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Synthesis, characterization, and self-assembled nanofibers of carbohydrate-functionalized mono- and di(2,2′:6′,2″-terpyridinyl)arenes†

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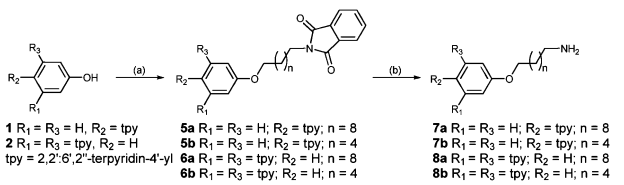
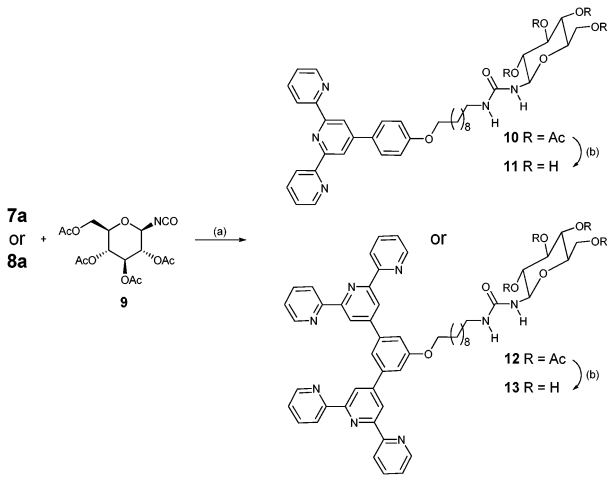
Self-assembly of novel linear and branched carbohydrate-functionalized mono- and di(2,2′:6′,2″-terpyridinyl)arenes afforded access to a series of twisted self-organized nanofibers.

Supramolecular-based assemblies, constructed *via* intermolecular non-covalent interactions, such as van der Waals forces, hydrogen bonding, ionic and coordinative interactions,[1,2] have been a major contributor to functional nanostructures.[3] Achiral bolaamphiphiles,[4,5] possessing a dumbbell shape and without internal structural perturbation, self-assembled into a linear ordered stacking pattern; whereas with internal disorder, helical motifs were realized.[6] Recently, gels[7–9] formed from small molecules have been investigated for their nanoscale chirality.[10–12] The appearance of a disaccharide, specifically furanosylfuranose or pyranosylpyranose (cellobiose), on terpyridine has been reported as a new class of oligopyridine ligands.[13] Some sugar-substituted oligopyridines have been used to form metal complexes of copper,[14–16] zinc,[16] iron,[17,18] ruthenium,[17] rhenium,[19] and technetium.[19] Herein, we report the construction of linear and branched carbohydrate-functionalized mono-4- and di-3,5-(2,2′:6′,2″-terpyridin-4′-yl)arenes as well as their self-assembly into twisted nanofibers, which have utilitarian potential in cell adhesion,[20] gene delivery,[21] and tissue engineering.[22,23]

Synthesis (Scheme 1) of the sugar-modified monomers began with the alkylation of 4-terpyridinylphenol[24] (**1**) and 3,5-di(terpyridinyl)phenol[25] (**2**) with either *N*-(10-bromodecyl)-phthalimide (**3**) or *N*-(6-bromohexyl)phthalimide (**4**) linkers to give imides **5a–6b**, followed by deprotection with hydrazine to afford the free amines **7a–8b**. Specifically, **7a** and **8a** (Scheme 2) were subsequently treated with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isocyanate[26] (**9**) to give (76–77%)



Scheme 1 *Reagents and conditions*: (a) **3** or **4**, K_2CO_3, DMF, 80 °C; (b) N_2H_4, EtOH, reflux.



Scheme 2 *Reagents and conditions*: (a) CH_2Cl_2, 30 °C; (b) Et_3N, MeOH, 30 °C.

10 and **12**, respectively. Their structures were established (^{1}H NMR) by the presence of peaks at 3.14 ppm (CH_2NHCO), 4.72 ppm (**10**) and 4.55 ppm (**12**) (CH_2NHCO) possessing the desired 2 : 1 ratio as well as five new peaks (^{13}C NMR) at 156.3, 169.8, 170.1, 170.9, and 171.4 ppm, corresponding to the urea and four ester carbonyl moieties, respectively. The ESI-MS spectra further support these structures by peaks at m/z 875.9 $[M + Na]^+$ (calcd m/z = 876.4) for **10** and m/z 1107.7 $[M + Na]^+$ (calcd m/z = 1107.5) for **12**.

The acetylated precursors were deprotected by using triethylamine in MeOH to give (~85%) the desired monomers **11** and **13**. Characterization of their structures was supported (^{1}H and ^{13}C NMR) by the disappearance of peaks assigned to the acetyl group and ESI-MS spectra of peaks at m/z 708.3 $[M + Na]^+$ (calcd m/z = 708.4) for **11** and m/z 939.6 $[M + Na]^+$ (calcd m/z = 939.4) for **13**.

The branched, sugar-functionalized, mono- and di(terpyridinyl)-arenes were obtained using the ubiquitous acrylate–diamine protocol for 1 → 2 *N*-branching.[27] Thus, Michael addition (Scheme 3) of the terminal amines **7b** and **8b** to methyl acrylate in MeOH and a mixed solvent of THF and MeOH, respectively, afforded (99%) the corresponding methyl diesters **14** and **15**. Their structures were confirmed by the appearance of peaks (^{13}C NMR) for the ester carbonyl groups at 173.2 ppm and the molecular ion peaks at m/z 597.3 $[M + H]^+$ (calcd m/z = 597.3) for **14** and m/z 828.4 $[M + H]^+$ (calcd m/z = 828.4) for **15** in ESI-MS spectra. Treatment of **14** and **15** with excess ethylenediamine in MeOH gave the diamines **16** and **17**, respectively, whose structures were supported by the disappearance (^{1}H NMR) of methyl

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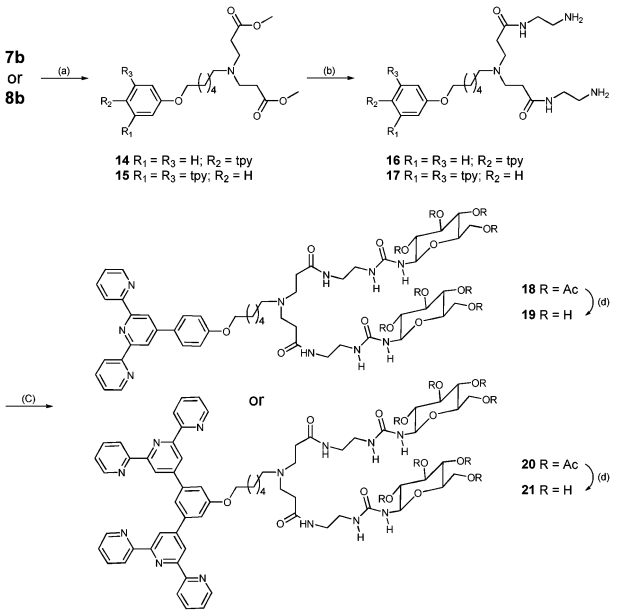

Scheme 3 *Reagents and conditions*: (a) methyl acrylate, MeOH–THF, 30 °C; (b) ethylenediamine, MeOH, 30 °C; (c) **9**, CH_2Cl_2, reflux, 3 h; (d) Et_3N, MeOH, 30 °C.

peaks and the appearance of triplets for the amide at 7.50 ppm (**16**) and 7.62 ppm (**17**). Reactions of **16** and **17** with 2.2 eq. isocyanate **9** in CH_2Cl_2 at 40 °C generated the branched acetylated monoterpyridine **18** (65%) and bisterpyridine **20** (43%), which were characterized by ^{1}H, ^{13}C, and 2D COSY NMR spectra, as well as confirmed by the ESI-MS peaks at m/z 1399.4 $[M + H]^+$ (calcd m/z = 1399.6) and m/z 1630.8 $[M + H]^+$ (calcd m/z = 1630.7), respectively. Further deprotection of **18** and **20** afforded the desired branched carbohydrate-functionalized monoterpyridine **19** (88%) and bisterpyridine **21** (84%), which were supported by [^{1}H NMR, $(CD_3)_2SO$] the peaks at 7.94 ppm (t) for CH_2CONH, 6.51 ppm (d) for CONH–Glu, and 6.04 ppm (t) for CH_2NHCO and also by (^{13}C NMR) peaks at 171.5 and 157.2 ppm, corresponding to the amide and urea carbonyl moieties, respectively. The MALDI-TOF mass spectra also confirmed the structures by peaks at m/z 1063.5 $[M + H]^+$ (calcd m/z = 1063.5) for **19** and m/z 1316.6 $[M + Na]^+$ (calcd m/z = 1316.6) for **21**.

The self-assembled fibers of **11**, **13**, and **21** were prepared by cooling a clear solution (1 mg mL^{-1}) in a suitable ratio (Fig. 1) of water and MeOH from 60 to 20 °C. The fibers could be redissolved upon warming, while upon cooling, they reformed, thereby, showing this process is completely reversible. Notably, when solutions of **13** and **21** were prepared with increasing concentrations (1 to 3 mg ml^{-1}; Table S1, ESI†) and cooled

Compound	H_2O:MeOH
11	1 : 1
13	MeOH
21	1 : 2

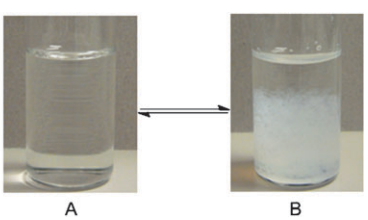

Fig. 1 A solution of **13** in MeOH (1 mg mL^{-1}) (A) at 60 °C and (B) at 20 °C.

from 60 to 20 °C, precipitates, partial gels, and steady gels were obtained, respectively; at higher concentrations, **11** remained a precipitate and **19** remained completely soluble. Herein we focused on the nanofiber precipitates. In comparison with compounds **11**, **13**, and **21**, **19** is highly soluble in both H_2O and MeOH at 20 °C due to its enhanced hydrophilic composition. However, a cloudy solution was formed by cooling the solution of **19** (1 mg ml^{-1}) in a less polar solvent, isopropyl alcohol, from 80 to 20 °C. TEM images of **19** (Fig. S1, ESI†) show spherical aggregates with diameters of 200–300 nm, suggesting that self-assembled morphologies are dependent on both solvent environment and the volume ratio of the hydrophilic and hydrophobic units.[28]

After cooling to 20 °C, the solutions of **11**, **13**, and **21** were allowed to set undisturbed for two days in sealed vials. Fig. 2 shows TEM images obtained from casting a dilute suspension (diluted ten times with the original solvent system) of the fibers onto a 200-mesh carbon-coated Cu grid. Low-magnification images (Fig. 2A, C, and E) show hyperbranched and intertwined networks of fibrous assemblies with lengths of several micrometres. These features are very similar to the supramolecular structures that had been found in gels formed from

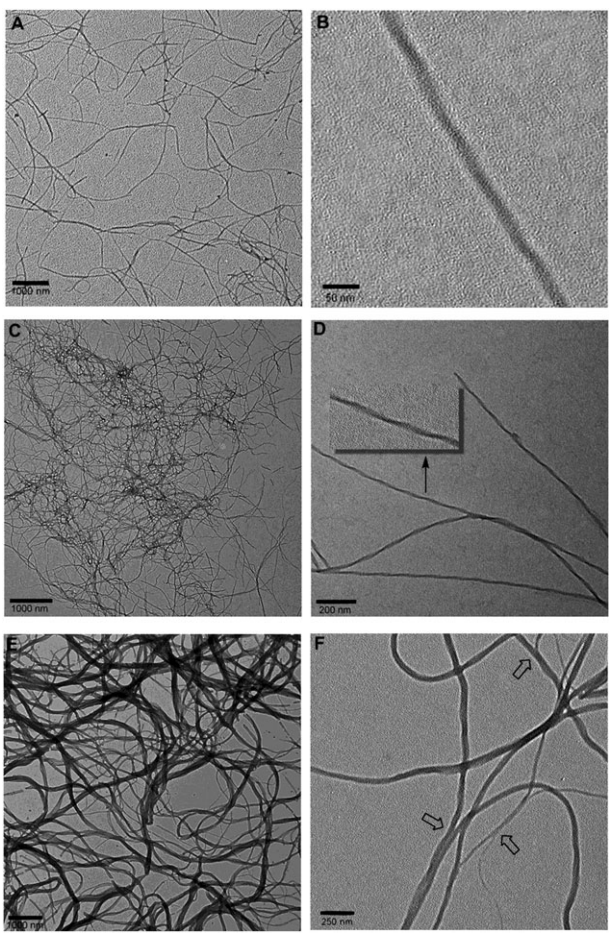

Fig. 2 TEM images of self-assembled **11** (A) in low magnification and (B) in high magnification. TEM images of self-assembled **13** (C) in low magnification, and (D) showing repeating twists (inset). TEM images of self-assembled **21** showing (E) three-dimensional networks and (F) merging points at arrows.

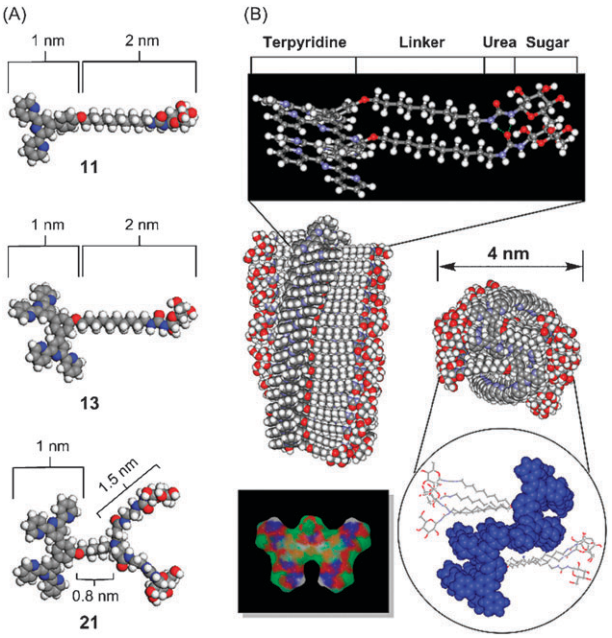

Fig. 3 (A) Space-filling representation of the minimized-energy structures of carbohydrate-functionalized terpyridines **11**, **13**, and **21** and (B) a proposed model of self-assembled nanofibers of **13** and a view of the bis(terpyridine) molecular surface with mapped electron rich (red) and poor (blue) regions.

low molecular-mass organic gelators.[7] In the cases of **11** and **13**, the supramolecular structures have regularly repeating twists (Fig. 2B and D) and diameters ranging from 4 to 100 nm (most fibers with 15–20 nm diameter). The self-assembled **21** (Fig. 2E) has an observed average diameter *ca.* 150 nm due presumably to the packing requirements of a greater molecular volume. Arrows in Fig. 2F show some merging points from which the small and primary fibers associate into large fibers.

Molecular modeling (ESI†) of the sugar-functionalized monoterpyridine **11** and bisterpyridines **13** and **21** revealed that the three monomers have a similar length (*ca.* 3 nm; Fig. 3A). The models of **11** and **13** show that the length contributed by the terpyridine portion is estimated to be 1 nm and the length of the aliphatic part to be *ca.* 2 nm. In the model of **21**, the lengths of linker and branch are about 0.8 nm and 1.5 nm, respectively. A proposed model for the fibers (Fig. 3B; shown unsolvated) shows the hydrophobic terpyridines stacked on the interior of the aggregate surrounded, or wrapped, by the hydrocarbon linkers and hydrophilic carbohydrates, which are oriented towards the exterior; this presumably reduces interfacial energy in a polar environment. Additionally, *H*-bonding interactions between the urea groups also facilitate the stacking. This feature is operative in the nanofibers reported by Meijer *et al.*,[11] as well as Jung and co-workers.[29] The 4 nm diameter of the modeled structure is consistent with observed TEM diameters of the primary fibers. Distances measured for a 360° twist in the fibers ranged from 100 to 150 nm. This corresponds to a twist angle between monomers from 1.0 to 1.4°, respectively, with a 4 Å distance between terpyridines. Further support for the proposed structure is given by considering the bis(terpyridine) molecular surface with the calculated regions of electron density color coded in red (electron rich) and blue (electron poor) (lower left of Fig. 3B), which presumably provides an electrostatic-based driving force component for aggregation. Bis(terpyridine) electrostatic attraction is estimated to decrease the total energy by $\sim$30 kcal mol^{-1} per stacked pair in the aggregate.

In summary, a series of carbohydrate-functionalized mono- and di(terpyridinyl)arenes has been synthesized by urea glucosidation of the terpyridinyl alkyl amines as well as characterized. By simply cooling homogeneous solutions of **11**, **13**, and **21** to 20 °C, self-assembled nanofibers formed; addition of KCl and Fe(II) destroyed the ordered arrays affording a colorless solution and new tpy–Fe(II)–tpy complex, respectively.

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Notes and references

1 J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, WILEY-VCH, Weinheim, 1995.
2 J.-M. Lehn, *Chem. Soc. Rev.*, 2007, **36**, 151.
3 J. L. Atwood and J. W. Steed, *Organic Nanostructures*, WILEY-VCH, Weinheim, 2008.
4 G. R. Newkome, G. R. Baker, M. J. Saunders, P. S. Russo, V. K. Gupta, Z. Yao, J. E. Miller and K. Bouillion, *J. Chem. Soc., Chem. Commun.*, 1986, 752.
5 G. R. Newkome, G. R. Baker, S. Arai, M. J. Saunders, P. S. Russo, K. J. Theriot, C. N. Moorefield, L. E. Rogers, J. E. Miller, T. R. Lieux, M. E. Murray, B. Phillips and L. Pascal, *J. Am. Chem. Soc.*, 1990, **112**, 8458.
6 G. R. Newkome, C. N. Moorefield, G. R. Baker, R. K. Behera, G. H. Escamilla and M. J. Saunders, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 917.
7 R. G. Weiss and P. Terech, *Molecular Gels-Materials with Self-Assembled Fibrillar Networks*, Springer, Dordrecht, 2006.
8 A. R. Hirst, B. Escuder, J. F. Miravet and D. K. Smith, *Angew. Chem., Int. Ed.*, 2008, **47**, 8002.
9 P. Dastidar, *Chem. Soc. Rev.*, 2008, **37**, 2699.
10 A. l. Brizard, R. Oda and I. Huc, *Low Molecular Mass Gelator: Chirality Effects in Self-assembled Fibrillar Networks*, Springer, Berlin/Heidelberg, 2005, p. 167.
11 C. C. Lee, C. Grenier, E. W. Meijer and A. P. H. J. Schenning, *Chem. Soc. Rev.*, 2009, **38**, 671.
12 D. K. Smith, *Chem. Soc. Rev.*, 2009, **38**, 684.
13 E. C. Constable, C. E. Housecroft and A. Mahmood, *Carbohydr. Res.*, 2006, **343**, 2567.
14 R. Roy and J. M. Kim, *Tetrahedron*, 2003, **59**, 3881.
15 S. Sakamoto, T. Tamura, T. Furukawa, Y. Komatsu, E. Ohtsuka, M. Kitamura and H. Inoue, *Nucleic Acids Res.*, 2003, **31**, 1416.
16 S. Orlandi, R. Annunziata, M. Benaglia, F. Cozzi and L. Manzoni, *Tetrahedron*, 2005, **61**, 10048.
17 E. C. Constable and S. Mundwiler, *Polyhedron*, 1999, **18**, 2433.
18 E. C. Constable, R. Frantz, C. E. Housecroft, J. Lacour and A. Mahmood, *Inorg. Chem.*, 2004, **43**, 4817.
19 M. Gottschaldt, D. Koth, D. Muller, I. Klette, S. Rau, H. Gorls, B. Schafer, R. P. Baum and S. Yano, *Chem.–Eur. J.*, 2007, **13**, 10273.
20 B.-S. Kim, D.-J. Hong, J. Ba and M. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 16333.
21 Y. Aoyama, T. Kanamori, T. Nakai, T. Sasaki, S. Horiuchi, S. Sando and T. Niidome, *J. Am. Chem. Soc.*, 2003, **125**, 3455.
22 J. D. Hartgerink, E. Beniash and S. I. Stupp, *Science*, 2001, **294**, 1684.
23 Y. b. Lim, K. S. Moon and M. Lee, *Chem. Soc. Rev.*, 2009, **38**, 925.
24 K. Hanabusa, T. Hirata, D. Inoue, M. Kimura and H. Shirai, *Colloids Surf., A*, 2000, **169**, 307.
25 P. Wang, C. N. Moorefield and G. R. Newkome, *Org. Lett.*, 2004, **6**, 1197.
26 Y. Ichikawa, Y. Matsukawa, T. Nishiyama and M. Isobe, *Eur. J. Org. Chem.*, 2004, 586.
27 G. R. Newkome and C. D. Shreiner, *Polymer*, 2008, **49**, 1.
28 J. H. Ryu, D. J. Hong and M. Lee, *Chem. Commun.*, 2008, 1043.
29 E. J. Cho, N. H. Kim, J. K. Kang and J. H. Jung, *Chem. Mater.*, 2009, **21**, 3.