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A cyclic trimer of 2-(2-aminophenoxy)propionic acid with a bowl-shaped structure

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ABSTRACT

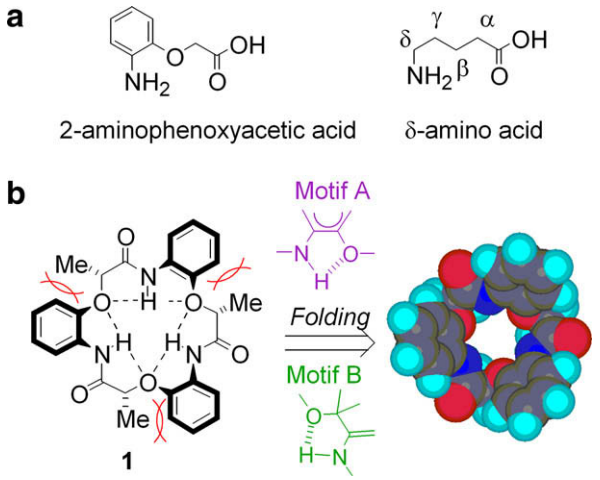
A cyclic trimer of (*R*)-2-(2-aminophenoxy)propanoic acid, a δ-amino acid analogue, was synthesized. Molecular mechanics calculations on the cyclic trimer predicted that a concave network of sequential hydrogen bonds forms a C_3-symmetric bowl-shaped structure. Evidence for this conformation was found in the NMR spectra of the trimer in D-chloroform. Although the single-crystal structure of the cyclic trimer indicates that chloroform could be included in the bowl-shaped structure, the conformation was not C_3-symmetric and the hydrogen bonding network was of a different mode. These different conformations between solid and solution were reasonably clear from IR spectra.

The C_3-symmetric molecular design fascinates us not only with its picturesque beauty but also for its potential advantages in asymmetric catalysis, molecular recognition, and materials science.[1] In the field of host-guest chemistry, simple cyclic triamides,[2] chiral cyclotriveratrylene,[3] cyclic tripeptides,[4] and cyclic pseudopeptides[5] have been reported to have C_3-symmetric bowl-shaped structures, and they have the potential to act as synthetic receptors.

Recently, we reported oligomers of 2-aminophenoxyacetic acid as a conformationally fixed analogue of δ-amino acid.[6] The oligomer as a foldamer had an induced helical structure. In this context, we are interested in whether the cyclic trimer **1** of 2-(2-aminophenoxy)alkanoic acid can be induced to have a bowl-shaped structure (Scheme 1).

The design relies on the formation of two five-membered hydrogen-bonded motifs (A and B) to stabilize the structure. A systematic survey of the Cambridge Structural Database[7] 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 motifs A and B into a cyclic trimer of 2-(2-aminophenoxy)propionic acid will result in 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. In addition to this, the side chain (Me group) on homochiral α-carbons has a steric effect to ruffle the cyclic backbone into a bowl-shaped structure. Thus, the steric effect and the concave network of sequential hydrogen bonds form a C_3-symmetric bowl-shaped structure of compound **1**. Here, we report on the synthesis and structural properties of the cyclic trimer **1** based on this foldamer design.

The desired cyclic trimer **1** was synthesized according to Scheme 2. Enantiopure (*R*)-2-(2-nitrophenoxy)propionic acid **5** was obtained by saponification of methyl (*R*)-2-(2-nitrophen-



Scheme 1. (a) 2-Aminophenoxyactetic acid as δ-amino acid analogue. (b) Folding of compound **1** by two motifs of hydrogen bonding and the steric effect.

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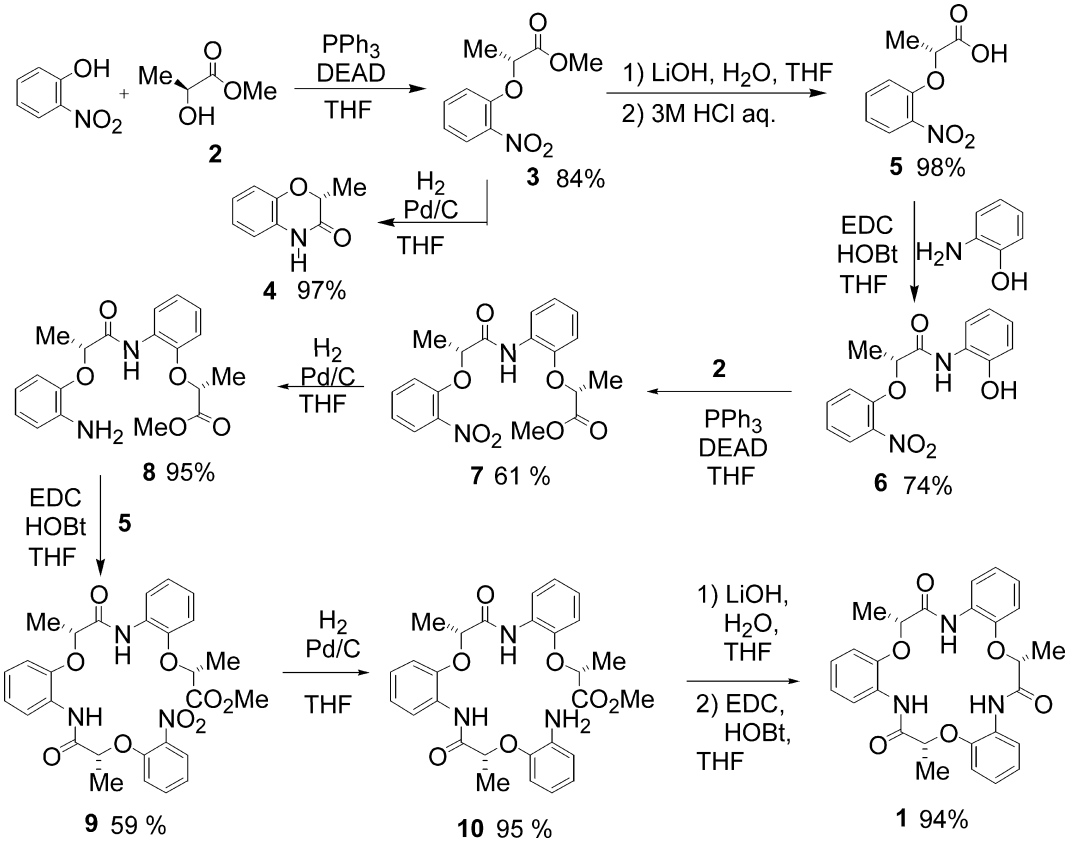


Scheme 2. Synthesis of compound **1**.

oxy)propionate **3**, which is easily prepared by using the Mitsunobu reaction[8] of methyl (*S*)-lactate **2** and 2-nitrophenol. The method of synthesizing the cyclic trimer is not straightforward, because we could not obtain methyl (*R*)-2-(2-aminophenoxy)propionate, which is necessary for the synthesis of the dimer by direct coupling. However, reduction of methyl (*R*)-2-(2-nitrophenoxy)propionate **3** resulted in the undesirable lactam, (*R*)-2-methyl-(2*H*)-1,4-benoxazin-3(4*H*)-one **4**. It is known that nitro group reduction and concomitant cyclization of several 2-nitrophenoxyacetate derivatives afford the corresponding lactams.[9] Therefore, we had to take a circuitous route to obtain the dimer structure. First, a coupling reaction of (*R*)-2-(2-nitrophenoxy)propionic acid with 2-aminophenol afforded *N*-2-hydroxyphenyl(*R*)-2-(2-nitrophenoxy)propionamide **6**. Then, the phenolic hydroxyl group was reacted with **2** under the conditions of Mitsunobu reaction to afford the dimer structure, which could be reduced to an amino group without undesirable concomitant cyclization. For the coupling reaction, we utilized standard conditions with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxy-1*H*-benztriazole (HOBt).[10] The trimer **9** was prepared by coupling of the reduced dimer **8** with (*R*)-2-(2-nitrophenoxy)propionic acid **5** under the standard conditions. After final reduction and saponification, the intramolecular coupling reaction afforded the desirable cyclic trimer **1**.

Fortunately, crystallization of **1** from chloroform/hexane afforded single crystals suitable for X-ray analysis (Fig. 1).[11] The solid state structure of compound **1** has three chloroform molecules that were cocrystallized in the asymmetric unit (Fig. 1a). One chloroform molecule (shown as a space filling model) was included in the bowl-shaped cavity, the others filled vacant space. However, the bowl-shaped structure was not C_3-symmetric (Fig. 1b). The intra- and intermolecular hydrogen bonds are summarized in Table 1. As predicted, two hydrogen-bonded motifs (A and B) combine to form the alternating three-centered and bifurcated hydrogen bonding network as per the original design. Surprisingly, one amide group flipped and directed the amide oxygen into the cavity so as to form two transannular hydrogen bonds, whose distances [N···O(H···O)] are 2.88 (2.06) and 2.84 Å (2.08 Å). As a result, two inward hydrogen atoms formed rare four-centered hydrogen bond that appears without positive charged H–N.[12] Since the outward hydrogen of the amide bonded to the amide of the adjacent bowl, the intermolecular hydrogen bonds arranged these bowls into a one-dimensional array with an intermolecular hydrogen bond distance N···O(H···O) of 2.85 Å (1.99 Å).

A C–H/O interaction between chloroform and an oxygen atom of the amide group occurred with all three chloroform guest molecules (Fig. 1a). The distances of C···O are 3.13, 3.23, and 3.15 Å, and they are within the mean C···O distance (3.32 Å) for $HCCl_3$ approaching oxygen.[13] In addition, the C_3-symmetrical shape of chloroform comfortably settled back into a pseudo-C_3-symmetric cavity through van der Waals contact.

To estimate the preferred conformation, we performed a conformational search for **1** by doing molecular mechanics calculations with Monte Carlo minimization procedures, using the MMFF94s force field[14] and GB/SA solvation treatment (chloroform)[15] as implemented in the MacroModel program.[16] As expected, the lowest-energy conformation of **1** was the C_3-symmetric bowl-shaped structure, which has a concave network of sequential hydrogen bonds (Fig. 2a). The calculations revealed two other conformers within 10 kJ mol^{-1} that have higher energies of +1.6 and +5.9 kJ mol^{-1} (Fig. 2b and c, respectively).

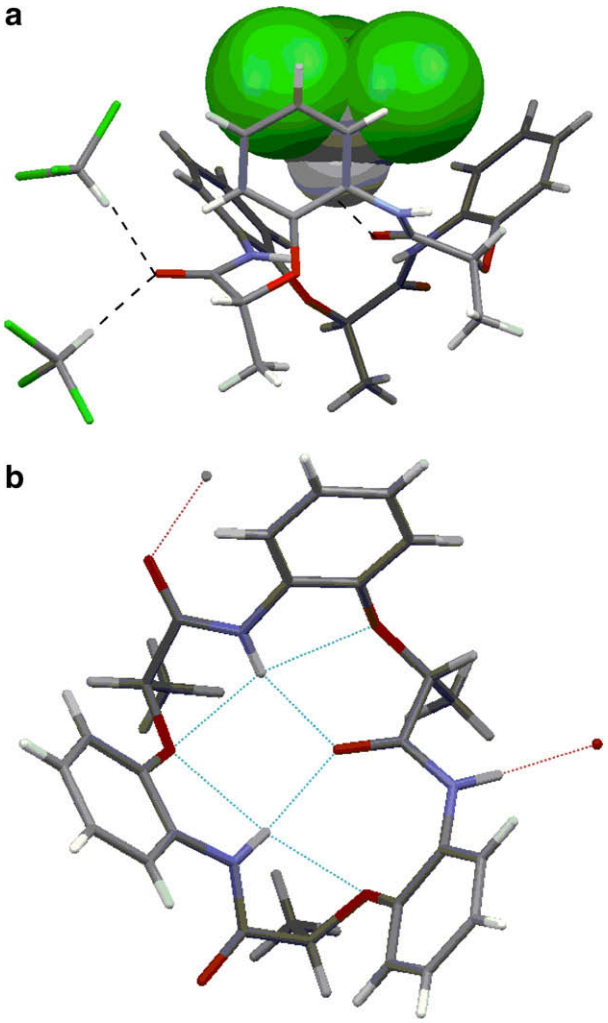
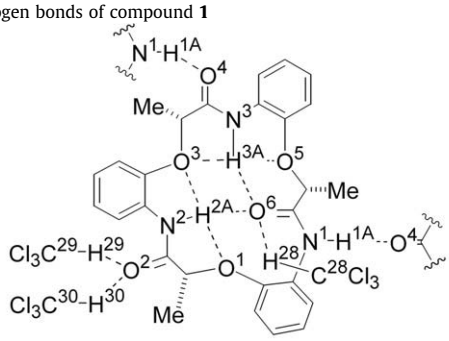


Figure 1. Crystal structure of **1** (a) Side view: one chloroform molecule (shown as a space filling model) in the bowl-shaped cavity. (a) Top view: intramolecular hydrogen bonds of **1**.

Table 1
Hydrogen bonds of compound **1**



	H-bonding	r / Å	θ / °	d / Å
Motif A	N2-H2A...O3	2.47	90.6	2.63
	N3-H3A...O5	2.43	95.7	2.65
Motif B	H-bonding	r / Å	θ / °	d / Å
	N2-H2A...O1	2.29	108.1	2.69
	N3-H3A...O3	2.28	108.2	2.67
	H-bonding	r / Å	θ / °	d / Å
	N2-H2A...O6	2.06	158.2	2.88
	N3-H3A...O6	2.08	147.8	2.84
	N1-H1A...O4	1.99	175.5	2.85
	H-bonding	r / Å	θ / °	d / Å
	C28-H28...O6	2.28	145.1	3.15
	C29-H29...O2	2.13	176.4	3.13
	C30-H30...O2	2.26	161.1	3.23

Although both are distorted C_3-symmetric bowl-shaped structures, all of their hydrogen bonds have motif A or B. As shown in Figure 2d, a different conformer having a flipped amide group was the next higher energetic state (+13.1 kJ mol^{-1}). The hydrogen bonding network is similar to the crystal structure mentioned above.

We investigated the conformational differences between the solution and solid state by measuring the IR spectra. In solution (2 mM in $CHCl_3$), the characteristic absorption bands of compound **1** are located at 3414 cm^{-1} (N–H) and 1684 cm^{-1} (C=O). They are almost the same values as for our previously reported foldamer, whose IR bands are located at 3401 and 1685 cm^{-1}(2 mM in $CHCl_3$).[6] On the other hand, the solid state IR spectra (KBr disk) showed amide H–N peaks (3245 and 3141 cm^{-1}) and C=O peaks (1684 and 1653 cm^{-1}). The hydrogen bonds in the solid state, as indicated by the N–H peaks' shift to a lower wave number, may be strengthened by increment of hydrogen bonds and conformational fixation. In particular, the shift of C=O from 1684 into 1653 cm^{-1} shows that the oxygen atoms of the amide carbonyls participate in strong hydrogen bonds with N–H.

In $CDCl_3$, ^{1}H NMR and ^{13}C NMR spectra of compound **1** show only one third of the peaks of the whole structure, which indicates a highly symmetric structure such as C_3 symmetry.[17] These spectra might suggest the presence of the rapid equilibrium among conformational isomers within the NMR time-scale. Although we performed the NOE study of compound **1**, observed NOEs were rationalized by these four conformational isomers. But no characteristic NOEs of the flipped amide group were detected. The NMR spectra of the variable temperature (VT) NMR study show high symmetry peaks even at −55 °C in $CDCl_3$ (−90 °C in CD_2Cl_2). This experiment suggests that conformational fixation of the flipped amide group would occur only in a highly concentrated state such as crystal. This means that the flipping of the amide group can be attributed to the forming of not transannular intramolecular hydrogen bonds but rather of intermolecular hydrogen bonds between the flipped N–H and the C=O of the adjacent bowl. It might well be that the unfavorable conformation of compound **1** predicted by the molecular mechanics calculations overcomes the energetic disadvantage in crystal by means of intermolecular hydrogen bonds, inclusion of three chloroform molecules, the packing force of crystal, and so on.

In summary, we prepared a cyclic trimer of 2-(2-aminophenoxy)propionic acid and elucidated the bowl-shaped structure with chloroform as a guest molecule by single-crystal X-ray analysis. The compound has a bowl-shaped structure in the solid state and in solution, but the conformation varies between states. This compound is a new bowl-shaped structure in supramolecular chemistry. Our ongoing research is focused on functionalizing the bowl-shaped structure for the purposes of host-guest chemistry.

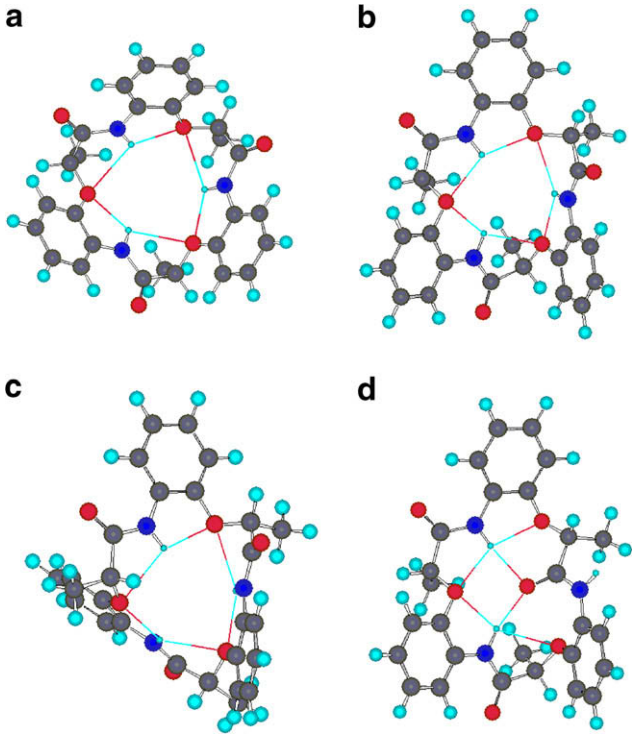


Figure 2. Representative conformations of **1** from a Monte Carlo conformational search. (a) Lowest-energy structure of C_3 symmetry (relative energy, 0 kJ mol^{-1}). (b) Distorted C_3-symmetric structure (relative energy, +1.6 kJ mol^{-1}). (c) Distorted C_3-symmetric structure (relative energy, +5.9 kJ mol^{-1}). (d) An amide flipped structure (relative energy, +13.1 kJ mol^{-1}).

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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.2009.07.029.

References and notes

1. (a) Gibson, S. E.; Castaldi, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4718–4720; (b) Moberg, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4721–4723; (c) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248–268.
2. (a) Katagiri, K.; Kato, T.; Masu, H.; Tominaga, M.; Azumaya, I. *Cryst. Growth Des.* **2009**, *9*, 1519–1524; (b) Imabeppu, F.; Katagiri, K.; Masu, H.; Kato, T.; Tominaga, M.; Therrien, B.; Takayanagi, H.; Kaji, E.; Yamaguchi, K.; Kagechika, H.; Azumaya, I. *Tetrahedron Lett.* **2006**, *47*, 413–416.
3. (a) Collet, A.; Jacques, J. *Tetrahedron Lett.* **1978**, *15*, 1265–1268; (b) Collet, A.; Gabard, J.; Jacques, J.; Cesario, M.; Guilhem, J.; Pascrd, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1630–1638; (c) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299–1308.
4. (a) Chakraborty, T. K.; Tapadar, S.; Raju, T. V.; Annapurna, J.; Singh, H. *Synlett* **2004**, 2484–2488; (b) Sonntag, L.-S.; Ivan, S.; Langer, M.; Conza, M. M.; Wennemers, H. *Synlett* **2004**, 1270–1272; (c) Haberhauser, G. *Synlett* **2004**, 1003–1006; (d) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem. Commun.* **2004**, 2044–2045; (e) Haberhauer, G.; Rominger, F. *Tetrahedron Lett.* **2002**, *43*, 6335–6338; (f) Haberhauer, G.; Somogyi, L., Jr.; Rebek, J. *Tetrahedron Lett.* **2000**, *41*, 5013–5016.
5. (a) Lee, K. H.; Lee, D. H.; Hwang, S.; Lee, O. S.; Chung, D. S.; Hong, J.-I. *Org. Lett.* **2003**, *5*, 1431–1433; (b) Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475–9486; (c) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155–163; (d) McDonald, D. Q.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 2073–2077; (e) Borchardt, A.; Still, W. C. *J. Am. Chem. Soc* **1994**, *116*, 7467–7468; (f) Borchardt, A.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 373–374; (g) Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111–5112.
6. Akazome, M.; Ishii, Y.; Nireki, T.; Ogura, K. *Tetrahedron Lett.* **2008**, *49*, 4430–4433.
7. Bilton, C.; Allen, F. H.; Shields, G. P.; Howard, J. A. K. *Acta Crystallogr., Sect. B* **2000**, *56*, 849–856.
8. Mistunobu, O. *Synthesis* **1981**, 1–28.
9. (a) Atkinson, P. J.; Bromidge, S. M.; Duxon, M. S.; Gaster, L. M.; Hadley, M. S.; Hammond, B.; Johnson, C. N.; Middlemiss, D. N.; North, S. E.; Price, G. W.; Rami, H. K.; Riley, G. J.; Scott, C. M.; Shaw, T. E.; Starr, K. R.; Stemp, G.; Thewlis, K. M.; Thomas, D. R.; Thompson, M.; Antonio, K. K.; Vong, A. K. K.; Watsona, J. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 737–741; (b) Breznik, M.; Hrast, V.; Mrcina, A.; Kikelj, D. *Tetrahedron: Asymmetry* **1999**, *10*, 153–167; (c) Sumida, M.; Niwata, S.; Fukami, H.; Tanaka, T.; Wakabayashi, K.; Bogerg, P. *J. Agric. Food Chem.* **1995**, *43*, 1929–1934.
10. Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2165–2168.
11. *Crystal data for* **1**: crystallization, $C_{30}H_{30}Cl_9N_3O_6$, Mr = 847.62, colorless plate, crystal $0.38 \times 0.08 \times 0.07$ mm^3, orthorhombic, space group $P2_12_12_1$, a = 9.4417(13), b = 15.756(2), and c = 25.669(4) Å, V = 3818.6(9) Å^3, T = 173 K, Z = 4, Dc = 1.474 g cm^{-3}, μ = 0.704 mm^{-1}, λ = 0.71073 Å, 8412 reflections collected, 2476 (R_{int} = 0.0283) independent reflections, 445 refined parameters, R_1 ($I > 2\sigma(I)$) = 0.0214, wR_2 (all data) = 0.0464. GOF(F^2) = 1.066. CCDC 733222. Three hydrogen atoms of amide were found from differential Fourier map and their coordination was refined. The distance between all of these N–H bonds is 0.86(4) Å.
12. (a) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1984**, *106*, 244–248; (b) Taylor, R.; Kennard, O.; Versichel, W. *J. Am.Chem. Soc.* **1983**, *105*, 5761–5766.
13. (a) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1989**, 179–180; (b) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290–296.
14. (a) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 720–729; (b) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730–748.
15. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129.
16. (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467; (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
17. The CD spectrum of **1** shows negative Cotton effect as well as our previously reported foldamer.[6] See Supplementary data for details.