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Construction of anomalously bent biphenyl structure using conformational properties of calix[4]amide

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Abstract—C_{2v}-symmetrical cyclic tetramers of aromatic amides were simply synthesized in moderate yield by condensation reaction of *N*,*N*′-dimethyl-1,3-phenylenediamine and isophthalic acid derivatives using dichlorotriphenylphosphorane. The calix[4]amides exist in 1,3-alternate structure with cis conformation of tertiary aromatic amides, which were shown to be a versatile scaffold leading to a bowl-shaped macrocyclic compound possessing a anomalously strained structure, a bent hinge angle between two aromatic ring planes of biphenyl moiety, via an intramolecular ligation reaction.

Since the discovery of the fullerenes,[1] nonplanar polycyclic aromatic compounds having a deformed alkyne and aromatic surface under highly strained environment have attracted considerable interest in the field of experimental and theoretical chemistry because of their many exploitable properties, such as specific reactivity for chemical transformation, and their unique electronic property.[2] Bowl-shaped π-conjugated compounds such as corannulene and sumanene have been reported as model fullerene compounds.[3] Recently, simpler nonplanar aromatic compounds consisting of pyrenes,[4] phenylacetylenes,[5] and related compounds[6] have been effectively constructed by using cyclophane chemistry.[7] Namely, intramolecular reactions of para- and meta-substituted rings in the cyclophane as precursors result in the formation of corresponding bent and distorted entities, due to the molecular strain of cyclic frameworks. Thus, proper rigid frameworks are a useful tool for the construction of bent structures, and much more rigid linkages between each aromatic ring are important for the highly distortional structures, because the conformation of the deformed entity was retained by the force of the rigid cyclic framework. Previously, we have reported the formation of cyclic oligomers of aromatic amides[8] based on the cis conformational preference of N-methylated amides.[9] Among these, a cyclic tetramer of 3-(methylamino)benzoic acid shows a stable and rigid structure with four *cis*-amide bonds. In this study, we demonstrate that the folded calix[4]amide structure is a useful scaffold for an easy synthesis of an unusual strained structure possessing a bent hinge angle between two aromatic rings in a biphenyl moiety, which is the fullerene fragment, especially higher fullerene ones.

We designed a novel C_{2v}-symmetric cyclic tetramer of tertiary aromatic amides (**1**) as a versatile scaffold for the synthesis of constrained compounds. This calix[4]amide was synthesized by a direct condensation reaction of *N*,*N*′-dimethyl-1,3-phenylenediamine with isophthalic acid using dichlorotriphenylphosphorane as a condensation reagent (Scheme 1), which is a very effective method for the construction of macrocyclic aromatic amide architectures.[10] The mixture of *N*,*N*′-dimethyl-1,3-phenylenediamine and isophthalic acid (1:1 in molar ratio) was treated with 2.4 equiv of Ph_3PCl_2 in 1,1,2,2-tetrachloroethane (50 mM) at 120 °C for 6 h. The crude product was purified by gel permeation chromatography to give the macrocyclic aromatic amide **1** as a major compound in a 41% yield.

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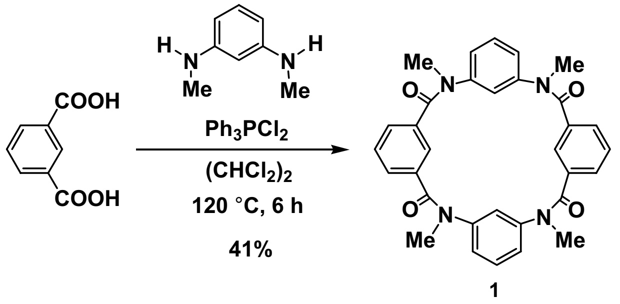


Scheme 1.

The structure of macrocycle **1** was determined by X-ray crystallographic analysis.[11] Single crystals were obtained from a mixture of chloroform and ethyl acetate solution (1:1) by a slow evaporation of the solvent at an ambient temperature for 4 days. The ORTEP views of the crystal structure corresponded to the 1,3-alternate structure, indicating two benzene rings pointing up and the other two benzene rings pointing down, resulting in a pseudo C_{2v}-symmetry (Fig. 1), which is similar to the crystal structure of the cyclic tetramer of 3-(methylamino)benzoic acid.[12] The cyclic molecule had a small cavity surrounded by four benzene rings. Each amide bond existed in cis conformation, where the torsion angles of the four amide bonds (C_{Ph}–C–N–C_{Ph}) were 39.2°, 32.1°, 30.0°, and 18.9°; those of Ar-CO were 54.4°, 65.2°, 50.5°, and 80.8°; and those of Ar-NC_{Me} were 79.0°, 71.7°, 75.0°, and 78.1° (averaged torsion angles in **1** were 30.1°, 59.3°, and 74.9°, respectively). The dihedral angles of two cofacial pairs of aromatic rings were highly bent, at 75.6° and 75.0°, which were ascribed to the rigid framework of macrocycle **1** bearing the cis-preference of the tertiary aromatic amide.

From the crystal structure of **1**, we anticipated a bowl-shaped macrocyclic compound with a severely distortional moiety, through intramolecular reaction in a functionalized C_{2v}-symmetrical calix[4]amide derived from meta-substituted isophthalic acid and *N*,*N*′-dimethyl-1,3-phenylenediamine. Thus, macrocycle **3** was synthesized according to Scheme 2. The condensation reaction of *N*,*N*′-dimethyl-1,3-phenylenediamine with 5-iodoisophthalic acid similarly gave macrocycle **2** (21%),[13] which was then converted to cross-linked macrocycle **3** in a 67% yield by a palladium-catalyzed intramolecular coupling reaction.

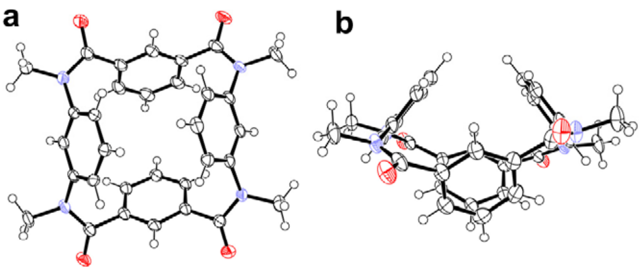
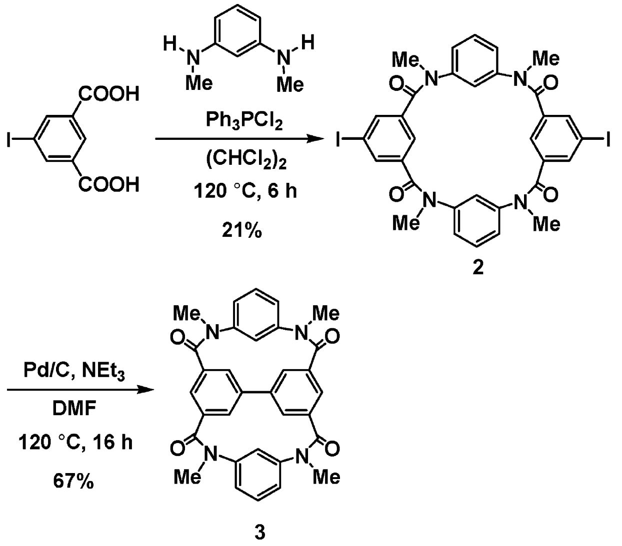


Figure 1. ORTEP view of the crystal structure of macrocycle **1**: (a) a top view and (b) a side view. The thermal ellipsoids are drawn at the 50% probability level (water molecules are omitted for simplicity).



Scheme 2.

A single crystal suitable for X-ray analysis was obtained by allowing a solution of **3** in chloroform/ethyl acetate/ethanol to stand at an ambient temperature for 1 week. The crystal structure of **3** indicates an unusual and interesting structural feature (Fig. 2).[11] The torsion angle of the tertiary aromatic amide and the hinge angle between a cofacial pair of non-cross-linked aromatic rings were similar to those of macrocycle **1**. However, the most significant aspect was that the hinge angle[14] between two the benzene rings in the cross-linked parts of **3** was 50.1° and 51.7°, and their torsion angle (C_4–C_5–C_{15}–C_{16}) was 0.2° and 8.5°.[15] That is, the framework of macrocycle **3**, due to the cis conformational preference of the tertiary aromatic amide, possessed considerable rigidity to generate a remarkable strained entity.

To evaluate this anomalous feature of the biphenyl moiety (**A**) embedded in macrocycle **3**, DFT calculations

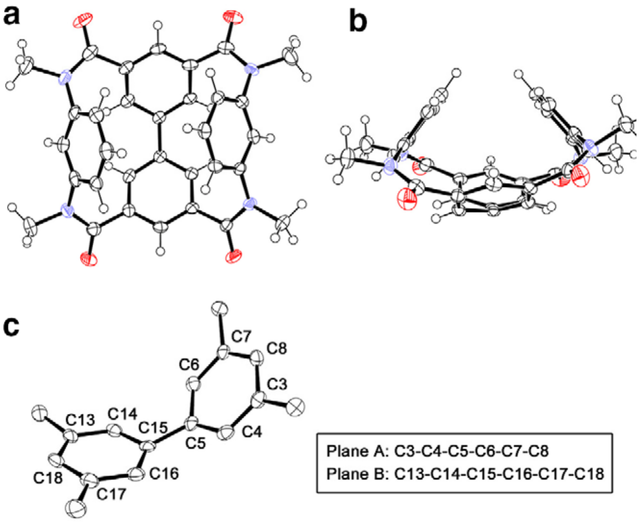


Figure 2. ORTEP view of the crystal structure of macrocycle **3**: (a) a top view; (b) a side view. The thermal ellipsoids are drawn at the 50% probability level (water molecules are omitted for simplicity); and (c) ORTEP view of the biphenyl moiety of **3**.

were performed on simple biphenyl as a model compound at the B3LYP/6-31G(d) level, resulting in an energy profile as a function of hinge angle and torsion angle of mutual phenyl rings (see Supplementary data). The gas phase calculations indicated that the structural strain of **A** was very high, and hence its relative energy was estimated to be much higher (16 kcal/mol) than that of the most stable simple biphenyl. Very limited examples of the strained biphenyl *in the ground state* have been reported. Therefore, the high yield in the synthesis of **3** was due to the conformational property of the partial structures during macrocyclization.

In conclusion, we have described that the synthesis of the bowl-shaped macrocycle with the highly strained moiety can be easily achieved by the intramolecular homocoupling reaction of the C_{2v}-symmetrical N-methylated calix[4]amide in a moderate yield. We believe that calix[4]amides with a rigid macrocyclic framework can be used as the scaffold for generating various distortional structures. The creation of a series of exceptional deformed molecules possessing alkyne and alkene parts, which are expected to exhibit a specific reactivity for chemical transformations and uncommon electronic properties, is currently under investigation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.062.

References and notes

1. (a) Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature* **1985**, *318*, 162–163; (b) Krätschmer, W.; Lamb, L. D.; Fostiropoulos, K.; Huffman, D. R. *Nature* **1990**, *347*, 354–358.
2. (a) *Carbon Rich Compounds 1*; de Meijere, A., Ed.; Springer: Berlin, 1998; (b) *Carbon Rich Compounds 2*; de Meijere, A., Ed.; Springer: Berlin, 1999.
3. (a) Sygula, A.; Rabideau, P. W. *J. Am. Chem. Soc.* **2000**, *122*, 6323–6324; (b) Bühl, M.; Hirsch, A. *Chem. Rev.* **2001**, *101*, 1153–1183; (c) Sakurai, H.; Daiko, T.; Hirao, T. *Science* **2003**, *301*, 1878.
4. (a) Bodwell, G. J.; Bridson, J. N.; Houghton, T. J.; Kennedy, J. W. J.; Mannion, M. R. *Chem. Eur. J.* **1999**, *5*, 1823–1827; (b) Bodwell, G. J.; Bridson, J. N.; Cyrański, M. K.; Kennedy, J. W. J.; Krygowski, T. M.; Mannion, M. R.; Miller, D. O. *J. Org. Chem.* **2003**, *68*, 2089–2098.
5. (a) Tobe, Y.; Fujii, T.; Matsumoto, H.; Naemura, K.; Achiba, Y.; Wakabayashi, T. *J. Am. Chem. Soc.* **1996**, *118*, 2758–2759; (b) Bunz, U. H. F.; Rubin, Y.; Tobe, Y. *Chem. Soc. Rev.* **1999**, *28*, 107–119; (c) Wandel, H.; Wiest, O. *J. Org. Chem.* **2002**, *67*, 388–393.
6. (a) Tani, K.; Seo, M.; Maeda, M.; Imagawa, K.; Nishiwaki, N.; Ariga, M.; Tohda, Y.; Higuchi, H.; Kuma, H. *Tetrahedron Lett.* **1995**, *36*, 1883–1886; (b) Lhoták, P.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 645–648; (c) Lahtinen, T.; Wegelius, E.; Linnanto, J.; Rissanen, K. *Eur. J. Org. Chem.* **2002**, 2935–2941; (d) Benniston, A. C.; Clegg, W.; Harriman, A.; Harrington, R. W.; Li, P.; Sams, C. *Tetrahedron Lett.* **2003**, *44*, 2665–2667.
7. (a) *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vols. 1 and 2, (b) *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, 2004; (c) Boekelheide, V. *Acc. Chem. Res.* **1980**, *13*, 65–70; (d) Gleiter, R.; Kratz, D. *Acc. Chem. Res.* **1993**, *26*, 311–318; (e) Nishimura, J.; Nakamura, Y.; Hayashida, Y.; Kudo, T. *Acc. Chem. Res.* **2000**, *33*, 679–686.
8. (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177–6180; (b) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Ito, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833–2838; (c) Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 5474–5475; (d) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649–10650; (e) Saito, S.; Toriumi, Y.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715–4720; (f) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277–5290; (g) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433–6442; (h) Tominaga, M.; Masu, H.; Katagiri, K.; Kato, T.; Azumaya, I. *Org. Lett.* **2005**, *7*, 3785–3787.
9. In this letter 'cis' and 'trans' are used to show the relative position of phenyl groups connected to the amide group. The designation can be easily understood at a glance; although, ordinarily, '*cis*-amide' and '*trans*-amide' should be named (*E*)- and (*Z*)-amide, respectively.
10. Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanagi, H. *Tetrahedron* **2003**, *59*, 2325–2331.
11. X-ray data were collected on a Bruker ApexII (for **1**) or Bruker Smart1000 (for **3**) CCD detector. The crystal structure was solved by direct method SHELXS-97 (Sheldrick, 1997), and refined by full-matrix least-squares method SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. *Crystal data for* **1**: $C_{32}H_{28}N_4O_4\cdot 3H_2O$; $M = 586.63$ g mol^{-1}, *Triclinic*, $P-1$, $T = 90$ K, $a = 9.0238(4)$, $b = 9.4099(4)$, $c = 17.4891(7)$ Å, $\alpha = 85.291(2)$, $\beta = 89.010(2)$, $\gamma = 80.224(2)°$, $V = 1458.54(11)$ Å^3, $Z = 2$, $D_c = 1.336$ M g m^{-3}, $\mu = 0.095$ mm^{-1}, GOF on $F^2 = 1.035$, $R_1 = 0.0610$, $wR_2 = 0.1152$ ($I > 2\sigma(I)$), $R_1 = 0.1152$, and $wR_2 = 0.1808$ (all data). CCDC-619689. *Crystal data for* **3**: $C_{32}H_{26}N_4O_4\cdot 1.25H_2O$; $M = 553.09$ g mol^{-1}, *Monoclinic*, $P2_1/c$, $T = 150$ K, $a = 19.495(3)$, $b = 8.6932(12)$, $c = 31.385(4)$ Å, $\beta = 94.567(2)°$, $V = 5302.0(12)$ Å^3, $Z = 8$, $D_c = 1.386$ M g m^{-3}, $\mu = 0.096$ mm^{-1}, GOF on $F^2 = 1.001$, $R_1 = 0.0684$, $wR_2 = 0.1519$ ($I > 2\sigma(I)$), $R_1 = 0.1559$, and $wR_2 = 0.1937$ (all data). CCDC-619690.
12. Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1996**, *37*, 5003–5006.
13. Most probably, a low yield of amide coupling reaction is ascribed to the steric hindrance of the iodine group in macrocycle **2**.
14. The hinge angle in the biphenyl moiety of **3** is defined by the angle formed by the planes A and B (Fig. 2c).
15. The crystals of **3** had two independent molecules in the asymmetric unit.