A Proline-based Macrocyclic Amide with S_4 Symmetry

Hee Choon Ahn, Sun-mi Yun, and Kihang Choi*
Department of Chemistry and Center for Electro- and Photo-Responsive Molecules, Korea University, Seoul 136-701, Korea

(Received October 4, 2007; CL-071099; E-mail: kchoi@korea.ac.kr)

A new square-shaped macrocyclic amide was prepared from *N*-(4-amino-2-nitrophenyl)proline (ANPP). The two enantiomers of ANPP were connected in an alternating sequence and then cyclized to the corresponding macrocyclic tetramer with S_4 symmetry. In this design, there is a central cavity approximately 7 Å in diameter and rigid aromatic rings and intramolecular hydrogen bonding help to reduce the conformational flexibility of the molecule.

Macrocycles have been widely used in molecular recognition studies, and many synthetic receptors for biologically and environmentally important molecules and ions have been constructed on the basis of macrocyclic scaffolds.[1] Macrocyclic structures are effective in reducing conformational flexibility and providing preorganized ligand binding sites when compared to their acyclic analogues. In particular, cyclic amides have received much attention as ideal candidates for novel macrocyclic scaffolds;[2] both symmetrical and unsymmetrical macrocycles can be synthesized from amino acid monomers in a stepwise manner, and the rigid amide bonds between the monomers not only reduce conformational flexibility but also provide the macrocycles potential sites for inter- or intramolecular hydrogen-bonding interactions.

Recently, we have reported that *N*-(2-nitrophenyl)proline (2-NPP) amides of primary amines have conformational preference for the intramolecular hydrogen bonds connecting the amide hydrogen, proline nitrogen, and nitro oxygen atoms.[3] A simple modeling study on 2-NPP phenylamide showed that the same bifurcated hydrogen bonding could also stabilize the lowest energy conformation of 2-NPP amides of aromatic amines. Because of the reduced conformational flexibility and the orthogonal arrangement of the two aromatic rings within 2-NPP phenylamide (Figure 1), we reasoned that *N*-(4-amino-2-nitrophenyl)proline (ANPP) might be used as a building block to construct a new square-shaped macrocyclic amide.

Simple conformational search studies showed that the homochiral linear tetramer of ANPP would prefer a helical conformation to a cyclic one and the corresponding cyclic tetramer with C_4 symmetry would have large ring strain (data not shown). On the other hand, the linear tetramer with an alternating sequence of (*R*)- and (*S*)-ANPP monomers would prefer a cyclic conformation so that macrocycle **1** with S_4 symmetry would have much lower ring strain.[4]

To obtain a detailed picture of the macrocycle, we performed a Monte Carlo conformation search.[5] The lowest energy conformation of macrocycle **1** has S_4 symmetry, as expected, (Figure 2) and the other low-energy conformations show only minor variations in the ring puckering of the proline moieties outside the molecule. The dimensions of the macrocycle are about 10×10 Å and similar to those of β-cyclodextrin, which

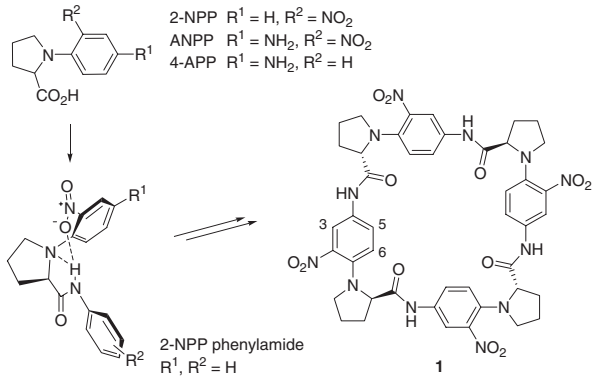


Figure 1. Conformational preference of 2-NPP phenylamide and structure of the cyclic tetramer of ANPP. The hydrogen bonds stabilizing the lowest conformer of 2-NPP phenylamide are indicated by dashed lines.

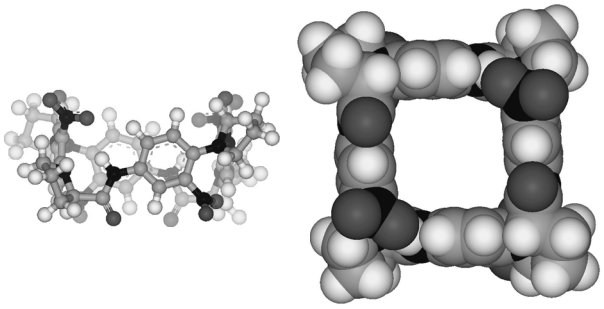
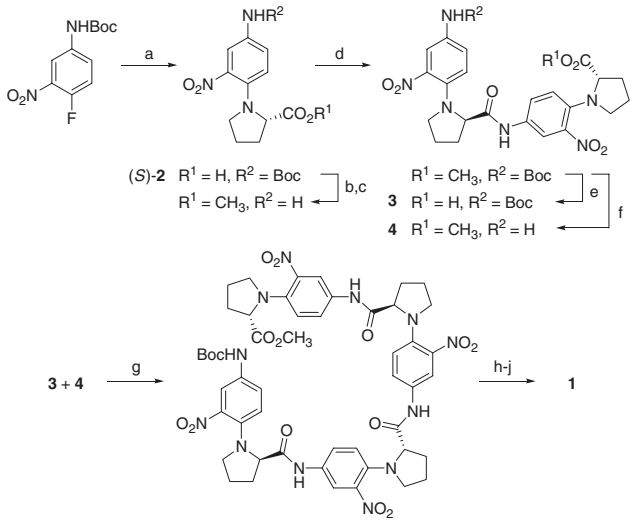


Figure 2. Lowest energy conformation of the cyclic tetramer of ANPP: a side view drawn with depth cues (left) and a top view with CPK representation (right). Progressively darker shades of gray represent H, C, O, and N, respectively.

has been widely used as a macrocyclic scaffold in molecular recognition studies.[6] In the center of macrocycle **1**, there is a cavity approximately 7 Å in diameter. Because the amide and nitro groups are located at the sterically congested corners, the cavity is lined mostly with the four phenyl rings.

The macrocycle synthesis began with the preparation of the two ANPP enantiomers (Scheme 1). (*S*)- and (*R*)-**2** were synthesized from the nucleophilic substitution reaction of Boc-protected 4-fluoro-3-nitroaniline[7] with L- and D-proline, respectively (Boc = *tert*-butoxycarbonyl). The corresponding amine component was prepared by protection of the carboxyl group as its methyl ester and deprotection of the amine group under acidic condition. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) was used as the coupling reagent to synthesize the dimer that was in turn converted into **3** or **4** by removal of the Boc group or hydrolysis of the methyl ester group, respectively. These two dimers with a free amine or carboxyl group were coupled togeth-



Scheme 1. Reagents and conditions: (a) L-proline, $NaHCO_3$, H_2O, EtOH, reflux, 80%; (b) MeI, K_2CO_3, DMF, 93%; (c) TFA, CH_2Cl_2; (d) (*R*)-**2**, BOP-Cl, DIEA, CH_2Cl_2, 87%; (e) LiOH, H_2O, MeOH, THF, 96%; (f) TFA, CH_2Cl_2; (g) BOP-Cl, DIEA, CH_2Cl_2, 73%; (h) LiOH, H_2O, MeOH, THF, 94%; (i) TFA, CH_2Cl_2; (j) BOP-Cl, DIEA, THF, 30%. TFA = trifluoroacetic acid, DIEA = *N*,*N*-diisopropylethylamine.

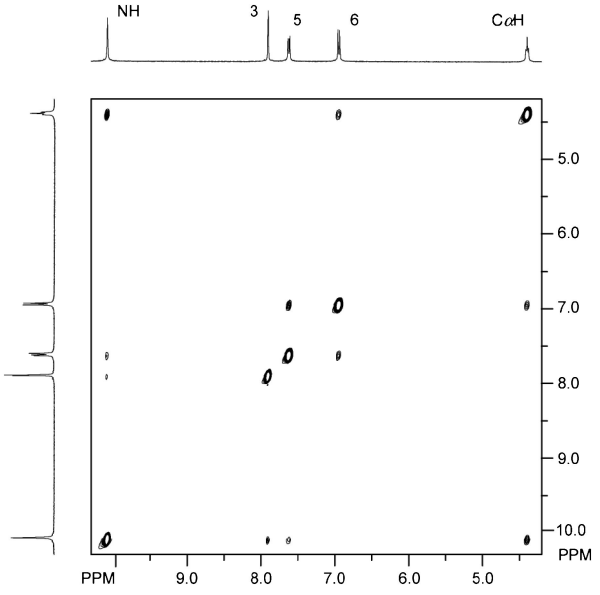


Figure 3. NOESY spectrum of macrocycle **1** in DMSO-d_6. The ^{1}H signals were assigned on the basis of their chemical shifts and splitting patterns. The mixing time was set as 300 ms with 400 MHz ^{1}H NMR frequency.

er to afford the tetramer. Sequential deprotection of the *N*- and *C*-terminal groups gave the linear precursor that was cyclized to macrocycle **1** under high dilution condition (1 mM) to minimize linear oligomer formation.

The structure of the macrocycle was initially confirmed by its simplified NMR spectrum and finally by high-resolution mass spectrometry.[8] A NOESY experiment showed all the expected NOEs between adjacent protons (Figure 3), and the diagonal and cross peaks in the 2D spectrum have the same signs indicating that the molecule has a long rotational correlation time presumably because of its large size.[9] Synthesis of another macrocycle was attempted by using (*R*)- and (*S*)-*N*-(4-aminophenyl)-proline (4-APP) as monomers. However, the corresponding tetrameric precursor showed very low solubility in common organic solvents and test reactions for the cyclization yielded inseparable mixtures. It seems that the intramolecular interactions between the nitro and amide groups of macrocycle **1** prevent intermolecular hydrogen bonding and thus reduce aggregation.

In summary, we have shown that a new macrocyclic amide can be synthesized from proline-based amino acids. In this square-shaped cyclic tetramer, the two enantiomers of ANPP are connected in an alternating sequence and the overall structure has S_4 symmetry. Incorporation of rigid aromatic rings and preorganization through intramolecular hydrogen bonding allowed to control the conformational flexibility of this large macrocycle. We are currently working on the development of various synthetic receptors based on this novel macrocyclic scaffold.

This work was partly supported by a Korea University Grant and the Korea Science and Engineering Foundation through CRM of Korea University.

References and Notes

1 a) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, Chichester, **2000**. b) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, Wiley-VCH, Weinheim, **1995**.
2 a) H. Ishida, M. Suga, K. Donowaki, K. Ohkubo, *J. Org. Chem.* **1995**, *60*, 5374. b) S. Kubik, R. Goddard, R. Kirchner, D. Nolting, J. Seidel, *Angew. Chem., Int. Ed.* **2001**, *40*, 2648. c) K. Choi, A. D. Hamilton, *J. Am. Chem. Soc.* **2003**, *125*, 10241. d) T. K. Chakraborty, S. Tapadar, S. K. Kumar, *Tetrahedron Lett.* **2002**, *43*, 1317. e) D. Mink, S. Mecozzi, J. Rebek, Jr., *Tetrahedron Lett.* **1998**, *39*, 5709. f) C. Boss, P. H. Rasmussen, A. R. Wartini, S. R. Waldvogel, *Tetrahedron Lett.* **2000**, *41*, 6327. g) G. Haberhauer, T. Oeser, F. Rominger, *Chem. Commun.* **2004**, 2044. h) G. Haberhauer, A. Pinter, T. Oeser, F. Rominger, *Eur. J. Org. Chem.* **2007**, 1779. i) H. Jiang, J.-M. Leger, P. Guionneau, I. Huc, *Org. Lett.* **2004**, *6*, 2985. j) P. S. Shirude, E. R. Gillies, S. Ladame, F. Godde, K. Shin-Ya, I. Huc, S. Balasubramanian, *J. Am. Chem. Soc.* **2007**, *129*, 11890. k) I. Azumaya, T. Okamoto, F. Imabeppu, H. Takayanagi, *Tetrahedron* **2003**, *59*, 2325. l) S. Jayaprakash, G. Pattenden, M. S. Viljoen, C. Wilson, *Tetrahedron* **2003**, *59*, 6637.
3 H. C. Ahn, K. Choi, *Org. Lett.* **2007**, *9*, 3853.
4 For cyclic amides with an alternating sequence of L- and D-α-amino acids, see: D. T. Bong, T. D. Clark, J. R. Granja, M. R. Ghadiri, *Angew. Chem., Int. Ed.* **2001**, *40*, 988.
5 Spartan'06 (Wavefunction, Inc.) was used for the calculations. A Monte Carlo conformation search was performed using the MMFF force field to find the lowest energy conformation, which was then used as an initial structure for the geometry optimization using the semiempirical AM1 model.
6 J. Szejtli, *Chem. Rev.* **1998**, *98*, 1743.
7 Y. Kuramoto, Y. Ohshita, J. Yoshida, A. Yazaki, M. Shiro, T. Koike, *J. Med. Chem.* **2003**, *46*, 1905.
8 Spectral data of macrocycle **1**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 4H), 7.90 (d, $^4J = 2.6$ Hz, 4H), 7.62 (dd, $^3J = 9.3$ Hz, $^4J = 2.6$ Hz, 4H), 6.94 (d, $^3J = 9.3$ Hz, 4H), 4.38–4.41 (m, 4H), 3.38–3.42 (m, 4H), 3.07–3.11 (m, 4H), 2.38–2.42 (m, 4H), 1.84–2.01 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 137.4, 136.6, 128.8, 125.1, 117.9, 115.7, 62.8, 51.5, 31.6, 24.3; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{44}H_{45}N_{12}O_{12}$, 933.3280; found 933.3276.
9 J. Keeler, *Understanding NMR Spectroscopy*, Wiley, Chichester, **2005**.

Published on the web (Advance View) November 27, 2007; doi:10.1246/cl.2008.10