

Alternation and tunable composition in hydrogen bonded supramolecular copolymers†

Thorsten Felder, Tom F. A. de Greef, Marko M. L. Nieuwenhuizen and
Rint P. Sijbesma*Cite this: *Chem. Commun.*, 2014,
50, 2455Received 29th August 2013,
Accepted 9th January 2014

DOI: 10.1039/c3cc46611f

www.rsc.org/chemcomm

Sequence control in supramolecular copolymers is limited by the selectivity of the associating monomer end groups. Here we introduce the use of monomers with aminopyrimidinone and aminohydroxy-naphthyridine quadruple hydrogen bonding end groups, which both homodimerize, but form even stronger heterodimers. These features allow the formation of supramolecular copolymers with a tunable composition and a preference for alternating sequences.

More than 20 years after the introduction of the term supramolecular polymers, the field continues to develop rapidly.^{1,2} Applications such as biomedical materials² and self-healing materials³ are being explored, and the details of supramolecular polymerization processes have become a subject of detailed study.⁴ However, in at least one aspect supramolecular polymers remain behind their covalent counterparts, *viz.* in control over monomer sequences in copolymers. The use of well-designed multiple hydrogen bonding units potentially provides the selectivity and strength to create the desired control. Self-complementary quadruple hydrogen bonding motifs⁵ have been shown to be useful in the formation of supramolecular homopolymers. In addition, a variety of complementary hydrogen bonding motifs has been reported,⁶ as well as the possibility to exploit these to form supramolecular copolymers with highly alternating structures in mixtures with a strict 1:1 stoichiometry.⁷ Another approach toward these highly alternating structures relies on self-sorting in mixtures of two AB-type heteroditopic monomers.⁸

Multiple hydrogen bonding units that are able to switch from self-complementary to complementary modes of complexation

would allow the formation of alternating copolymers with tunable composition and a degree of alternation that depends on the selectivity of heterocomplexation.⁹ Here we describe the combination of two quadruple hydrogen bonding units, amino-pyrimidinones (AminoUPy) and amino-hydroxy-naphthyridines (NaPyO), in which this capability is inherently present. Monomers functionalized with two of these units form supramolecular polymers. The selectivity for heterocomplexation results in the formation of copolymers with tunable composition and a preference for alternating sequences when the monomers are mixed in solution.

In supramolecular polymers, extensive use has been made of the strong self-association¹⁰ ($K_{\text{dim}} = 6 \times 10^7 \text{ M}^{-1}$ in CHCl_3) of the 2-ureido-4[1H]-pyrimidinone (UPy) unit *via* a DDAA motif of hydrogen bonding sites. UPy's are also able to form heterodimers with 2,7-diamido-1,8-naphthyridine (NaPy).¹¹ They do so with high selectivity *via* a complementary ADDA-DAAD motif upon their tautomerization into the 6[1H]-form ($K_{\text{ass}} = 5 \times 10^6 \text{ M}^{-1}$ in CHCl_3). UPy-NaPy hetero-complexation has been used to form supramolecular copolymers from bifunctional bisUPy and bisNaPy monomers.^{11b} Alternating copolymers are formed over a broad composition range. However, the incapability of the NaPy unit to form homodimers means that the NaPy monomers act as end-cappers of the supramolecular polymer when they are present in excess to the bis-UPy monomers (Fig. 1a).

In order to obtain a system that maintains a high degree of polymerization (DP) over the whole composition range, both hydrogen bonding units must have the capability to self-associate (Fig. 1b). The NaPyO binding unit is capable of forming a homodimeric complex *via* the formation of quadruple hydrogen bonds *via* linear acceptor-donor-acceptor-donor (ADAD) arrays.¹² UPys with electron donating substituents at the 6-position are present in the enol-tautomeric form and are also able to dimerize using ADAD hydrogen bonding arrays.¹³ Consequently, a combination of both dimers is expected to result in the formation of a heterodimer (Scheme 1).

Monofunctional NaPyO binding units **1** and **2** and the bifunctional derivative **4** (Chart 1) were prepared on a multigram scale in high yields using a straightforward procedure from

Laboratory of Macromolecular and Organic Chemistry and Institute for Complex Molecular Systems, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands. E-mail: r.p.sijbesma@tue.nl

† Electronic supplementary information (ESI) available: General methods; synthetic procedures; determination of the dimerization constants using ¹H-NMR; determination of the association constants using UV-Vis titration experiments; curve fitting procedure of the UV-Vis titration data at a single wavelength; variable temperature ¹H-NMR experiments; determination of the concentration dependence of the specific viscosity using dilution experiments; viscosity titration experiments. See DOI: 10.1039/c3cc46611f

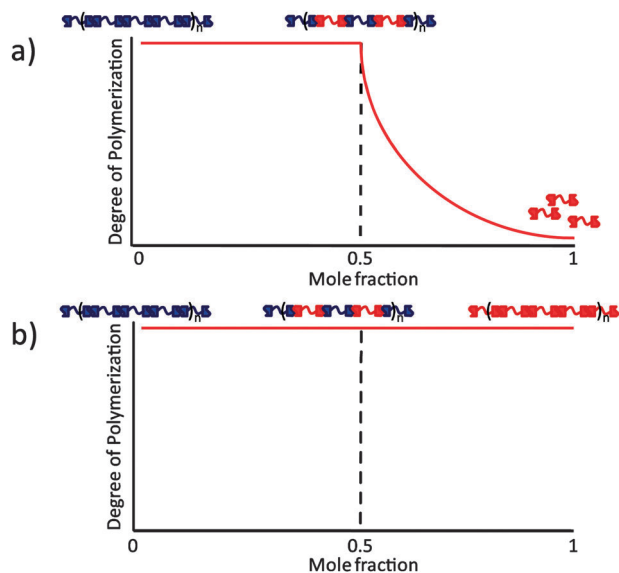
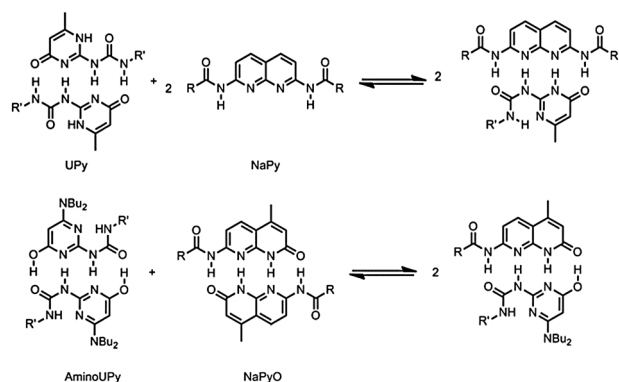


Fig. 1 (a) Supramolecular copolymerization of bisUPy and bisNaPy monomers. The NaPy unit, which does not homodimerize, acts as a chain stopper when the bisNaPy monomer is present in excess. (b) Copolymer formation between two monomer species capable of homo- as well as hetero dimerization. Shown is a case in which the binding constants are approximately equal.



Scheme 1 Top: heterodimerization between typical UPy and NaPy groups. Only the UPy unit can self-dimerize. Bottom: heterodimerization between AminoUPy and NaPyO. Both units can form homodimers as well as heterodimers.

1,8-naphthyridin-2(1H)-one by reaction with aliphatic acyl chlorides (see ESI†). Naphthyridines **1** and **2** and AminoUPy **3** served as model compounds to investigate the strength and selectivity of binding. Bifunctional derivatives NaPyO **4** (NaPyO end-group functionalization >99%) having a polymeric spacer of pTHF₂₀₀₀ ($M_n = 2000$) and bisUPy **5** containing a short aliphatic spacer group were prepared to study the formation of NaPyO–UPy supramolecular copolymers.

Homodimerization constants K_{dim} of the NaPyO model compounds **1** and **2** were determined through fitting of concentration dependent NMR chemical shift data (CDCl_3 , 25 °C) and were determined to be $K_{\text{dim}}(\mathbf{1}) = 6 \pm 1 \times 10^3 \text{ M}^{-1}$ ($\Delta G^\circ = -21.6 \text{ kJ mol}^{-1}$) and $K_{\text{dim}}(\mathbf{2}) = 8 \pm 4 \times 10^3 \text{ M}^{-1}$ ($\Delta G^\circ = -22.3 \text{ kJ mol}^{-1}$), respectively. The dimerization constant of AminoUPy **3** (Chart 1) was reported earlier^{13b} and has a value of

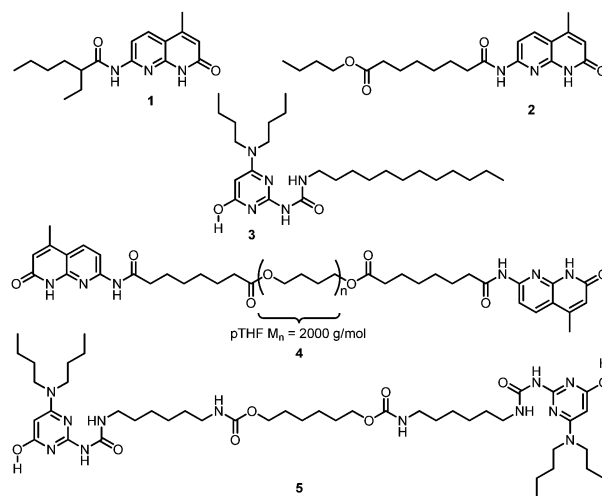


Chart 1

$K_{\text{dim}}(\mathbf{3}) = 9.0 \times 10^5 \text{ M}^{-1}$ ($\Delta G^\circ = -34.0 \text{ kJ mol}^{-1}$). Hetero-complexation of AminoUPy–NaPyO was determined utilizing compounds **1**, **2** and **3** by UV/Vis titration experiments in CHCl_3 at a constant concentration of naphthyridine, $[\text{NaPyO}] = 2.5 \times 10^{-4} \text{ M}$ (see ESI†). K_{ass} was obtained by appropriate fitting of the received binding curves to a model describing homodimerization of both components as well as heteroassociation between the components. The heteroassociation constants of the complexes were determined to be $K_{\text{ass}}(\mathbf{1-3}) = 5.3 \pm 0.3 \times 10^5 \text{ M}^{-1}$ ($\Delta G^\circ = -32.5 \text{ kJ mol}^{-1}$) and $K_{\text{ass}}(\mathbf{2-3}) = 2.7 \pm 0.2 \times 10^5 \text{ M}^{-1}$ ($\Delta G^\circ = -31.0 \text{ kJ mol}^{-1}$). Based on the free energy change obtained for the individual binding events, the free energy change for the formation of heterocomplexes from homocomplexes is calculated to be negative ($\Delta G^\circ = -9.4 \text{ kJ mol}^{-1}$ for complex **1-3** and -5.7 kJ mol^{-1} for complex **2-3**) and therefore the heterocomplex is favored over the homocomplexes in equimolar mixtures of the components (Table 1).

¹H-NMR spectroscopy was also used to study the preference for heterocomplexation. However, spectra from equimolar mixtures (10 mM, CDCl_3) of NaPyO **1** and UPy **3** at 298 K exhibit broadened signals particularly in the aromatic region (see ESI†). Therefore, the measurements were also performed at lower temperatures where sharpening and splitting of the peaks occurred. The recorded low temperature NMR spectra showed multiple sets of signals, which were assigned to the homo- and heterodimeric species in solution. Upon integration of the respective signals, the selectivity of the heterocomplex **1-3** was determined to be 73% at 263 K. Further lowering of the temperature led to an increased selectivity of 79% at 248 K.

Bis-functionalized derivatives **4** and **5** (Chart 1) form supramolecular homopolymers in chloroform, as shown by the concentration dependence of the specific viscosities (η_{sp}) which

Table 1 Heterocomplexation selectivity for quadruple hydrogen bonding units

Equilibrium	[Heterodimer]/[homodimer]	
	298 K (UV)	248 K (NMR)
$\mathbf{1-1} + \mathbf{3-3} \rightarrow \mathbf{2} (\mathbf{1-3})$	3.6	3.8
$\mathbf{2-2} + \mathbf{3-3} \rightarrow \mathbf{2} (\mathbf{2-3})$	3.7	n.d.



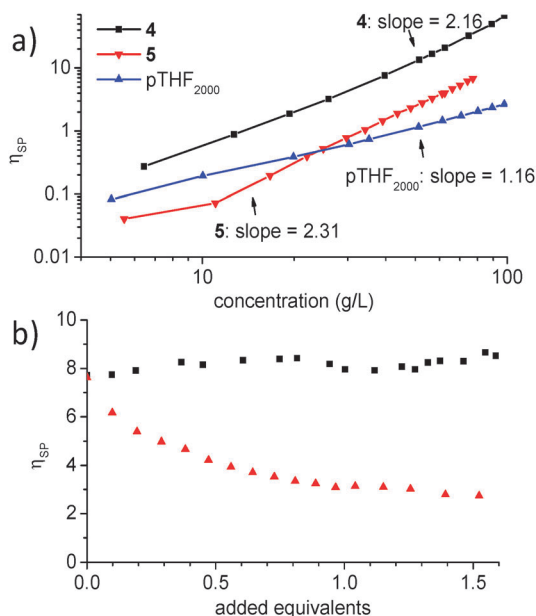


Fig. 2 (a) Concentration dependent specific viscosities of **4**, **5** and pTHF₂₀₀₀ in chloroform. **4** and **5** exhibit a strong concentration dependence of the solution viscosity indicating the formation of supramolecular polymers. (b) Viscosity titration of a 39 g L⁻¹ bisNaPyO **4** solution with bisUPy **5** (■) and with UPy stopper **3** (▲) in chloroform.

scale with concentration as $\eta_{sp} \sim c^{2.16}$ and $\eta_{sp} \sim c^{2.31}$, respectively (Fig. 2a). In contrast to the strong concentration dependence of the viscosity of the bifunctionalized monomers, η_{sp} of unfunctionalized polytetrahydrofuran with a molecular weight of 2000 g mol⁻¹ (the length of the linker in **4**) is low and shows a nearly linear increase of η_{sp} with concentration. Supramolecular copolymerization was probed by measuring the specific viscosity of a 39 g L⁻¹ NaPyO monomer **4** solution to which increasing amounts of UPy monomer **5** were added. The experiment resulted in a viscosity plot displaying a constant value at $\eta_{sp} = 8.5$ over the whole measured composition range up to 1.6 equiv. of **5**. This observation can be understood by a continuous incorporation of the UPy monomer into the preformed NaPyO homo polymer chain, which at a monomer ratio of 1:1 (1 equivalent **5** in **4**) results in UPy-NaPyO supramolecular copolymers with preferred alternation and without exhibiting a significant change in solution viscosity. Upon further addition of >1 equiv. of **5** to the solution, no considerable change in η_{sp} was observed. In contrast, a titration of bisNaPyO **4** with 1.55 equivalents of monoUPy **3** showed a progressive drop in viscosity from the pure solution of **4** ($\eta_{sp} = 7.6$) to $\eta_{sp} = 2.7$ (Fig. 2b).

Heterodimerization of the 1,8-naphthyridin-2(1*H*)-one derivative to UPy derivatives with high binding strength and modest selectivity has been demonstrated. This allowed formation of supramolecular copolymers with tunable composition from bifunctional monomers over a broad mixing ratio without a notable influence on solution viscosity. Heteroselectivity results in preferred alternation of monomeric units in the copolymer, although the alternation is incomplete. The actual degree of alternation is determined by the heterocomplexation equilibrium. Although the supramolecular copolymer has certain analogies with alternating covalent copolymers obtained by radical copolymerization, an essential difference is

that the degree of alternation in radical polymerizations is determined by kinetics, while in the supramolecular polymers it is determined by the ratio of equilibrium constants.

Further improvement in the system may therefore be achieved by increasing the selectivity of heterocomplexation. The origin of heteroselectivity in the NaPyO-UPy system appears not to be related to improved steric complementarity in the heterodimer, since crystal structures and energy minimized structures of the DADA arrays in both components show that they are linear within 0.1 Å.^{13b,14} Therefore, we propose that electronic complementarity, *i.e.* matching of the strongest acceptor and donor sites is responsible for the observed selectivity. Current efforts are focused on improving the selectivity in donor-acceptor arrays optimized for electronic complementarity.

This research was partially supported by NanoNed, a national nanotechnology program coordinated by the Dutch Ministry of Economic Affairs (Project EMM.7126).

Notes and references

- (a) 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**, 5687–5754; (b) T. Aida, E. W. Meijer and S. I. Stupp, *Science*, 2012, **335**, 813–817.
- P. Y. W. Dankers, M. C. Harmsen, L. A. Brouwer, M. J. A. Van Luyn and E. W. Meijer, *Nat. Mater.*, 2005, **4**, 568–574.
- P. Cordier, F. Tournilhac, C. Soulié-Ziakovic and L. Leibler, *Nature*, 2008, **451**, 977–980.
- P. A. Korevaar, S. J. George, A. J. Markvoort, M. M. J. Smulders, P. A. J. Hilbers, A. P. H. J. Schenning, T. F. A. De Greef and E. W. Meijer, *Nature*, 2012, **481**, 492–496.
- (a) R. P. Sijbesma and E. W. Meijer, *Chem. Commun.*, 2003, 5–16; (b) Y. Hisamatsu, N. Shirai, S. Ikeda and K. Odashima, *Org. Lett.*, 2009, **11**, 4342–4345; (c) V. G. H. Lafitte, A. E. Aliev, E. Greco, K. Bala, P. Golding and H. C. Hailes, *New J. Chem.*, 2011, **35**, 1522–1527; (d) X. Li, Y. Fang, P. Deng, J. Hu, T. Li, W. Feng and L. Yuan, *Org. Lett.*, 2011, **13**, 4628–4631.
- (a) S. K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1988, **110**, 1318–1319; (b) Y. Hisamatsu, N. Shirai, S. Ikeda and K. Odashima, *Org. Lett.*, 2010, **12**, 1776–1779; (c) B. A. Blight, C. A. Hunter, D. A. Leigh, H. McNab and P. I. T. Thomson, *Nat. Chem.*, 2011, **3**, 244–248; (d) M. L. Pellizzaro, S. A. Barrett, J. Fisher and A. J. Wilson, *Org. Biomol. Chem.*, 2012, **10**, 4899–4906.
- (a) V. Berl, M. Schmutz, M. J. Krische, R. G. Khoury and J.-M. Lehn, *Chem.-Eur. J.*, 2002, **8**, 1227–1244; (b) S. Sivakova, D. A. Bohnsack, M. E. Mackay, P. Suwanmala and S. J. Rowan, *J. Am. Chem. Soc.*, 2005, **127**, 18202–18211; (c) O. A. Scherman, G. B. W. L. Lighthart, H. Ohkawa, R. P. Sijbesma and E. W. Meijer, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 11850–11855; (d) T. Park and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2006, **128**, 13986–13987; (e) K. P. Nair, V. Breedveld and M. Weck, *Macromolecules*, 2008, **41**, 3429–3438.
- (a) F. Wang, C. Han, C. He, Q. Zhou, J. Zhang, C. Wang, N. Li and F. Huang, *J. Am. Chem. Soc.*, 2008, **130**, 11254–11255; (b) N. Tomimasu, A. Kanaya, Y. Takashima, H. Yamaguchi and A. Harada, *J. Am. Chem. Soc.*, 2009, **131**, 12339–12343.
- M. L. Pellizzaro, K. A. Houton and A. J. Wilson, *Chem. Sci.*, 2013, **4**, 1825–1829.
- F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761–6769.
- (a) X.-Q. Li, X.-K. Jiang, X.-Z. Wang and Z.-T. Li, *Tetrahedron*, 2004, **60**, 2063–2069; (b) G. W. B. L. Lighthart, H. Ohkawa, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 810–811.
- S. Goswami, S. Dey, J. F. Gallagher, A. J. Lough, S. Garcia-Granda, L. Torre-Fernández, I. Alkorta and J. Elguero, *J. Mol. Struct.*, 2007, **846**, 97–107.
- (a) V. G. H. Lafitte, A. E. Aliev, H. C. Hailes, K. Bala and P. Golding, *J. Org. Chem.*, 2005, **70**, 2701–2707; (b) T. F. A. de Greef, G. Ercolani, G. B. W. L. Lighthart, E. W. Meijer and R. P. Sijbesma, *J. Am. Chem. Soc.*, 2008, **130**, 13755–13764.
- B. Ośmiałowski, E. Kolehmainen, E. Kalenius, B. Behera, R. Kauppinen and E. Sievänen, *Struct. Chem.*, 2011, **22**, 1143–1151.

