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## pH-Responsive single-layer honeycomb supramolecular organic frameworks that exhibit antimicrobial activity

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**Two two-dimensional (2D) single-layer supramolecular organic frameworks (SOFs) have been constructed in water. One framework displays pH-responsive self-assembly and de-assembly and both exhibit activity against methicillin-resistant *Staphylococcus aureus*.**

Two-dimensional (2D) single-layer molecular networks have received considerable interest in recent years due to their unique structural feature and potential functions in sensing, analytical, environmental and materials fields.<sup>1-6</sup> By controlling the polymerization<sup>7-9</sup> or self-assembly<sup>10</sup> of organic components on solid surfaces, several kinds of single-layer networks have been constructed. Kim and co-workers reported the solution-phase synthesis of single-monomer-thick 2D organic polymers through shape-directed covalent self-assembly of a cucurbit[6]uril precursor,<sup>11</sup> while Zhao and co-workers described the solution-phase formation of another kind of single-layer 2D polymers from the coupling of preorganized triptycene tricatechol with 1,4-benzene- or 4,4'-biphenyldiboronic acids.<sup>12</sup> We and other groups have recently developed a highly efficient self-assembly strategy for generating homogeneous 2D supramolecular organic frameworks (SOFs) in water.<sup>13-17</sup> However, their potential applications have not been exploited and responsive covalent and supramolecular systems are not available either. We herein describe the formation of two 2D honeycomb single-layer SOFs from viologen-appended rigid triangular monomer **1** and linear flexible monomers **2a** and **2b**, which bear two 2,6-dioxy or 2-

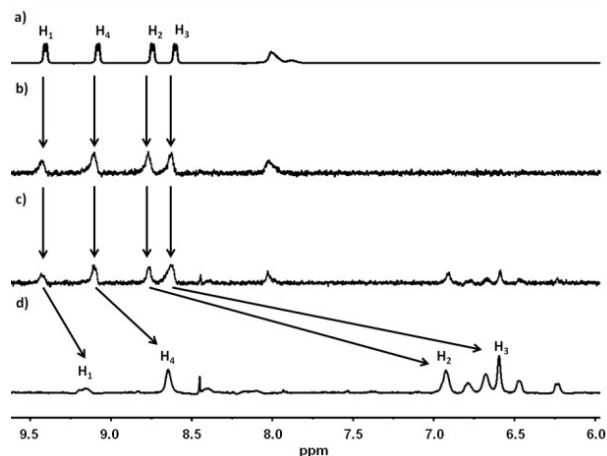
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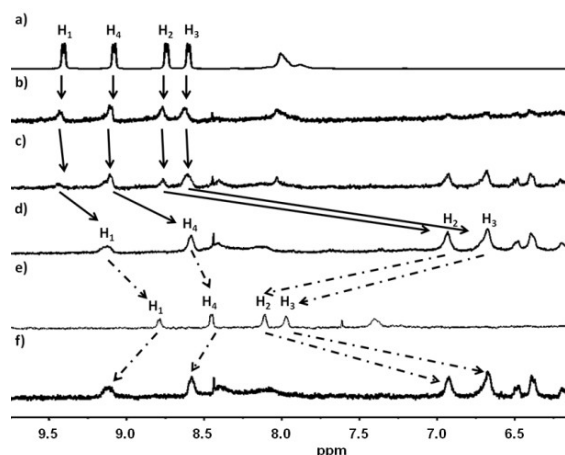
hydroxy-6-amino naphthalene subunits, respectively, by the encapsulation of cucurbit[8]uril (CB[8]) for the donor-acceptor dimers between the electron-rich naphthalene subunits of **2a** or **2b** and the electron-deficient viologen subunits of **1**. We further demonstrate that the assembly of the SOF from diamine **2b** can be tuned reversibly by changing the pH of the medium and both SOFs exhibit activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

Compounds **1**<sup>14</sup> and **2a**<sup>15</sup> were prepared according to reported methods. The synthesis of **2b** is shown in the supporting information. Compounds **2a** and **2b** has low solubility in water. Upon mixing with **1**, their solubility was increased substantially. Thus, <sup>1</sup>H NMR spectra of the 1:1.5 mixtures of **1** (1.0 mM) with **2a** and **2b** in D<sub>2</sub>O were recorded (Fig. 1 and 2). For both spectra, the signals of **1** in the downfield area did not display discernible shifting compared to the signals of the pure sample of the same concentration. The signals of the aromatic protons of **2a** and **2b** did not appear in the spectrum. This may be ascribed to the low resolution of their spectrum in water.



**Fig. 1** <sup>1</sup>H NMR spectra (400 MHz) of (a) **1** + **2a**, (b) **1** + **2a** + CB[8] (1.0 mM), (c) **1** + **2a** + CB[8] (2.0 mM), (d) **1** + **2a** + CB[8] (3.0 mM) in D<sub>2</sub>O at 25 °C ([**1**] = 1.0 mM, [**2a**] = 1.5 mM).

Adding CB[8] to the above mixture led to the decrease of the resolution of the spectrum of **1**. Upon addition of 3.0 equivalent of CB[8] which was relative to **1**, the mixture gave rise to a new set of signals. In particular, the signals of H-1-4 (see the structure), which were assigned on the basis of 2D COSY  $^1\text{H}$  NMR experiments (Fig. S1 and S2), of the bipyridinium subunits of **1** shifted upfield pronouncedly, and the shifting extent of H-2 (from 8.8 to 6.9 ppm) and H-3 (from 8.6 to 6.6 ppm) was obviously higher than that of H-1 and H-4 (Fig. 1d). In addition, the signals of the naphthalene subunits of **2a** appeared even though overlapping occurred. These signals were not observed from the spectrum of the mixture of **1** and **2a** (Fig. 1a), probably due to their intra- and intermolecular stacking and interaction with **1**, which were expected to reduce the resolution of the signals. These observations provides the first evidence that CB[8] enhanced the stacking or dimerization of the bipyridinium subunits of **1** and the naphthalene subunits of **2a** by encapsulating the dimers, which suggested a 1:1.5:3 binding stoichiometry.<sup>15</sup>



**Fig. 2**  $^1\text{H}$  NMR spectra (400 MHz) of (a) **1** + **2b**, (b) **1** + **2b** + CB[8] (1.0 mM), (c) **1** + **2b** + CB[8] (2.0 mM), (d) **1** + **2b** + CB[8] (3.0 mM), (e) **1** + **2b** + CB[8] (3.0 mM) + DCl (3.0 mM), and (f) **1** + **2b** + CB[8] (3.0 mM) + DCl (3.0 mM) + NaOD (3.0 mM) in  $\text{D}_2\text{O}$  at 25 °C. ( $[\mathbf{1}] = 1.0 \text{ mM}$ ,  $[\mathbf{2b}] = 1.5 \text{ mM}$ ).

Results were similar to those of the above mixture of **1**, **2a** and CB[8] were also observed for the mixture of **1**, **2b** and CB[8] (Fig. 2a-2d), which suggested that CB[8] also encapsulated the dimers of the 2-hydroxy-6-amino subunits of **2b**. Upon adding the DCl solution of the molar amount that was equal to that of the 2-hydroxy-6-amino subunits of **2b**, a new set of signals was observed for the H-1-4 protons of **1**. Compared with those of **1**, the signals of H-2,3 shifted downfield, while the H-1,4 signals shifted upfield (Fig. 2e), which indicated that the bipyridinium subunits of **1** were still encapsulated by CB[8], which should be in a 1:1 encapsulation motif,<sup>18</sup> even though the protonated aminonaphthalene subunits of **2b** moved out from the hydrophobic cavity of CB[8] due to the fact that protonated 2-hydroxy-6-aminonaphthalene subunits became hydrophilic. Further addition of NaOD led to the deprotonation of the ammonium groups and

consequently the recovery of the encapsulation of CB[8] for the bipyridinium/naphthalene dimers, as indicated by the  $^1\text{H}$  NMR spectrum (Fig. 2f).

Probably due to the formation of large supramolecular polymeric aggregates, the resolution of the  $^1\text{H}$  NMR spectra of the above two three-component mixtures was quite low.  $^1\text{H}$  NMR dilution experiments ( $[\mathbf{1}]$ : 1.0 mM to 0.125 mM) were conducted to evaluate the stability of the supramolecular entities (Fig. S3 and S4). No discernible shifting was observed for the signals in the downfield area. This observation supported that no de-aggregation occurred within the investigated concentration range. Increasing the temperature from 25 °C to 60 °C did not cause distinct shifting of these downfield signals in both spectra (Fig. S5 and S6), even though the resolution of the spectra increased slightly. This result also reflected the high stability of the two supramolecular entities at increased temperature.

Diffusion-ordered NMR spectroscopic (DOSY) experiments were also carried out for both three-component mixtures ( $[\mathbf{1}] = 1.0 \text{ mM}$ ). The signals of the three components in either of the mixtures exhibited the identical diffusion coefficient ( $D$ ), being ca.  $1.0 \times 10^{-10}$  and  $1.1 \times 10^{-10} \text{ m}^2/\text{s}$ , respectively (Fig. S7 and S8). Both values were obviously lower than that ( $1.9 \times 10^{-10} \text{ m}^2/\text{s}$ ) of the free **1** of the same concentration, further supporting the engagement of large supramolecular entities.

The absorption spectra of the two three-component mixtures were also recorded in water (Fig. S9-S11). The two spectra exhibited an absorption band centred at 605 and 660 nm, respectively, which could be readily ascribed to the charge-transfer absorption between the electron-rich 2,6-dioxynaphthalene subunits of **2a** or 2-hydroxy-6-aminonaphthalene subunits of **2b** and the electron-deficient bipyridinium subunits of **1**, with the molar absorption coefficient ( $\epsilon$ ) being calculated as 396 and  $696 \text{ M}^{-1}\text{cm}^{-1}$ , respectively. Both absorbance obeyed Beer's law within the investigated concentration range, suggesting that the supramolecular entities were stable and did not decompose within the concentration range investigated.

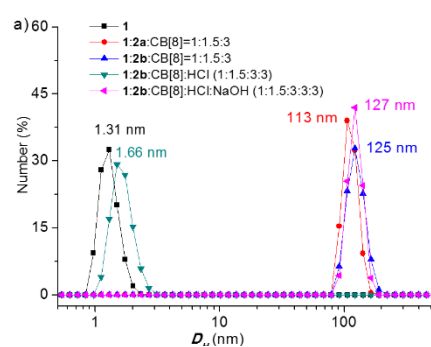
For the mixture of **2b**, adding 2 equivalent of hydrochloric acid, relative to that of **2b**, caused the charge-transfer absorption to vanish. Upon adding the same amount of sodium hydroxide, the charge-transfer absorption recovered to the identical extent (Fig. S9). These observations again illustrated the responsiveness of the supramolecular entities of **2b** to pH of the solution.

Compounds **2a** and **2b** exhibited strong fluorescence centred at 370 and 430 nm, respectively, whereas compound **1** and CB[8] had no fluorescence. For the two three-component mixtures, the fluorescence of **2a** and **2b** was quenched substantially. In contrast, no quenching was observed in the absence of CB[8] (Fig. S12). These results again could be ascribed to the above mentioned charge-transfer complexation, which promoted the quenching of the fluorescence of the naphthalene subunits of **2a** or **2b** by the bipyridinium subunits of **1** in the cavity of CB[8] (Fig. S12). For the three-component mixture of **2b**, adding hydrochloric acid, two equivalents relative to that of **2b**, induced the

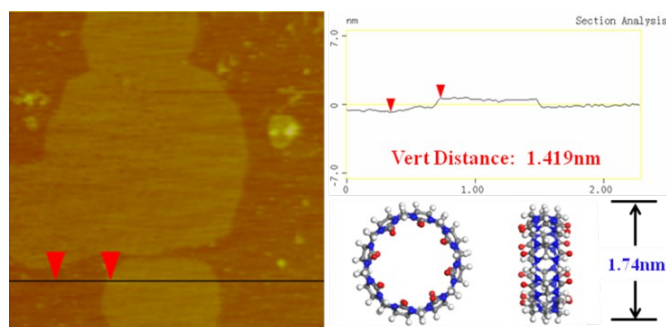
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enhancement of the fluorescence of **2b**. The intensity of the fluorescence was comparable to that of protonated **2b**, indicating that the addition of hydrochloric acid caused the de-aggregation of the three-component supramolecular systems due to electronic repulsion. Upon adding NaOH to neutralize the acid, the fluorescence of **2b** was quenched again as a result of the recombination of the three components into supramolecular entities (Fig. S12).

Dynamic light scattering (DLS) experiments were performed for the two three-component mixtures (1:1.5:3) in water to estimate their hydrodynamic diameters ( $D_H$ ) values. At  $[1] = 0.3$  mM, their  $D_H$  values were determined to be 113 and 125 nm, respectively (Fig. 3a). The values further increased with the concentration increase and reached the large values of 1240 and 1450 nm, respectively, at  $[1] = 1.5$  mM (Fig. S13). Because it had been established that the 1D stacking of **1** is inhibited by the three aliphatic side chains,<sup>13,14</sup> the large  $D_H$  values suggested that the two mixtures should form supramolecular entities in the 2D space. DLS experiments also showed that the mixture of **2b** could undergo reversible de-assembly (pH<5) and re-self-assembly (pH = 7-10) by alternately adding HCl and NaOH (Fig. 3a and 3b). The small  $D_H$  values revealed after acidifying **2b** clearly supported the de-assembly of the supramolecular entities, which is in accordance with the above <sup>1</sup>H NMR, absorption and fluorescence experiments. Heating the two solutions to 100 °C and then cooled to ambient temperature, their  $D_H$  values were not changed, indicating a high stability of the frameworks.



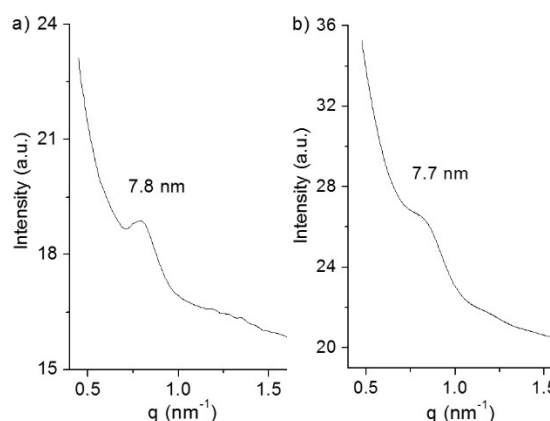
**Fig. 3** a) DLS results of **1** and the mixtures of **1**, **2a** and **2b** (without and with the addition of HCl and subsequently NaOH), and CB[8] in water at 25 °C. The data represent the hydrodynamic diameters ( $D_H$ ) ( $[1] = 0.3$  mM). b)  $D_H$  of the mixture of **2b** with the alternate addition of 2 equiv, relative to **2b**, of HCl and NaOH.



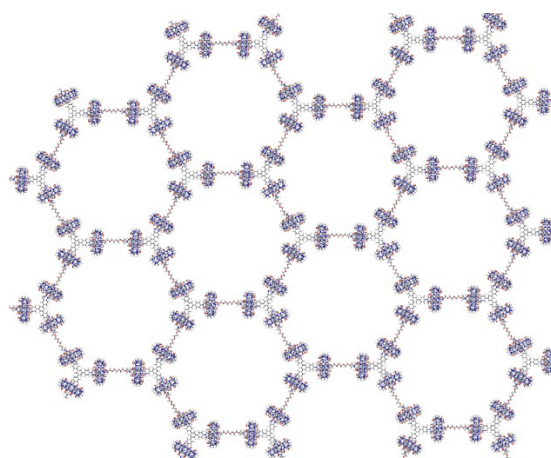
**Fig. 4** Tapping-mode AFM image and cross-section analysis of the sample prepared by evaporating the aqueous solution of **1**, **2a** and CB[8] (1:1.5:3) in water ( $[1] = 10$   $\mu$ M).

Transmission electron microscopy (TEM) was then utilized to investigate the morphology of the two supramolecular entities. Both mixtures gave rise to large sheet-like structures with lateral sizes being up to several micrometers (Fig. S14), which supported the formation of 2D supramolecular entities. Atomic force microscopy (AFM) was then used to measure the height of these sheet-like structures. A thickness of 1.4 nm (Fig. 4) and 1.3 nm (Fig. S15) was estimated for the two three-component mixtures. For the single-layer of a 2D polymer formed by the two mixtures, the thickness should be less than 1.74 nm of the diameter of CB[8].<sup>15</sup> Thus, these values supported that the sheet-like structures should be of single-layer.

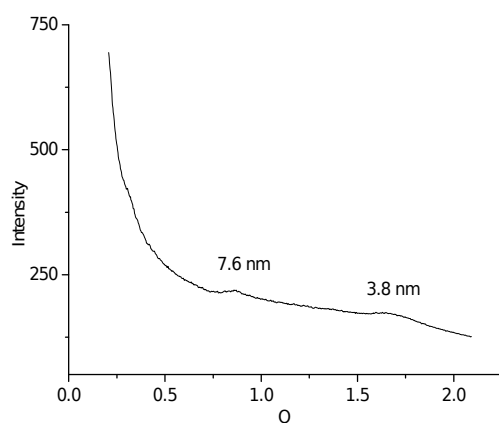
Solution-phase small angle X-ray scattering (SAXS) experiments were then conducted for the two 2D single-layer supramolecular polymers in water. Both samples gave rise to a broad but clear scattering peak corresponding to the d-spacing centred at 7.8 and 7.7 nm, respectively (Fig. 5). Considering the dynamic feature of the new self-assembled structures, these values matched well with the calculated value (7.4 nm) for the {100} spacing of the supramolecular organic frameworks (SOFs), thus providing evidence for the periodicity of the 2D monolayer structure (Fig. 6). Grazing-incidence (GI)-SAXS experiment was also performed for the solution of **1**, **2a** and CB[8] in water. The profile exhibited two broad peaks centred at 7.6 and 3.6 nm, respectively (Fig. 7), which corresponded to the {100} and {200} spacings of the 2D SOF.



**Fig. 5** Solution-phase small-angle X-ray (SAXS) scattering profile of the mixture of a) **1**, **2a** and CB[8] (1:1.5:3) and b) **1**, **2b** and CB[8] (1:1.5:3) in water at 25 °C ([**1**] = 1.5 mM).



**Fig. 6** Schematic representation of the 2D honeycomb monolayer SOFs formed by **1**, **2a** or **2b** and CB[8] in water.



**Fig. 7** GI-SAXS patterns of the solution of compounds **1**, **2a** and CB[8] (1:1.5:3) ([**1**] = 1.5 mM) in water at 25°C.

The 2D SOFs may be regarded as layered cationic supramolecular polyelectrolytes. Their antimicrobial activity was also tested by using agar diffusion assays of methicillin-resistant *Staphylococcus aureus* (MRSA) as a test strain (Fig. S16 and S17). The assays showed that both SOFs exhibited medium activity against the tested MRSA in a dose-dependent manner. In contrast, compounds **1**, **2a**, **2b**, or CB[8] of the identical concentration did not show any detectable activity. Thus, the activity exhibited by the two SOFs is tentatively attributed to their increased cation concentration in the 2D space on the surface of MRSA.<sup>19</sup>

In summary, we have constructed two single-layer 2D honeycomb supramolecular organic

frameworks in water with {100} spacing larger than 7 nm by using encapsulation-enhanced donor-acceptor interaction as driving force. The SOF constructed from 2-hydroxy-6-aminonaphthalene-derived monomer exhibits pH-responsive self-assembly and de-assembly. The new SOFs also display interesting antibacterial activity due to the ion enriching effect produced by their periodic framework. This work further establishes that the formation of periodic supramolecular organic frameworks in solution can allow for the use of flexible monomers. In the future, we will explore the possibility of using flexible monomers to build 3D SOFs.

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## Notes and references

- 1 P. Payamyar, B. T. King, H. C. Öttinger and A. D. Schlüter, *Chem. Commun.*, 2016, **52**, 18–34.
- 2 J. W. Colson and W. R. Dichtel, *Nat. Chem.*, 2013, **5**, 453–465.
- 3 H. Wang, D.-W. Zhang, X. Zhao and Z.-T. Li, *Acta Chimica Sinica*, 2015, **73**, 471–479; L. Chen, Y.-C. Zhang, W.-K. Wang, J. Tian, L. Zhang, H. Wang, D.-W. Zhang and Z.-T. Li, *Chin. Chem. Lett.*, 2015, **26**, 811–816; T. Wang and Z. Li, *Imag. Sci. Photochem.*, 2015, **33**, 3–14; D.-W. Zhang, J. Tian, L. Chen, L. Zhang and Z.-T. Li, *Chem. Asian J.*, 2015, **10**, 56–68.
- 4 Y.-j. Li and Y.-l. Li, *Gaofenzi Xuebao*, 2015, 147–165.
- 5 X. Zhuang, Y. Mai, D. Wu, F. Zhang and X. Feng, *Adv. Mater.*, 2015, **27**, 403–427.
- 6 S.-L. Cai, W.-G. Zhang, R. N. Zuckermann, Z.-T. Li, X. Zhao and Y. Liu, *Adv. Mater.*, 2015, **27**, 5762–5770.
- 7 L. Grill, M. Dyer, L. Lafferentz, M. Persson, M. V. Peters and S. Hecht, *Nat. Nanotechnol.*, 2007, **2**, 687–691; L. Lafferentz, V. Eberhardt, C. Dri, C. Africh, G. Comelli, F. Esch, S. Hecht and L. Grill, *Nat. Chem.*, 2012, **4**, 215–220.
- 8 P. Kissel, R. Erni, W. B. Schweizer, M. D. Rossell, B. T. King, T. Bauer, S. Götzinger, A. D. Schlüter and J. Sakamoto, *Nat. Chem.*, 2012, **4**, 287–291; R. Bhola, P. Payamyar, D. J. Murray, B. Kumar, A. J. Teator, M. U. Schmidt, S. M. Hammer, A. Saha, J. Sakamoto, A. D. Schlüter and B. T. King, *J. Am. Chem. Soc.*, 2013, **135**, 14134–14141.
- 9 D. J. Murray, D. D. Patterson, P. Payamyar, R. Bhola, W. Song, M. Lackinger, A. D. Schlüter and B. T. King, *J. Am. Chem. Soc.*, 2015, **137**, 3450–3453; W. Dai, F. Shao, J. Szczerbinski, R. McCaffrey, R. Zenobi, Y. Jin,

## COMMUNICATION

- A. D. Schlüter and W. Zhang, *Angew. Chem. Int. Ed.*, 2016, **55**, 213–217.
- 10 L.-J. Wan, *Acc. Chem. Res.*, 2006, **39**, 334–342; Y. Yang and C. Wang, *Chem. Soc. Rev.*, 2009, **38**, 2576–2589; K. S. Mali, J. Adisoejoso, E. Ghijsen, I. De Cat and S. De Feyter, *Acc. Chem. Res.*, 2012, **45**, 1309–1320; M. Lackinger, *Polym. Int.*, 2015, **64**, 1073–1078; Z. Mu, L. Shu, H. Fuchs, M. Mayor, L. Chi, *J. Am. Chem. Soc.*, 2008, **130**, 10840–10841; M. Vybornyi, A. V. Rudnev, S. M. Langenegger, T. Wandlowski, G. Calzaferri and R. Häner, *Angew. Chem. Int. Ed.*, 2013, **52**, 11488–11493; M. Vybornyi, A. Rudnev, R. Häner, *Chem. Mater.*, 2015, **27**, 1426–1431.
- 11 K. Baek, G. Yun, Y. Kim, D. Kim, R. Hota, I. Hwang, D. Xu, Y. H. Ko, G. H. Gu, J. H. Suh, C. G. Park, B. J. Sung and K. Kim, *J. Am. Chem. Soc.*, 2013, **135**, 6523–6528.
- 12 T.-Y. Zhou, F. Lin, Z.-T. Li and Xin Zhao, *Macromolecules*, 2013, **46**, 7745–7752.
- 13 K.-D. Zhang, J. Tian, D. Hanifi, Y. Zhang, A. C.-H. Sue, T.-Y. Zhou, L. Zhang, X. Zhao, Y. Liu and Z.-T. Li, *J. Am. Chem. Soc.*, 2013, **135**, 17913–17918; J. Tian, T.-Y. Zhou, S.-C. Zhang, S. Aloni, M. V. Altoe, S.-H. Xie, H. Wang, D.-W. Zhang, X. Zhao, Y. Liu and Z.-T. Li, *Nat. Commun.*, 2014, **5**, 5574.
- 14 L. Zhang, T.-Y. Zhou, J. Tian, H. Wang, D.-W. Zhang, X. Zhao, Y. Liu and Z.-T. Li, *Polym. Chem.*, 2014, **5**, 4715–4721.
- 15 X. Zhang, C.-B. Nie, T.-Y. Zhou, Q.-Y. Qi, J. Fu, X.-Z. Wang, L. Dai, Y. Chen and X. Zhao, *Polym. Chem.*, 2015, **6**, 1923–1927.
- 16 S.-Q. Xu, X. Zhang, C.-B. Nie, Z.-F. Pang, X.-N. Xu and X. Zhao, *Chem. Commun.*, 2015, **51**, 16417–16420.
- 17 M. Pfeiffermann, R. Dong, R. Graf, W. Zajaczkowski, T. Gorelik, W. Pisula, A. Narita, K. Müllen and X. Feng, *J. Am. Chem. Soc.*, 2015, **137**, 14525–14532.
- 18 K. Kim, D. Kim, J. W. Lee, Y. H. Ko and K. Kim, *Chem. Commun.*, 2004, 848–849.
- 19 R. Tejero, D. Lopez, F. Lopez-Fabal, J. L. Gomez-Garces and M. Fernandez-Garcia, *Polym. Chem.*, 2015, **6**, 3449–3459; L. D. de Melo Carrasco, J. L. M. Sampaio and A. M. Carmona-Ribeiro, *Int. J. Mol. Sci.*, 2015, **16**, 6337–6352.