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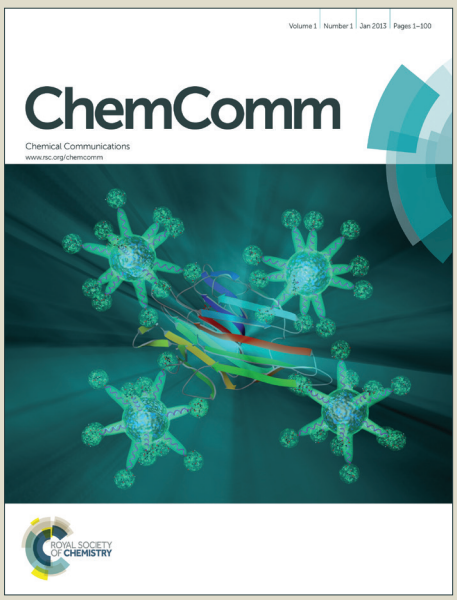

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Alternation and Tunable Composition in Hydrogen Bonding Supramolecular Copolymers

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

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 aminohydroxynaphthyridine 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 developing rapidly.[1,2]Applications such as biomedical materials[2] and self-healing materials[3] 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 sequence 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 motifs[5] 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. 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-association[10] (K_{dim} = 6 × 10^7 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_{ass} = 5×10^6 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 endcappers of the supramolecular polymer when they are present in excess to the bis-UPy monomers (Figure 1a).

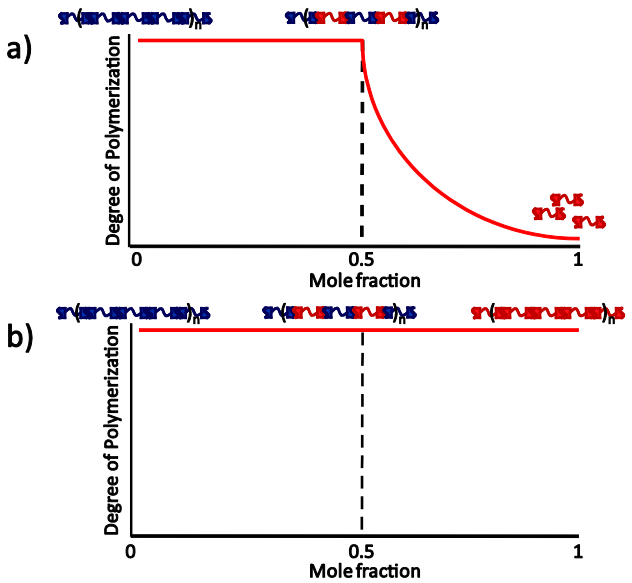
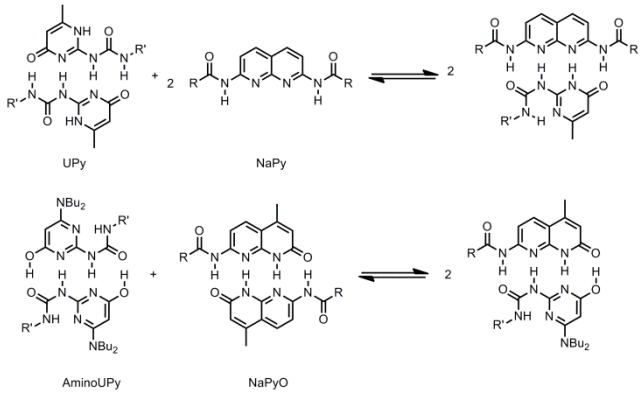


Figure 1. (a) Supramolecular copolymerization of bisUPy and bisNaPy monomers. The NaPy unit, which does not homodimerize, acts a as chain stopper when the bisNaPy monomer is present in excess (b) Copolymer formation between two monomer species capable of homo- as well as hetero dimerization. Shown is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

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 (Figure 1b). The NaPyO binding unit is capable of forming a homo-dimeric 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-

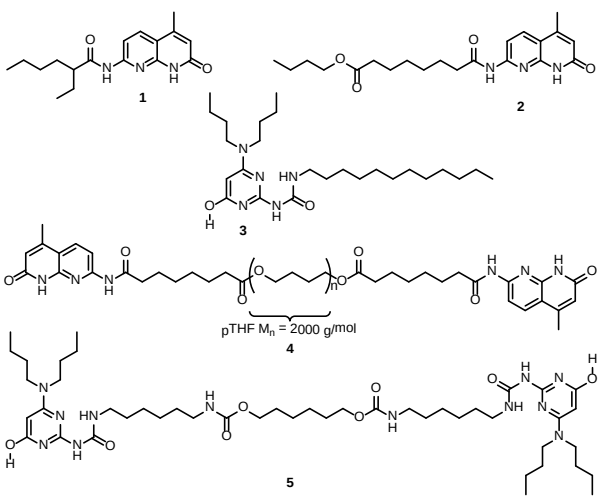
position are present in the enol-tautomeric form and are also able to dimerize using ADAD hydrogen bonding arrays.[13] Consequently, a combination of both dimers is expected to result in the formation of a heterodimer (Scheme 1).



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.

Preparation of monofunctional NaPyO binding units **1** and **2** and bifunctional derivative **4** (Chart 1) was performed on multigram scale in high yields using a straightforward procedure from 1,8-naphthyridin-2(1*H*)-one by reaction with aliphatic acyl chlorides (see Supporting Information). Naphthyridines **1** and **2** and AminoUPy **3** served as model compounds to investigate strength and selectivity of binding. Bifunctional derivatives NaPyO **4** (NaPyO end-group functionalization >99%) having a polymeric spacer of $pTHF_{2000}$ (M_n = 2,000) and bisUPy **5** containing a short aliphatic spacer group were prepared to study the formation of NaPyO–UPy supramolecular copolymers.

Chart 1.



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_{dim}(**1**) = 6 ± 1 × 10^3 M^{-1} (ΔG°= -21.6 kJ/mol) and K_{dim}(**2**) = 8 ± 4 × 10^3 M^{-1} (ΔG°= -22.3 kJ/mol), respectively. The dimerization constant of AminoUPy **3** (Chart 1) was reported earlier[13b] and has a value of K_{dim}(**3**) = 9.0 × 10^5 M^{-1} (ΔG°= -34.0 kJ/mol). Heterocomplexation of AminoUPy–NaPyO was determined utilizing compounds **1**,**2** and **3** by UV/Vis titration experiments in $CHCl_3$ at constant concentration of the naphthyridine, [NaPyO] = 2.5 × 10^{-4} M. (see Supporting Information). 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_{ass}(**1**·**3**) = 5.3 ± 0.3 × 10^5 M^{-1} (ΔG°= -32.5 kJ/mol) and K_{ass}(**2**·**3**) = 2.7 ± 0.2 × 10^5 M^{-1} (ΔG°= -31.0 kJ/mol). Based on the 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 (ΔG°= -9.4 kJ/mol for complex **1**·**3** and -5.7 kJ/mol for complex **2**·**3**) and therefore the heterocomplex is favored over the homocomplexes in equimolar mixtures of the components. (Table 1).

Table 1. Heterocomplexation selectivity for quadruple hydrogen bonding units

Equilibrium	[heterodimer] / [homodimer]	
	298K (UV)	248K (NMR)
1·1 + **3·3** → 2 (**1·3**)	3.6	3.8
2·2 + **3·3** → 2 (**2·3**)	3.7	n.d.

^{1}H-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 Supporting Information). 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. From integration of the respective signals, 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 is shown by the concentration dependence of the specific viscosities (η_{sp}) which scale with concentration as $\eta_{sp} \sim C^{2.16}$ and $\eta_{sp} \sim C^{2.31}$, respectively (Figure 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 (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 39 g/L solutions NaPyO monomer **4** to which increasing amounts of UPy monomer **5** were added. The experiment resulted in a viscosity plot displaying an constant value at η_{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 copolymer 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** (η_{sp} = 7.6) to η_{sp} = 2.7 (Figure 2b).

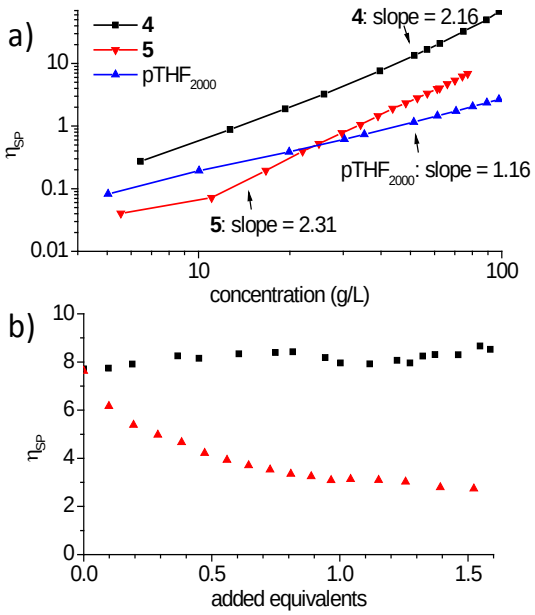


Figure 2. (a) Concentration dependent specific viscosities of **4**, **5** and $pTHF_{2000}$ in chloroform. **4** and **5** exhibit a strong concentration dependence of the solution viscosity indicating the formation of supramolecular polymers. b) Viscosity titration of a 39 g/L bisNaPyO **4** solution with bisUPy **5** (■) and with UPy stopper **3** (▲) in chloroform.

Conclusions

Heterodimerization of 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 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 a 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 selectivity in donor acceptor arrays optimized for electronic complementarity.

Acknowledgement

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

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† Electronic Supplementary Information (ESI) available: General Methods; Synthetic procedures; Determination of the dimerization constants using ^{1}H-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 ^{1}H-NMR experiments; Determination of the concentration dependence of the specific viscosity using dilution experiments; Viscosity titration experiments. See DOI: 10.1039/b000000x/

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