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## COMMUNICATION

## A new family of "*clicked*" estradiol-based low-molecular-weight gelators having highly symmetry-dependent gelation ability<sup>†</sup><sup>‡</sup>

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Reported herein is the discovery of a novel family of "*clicked*" estradiol-based LMWGs whose gelation ability highly depends on the gelator symmetry. These LMWGs that gel different organic solvents in the presence of  $H_2O$  even at concentrations as low as 0.04 wt% are readily accessible using "*click*" chemistry.

The search for physical gels derived from low-molecular-weight gelators (LMWGs) is currently an area of growing interest due to their physical properties and practical applications in different fields. Structurally diverse gelators that self-assemble into entangled 3D networks through cooperative noncovalent interactions have been reported.<sup>1</sup> However, in spite of the remarkable achievements of supramolecular chemistry in the controlled self-assembly of small molecules, the structural requirements for these LMWGs are still poorly understood. Therefore, a rational correlation between the molecular structure and the gelation ability is a challenging goal.

"Click" chemistry has emerged as a versatile tool in different areas of research.<sup>2</sup> Although this methodology has been widely applied for the synthesis of polymeric gelators,<sup>3</sup> examples of the use of "click" chemistry for the preparation of LMWGs gels are scarce.<sup>4</sup> During the course of our research program<sup>5</sup> directed to the preparation of natural product based macrocycles,<sup>6</sup> we observed that  $C_2$  symmetric ethynylestradiol-based precursor **2a** formed swellable materials in aqueous DMSO (Scheme 1). Subsequently, structurally diverse related dimeric hybrids such as TMS-protected dimers **1a–d** and terminal bis-alkynes **2a–d** 

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<sup>‡</sup> The paper is dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.



Scheme 1 "Clicked" estradiol-based dimers.

were tested for gelation properties.<sup>6</sup> o- and p-Phenyl disubstituted derivatives **2a–b** were able to gel different non-protic polar solvents such as DMSO, DMA, DMF and *N*-methylpyrrolidone upon addition of water, gently heating and subsequently cooling to room temperature. In this way robust and transparent gels at concentrations below 1 wt% were obtained. It is worth noting that the use of simple and easy to make estrone derivatives like **2** as "gelating" scaffolds is unknown.<sup>7</sup>

Once demonstrated the gelation ability of dimers 2a-b the structural requirements for these compounds as LMWGs and their mode of aggregation were investigated by varying systematically the different fragments within these amphiphilic molecules. The critical gelation concentration (CGC) of the gelators prepared through this work in DMSO/H<sub>2</sub>O (3/1 v/v) was next determined. Firstly, C2 symmetric estradiol-based compounds 3a-c lacking an ethynyl fragment at C-17 were prepared and tested. Estradiol-based dimers o-3a (2.3 mg mL<sup>-1</sup>) and p-3b (3.0 mg mL<sup>-1</sup>) were efficient gelators albeit slightly worse than compounds o-2a (1.5 mg mL<sup>-1</sup>) and p-2b (2.3 mg mL<sup>-1</sup>). Thence, the terminal triple bond located at C-17 is not crucial for the gelation process. By contrast, a change in the nature of the triazole-linked spacers seems to alter the gelation event. In fact, derivatives 2c and 2d bearing aliphatic taddol and ferrocenyl linkers, respectively, were inefficient in gelling any aqueous organic solvent tested. The absence of hydroxyl

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Complete experimental procedures and compound characterization data for the products described in the text, and the physicochemical characterization of the gels, including SEM and TEM data, as well as X-ray data for compound **3b**. CCDC 786367. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13251b

groups in bis-acetylated *o*-phenyl **4a** and the location of bulky TMS-alkynyl groups in dimers **1a–d** inhibited gelation providing only precipitates.

To establish the role of potential stacking interactions in assembling the gel, dimers **3e–f** bearing extended aromatic linkers were prepared (Scheme 1). Both biphenyl **3e** (1.5 mg mL<sup>-1</sup>) and fluorene **3f** (1.5 mg mL<sup>-1</sup>) derivatives produced improved CGC values with respect to those of the *p*-phenyl **3b** (2.3 mg mL<sup>-1</sup>) and **3a** (3 mg mL<sup>-1</sup>) counterparts.

With the aim to identify the minimum structural requirements needed for gelation we synthesized a series of monomers presenting phenyl **5–6** and pyrenyl **7–8** aromatic groups (Scheme 2). However, neither phenyl (**5–6**) nor pyrenyl (**7–8**) monomers gelled any solvent tested producing either precipitates or crystals.

The symmetry of the gelating agent was next addressed.  $C_3$  symmetric trimers **9a–b**<sup>6</sup> and **10** and  $C_2$  symmetric tetramer **11** were studied (Scheme 2). Trimeric structures **9a–b** and **10** did not form gels providing basically precipitates in all solvents tested. These results strongly contrast with the  $C_2$  symmetric tetramer **11**, which gelled DMSO/H<sub>2</sub>O (3/1 v/v) at concentrations as low as 0.37 mg mL<sup>-1</sup> (0.04 wt%). Furthermore, tetramer **11** was able to gel a wider range of aqueous solvents (DMSO, DMF, DMA, *N*-methylpyrrolidone, Py, AcOH and dioxane). These results demonstrate that tetrameric compound **11** is much more efficient than their dimeric analogues. In fact, tetramer **11** immobilizes aqueous solvents such as DMSO, DMF, DMA, and *N*-methylpyrrolidone at concentrations below 1.0 mg mL<sup>-1</sup> therefore falling into the category of "super-gelators".<sup>8</sup>



Scheme 2 "Clicked" estradiol-based compounds 5–11.

Results above show that the gelation ability of this new family of LMWGs is symmetry-dependent. In fact, while  $C_2$  symmetric dimeric and tetrameric estradiol-based structures



Fig. 1 Sol-gel transition temperatures (Tg) for gels 2a–b, 3a–b, 3e–f and 11/DMSO/H<sub>2</sub>O (3/1 v/v) as a function of gelator concentration measured by the "dropping ball method".

behave as LMWGs, their monomeric and  $C_3$  symmetric trimeric analogues do not.

To compare the thermal behaviour of the gels prepared throughout this work, **2a–b**, **3a–b**, **3e–f** and **11**/DMSO/H<sub>2</sub>O (3/1 v/v) gels with concentrations varying from 0.4 to 8.0 mg mL<sup>-1</sup> were studied by the "dropping ball method".<sup>9</sup> Fig. 1 shows that thermal stability of the gels prepared from gelators at different concentrations correlates well with their gelation ability and CGC values. Thus, gels derived from ethynyl estradiol-based dimers *o*-**2a** and *p*-**2b** present higher Tg than their dimeric analogues *o*-**3a** and *p*-**3b**, respectively. Furthermore, gels obtained from *o*-phenyl **2a** and **3a** are more resistant toward temperature than those prepared from *p*-phenyl **2b** and **3b**. A real improvement of thermal stability is attained when extended aromatic linkers (compare **3e** and **3f** with **3b**) or a  $C_2$  symmetric tetrameric core (compare **11** with **3a**) is employed.

The scanning electron microscopy (SEM) image of the xerogel of **3a** reveals well-defined shape fibers that are about  $2-30 \ \mu\text{m}$  wide and  $110-540 \ \mu\text{m}$  long. In most cases, these thick fibers have a tendency to form right-handed twisted ribbon morphology with a regular pitch (Fig. 2a). Furthermore, these fibers can undergo further aggregation giving rise to wire-like fiber bundles in the gel network (Fig. 2b). To get some insight into the interlayer interactions on the fiber structures, a high resolution transmission electron microscopy (HRTEM) characterization was carried out. The inset (Fig. 2c) shows a higher magnification micrograph of the end of the fibers, confirming that one fiber consists of many lamellae having crystalline domains.<sup>10</sup> Fig. 2e reveals a complex microstructure, where an amorphous matrix contains highly ordered crystallized



Fig. 2 SEM and TEM images of the xerogel of  $3a (0.7 \text{ wt\%})/\text{DMSO}/\text{H}_2\text{O} (v/v 2:1)$ . For additional images of 3a and 11 see the ESI.†

domains randomly oriented. An average interplanar distance of 3.6 Å between planes can be measured and fits well with the typical distance reported for  $\pi$ - $\pi$  stacking aromatic interactions.

A possible aggregation model for these  $C_2$  symmetric gelators may be based on the molecular structure of 3b-3CHCl<sub>3</sub>§. which was established by X-ray analysis (Fig. 3). This estradiol-based dimer forms infinite chains through O-H···O hydrogen bonds between terminal hydroxyl groups. These chains are closely assembled forming molecular planes through C(benzene)– $H \cdot \cdot \cdot O$ ,  $C(methylene) - H \cdots N$ and C(triazole)–H··· $\pi$  interactions (see ESI<sup>†</sup>). In the molecular planes, C-H axial bonds of one estradiol moiety are oriented towards the  $\pi$  cloud of the neighboring estradiol fragment. Layers are assembled through C(methylene)-H...N interactions and a  $\pi \cdots \pi$  stacking of the triazole moieties with an average interplanar distance of 3.5–3.6 Å. In the crystal, layers assembly for **3b** forms tubular voids of *ca*. 643  $Å^{3,11}$  It should be noted that although the crystal structure of  $3b^{12}$  may help to understand the self-assembling process of "clicked" gelators, great care must be taken because the single crystals were obtained from a solvent mixture (CHCl<sub>3</sub>/MeOH/hexanes) of different nature compared to that of the gel matrix. In this context, it is most likely that assembly in the gel state is initially driven by hydrophobic forces between estradiol fragments favoring  $\pi$ -stacking of the aromatic linkers and then lateral and directional hydroxyl groups at C-17 facilitate linear hydrogen-bonded polymeric chains.<sup>13</sup> In fact, C<sub>2</sub> symmetric dimeric and tetrameric structures would favor the formation of linear hydrogen-bonded aggregates by enforcing alignment along the axis oriented parallel to the hydrogen bonds between hydroxyl groups forming arrays of supramolecular polymeric chains that further assemble into fibres (see ESI<sup>†</sup>).



**Fig. 3** Crystal packing views showing layers assembly along the a axis with solvent molecules omitted for clarity (top), and a tubular void along the a axis including solvent molecules (bottom).

In summary, we reported the discovery of a novel family of estradiol-based LMWGs that gel different organic solvents in the presence of  $H_2O$  even at concentrations as low as 0.04 wt%. These compounds are readily accessible using "*click*" chemistry from commercially available starting materials. A structure– property relationship study for these gelators shows that their gelation ability depends on the gelator symmetry. ATR-IR and X-ray diffraction studies indicate that directional hydrogen bonding, van der Waals and  $\pi$ -stacking interactions may be responsible for the self-assembly process. SEM and TEM studies reveal the formation of multilamellar right-handed twisted ribbons.

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## Notes and references

§ X-Ray data for **3b**·3CHCl3:  $C_{53}H_{63}Cl_9N_6O_4$ ,  $M_r = 1167.14$ , triclinic,  $P1, a = 6.6681(5), b = 11.0049(11), c = 21.379(2) \text{ Å}, \alpha = 91.410(8)^\circ$ ,  $\beta = 95.287(7)^\circ$ ,  $\gamma = 106.366(8)^\circ$ ,  $V = 1496.8(2) \text{ Å}^3$ , Z = 1, T = 120(2) K,  $2\theta_{\text{max}} = 50.06$ , 22870/10521 reflns. collected/independent,  $R_{\text{int}} = 0.1072, R_1[I > 2\sigma(I)] = 0.1092$ , w $R_2$ (all data) = 0.2675, Flack parameter 0.12(14).

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- 13 The presence of hydrogen bonded OH groups in the gel state is corroborated by the ATR-IR spectrum of **3a**/DMSO-d<sub>6</sub>/D<sub>2</sub>O (3/1 v/v) gel, after subtraction of the solvent-basedbackground, which showed a broad band at 3426 cm<sup>-1</sup>.