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Facile synthesis of a chiral polymeric helix; folding by intramolecular hydrogen bonding†

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Received (in Cambridge, UK) 8th October 2003, Accepted 31st October 2003
First published as an Advance Article on the web 25th November 2003

In a single condensation step, a poly-ureidophthalimide is synthesized, which folds into a chiral, helical architecture according to circular dichroism spectroscopy.

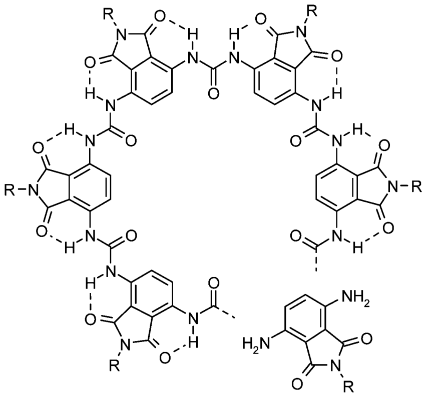
The helix, being a fundamental structure in realizing the biological activity of naturally occurring macromolecules, is expected to lead to a broad range of applications, including molecular recognition, and molecular scaffold functions.[1] Of the various synthetic helices,[2] the foldamers[3,4] are most similar to the natural α-helix, compared to helicenes[5] or supramolecular helices.[6] Aliphatic peptidometic homologues,[7] as well as aromatic oligo-amides,[8] have been demonstrated to adopt helical conformations through non-covalent intramolecular interactions.

Using *para*- instead of *meta*[8]-substituted aromatic units, urea[9] based aromatic helices may also be formed with an estimated 6–8 units per turn (Scheme 1). Imide oxygens are suitable to orientate the *para*-positioned urea groups, while imide nitrogens allow the incorporation of any primary amine containing functionality. In this case, a chiral amine is incorporated to permit investigation of the chiral, helical architecture in dilute solution using circular dichroism spectroscopy. After a two step conversion of the amine into a monomer, a true polymer is formed in a single, swift condensation step. In addition, corresponding oligomers have been obtained by chromatographic separations.

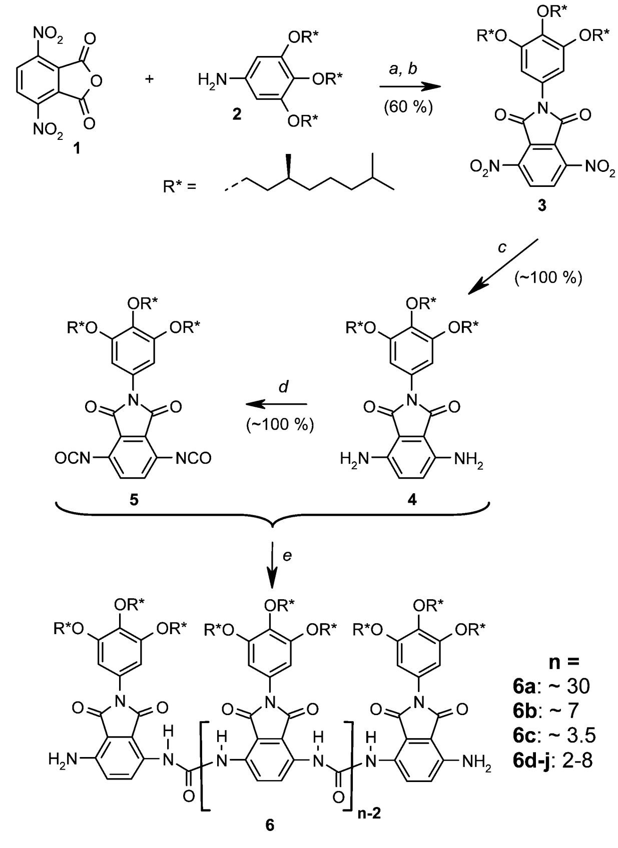
Backbone building block, 3,6-dinitrophthalic anhydride (**1**), was synthesized by nitration of 1,5-dinitronaphthalene and subsequent oxidation,[10] followed by ring closure of the obtained diacid using acetic anhydride.[11] Anhydride **1** was reacted with 1.6 equiv. of chiral 3,4,5-tris[(*S*)-3,7-dimethyloctyloxy]aniline (**2**) to obtain 3,6-dinitrophthalimide **3** (Scheme 2).[12] Dinitro compound **3** was catalytically hydrogenated on Pd to diamino compound **4**; diisocyanato monomer **5** was obtained by treating diamine **4** with an excess of phosgene. Equimolar amounts of diamino monomer **4** and diisocyanato monomer **5** were copolymerized in toluene using 4-dimethylaminopyridine as a catalyst, to afford poly-ureidophthalimide **6**.

Polymer **6** was subjected to column chromatography to divide the mixture into high (**6a**), intermediate (**6b**), and low (**6c**) molecular weight fractions. The average chain length of the mixtures **6a–c** was determined by ^{1}H-NMR endgroup analysis, using the integral ratio between the signals of the termini (amine protons at 5.18 ppm and aromatic phthalimide protons at 6.95 and 8.48 ppm) and the signals of the aromatic phthalimide protons in the main chain (8.73 ppm). For polymer **6a**, an average value as high as 30 units was calculated. Average values of 7 and 3.5 units were calculated for **6b** and **6c**, respectively. The oligomers (dimer up to octamer **6d–j**) were obtained by preparative, reversed phase HPLC[13] (see Supplementary information for polydispersities).

The appearance of urea protons at 9.0 ppm is indicative of intramolecular hydrogen bonding. The chiral architectures were investigated in detail with CD-spectroscopy (Fig. 1). Polymer **6a** (~ 30 units) folds into a chiral structure with a very high degree of ordering in THF ($g = -0.012$). Remarkably, **6b** (~ 7 units) shows only a minor Cotton effect, while **6c** (~ 3.5 units) shows no Cotton effect at all. The dimer up to the hexamer **6d–h** show no Cotton effects either, while the heptamer **6i** and octamer **6j** show minor effects.[13]



Scheme 1 Chemical structure of a turn of the designed polymeric helix, together with a diamino functionalized monomer.



Scheme 2 Synthesis of poly-ureidophthalimide **6**. *Reagents and conditions*: a) acetonitrile, 80 °C; b) acetic anhydride, 100 °C; c) H_2(g), Pd/C, THF–EtOH–water; d) phosgene in toluene, 110 °C; e) 4-dimethylaminopyridine, toluene, 80 °C.

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† Electronic Supplementary Information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b312407j/

DOI: 10.1039/b312407j

Indeed, it is most likely that the poly-ureidophthalimide **6** folds into a helical architecture with a pitch of approximately 6–8 units. In agreement with earlier studied foldamers,[4] only chains that complete one pitch of the helix (**6b**) can fold into a stable architecture in which chirality is transferred from the CD-silent peripheral side chains, to the accurately positioned, CD-active phthalimide chromophores. In longer systems, pitches become 'sandwiched' between turns below and above, and order is only increased (**6a**).

On the other hand, in $CHCl_3$, no Cotton effect is observed for ureidophthalimides **6a–c**, suggesting a non-chiral conformation of the polymer chains in this solvent. This might be rationalized by interference of the intramolecular imide–urea hydrogen bonding by $CHCl_3$ (H-bond donor), while the ether oxygen of THF (H-bond acceptor) might increase the *syn*-coplanarity between two adjacent urea protons.[14] Denaturation experiments show that the chiral, helical aggregates in THF are unusually insensitive to the addition of $CHCl_3$.[4] Finally, above 50 vol% $CHCl_3$, a fairly sharp transition is observed, which corresponds to the unfolding of a highly ordered aggregate (Fig. 2).

It is worth mentioning that hysteresis accompanies the folding process of the chiral helix. It takes a long time (1 h) before the system reaches equilibrium after the addition of more $CHCl_3$. Also, order is hardly lost upon raising the temperature (45% at 55 °C, compared to 100% at 20 °C for **6a** in THF), while upon cooling, the architectures need at least several hours to regain their maximal ordering. Apparently, order and stability are optimally balanced for this poly-ureidophthalimide, since stronger hydrogen bonding and π–π stacking interactions will occur at the expense of reversibility and flexibility of the helical architecture.[15]

Currently, we are unravelling the exact intra- and intermolecular ordering phenomena in more detail, but already we can conclude, that the highly ordered, poly-ureidophthalimide helix is an easily accessible, truly polymeric scaffold enclosing an interesting hollow core, with potential applications in biological or materials science.

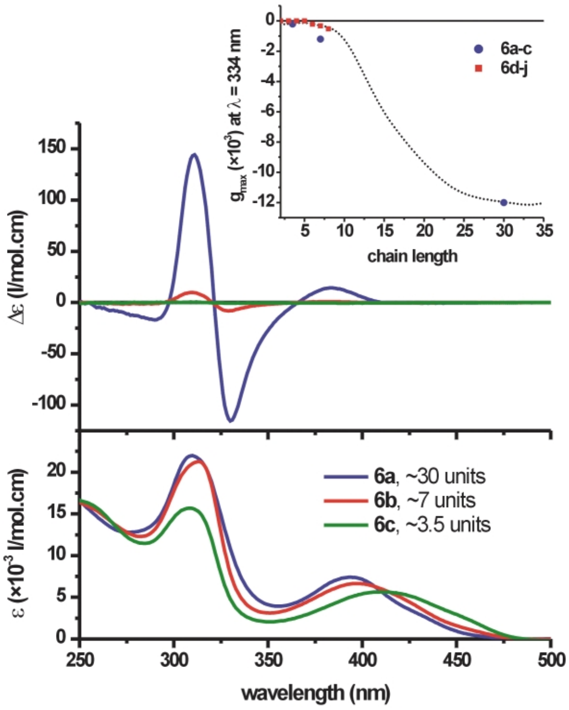

Fig. 1 UV-Vis (bottom) and CD spectra (top) of ureidophthalimides **6a–c** in THF (~0.03 g ml^{-1}), per mole monomeric units, together with the chain length dependence of the Cotton effect (inset).

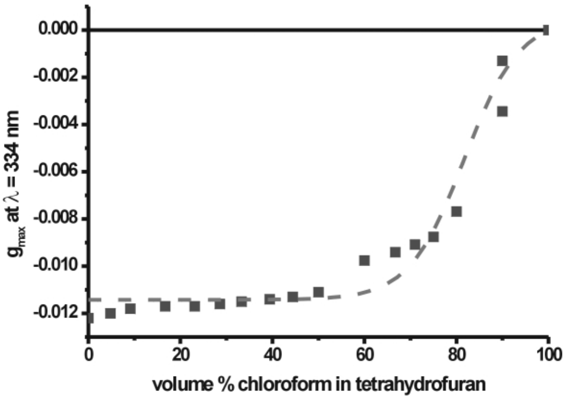

Fig. 2 Denaturation curve of helical polymer **6a**.

Notes and references

1 T. Nakano and Y. Okamoto, *Chem. Rev.*, 2001, **101**, 4013.
2 C. Schmuck, *Angew. Chem., Int. Ed.*, 2003, **42**, 2448.
3 D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1996, **118**, 13071.
4 D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893.
5 B. Kiupel, C. Niederalt, M. Nieger, S. Grimme and F. Vögtle, *Angew. Chem., Int. Ed.*, 1998, **37**, 3031; L. Vyklický, S. H. Eichhorn and T. J. Katz, *Chem. Mater.*, 2003, **15**, 3594.
6 J.-M. Lehn, J.-C. Homo and M. Schmutz, *Angew. Chem., Int. Ed.*, 2000, **38**, 233; V. Berl, M. J. Krische, I. Huc, J.-M. Lehn and M. Schmutz, *Chem. Eur. J.*, 2000, **6**, 1938; F. Würthner, S. Yao and U. Beginn, *Angew. Chem., Int. Ed.*, 2003, **42**, 3247.
7 R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; K. Gademann, A. Häne, M. Rueping, B. Jaun and D. Seebach, *Angew. Chem., Int. Ed.*, 2003, **42**, 1534; D. Seebach, L. Schaeffer, M. Brenner and D. Hoyer, *Angew. Chem., Int. Ed.*, 2003, **42**, 776.
8 Y. Hamuro, S. J. Geib and A. D. Hamilton, *J. Am. Chem. Soc.*, 1997, **119**, 10587; H. Jiang, J.-M. Léger and I. Huc, *J. Am. Chem. Soc.*, 2003, **125**, 3448; C. Dolain, V. Maurizot and I. Huc, *Angew. Chem., Int. Ed.*, 2003, **42**, 2738; V. Berl, I. Huc, R. G. Khoury, M. J. Krische and J.-M. Lehn, *Nature*, 2000, **407**, 720; X. Yang, A. L. Brown, M. Furukawa, S. Li, W. E. Gardiner, E. J. Bukowski, F. V. Bright, C. Zheng, X. C. Zeng and B. Gong, *Chem. Commun.*, 2003, 56; B. Gong, *Chem. Eur. J.*, 2001, **7**, 4336; R. D. Parra, B. Gong and X. C. Zeng, *J. Phys. Chem.*, 2001, **115**, 6036.
9 C. Hemmerlin, M. Marraud, D. Rognan, R. Graff, V. Semety, J.-P. Briand and G. Guichard, *Helv. Chim. Acta*, 2002, **85**, 3692; P. S. Corbin, S. C. Zimmerman, P. A. Thiessen, N. A. Hawryluk and T. J. Murray, *J. Am. Chem. Soc.*, 2001, **123**, 10475.
10 T. Momose and M. Torigoe, *J. Pharm. Soc. Jpn.*, 1951, **71**, 977.
11 J. L. Meek, *J. Chromatogr.*, 1983, **266**, 401.
12 K. Pieterse, *PhD Thesis: Electron deficient materials based on azaheterocycles*, Technische Universiteit Eindhoven, Eindhoven, 2001.
13 Results to be published.
14 Broadening of the ^{1}H-NMR signals is much more pronounced in THF-d_8 than in $CDCl_3$, and disappears upon addition of HFIP. Infrared spectroscopy shows the urea NH stretch vibration at 3354 cm^{-1} in $CHCl_3$ and at 3341 cm^{-1} in THF.
15 J. J. van Gorp, J. A. J. M. Vekemans and E. W. Meijer, *J. Am. Chem. Soc.*, 2002, **124**, 14759.