of **1** and the amount of HCl presented in the mixture. Thus, a careful preparation of the MGS is necessary to ensure reproducible and optimal conditions for the formation of transient gels. Due to the strong hydrogen-bonding network of the metastable gels, an additional energetic contribution (*e.g.* mechanical stress, heat) is required to accelerate the irreversible transition to the thermodynamically stable equilibrium position,

which otherwise will simply take place over time. All the products were unequivocally characterized by NMR and elemental analysis, as well as by XRD in the case of crystalline **4** obtained from MGS **2**.<sup>26</sup>

The exceptional ability of chiral *trans*-1,2-diaminocyclohexane to behave as an assembler of supramolecular hydrogen-bonding structures has been previously reported,<sup>41</sup> and it is in perfect agreement with our observations. Indeed, the proposed plausible gelation mechanism based on the HCl-induced ionic dissociation-exchange of **1** and the formation of a transient chloride-containing assembly in solution, resembling that in the crystalline state,<sup>38,40</sup> are supported by the series of experimental evidence discussed along the different sections of this manuscript, namely:

(1) the formation of jelly aggregates with much lower stability when either (a) the MGS was prepared using (1*R*,2*R*)-1,2-diaminocyclohexane and L-tartaric acid instead of its pre-organized hydrogen-bonded polymeric salt **1**, favouring a much faster formation of the dichloride salt **4**; (b) the tartaric acid counterpart was eliminated from the multicomponent solution; (c) the use of aged MGS (which is most likely on its way to the equilibrium position); (d) the tartaric acid or the diaminocyclohexane was exchanged by alternative diacids or diamines respectively (which cannot replicate the strongly hydrogen-bonded, ion-paired situation of **1**), or (e) non-enantiomerically pure MGS solutions were used.

(2) the thermodynamic formation of dichloride salt **4** as a crystalline solid from the initial MGS or an amorphous solid after destruction of the gel phase;

(3) the delicate balance between the concentration of each component to maximize the half-life of the transient gels;

(4) the evidence of transient gelation even when highly concentrated MGS solutions were used (despite the solubility limitations of the system).

## Conclusions

The formation of supramolecular organogels is a result of a well-balanced combination of numerous non-covalent interactions, including those between gelator–gelator, gelator–solvent, aggregate–solvent and solvent–solvent molecules. Usually, a lack of control over these interactions caused an unpredictable competition between crystallisation and gelation phenomena. The peculiar synergistic multicomponent gelator solution described in this manuscript [*ca.* 0.13 M (1*R*,2*R*)-1,2-diaminocyclohexane L-tartrate in MeOH + 2.4 equiv. HCl (37 wt.% in aqueous solution)] has showed a remarkable ability to kinetically frustrate a crystallisation process allowing the evolution of transient gel aggregates at low temperatures and in a number of oxygenated and nitrogenated solvents with moderate polarity. The foregoing results support a gelation mechanism based on the self-assembly of the tartrate salt resembling somehow that in the crystalline state. The experimental evidence points out a key role of the (1*R*,2*R*)-1,2-diaminocyclohexane as the major structural director of the assembly process, whereas the complementary tartaric acid partner acts as an important extender and stabilizer of the supramolecular network. The hydrochloric acid is involved in the solubilisation of the salt through a thermodynamic ionic dissociation-exchange process, which ends up with

the formation and segregation of (1*R*,2*R*)-1,2-diaminocyclohexane dihydrochloride salt. As a consequence, an irreversible destruction of the gel takes place, which indicates the metastable nature of this phase that cannot be accessed from the thermodynamically equilibrated state. Despite the expected disturbance of the hydrogen-bonding caused by the presence of methanol and HCl, the real extension of such disruption is not yet clear in the MGS (which most likely denotes a highly organized hydrogen-bonded liquid system as observed in liquid water). In this sense, both MGS and its gels represent an extraordinary example of persistence of memory of the parent assembly of **1** for a considerable length of time, showing similarities with the standard colloidal gels.<sup>42</sup>

It seems evident that the formation of the described transient gels depends on the ability to maintain a judicious balance between the above-mentioned non-covalent interactions (especially anisotropic interactions between aggregate and solvent molecules) with different energetic contributions and a significant electrostatic component.<sup>43</sup> In this sense, besides the chloride-bridged transient assembly, the possibility of MeOH-induced microsolvation<sup>44</sup> processes to allow the fine-tuning of the hydrogen-bonding pattern should be also considered. Moreover, it would be desirable to gain insights into a number of important physical-chemical aspects such as the exact mode of cation–anion association, the dissociation enthalpies of the critical bonds, the exact nature of the supramolecular nucleating species<sup>45</sup> before crystallisation of **4** or the interplay between the solvent system and the salt **1** in promoting the optimal ion-pairing for the stable self-assembly growth. Nevertheless, the significant complexity of this particular cooperative multicomponent liquid system makes the performance of the required experimental/theoretical<sup>46</sup> studies still a great scientific challenge.

Undoubtedly, the isolation and study of MGS-based gels provide an interesting perspective for the development of new gelators and a versatile platform for the study of pre-existing interfaces during molecular crystallisation. Moreover, we have recently found that some polar aprotic solvents like DMSO could, at least to some extent, replace MeOH in the gelator solution. Further investigations directed towards the detailed study of these new gelator solutions, extending the lifetime of the transient gels based on calculated solubility parameters and Teas plots, controlling the kinetics of their structural transitions and understanding the dynamic of the hydrogen-bonded network are currently underway in our laboratories.

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