

Cite this: *Chem. Commun.*, 2011, **47**, 10281–10283

www.rsc.org/chemcomm

COMMUNICATION

A new family of “clicked” estradiol-based low-molecular-weight gelators having highly symmetry-dependent gelation ability†‡

Pedro Ramírez-López,^{*a} María C. de la Torre,^{*a} María Asenjo,^a Julio Ramírez-Castellanos,^b José M. González-Calbet,^b Alejandra Rodríguez-Gimeno,^c Carmen Ramírez de Arellano^c and Miguel A. Sierra^{*d}

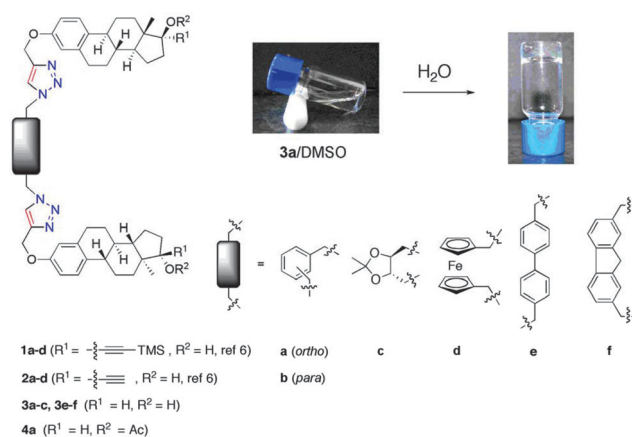
Received 1st June 2011, Accepted 3rd August 2011

DOI: 10.1039/c1cc13251b

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 H₂O 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.¹ 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.² Although this methodology has been widely applied for the synthesis of polymeric gelators,³ examples of the use of “click” chemistry for the preparation of LMWGs gels are scarce.⁴ During the course of our research program⁵ directed to the preparation of natural product based macrocycles,⁶ we observed that C₂ 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**



Scheme 1 “Clicked” estradiol-based dimers.

were tested for gelation properties.⁶ *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.⁷

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/H₂O (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⁻¹) and *p*-**3b** (3.0 mg mL⁻¹) were efficient gelators albeit slightly worse than compounds *o*-**2a** (1.5 mg mL⁻¹) and *p*-**2b** (2.3 mg mL⁻¹). 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

^a Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain. E-mail: pedror@iqog.csic.es (PR-L), ctorre@iqog.csic.es (MCT)

^b Departamento de Química Inorgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

^c Departamento de Química Orgánica, Universidad de Valencia, 46100-Valencia, Spain

^d Departamento de Química Orgánica. UCM, 28040 Madrid, Spain. E-mail: sierraor@quim.ucm.es (MAS)

† 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

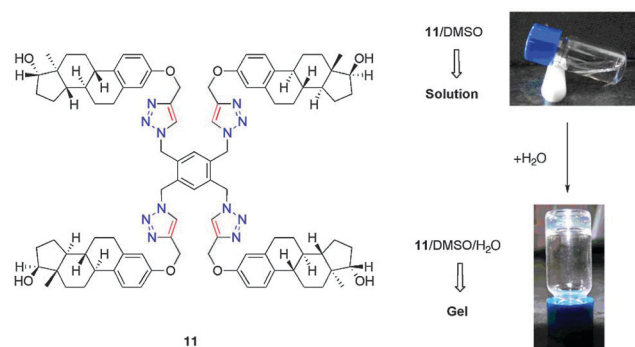
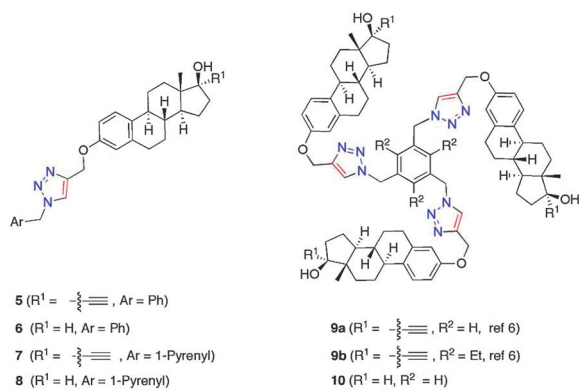
‡ The paper is dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

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⁻¹) and fluorene **3f** (1.5 mg mL⁻¹) derivatives produced improved CGC values with respect to those of the *p*-phenyl **3b** (2.3 mg mL⁻¹) and **3a** (3 mg mL⁻¹) 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. C₃ symmetric trimers **9a–b**⁶ and **10** and C₂ 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 C₂ symmetric tetramer **11**, which gelled DMSO/H₂O (3/1 v/v) at concentrations as low as 0.37 mg mL⁻¹ (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⁻¹ therefore falling into the category of “super-gelators”.⁸



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 C₂ symmetric dimeric and tetrameric estradiol-based structures

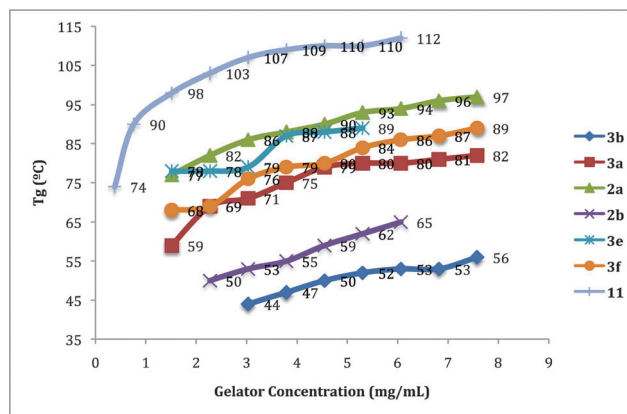


Fig. 1 Sol-gel transition temperatures (T_g) for gels **2a–b**, **3a–b**, **3e–f** and **11**/DMSO/H₂O (3/1 v/v) as a function of gelator concentration measured by the “dropping ball method”.

behave as LMWGs, their monomeric and C₃ 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/H₂O (3/1 v/v) gels with concentrations varying from 0.4 to 8.0 mg mL⁻¹ were studied by the “dropping ball method”.⁹ 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 T_g 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 C₂ 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 μm wide and 110–540 μm 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.¹⁰ Fig. 2e reveals a complex microstructure, where an amorphous matrix contains highly ordered crystallized

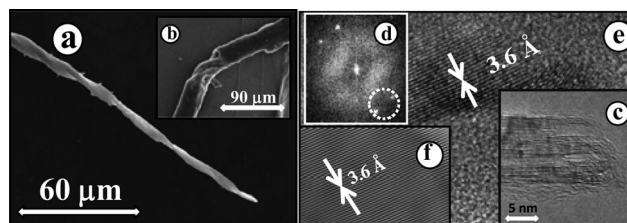


Fig. 2 SEM and TEM images of the xerogel of **3a** (0.7 wt%)/DMSO/H₂O (v/v 2: 1). For additional images of **3a** and **11** see the ESI.†

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 π - π stacking aromatic interactions.

A possible aggregation model for these C_2 symmetric gelators may be based on the molecular structure of **3b**·3CHCl₃, 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...O, C(methylene)-H...N and C(triazole)-H... π interactions (see ESI†). In the molecular planes, C-H axial bonds of one estradiol moiety are oriented towards the π cloud of the neighboring estradiol fragment. Layers are assembled through C(methylene)-H...N interactions and a π - π 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 Å³.¹¹ 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 (CHCl₃/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 π -stacking of the aromatic linkers and then lateral and directional hydroxyl groups at C-17 facilitate linear hydrogen-bonded polymeric chains.¹³ In fact, C_2 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†).

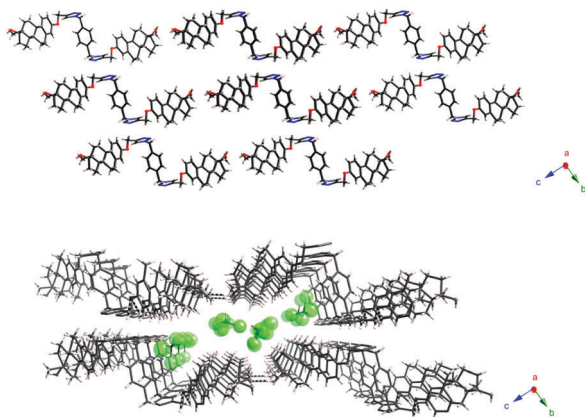


Fig. 3 Crystal packing views showing layers assembly along the *a* axis with solvent molecules omitted for clarity (top), and a tubular void along the *a* axis including solvent molecules (bottom).

In summary, we reported the discovery of a novel family of estradiol-based LMWGs that gel different organic solvents in the presence of H₂O 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 π -stacking interactions may be responsible for the self-assembly process. SEM and TEM studies reveal the formation of multilamellar right-handed twisted ribbons.

Financial support by the Spanish MCINN (CTQ2010-20714 and CSD2007-0006) and the CAM (P2009/PPQ1634) is acknowledged. P.R.-L. and M.A. thank the CSIC-JAE Program for postdoctoral and predoctoral grants, respectively.

Notes and references

§ X-Ray data for **3b**·3CHCl₃: C₅₃H₆₃Cl₉N₆O₄, *M_r* = 1167.14, triclinic, *P*1, *a* = 6.6681(5), *b* = 11.0049(11), *c* = 21.379(2) Å, α = 91.410(8)°, β = 95.287(7)°, γ = 106.366(8)°, *V* = 1496.8(2) Å³, *Z* = 1, *T* = 120(2) K, *2* θ _{max} = 50.06, 22870/10521 reflns. collected/independent, *R*_{int} = 0.1072, *R*₁[*I* > 2 σ (*I*)] = 0.1092, *wR*₂(all data) = 0.2675, Flack parameter 0.12(14).

- For a collection of review articles on LMWGs, see: J. H. van Esch and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2000, **39**, 2263; O. Gronwald and S. Shinkai, *Chem.–Eur. J.*, 2001, **7**, 4328; M. de Loos, B. L. Feringa and J. H. van Esch, *Eur. J. Org. Chem.*, 2005, 3615; M. George and R. G. Weiss, *Acc. Chem. Res.*, 2006, **39**, 489; A. R. Hirst, B. Escuder, J. F. Miravet and D. K. Smith, *Angew. Chem., Int. Ed.*, 2008, **47**, 8002, and references therein.
- M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952.
- S. M. Park, Y. S. Lee and B. H. Kim, *Chem. Commun.*, 2003, 2912; G. Godeau and P. Barthèlèmy, *Langmuir*, 2009, **25**, 8447; J. Lu, J. Hu, Y. Song and Y. Ju, *Org. Lett.*, 2011, **13**, 3372.
- N. Tzokova, C. M. Fernyhough, P. D. Topham, N. Sandon, D. J. Adams, M. F. Butler, S. P. Armes and A. J. Ryan, *Langmuir*, 2009, **25**, 2479; W. H. Binder and R. Sachsenhofer, *Click Chemistry on Supramolecular Materials, in Click Chemistry for Biotechnology and Materials Science*, ed. J. Lahann, John Wiley & Sons, Ltd, Chichester, UK, 2009 and references therein.
- M. C. de la Torre, A. M. Deometrio, E. Álvaro, I. García and M. A. Sierra, *Org. Lett.*, 2006, **8**, 593; E. Álvaro, M. C. de la Torre and M. A. Sierra, *Chem.–Eur. J.*, 2006, **12**, 6403; M. A. Sierra, R. M. Torres, M. C. de la Torre and E. Álvaro, *J. Org. Chem.*, 2007, **72**, 4213.
- H. E. Montenegro, P. Ramírez-López, M. C. de la Torre, M. Asenjo and M. A. Sierra, *Chem.–Eur. J.*, 2010, **16**, 3798; P. Ramírez-López, M. C. de la Torre, H. E. Montenegro, M. Asenjo and M. A. Sierra, *Org. Lett.*, 2008, **10**, 3555.
- For cholesterol-based organogels, see: J. H. Jung, Y. Ono and S. Shinkai, *Angew. Chem., Int. Ed.*, 2000, **39**, 1862; J. H. Jung, H. Kobayashi, M. Masuda, T. Shimizu and S. Shinkai, *J. Am. Chem. Soc.*, 2001, **123**, 8785 and references therein. For a review on bile acid-based organogels, see: P. Babu, N. M. Sangeetha and U. Maitra, *Macromol. Symp.*, 2006, **241**, 60.
- J. Liu, P. He, J. Yan, X. Fang, J. Peng, K. Liu and Y. Fang, *Adv. Mater.*, 2008, **20**, 2508 and references therein.
- Dropping ball method: A. Takahashi, M. Sakai and T. Kato, *Polym. J.*, 1980, **12**, 335.
- Fig. 2d shows the Fast Fourier Transform (FFT) pattern corresponding to the xerogel of **3a**, which is obtained from the digitized experimental HRTEM image. Few discrete and weak diffraction spots (marked by a dashed circle) confirm the presence of crystalline domains.
- Molecular voids: PLATON-SQUEEZE, A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7Crystal voids host CHCl₃ molecules by means of C-H...N, C-H...O and C-H...Cl interactions and C-Cl...Cl-C type II contacts, see: N. Ramasubbu, R. Parthasarathy and P. Murray-Rust, *J. Am. Chem. Soc.*, 1986, **108**, 4308.
- CCDC 786367.
- The presence of hydrogen bonded OH groups in the gel state is corroborated by the ATR-IR spectrum of **3a**/DMSO-*d*₆/D₂O (3/1 v/v) gel, after subtraction of the solvent-based background, which showed a broad band at 3426 cm⁻¹.