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Induced helix of 2-(2-aminophenoxy)alkanoic acid oligomers as a δ-peptidomimetic foldamer

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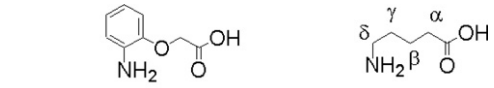
ABSTRACT

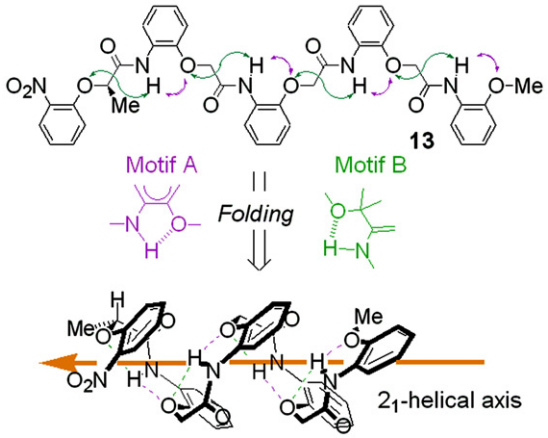
Peptidomimetic foldamers were synthesized by oligomerizing derivatives of the δ-amino acid analogue, 2-(2-aminophenoxy)alkanoic acid. Single-crystal analysis of the tetramer reveals a 2_1-helical secondary structure stabilized by hydrogen bonding and the coiled stacking of aromatic rings. The *M*-helicity of 2-aminophenoxyacetic acid oligomers was induced by the incorporation of only a single chiral carbon of the N-terminal (*R*)-2-(2-nitrophenoxy)propionamide moiety. The solution state CD spectra demonstrated that the resulting helix induced a substantial Cotton effect. The secondary structure was further characterized by IR and NMR spectroscopy.

The term 'foldamer' has been abundantly used in the field of supramolecular chemistry and refers to any functional oligomer that folds into a conformationally ordered state by noncovalent bonds.[1] A focus of foldamer research has been to design peptidemimetic oligomers to form helices that are stabilized by the formation of hydrogen bonds.[2,3] Along with β- and γ-amino acids,[4] various δ-amino acids such as quinoline-derived oligoamides,[5] cyclohexylether amino acids,[6] carbohydrate *δ*-amino acids,[7] and 2-aminomethyl-phenyl-acetic acids[8] have been used as the repeating subunits of foldamers. In this context, we were interested in the oligomers of 2-aminophenoxyacetic acid that is regarded as a conformationally fixed analogue of δ-amino acid (Scheme 1). Here we report that the oligomers of 2-aminophenoxyacetic acid and its α-methyl derivative form a hybrid type of chiral helical foldamer combining both an aromatic and an aliphatic backbone.[9]

Our design relies on the formation of two five-membered hydrogen bonded motifs (A and B) to stabilize the structure (Scheme 2). A systematic survey of the Cambridge Structural Database[10] has indicated that motifs such as A and B have a respective 79.2% and 73.2% probability of forming intramolecular hydrogen bonds. The combination of both motifs A and B into a 2-aminophenoxyacetic acid oligomer will result in the formation of a three-centered hydrogen bond, where the hydrogen of the amide group binds to both of the neighboring ether oxygen atoms. In other words, the ether oxygen acts as an acceptor of two amide hydrogens to form a chelated (or bifurcated) hydrogen bond. If the three-centered and the bifurcated hydrogen bonding elements



Scheme 1. 2-Aminophenoxyactetic acid as δ-amino acid analogue.



Scheme 2. Folding of compound **13** by two motifs of hydrogen bonding.

are sequentially repeated to form a concave network, a new type of helical foldamer should be formed.

The methods for synthesizing the oligomers (**4**, **6**, and **8**) are summarized in Scheme 3. Although standard peptide synthesis

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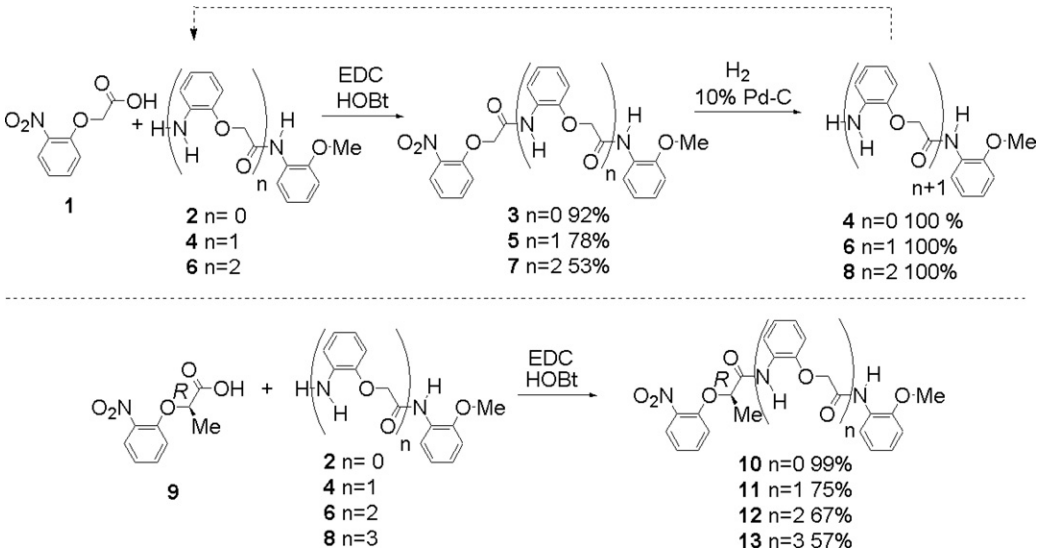


Scheme 3. Synthetic routes to compounds **10**–**13**.

requires the protection of the amino acid prior to coupling, we have developed a route which bypasses the protection of the amino group: we employed a nitro group as a synthetic precursor of the amino group. Since nitro group is tolerant to the coupling reaction of a carboxyl acid with an amine, we transformed it into the amino group after the coupling reaction. The starting materials are commercially available 2-nitrophenoxyacetic acid (**1**) and chiral (*R*)-2-(2-nitrophenoxy)propionic acid (**9**) that can be prepared by the Mitsunobu reaction[11] of (*S*)-lactic acid and 2-nitrophenol. The achiral oligomer (**4**) was synthesized from **1** by coupling with 2-methoxyaniline (**2**) and subsequent reduction. For the coupling reaction, we utilized standard conditions using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxy-1*H*-benztriazole (HOBt).[12] The resulting **4** is the starting material for the preparation of **6**, which is the synthetic precursor of **8**. A series of compounds (**10**–**13**) was synthesized by repeating these steps.

In order to characterize the folding of the compounds (**10**–**13**) in a solution, their circular dichroism (CD) spectra were measured. In Figure 1, the CD spectra of compound **12** in methanol, dichloromethane, and cyclohexane are shown. Among these solvents, methanol affords the weakest Cotton effect presumably because the solvent competes with hydrogen bonding which stabilizes the folded structure. In cyclohexane, inclusion of a single N-terminal chiral carbon of the trimer induced a strong Cotton effect in the CD spectrum, which suggesting the helical induction and main chain propagation.

Thus, we measured the CD spectra of compounds (**10**–**13**) in either cyclohexane or a mixture of cyclohexane and dichloromethane (19:1) (when required by limited solubility in cyclohexane) (Fig. 2). The Cotton effect observed in the CD spectra of compound **12** showed a strong induced Cotton effect, whereas with the shorter oligomers **10** and **11** it was not as pronounced. Surprisingly, the longest oligomer **13** displayed a slightly weaker CD signal than that of **12** in the same solvent. However, the molar absorptivity of **13** was comparable to the compound **12** in inten-

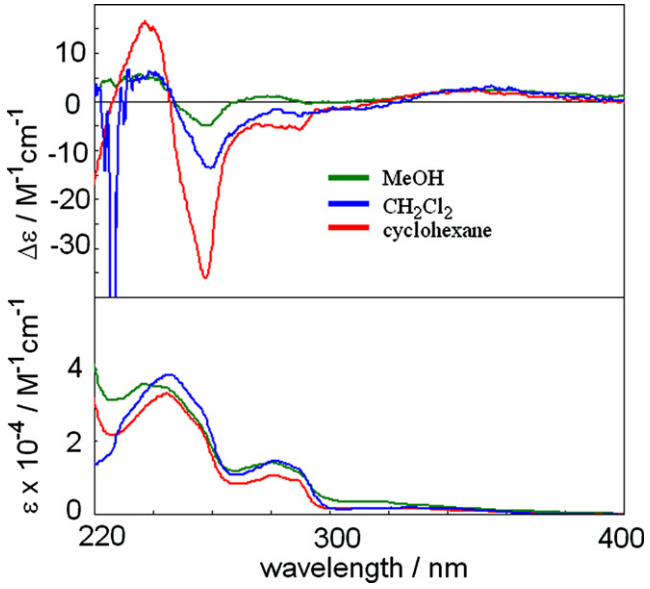


Figure 1. Solvent effect on CD (top) and UV (bottom) spectra of **12** (3.0×10^{-5} M).

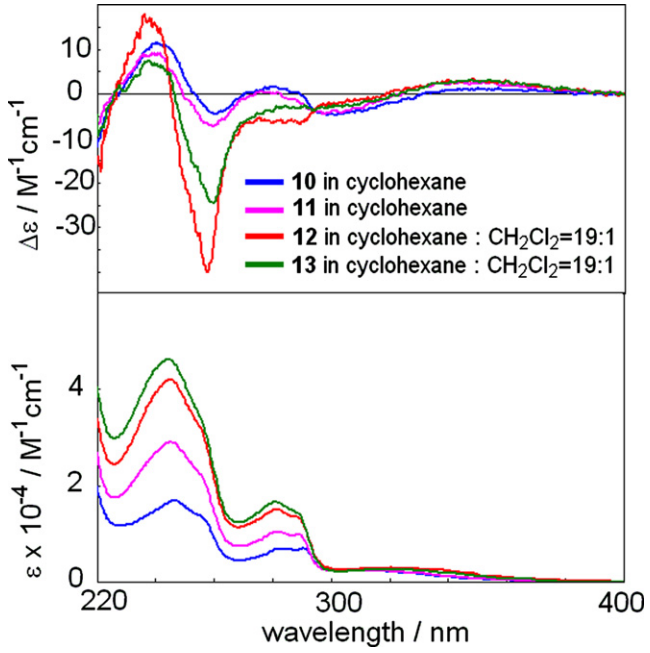


Figure 2. CD (top) and UV (bottom) spectra of **10**–**13** (3.0×10^{-5} M).

sity, suggesting a. hypochromic effect caused by the stacking of the benzene rings. As CD essentially explores the anisotropy of a compound's UV spectra, hypochromic effects should carry over into the CD, thereby leading us to conclude that a more direct method was required to determine the structure. Single-crystal X-ray analysis of compound **13** (vide infra) confirmed the stacking of the benzene rings. Similar hypochromism has been demonstrated in the DNA duplex[13] and also artificial foldamers[14] with stacked aromatic rings.

The CD spectra of these oligomers demonstrate that a single chiral center at the N-terminus can induce helical structure through an extended oligomer. However, it is difficult to estimate the degree of formation of the helix in solution. For example, as mentioned above, solvent can interrupt the hydrogen bond network to destabilize the helical state of **12**. Fortunately, single-crystal **X**-ray analysis could be performed to reveal that the solid state structure of compound **13** folds itself into 2_1-helical conformation (Fig. 3).[15] Clearly, the chirality of the (*R*)-2-(2-nitrophenoxy)propionamide moiety induces *M*-helicity, which is similar to the *P*-helix (α-helix) common to natural L-amino acid-based peptides.

As shown in schematic drawing in Figure 3b, hydrogen bonding plays an important role in folding the chain. As predicted, two hydrogen bonding motifs (A and B) combine to form the alternating three-centered and bifurcated hydrogen bonding network as per the original design. The intermolecular hydrogen bonds are summarized in Table 1. In addition to two motifs A and B, one oxygen atom of the terminal nitro group forms an additional hydrogen bond to the network.

It is noteworthy that the benzene–benzene interactions form a 'parallel stacked and displaced' structure in the helical structure[16] with the ring center-ring center distances of 5.05, 5.10, and 5.15 Å, respectively (Fig. 4). This stacking geometry would not only stabilize the folding structure to some extent and but would also lead to the hypochromic effect observed in a case of **13** in Figure 2. Similar aromatic interactions are observed in natural proteins[17] as well as artificial supramolecular aggregates.[18]

It is significant that a single chiral carbon can induce an *M*-helical structure to propagate through multiple achiral residues.[5c,19] Also significant is that the 2_1-helical structure of the 2-(2-aminophenoxy)alkanoic acid oligomer will project its side chains in good alignment (4.67, 5.16, and 5.19 Å compared to 5.4 Å) with that of the distance between side chains exhibited by an α-peptidic 3.6_1 helix in natural proteins (Fig. 4).[4a]

Solid-state IR spectra showed an amide H–N peak at 3399 cm^{-1} and CO 1685 cm^{-1}. Even in the solution (5 mM in $CHCl_3$), both IR bands of compound **13** are located at 3401 cm^{-1} and 1685 cm^{-1}, respectively, which are consistent with those of a solid state. These

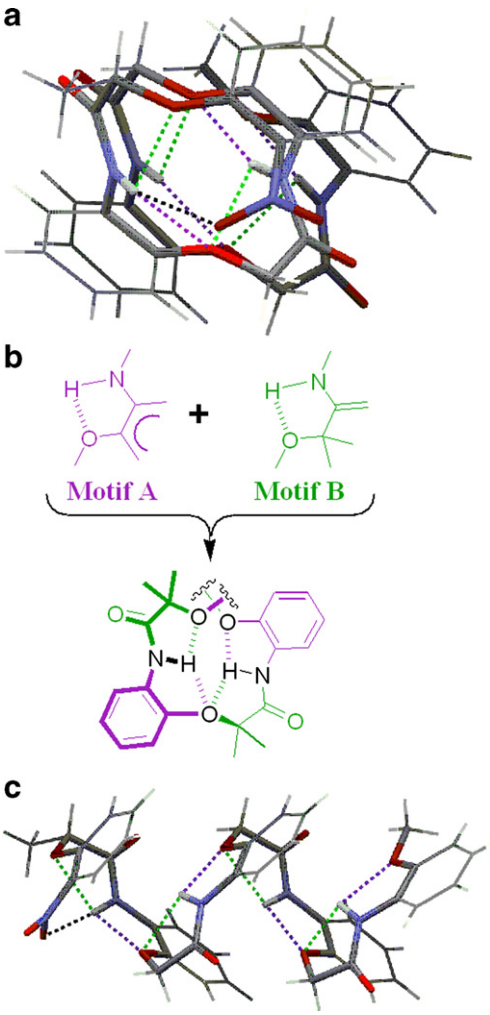
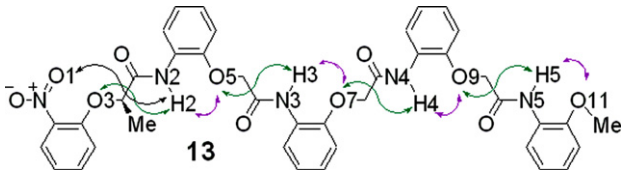


Figure 3. Crystal structure of **13** (only backbone atoms are shown as capped sticks): (a) top view; (b) schematic drawing of intramolecular hydrogen bonds; (c) side view.

Table 1
Intramolecular hydrogen bonding of compound **13**[a]



	H-bonding	*r*/Å	*θ*/°	*d*/Å
Motif A	N2–H2···O5	2.50	93.8	2.62
	N3–H3···O7	2.27	101.0	2.59
	N4–H4···O9	2.29	101.3	2.60
	N5–H5···O11	2.34	93.9	2.56
Motif B	H-bonding	*r*/Å	*θ*/°	*d*/Å
	N2–H2···O3	2.30	106.3	2.68
	N3–H3···O5	2.26	110.1	2.70
	N4–H4···O7	2.27	109.4	2.69
	N5–H5···O9	2.31	105.8	2.69
	H-bonding	*r*/Å	*θ*/°	*d*/Å
	N2–H2···O1	2.50	162.1	3.35

[a] Hydrogen atoms were placed in calculated positions (N–H bond: 0.88Å)

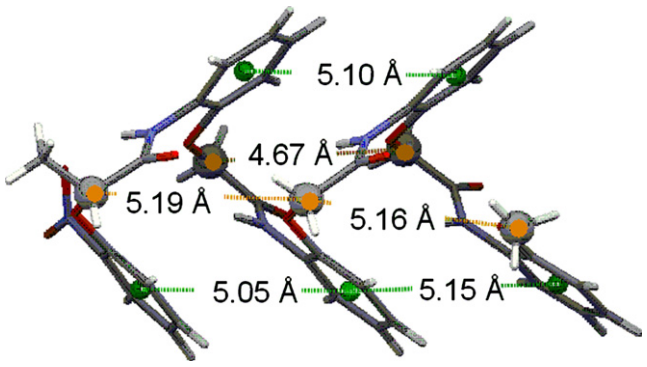


Figure 4. Crystal structure of **13**: distances between centroids (green balls) of benzene rings and distances between peptidemimetic α-carbons (orange).

results support formation of hydrogen bonding in both solution and the solid state.

As mentioned above, a single N-terminal chiral carbon of the tetramer induced strong Cotton effect of the CD spectrum in cyclohexane, suggesting induction of helicity through the other achiral subunits. In $CDCl_3$, H NMR spectra of compound **13** shows that six protons of three methylenes (4.35, 4.43, 4.52, 4.60, 4.66, and 4.75) have geminal coupling (J = 15 Hz). However, no geminal coupling is observed in DMSO-d_6, which acts as a hydrogen bond acceptor to break intramolecular hydrogen bonds, indicating that in the non-polar solvent the conformation is restricted causing the resonances from the diastereotopic protons to split each other. Further supporting this model, four singlet peaks of amide protons in $CDCl_3$ (δ 8.38, 8.85, 8.89, and 9.31 ppm) shifted to the lower field in DMSO-d_6 [δ 9.25, 9.59, and 9.64 (2H) ppm].

In summary, we have prepared a new class of foldamers based on peptidomimetics of δ-amino acids stabilized by a complex hydrogen bonded network. These foldamers will provide a type of structured artificial peptides with possible applications to biochemistry and drug design. Our ongoing research is focused on further characterizing the structure and properties of these novel foldamers in detail.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.003.

References and notes

1. (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180; (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011; (c) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252–262.
2. (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 446–448; (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529–7541; (c) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587–10593.
3. (a) Berl, V.; Huc, I.; Khoury, R. G.; Krische, M. J.; Lehn, J.-M. *Nature* **2000**, *407*, 720–723; (b) Berl, V.; Huc, I.; Khoury, R. G.; Lehn, J.-M. *Chem. Eur. J.* **2001**, *7*, 2798–2809; (c) Berl, V.; Huc, I.; Khoury, R. G.; Lehn, J.-M. *Chem. Eur. J.* **2001**, *7*, 2810–2820; (d) Huc, I. *Eur. J. Org. Chem.* **2004**, 17–29.
4. (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (c) Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers* **2006**, *84*, 23–37.
5. (a) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448–3449; (b) Jiang, H.; Léger, J.-M.; Dolain, C.; Guionneau, P.; Huc, I. *Tetrahedron* **2003**, *59*, 8365–8374; (c) Dolain, C.; Jiang, H.; Léger, J.-M.; Gornitzka, P.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 12943–12951; (d) Delsuc, N.; Godde, F.; Kauffmann, B.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2007**, *129*, 11348–11349.
6. (a) Koert, U. *J. Prakt. Chem.* **2000**, *342*, 325–333; (b) Arndt, H.-D.; Ziemer, B.; Koert, U. *Org. Lett.* **2004**, *6*, 3269–3272; (c) Arndt, H.-D.; Knoll, A.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2076–2078.
7. (a) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2041–2042; (b) Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2199–2202; (c) Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195–2198; (d) Brittain, D. E. A.; Watterson, M. P.; Claridge, T. D. W.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655–3665; (e) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666–3679; (f) Suhara, Y.; Ichikawa, M.; Hildreth, J. E. K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2549–2552.
8. Raynal, N.; Averlant-Petit, M.-C.; Bergé, G.; Didierjean, C.; Marraud, M.; Duru, C.; Martinez, J.; Amblard, M. *Tetrahedron Lett.* **2007**, *48*, 1787–1790.
9. (a) Srinivas, D.; Gonnade, R.; Ravindranathan, S.; Sanjayan, G. J. *J. Org. Chem.* **2007**, *72*, 7022–7025; (b) Baruah, P. K.; Sreedevi, N. K.; Gonnade, R.; Ravindranathan, S. R.; Damodaran, K.; Hofmann, H.-J.; Sanjayan, G. J. *J. Org. Chem.* **2007**, *72*, 636–639; (c) Srinivas, D.; Gonnade, R.; Ravindranathan, S.; Sanjayan, G. J. *Tetrahedron* **2006**, *62*, 10141–10146.
10. Bilton, C.; Allen, F. H.; Shields, G. P.; Howard, J. A. K. *Acta Crsytallogr., Sect. B* **2000**, *56*, 849–856.
11. Mistunobu, O. *Synthesis* **1981**, 1–28.
12. Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2165–2168.
13. (a) Tinoco, I.; Sauer, K.; Wang, J. C. *Biophysical Chemistry*; Prentice-Hall: New Jersey, 1985; (b) Cantor, C. R.; Schimmel, P. R. *Biophys. Chem.* **1980**.
14. (a) Goto, H.; Katagiri, H.; Furusho, Y.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 7176–7178; (b) Nakano, T.; Takewaki, K.; Yada, T.; Okamoto, Y. . Y. *J. Am. Chem. Soc.* **2001**, *123*, 9182–9183; (c) Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114–3121; (d) Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793–1796.
15. *Crystal data for* **13**: Crystallization, $C_{40}H_{37}N_5O_{11}$, M_r = 763.75, colorless plate, crystal size 0.31 × 0.10 × 0.06 mm^3, orthorhombic, space group $P2_12_12_1$, a = 9.7196(8), b = 13.5602(11), and c = 27.374(2) Å, V = 3607.9(5) Å^3, T = 173 K, Z = 4, D_c = 1.406 g cm^{-3}, μ = 0.104 mm^{-1}, λ = 0.71073 Å, 16882 reflections collected, 6159 (R_{int} = 0.0481) independent reflections, 508 refined parameters, R_1 ($I > 2\sigma(I)$) = 0.0495, wR_2 (all data) = 0.1235. CCDC-682493.
16. (a) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768–4774; (b) Hobza, P.; Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 3500–3506; (c) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104–112.
17. In proteins, π–π interactions on their side chains have already been investigated to reveal the edge-to-face interaction between benzene rings to be important: (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23–28; (b) Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 5921–5927; (c) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995–8001.
18. (a) Slawin, A. M.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1070–1072; (b) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534; (c) Lewis, F. D.; Yang, J.-S.; Stern, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 12029–13037; (d) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651–668.
19. (a) Inai, Y.; Kurikawa, Y.; Harabayashi, T. *Macromolecules* **1999**, *32*, 4575–4581; (b) Obata, K.; Kabuto, C.; Kira, M. *J. Am. Chem. Soc.* **1997**, *119*, 11345–11346.