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Cooperative self-assembly of linear organogelators. Amplification of chirality and crystal growth of pharmaceutical ingredients†

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Linear organogelators 1 and 2, which self-assemble cooperatively into fibrillar structures, act as efficient crystal growth media for common pharmaceutical ingredients like ASP, CAF, IND and CBZ.

The self-assembly of low-molecular-weight organogelators (LMWGs) renders supramolecular gels by the operation of hierarchical non-covalent forces. These organized structures are being applied in a number of research areas like drug delivery systems, biomaterials, electronic devices, and templates for nanostructures.[1] Particularly interesting is the exploitation of supramolecular gels as media for the crystal growth of molecular species since it is possible to attain different polymorphs and crystal habits, a key issue in pharmaceutical industry.[2] To the best of our knowledge, the mineralization of hydroxyapatite directed by the fibres resulting in the self-assembly of an amphiphilic peptide,[3] the growth of calcium carbonate into a bis-urea hydrogel,[4] and the crystal growth of a variety of pharmaceuticals into bis-urea based gels[5] are the scarce examples of the use of LMWGs as the crystallization media. An outstanding advantage of supramolecular gels over conventional hydrogels—amply utilized for the growth of crystals of different nature—is that the sol-to-gel transition can be modulated by a number of stimuli like pH, sonication, light irradiation, or addition of anions.[6]

Most of the reported organogelators self-assemble into monodimensional fibrillar structures that originate the gel upon capturing the solvent. Therefore, from a conceptual point of view, the formation of a supramolecular gel can be considered as an example of supramolecular polymerization in which single supramolecular polymers bundle to form the gel.[7] The supramolecular polymerization processes involving chiral building blocks are of special significance since they have been shown as powerful tools to investigate the amplification of chirality, that is, the process in which minute enantiomeric excesses are able to convert racemates into enantiomerically enriched mixtures.[8] Herein, the supramolecular polymerization mechanism, the amplification of chirality experienced by achiral **1** upon adding small amounts of chiral **2**, and the use of these organogelators as crystal growth media for common pharmaceutical ingredients like aspirin (ASP), caffeine (CAF), indomethacin (IND) and carbamazepine (CBZ) (Fig. 1) are investigated.

Organogelators **1** and **2** are readily prepared in only four synthetic steps following previously reported procedures (Scheme S1, ESI†).[9] All the intermediates and the final compounds have been fully characterized by NMR and FTIR spectroscopy and HRMS (ESI) spectrometry (see ESI†). We have initially utilized FTIR spectroscopy to evaluate the strength of the H-bonding interactions and also the interdigitation of the peripheral paraffinic side chains, responsible for the gelation of these compounds. The stretching N–H and amide I bands as well as the bending amide II band of **1** ($\nu \sim 3277$, 1633, and 1544 cm^{-1}) and **2** ($\nu \sim 3290$, 1635, and 1543 cm^{-1}) suggest that the amide groups are strongly H-bonded (Fig. S1, ESI†).[10a,b] However, a more efficient interdigitation of the alkyl chains in compound **1** ($\nu \sim 2921$ and 2853 cm^{-1}) in comparison to compound **2** ($\nu \sim 2954$, 2927 and 2868 cm^{-1}) can be inferred from the sharp waves corresponding to the $-CH_2-$ groups (Fig. S1, ESI†).[10c]

The self-assembly mechanism of the chiral organogelator **2** has been investigated by circular dichroism (CD) in methylcyclohexane (MCH) (Fig. 2). The bisignated Cotton effect—with a positive maximum at 222 nm and a negative maximum at 266 nm—implies the organization of compound **2** into left-handed helical structures.[11] Variable temperature (VT) CD experiments

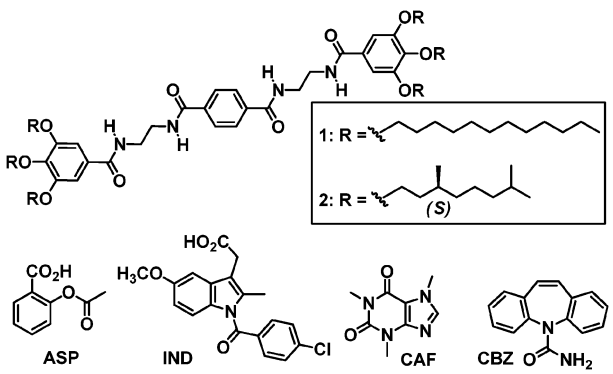

Fig. 1 Chemical structure of the organogelators **1** and **2**, and aspirin (ASP), caffeine (CAF), indomethacin (IND), and carbamazepine (CBZ).

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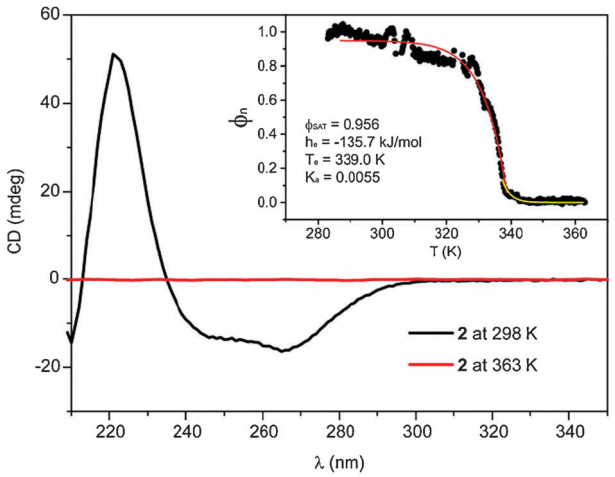

Fig. 2 CD spectra of **2** (MCH, 1×10^{-5} M). The inset depicts the melting curve from 363 to 283 K at intervals of 1 K min^{-1}. Red and yellow lines in the inset are the fits corresponding to the elongation and nucleation processes, respectively.

show that the sample becomes CD-silent upon heating at 363 K the resulting melting curve being non-sigmoidal which supports a nucleation–elongation mechanism.[7] Fitting these data to eqn (1) and (2) allows the extraction of relevant thermodynamic information like the enthalpy released during elongation (h_e), the temperature at which the nucleation regime changes into elongation (T_e), and the degree of cooperativity expressed by K_a.[12]

$$\phi_n = \phi_{SAT}\left(1 - \exp\left[\frac{-h_e}{RT_e^2}(T - T_e)\right]\right) \quad (1)$$

$$\phi_n = K_a^{1/3}\exp\left[(2/3K_a^{-1/3} - 1)\frac{h_e}{RT_e^2}(T - T_e)\right] \quad (2)$$

The supramolecular polymerization of chiral **2** is highly exothermic ($h_e = -135.7$ kJ mol^{-1}), with K_a and T_e values of 5.5×10^{-3} and 339 K, respectively. These data imply that the combination of four H-bonded amide groups, the π–π stacking of the three benzene rings and the van der Waals interactions between the peripheral chains strongly reinforce the self-assembly of these organogelators in comparison with other linear bis-amides previously reported by our group that did not show a significant chirooptical response.[13]

The dynamic character of supramolecular polymers allows the intercalation of minute amounts of chiral species in a columnar supramolecular structure formed from achiral monomeric units. This amplification of chirality results in the conversion of an equimolar mixture of *P*- and *M*-type helices into an enantiomerically enriched mixture, in which only one of the two helices predominates.[8] The addition of increasing amounts of chiral **2** into a solution of achiral **1**, keeping constant the total concentration of the mixture, leads to the appearance of a chirooptical response that varies non-linearly with the amount of the chiral tetra-amide added (Fig. S2, ESI†).[8,14]

It is well-established that LMWGs usually self-assemble into monodimensional fibrillar structures with a strong trend to bundle. The resulting bundles of fibers originate the gel upon capturing the solvent. The FTIR and VT-CD data extracted

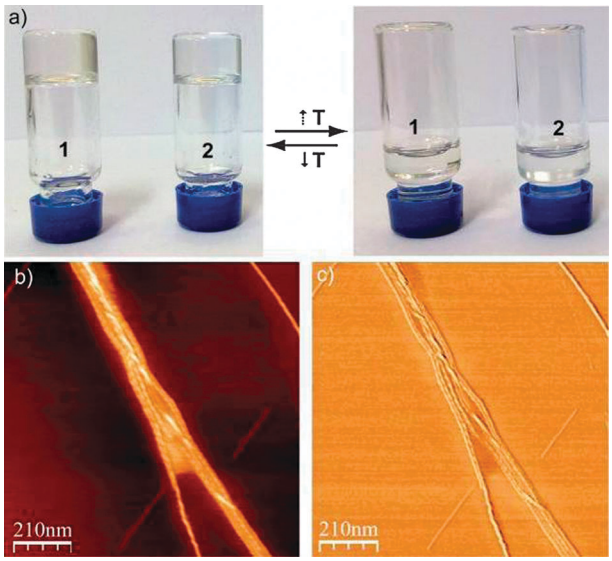

Fig. 3 (a) Pictures of the gel–sol phase transitions of **1** and **2** (toluene, 1 wt%, respectively). AFM height (b) and phase (c) images of the diluted (1×10^{-5} M in toluene) gel of **2** onto HOPG (*z* scale = 15 nm).

for **1** and **2** indicate that these compounds self-assemble into helical, columnar supramolecular structures that, subsequently, interact through the peripheral paraffinic chains. The resulting bundles of fibers could form organogels. In fact, both **1** and **2** readily form colorless and highly transparent gels in toluene at a concentration of 1 wt%. These organogels were verified to be stable by inversion of the glass vial and experience a gel-to-sol transition upon heating (Fig. 3). The morphology of the supramolecular gels formed from **1** and **2** has been firstly studied by scanning electron microscopy (SEM). The SEM images demonstrate a very different morphology of the gels formed from achiral **1** or chiral **2**: while the organogel formed from **1** exhibits a dense network of intertwined fibrillar structures, this fibrillar network is not visualized in the organogel formed from **2** in which a smooth surface of globular aggregates with no pores between them is observed (Fig. S3, ESI†). To characterize the fine structure of the fibres constitutive of the gel, we have carried out an atomic force microscopy (AFM) analysis at different concentrations and surfaces. AFM images of the xerogels of **1** and **2** at 1×10^{-4} M in toluene, and using HOPG or mica as surfaces, confirm that the bundles are formed by intertwined long chiral fibres (Fig. S4 and S5, ESI†). The fibrillar nature of the aggregates formed by the self-assembly of gelator **2** is maintained even at very low concentration (1×10^{-5} M in toluene). Under these conditions, the AFM images also clearly show the presence of left-handed intertwined helical nanofibers in good agreement with the CD measurements performed in solution (Fig. 3b and c and Fig. S6, ESI†).

The gels formed from **1** and **2** have been utilized as the crystallization media for APIs like ASP, CAF, IND or CBZ that have been reported to crystallize in toluene as solvent (Table 1). All the crystallization experiments were done per duplicate. The crystals obtained inside the organogels can be easily recovered by successive rinsing of the mixture with toluene, shaking and filtering. This procedure does not alter the polymorphic outcome of the studied APIs and avoids the addition of any other chemical species.[5] The first entry in Table 1

Table 1 Crystallization of APIs in gels **1** and **2**, and in toluene as solvent[a]

API	Compound **1**	Compound **2**	Toluene
CBZ	III	II + III	III
ASP	I	I	I
CAF	II (β)	II (β)	II (β)
IND	III (β)	III (β)	III (β)

[a] Crystallization performed at a concentration of 1 wt% for both organogelator and API. In brackets, the Greek notation of polymorphs II and III of CAF and IND, respectively, is included.

shows the difference found in the polymorphism of CBZ crystallized inside the organogel prepared from **1** and **2** at 1 wt%. The XRD pattern of the CBZ crystals before and after washing with toluene remains unaltered (Fig. S7 and Tables S2–S7, ESI†). The XRD analysis of the CBZ crystals obtained from the gel of achiral **1** corresponds to polymorph III (Fig. S7 and Tables S2 and S5, ESI†, and Table 1), similarly to the crystals formed upon crystallization of CBZ in toluene (Fig. S8 and Table S8, ESI†).[15] However, the X-ray diffractogram of the crystals obtained inside organogel **2** and also in the organogel formed upon mixing **1** and **2** in a 9/1 ratio, respectively, shows peaks corresponding to a mixture of polymorphs II and III (Fig. S7 and S9, and Tables S3 and S6, ESI†).[15] It is well-known that the crystallization of CBZ in toluene is unreliable and is often controlled by rates of cooling and agitation. Therefore, the changes observed in the polymorphism of CBZ could be ascribed to the retardation of diffusion, nucleation and convection currents present in the crystal growth media and/or to a heteronucleation phenomenon.[16] The different polymorphic outcome of CBZ (1 wt%) upon modifying the concentration of organogelators **1** or **2** in toluene could be ascribed to heteronucleation (Table S1, and Fig. S10 and S11, ESI†). In addition, the different morphology of the organogels formed from achiral **1** and chiral **2**, demonstrated by the corresponding SEM images, could induce changes in the diffusion, nucleation and convection currents thus conditioning the polymorphic outcome of CBZ.

We have also tested the crystallization of ASP and CAF—able to crystallize into two polymorphs[17,18]—and IND, that can crystallize into four polymorphs,[19] inside the organogels obtained from **1** and **2** in comparison with toluene. These APIs did not exhibit any polymorphic difference as demonstrated by the corresponding X-ray diffraction (XRD) data (Fig. S12–S14, ESI†). Optical images of the CAF, and IND crystals obtained inside organogelators **1** and **2**, and also from pure solvent show a dense network of needle-like objects of bigger size than those observed in the solvent (Fig. S15, ESI†). In good correlation with the data previously reported for bis-urea based organogelators,[5] amides **1** and **2** act as efficient crystallization media for these APIs, although no differences in their polymorphism are observed.

In summary, we report on the cooperative supramolecular polymerization and amplification of chirality of simple, linear tetra-amides that self-assemble into helical structures by the operation of amide C═O···H–N H-bonds. These helical fibers have been visualized by AFM imaging. The interaction of single helical, columnar aggregates into bundles allows the gelation of toluene. The toluene organogels formed from **1** and **2** have been utilized as crystal growth media for common APIs like ASP, CAF, IND and CBZ. The crystals obtained inside the organogels can be easily recovered by successive rinsing of the mixture with toluene, shaking and filtering. This procedure does not alter the polymorphic outcome of the studied APIs and avoids the addition of any other chemical species and does not alter the crystallization outcome of the crystals.

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Notes and references

1 For recent reviews on LMWGs, see: (*a*) J. van Esch and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2000, **39**, 2263; (*b*) M. George and R. G. Weiss, *Acc. Chem. Res.*, 2006, **39**, 489; (*c*) M. Sada, N. Takeuchi, M. Fujita, M. Numata and S. Shinkai, *Chem. Soc. Rev.*, 2007, **36**, 415; (*d*) A. Ajayaghosh, V. K. Praveen and C. Vijayakumar, *Chem. Soc. Rev.*, 2008, **37**, 109; (*e*) J. W. Steed, *Chem. Soc. Rev.*, 2010, **46**, 3686; (*f*) J. W. Steed, *Chem. Commun.*, 2011, **47**, 1379.
2 (*a*) G. R. Desiraju, *Cryst. Growth Des.*, 2008, **8**, 3; (*b*) G. P. Stahly, *Cryst. Growth Des.*, 2007, **7**, 1007.
3 J. D. Hartgerink, E. Beniash and S. I. Stupp, *Science*, 2001, **294**, 1684.
4 L. A. Estroff, L. Addadi, S. Weiner and A. D. Hamilton, *Org. Biomol. Chem.*, 2004, **2**, 137.
5 J. A. Foster, M.-O. M. Piepenbrock, G. O. Lloyd, N. Clarke, J. A. K. Howard and J. W. Steed, *Nat. Chem.*, 2010, **2**, 1037.
6 (*a*) M.-O. M. Piepenbrock, G. O. Lloyd, N. Clarke and J. W. Steed, *Chem. Rev.*, 2010, **110**, 1960; (*b*) A. R. Hirst, B. Escuder, J. F. Miravet and D. K. Smith, *Angew. Chem., Int. Ed.*, 2008, **47**, 80028; (*c*) H. Maeda, *Chem.–Eur. J.*, 2008, **36**, 11274.
7 T. F. A. De Greef, M. M. J. Smulders, M. Wolffs, A. P. H. J. Schenning, R. P. Sijbesma and E. W. Meijer, *Chem. Rev.*, 2009, **109**, 5687.
8 A. R. A. Palmans, *Angew. Chem., Int. Ed.*, 2007, **46**, 8948.
9 (*a*) P. Mukhopadhyay, Y. Iwashita, M. Shirakawa, S. Kawano, N. Fujita and S. Shinkai, *Angew. Chem., Int. Ed.*, 2006, **45**, 1592; (*b*) S. Ghosh, X.-Q. Li, V. Stepanenko and F. Würthner, *Chem.–Eur. J.*, 2008, **14**, 11343.
10 (*a*) S. Prasanthkumar, A. Saeki, S. Seki and A. Ajayaghosh, *J. Am. Chem. Soc.*, 2010, **132**, 8866; (*b*) J. Puigmartí-Luis, V. Laukhin, A. P. del Pino, J. Vidal-Gancedo, C. Rovira, V. N. Laukhin and D. B. Amabilino, *Angew. Chem., Int. Ed.*, 2007, **46**, 238; (*c*) T. Nakanishi, T. Michinobu, K. Yoshida, N. Shirahata, K. Ariga, H. Möhwald and D. G. Kurth, *Adv. Mater.*, 2008, **20**, 443.
11 *Stereochemistry of Organic Compounds*, ed. E. L. Eliel, S. H. Wilen and L. N. Mander, Wiley-Interscience, Chichester, UK, 1994.
12 (*a*) P. Jonkheijm, P. van der Schoot, A. P. H. J. Schenning and E. W. Meijer, *Science*, 2006, **313**, 80; (*b*) M. M. J. Smulders, A. P. H. J. Schenning and E. W. Meijer, *J. Am. Chem. Soc.*, 2008, **130**, 606.
13 F. Aparicio, F. Vicente and L. Sánchez, *Chem. Commun.*, 2010, **46**, 8356.
14 Unfortunately, the chemical structure of the organogelators impedes to record CD spectra in toluene since the solvent absorbance will overlap with the dichroic response of the chiral compound.
15 (*a*) A. L. Grzesiak, M. D. Lang, K. Kim and A. J. Matzger, *J. Pharm. Sci.*, 2003, **92**, 2260; (*b*) M. M. J. Lowes, M. R. Cairo, a. P. Lotter and J. G. van der Watt, *J. Pharm. Sci.*, 1987, **76**, 744; (*c*) J. P. Reboul, B. Cristau, J. C. Soyfer and J. P. Astier, *Acta Crystallogr., Sect. B*, 1981, **37**, 1844; (*d*) M. D. Lang, J. W. Kampf and A. J. Matzger, *J. Pharm. Sci.*, 2002, **91**, 1186; (*e*) J.-B. Arlin, L. S. Price, S. L. Price and A. J. Florence, *Chem. Commun.*, 2011, **47**, 7074.
16 *Crystal Growth in Gels*, ed. H. K. Henisch, Pennsylvania State University Press, University Park, 1970.
17 (*a*) A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem., Int. Ed.*, 2007, **46**, 615; (*b*) A. D. Bond, R. Boese and G. R. Desiraju, *Angew. Chem., Int. Ed.*, 2007, **46**, 618.
18 (*a*) D. J. Sutor, *Acta Crystallogr.*, 1958, **11**, 453; (*b*) G. D. Enright, V. V. Terskikh, D. H. Brouwer and J. A. Ripmeester, *Cryst. Growth Des.*, 2007, **7**, 1406.
19 N. Kaneniwa, M. Otsuka and T. Hayashi, *Chem. Pharm. Bull.*, 1985, **33**, 3447.