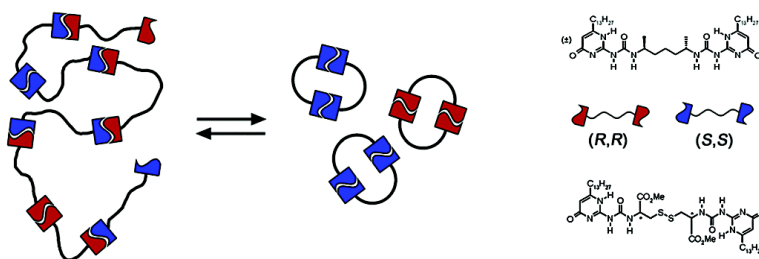## Communication

Enantioselective Cyclization of Racemic Supramolecular Polymers

A. Tessa ten Cate, Patricia Y. W. Dankers, Huub Kooijman,
Anthony L. Spek, Rint P. Sijbesma, and E. W. Meijer

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Enantioselective Cyclization of Racemic Supramolecular Polymers

A. Tessa ten Cate,† Patricia Y. W. Dankers,† Huub Kooijman,‡ Anthony L. Spek,‡
Rint P. Sijbesma,*,† and E. W. Meijer*,†

*Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O. Box 513,
5600 MB Eindhoven, The Netherlands, and Bijvoet Center for Biomolecular Research, Crystal and
Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*

Received January 22, 2003; E-mail: r.p.sijbesma@tue.nl; e.w.meijer@tue.nl

Stereoselective association plays an important role in chemistry and biology, for example, in recognition processes, asymmetric catalysis, and chiral chromatographic separations.[1] The phenomenon is based on a difference in interaction energy between molecules of equal and of opposite configuration, and the degree of selectivity is dependent on the strength of the intermolecular interaction, which may be different in different physical states. Since Pasteur's discovery of spontaneous resolution,[2] discrimination in the solid state has received much attention, and many examples of conglomerate crystallizations have been reported. Enantioselective self-association in solution is a much less studied subject. Nonequivalence between the ^1H NMR spectra of pure enantiomers and racemic mixtures has been reported for a number of associating molecules.[3] However, in most cases, the selectivity was limited, probably due to the dynamic nature and low stability of the aggregates. Much higher selectivities have been observed for stronger interactions in metal−ligand complexes[4] and assemblies based on multiple hydrogen bonding.[5] Homochiral supramolecular polymerization of xylylene-bridged bis(cyclic peptide)s was described recently.[6] Furthermore, heterochiral dimerization by $\pi-\pi$ stacking was reported for octahedral eilatin complexes.[7]
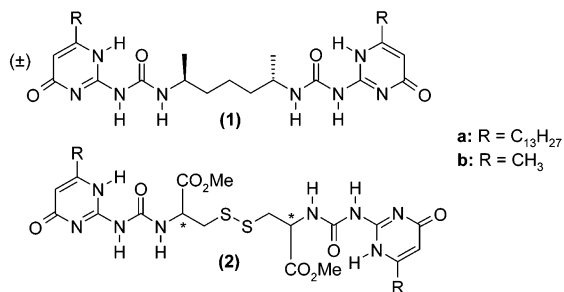
By designing complexes that possess high stability, we are also aiming at closing the gap between stereoselectivity in crystals and in solution. On the basis of the knowledge gained from crystals, we propose that C_2-symmetrical units would preferably form enantioselective "conglomerates". Previously, we have shown that dimerization of quadruply hydrogen bonding 2-ureido-4[1H]-pyrimidinone (UPy)[8] derivatives (Figure 1) is very strong and has an association constant of 6×10^7 M^{-1} in CDCl$_3$.[8b] Bifunctional molecules based on the UPy moiety may form randomly coiled supramolecular polymers as well as cyclic oligomers in solution,[9] depending on the external conditions and on the geometry of the monomer. Ring-chain equilibria are characterized by a critical concentration,[10] below which only cyclic species are present and above which the concentration of cyclic oligomers is constant and polymeric aggregates are formed. We report here that dimerization
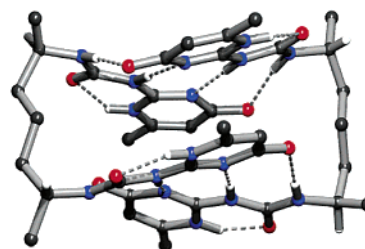
† Eindhoven University of Technology.
‡ Utrecht University.

Figure 1. Crystal structure of **1b**, showing enantioselective dimerization. Hydrogen atoms not involved in hydrogen bonds and not bonded to chiral centra are omitted for clarity.[13]

of chiral bifunctional UPy derivatives **1** and **2** in solution selectively produces homochiral assemblies.

Monomer **1a** was synthesized as a diastereomeric mixture from 2,6-diisocyanatoheptane and 6-tridecylisocytosine. Racemic **1a** was separated from the meso stereoisomer by flash column chromatography. In contrast to spectra of similar compounds, ^1H NMR spectra of **1a** show a single peak for each proton attached to the UPy unit, over a broad concentration range (5−300 mM), demonstrating that **1a** is present in solution as a single type of hydrogen-bonded aggregate. On the basis of ^1H NMR diffusion measurements,[11] this aggregate was estimated to be dimeric in size.[12] The solution viscosity of **1a** in chloroform was measured for concentrations up to 94 mM and was found to be only slightly higher than that of the solvent (specific viscosity below 0.5). Furthermore, the specific viscosity increased linearly with concentration, characteristic for aggregates of constant size. Together, these results demonstrate that racemic **1a** forms cyclic dimers in chloroform solution and has a critical concentration above 300 mM. From ^1H NMR spectra, it was concluded that the dimer of **1a** is fully symmetrical. Molecular models show that this is only possible if the dimers are homochiral, as heterochiral dimers have lower symmetry, leading to doubling of the number of peaks in the ^1H NMR spectra. Enantioselective dimerization was confirmed by single-crystal X-ray analysis of derivative **1b** (Figure 1). Homochiral dimers of different chirality alternated in racemic crystals (space group P-1), obtained from dimethyl sulfoxide−acetic acid mixtures.

To study enantioselective dimerization in detail, (R,R)-**2a** and (S,S)-**2a** were synthesized from enantiomerically pure cystine methyl esters, and solutions of the enantiomers were compared to solutions of the racemic mixture. In the ^1H NMR spectra of the pure substances at 30 mM, four peaks were observed for the pyrimidinone alkylidene proton between 5.7 and 6.1 ppm (Figure 2, bottom), which were all assigned to cyclic assemblies. The ^1H NMR spectrum of the racemic mixture at 30 mM was indistinguishable from that of the pure enantiomers, indicating again that only homochiral cyclic species were formed in solution. Upon increasing the concentration of the enantiomerically pure solutions, an additional peak was observed (Figure 2, top), which was assigned
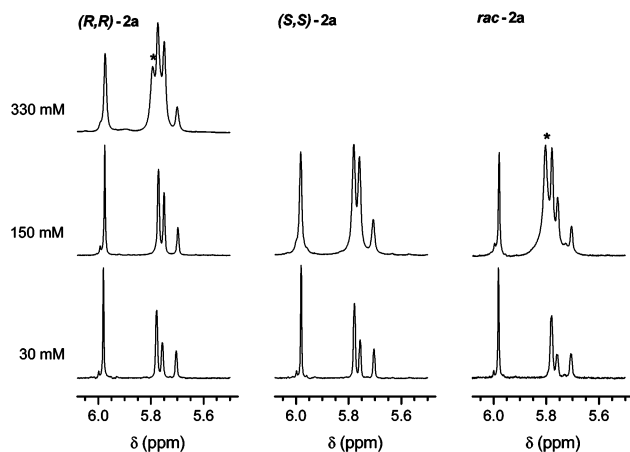
Figure 2. Alkylidene region of ^{1}H NMR spectra of (R,R)-**2a**, (S,S)-**2a**, and a racemic mixture in CDCl$_3$; asterisks denote peaks assigned to polymeric aggregates.
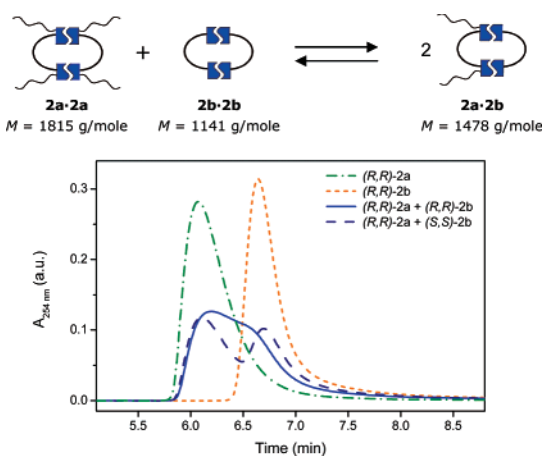

Figure 3. Schematic representation of the equilibrium between homo- and heterodimers of **2a** and **2b** and corresponding molecular weights (top) and results of SEC experiments with mixtures of **2a** and **2b** (bottom).

to a random coil polymeric aggregate with a low diffusion coefficient[14] as determined by ^{1}H NMR spectroscopy. On the basis of ^{1}H NMR spectra, the critical concentration for (R,R)-**2a** was determined to be 270 ± 20 mM (294 K). Remarkably, for the racemic mixture, a peak corresponding to a polymeric aggregate was already observed at 150 mM, and the critical concentration for racemic **2a** was determined to be 120 ± 20 mM (294 K). The large decrease in critical concentration is a very interesting phenomenon and is in full agreement with enantioselective cyclization in combination with the presence of both enantiopure and racemic dyads in linear hydrogen-bonded assemblies. If all dyads would have the same cyclization constant, the critical concentration would be the same as for the enantiomerically pure solutions. However, if only homochiral dyads can form cyclic aggregates, the critical concentration will be decreased.[15]

Size exclusion chromatography (SEC) has been demonstrated to be an effective tool to study the size of supramolecular aggregates.[16] To use the molecular size of the cyclic dimers as a probe for stereoselectivity, derivative **2b** was synthesized, which lacks the long alkyl tail on the pyrimidinone ring and has a lower molecular weight than **2a**. In dilute solutions containing mixtures of (R,R)-**2a** and (R,R)-**2b**, homochiral homo- and heterodimers of three different sizes[17] are formed (Figure 3, top). Conversely, solutions of (S,S)-**2a** and (R,R)-**2b** will contain only the two

homodimers (equilibrium fully to the left side), if cyclization indeed occurs enantioselectively. SEC experiments confirmed the expected behavior (Figure 3, bottom). While the chromatogram of (S,S)-**2a** with (R,R)-**2b** contains only two peaks corresponding to the homodimers, the chromatogram of (R,R)-**2a** with (R,R)-**2b** shows one broad combined signal of homo- and heterodimers.

In conclusion, we have demonstrated the selective formation of homochiral cyclic dimers of UPy derivatives **1** and **2** in chloroform solution. The preorganization of the monomers and the combined binding strength of the eight hydrogen bonds result in a very high stability of the cyclic aggregates with pronounced selectivity between homochiral and heterochiral cyclic species, usually only found in the crystalline state.

Supporting Information Available: Experimental details of synthesis and characterization of **1** and **2a/b** (PDF). Atomic displacement ellipsoid plot and X-ray crystallographic file in CIF format for **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Gübitz, G.; Schmid, M. G. *Biopharm. Drug Dispos.* **2001**, *22*, 291. (b) Schurig, V. *J. Chromatogr., A* **2001**, *906*, 275.
(2) Pasteur, L. *C. R. Hebd. Seances Acad. Sci.* **1853**, *37*, 162.
(3) (a) Dobashi, A.; Saito, N.; Motoyama, Y.; Hara, S. *J. Am. Chem. Soc.* **1986**, *108*, 307. (b) Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873. (c) Giordano, C.; Restelli, A.; Villa, M.; Annunziata, R. *J. Org. Chem.* **1991**, *56*, 2270. (d) Jursic, B. S.; Goldberg, S. I. *J. Org. Chem.* **1992**, *57*, 7172. (e) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.
(4) For example, see: (a) Masood, M. A.; Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 928. (b) Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 932. (c) Xu, J.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2878. (d) Vincent, J.-M.; Philouze, C.; Pianet, I.; Verlhac, J.-B. *Chem.-Eur. J.* **2000**, *6*, 3595.
(5) For example, see: (a) Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498. (b) Shi, X.; Fettinger, J. C.; Cai, M.; Davis, J. T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3124. (c) Murguly, E.; McDonald, R.; Branda, N. R. *Org. Lett.* **2000**, *2*, 3169. (d) Shi, X.; Fettinger, J. C.; Davis, J. T. *J. Am. Chem. Soc.* **2001**, *123*, 6738.
(6) Ishida, Y.; Aida, T. *J. Am. Chem. Soc.* **2002**, *124*, 14017.
(7) Gut, D.; Rudi, A.; Kopilov, J.; Goldberg, I.; Kol, M. *J. Am. Chem. Soc.* **2002**, *124*, 5449.
(8) (a) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761. (b) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487.
(9) (a) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601. (b) Folmer, B. J. B.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2001**, *123*, 2093.
(10) (a) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600. (b) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901. (c) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *Macromolecules* **2001**, *34*, 3815.
(11) Diffusion measurements were performed using a bipolar pulse pair (BPP) pulse sequence; for details, see: Wu, D.; Chen, A.; Johnson C. S., Jr. *J. Magn. Reson., Ser. A* **1995**, *115*, 260.
(12) The diffusion coefficient of the aggregate of **1** was found to be similar to that of the internal reference, heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (M = 1429 g/mol), denoting a dimeric size ($M_{1\cdot1}$ = 1817 g/mol).
(13) Crystal data of **1b**: 2C$_{19}$H$_{28}$N$_8$O$_4$·3C$_2$H$_4$O$_2$, colorless, triclinic, space group P-1 (No. 2), a = 10.8659(10), b = 14.784(2), c = 16.870(3) Å, α = 82.746(12), β = 82.149(10), γ = 75.847(12)°, V = 2590.9(6) Å^3, Z = 2, 71 935 reflections measured, 11 813 unique, 150 K, Mo Kα radiation, θ^{max} = 27.5°, refined on F^2, 331 parameters (including N- - -H coordinates), wR2 = 0.1333, R1 = 0.0501 for 7020 I > 2σ(I), S = 1.038, −0.27, and 0.42 e Å^{-3}.
(14) Diffusion coefficients relative to the internal reference[12] for peaks assigned to cyclic assemblies ranged between 0.67 and 0.91, while peaks assigned to polymers displayed a relative diffusion coefficient of 0.32.
(15) For details, see Supporting Information.
(16) (a) Seto, C. T.; Mathias, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1321. (b) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314.
(17) ^{1}H NMR experiments have shown that in solutions of **2a/b** at concentrations used for SEC (<2 mM) primarily dimeric aggregates are present. Furthermore, heterodimerization was confirmed by ^{1}H NMR spectroscopy of mixtures of (R,R)-**2a** and (R,R)-**2b**.

JA034273G