

Calix[3]amides—bowl-shaped cyclic trimers toward building block for molecular recognition: self-complementary dimeric structure in the crystal

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Abstract—Bowl-shaped cyclic trimers of aromatic amides were simply synthesized in high yield by condensation reaction of *meta*-substituted 3-(alkylamino)benzoic acid using dichlorotriphenylphosphorane. The cyclic amides exist in *syn* conformation, which has a small chiral cavity, and a pair of each enantiomeric conformer formed a dimeric structure in the crystal.

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Macrocyclic structures with a cavity are often seen in compounds that have molecular recognition abilities.¹ Calixarenes² and cyclodextrins³ are examples that have been extensively studied. A feature of these classes of compounds is a structure constructed by a repeated monomer unit, which can be synthesized by a single step reaction from an appropriate monomer. This multi-component cyclization reaction is often successful when the linkage places two monomer units in the same direction. In the course of our studies on the stereochemistry of aromatic amides,⁴ we found that a cyclic structure could easily be constructed using conformational alteration by N-alkylation of aromatic amides from *trans* to *cis*.⁵ Using this structural property, 3-(methylamino)benzoic acid was coupled with itself by a one-step reaction using tetrachlorosilane to give a mixture consisting mainly of cyclized trimer **1** of the monomer.⁶

The trimer has a bowl shape with a small cavity, which may be suitable to construct a molecular recognition site (Fig. 1).

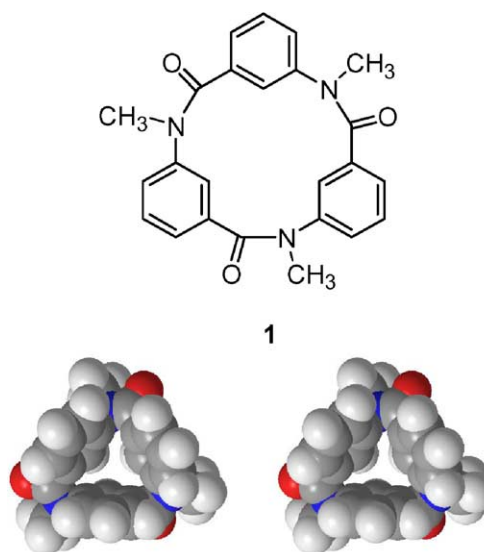


Figure 1. Structural formula and stereoview of the crystal structure⁶ in a space filling model of **1**.

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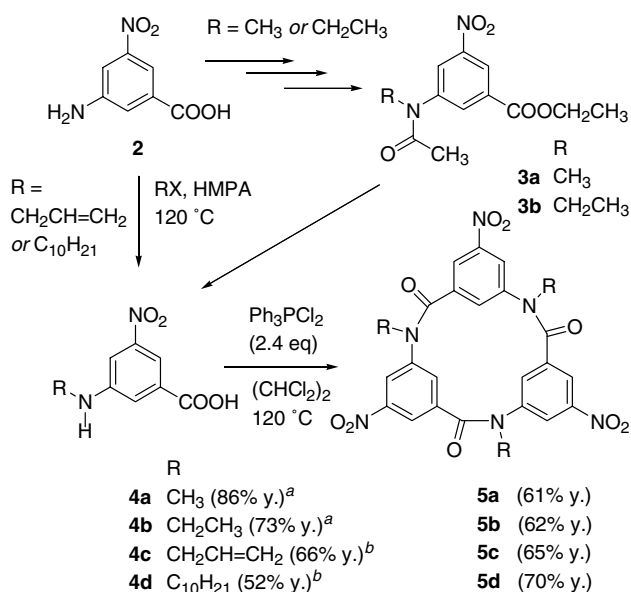
The trimer **1** was originally synthesized by Ollis and co-workers⁷ stepwise using a hydrolysis of an ester and activation to acid chloride at the carboxylic acid terminal. However, no functionalized derivative has been synthesized. As we reported previously, while searching for an effective condensation reagent to couple a carboxylic acid with an *N*-alkylated aniline with low nucleophilicity, we found that dichlorotriphenylphosphorane was highly effective in the one-step cyclization reaction of *N*-methylaminobenzoic acids.⁸ The yield of trimer is the highest among the cyclized oligomers obtained in relatively mild conditions, so this reagent is suitable for the synthesis of various functionalized cyclic aromatic amides.

Here we report a simple, one-step synthesis of cyclic trimers of 3-(alkylamino)-5-nitrobenzoic acid. We also report the characteristic crystal structure of nitro and amino derivatives obtained by the catalytic reduction of the corresponding nitro derivative. These cyclic aromatic amides would be classified as ‘calixamide’ and are a suitable skeleton for producing a new class of cyclic oligomers toward molecular recognition.

The calix[3]amides **5a–d** with various alkyl groups on the nitrogen atoms were synthesized by a one-step cyclization of 3-(alkylamino)-5-nitrobenzoic acid as a monomer using dichlorotriphenylphosphorane as a condensation reagent in a method that is very effective for macrocyclic aromatic amide construction (Scheme 1). In the case that alkyl groups on the nitrogen atoms are methyl or ethyl groups, the *N*-alkylated monomer was synthesized from commercially available 3-amino-5-nitrobenzoic acid as a starting material by the usual protection–deprotection steps including *N*-alkylation (see Supplementary data). Contrarily, *N*-allylated or *N*-decylated monomer was simply synthesized by a one-

step reaction from 3-amino-5-nitrobenzoic acid in relatively high yield without any difficulty for purification of the reaction mixture. These *N*-substituted monomers were cyclized by dichlorotriphenylphosphorane in 1,1,2,2-tetrachloroethane at 120 °C to give the corresponding cyclic trimer as a major compound in high yield. This is because the amino and carboxyl groups at the end of chained trimer with two amide connections are close together due to the *cis* conformational preference of tertiary amide that holds two substituents of amide at a direction of 60°. In these syntheses, it is notable that the calix[3]amides **5c** and **5d** could be synthesized by just two steps from the commercially available starting material.

X-ray single crystal structure analysis was carried out for crystals of the calix[3]amides **5a** and **5b**,¹⁰ which were obtained by recrystallization from CH₃OH–CHCl₃. All compounds have *syn* conformation in the crystal, where the three *N*-phenyl groups are directed to the same side. The cyclic compounds have a small cavity surrounded by three substituted-benzene rings. The conformations have a molecular chirality based on the direction of the amide bonds in the *syn* conformation. The unit cell has the same number of enantiomeric conformers, which results in the crystals having no chiral property. Interestingly, these enantiomeric conformers existed in dimeric, complementary form in the crystal where the cavity of one molecule was filled with the nitro group of another enantiomeric conformer. The crystal structure and dimeric feature of compound **5b** is shown in Figure 2. Two oxygen atoms with high electronegativity (red area) of the nitro group in a cavity seemed to be directed to the relatively electropositive (blue area) of the ring center of the two aromatic rings of the cavity. The distance between the two aromatic planes (distance A in Fig. 3) is 3.202 Å and the horizontal distance between centers of



Scheme 1. (a) The yield was calculated through the reactions from **2** via **3a** or **3b**. (b) The yield was calculated for the direct alkylation from **2** based on the halide (RX).

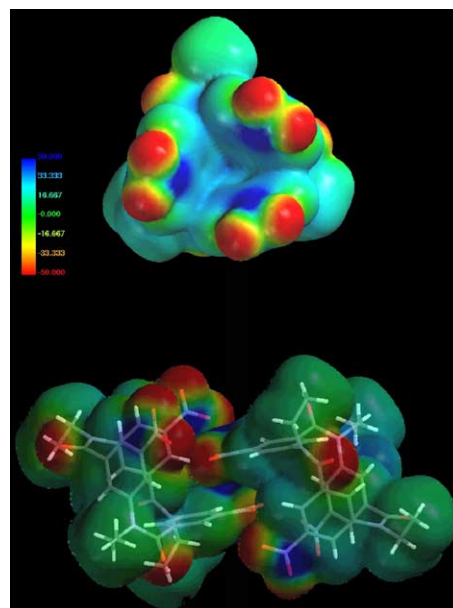


Figure 2. Static potential map⁹ of compound **5b** based on the crystal structure and the dimeric feature.

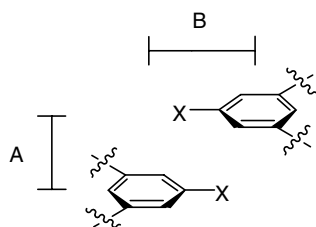


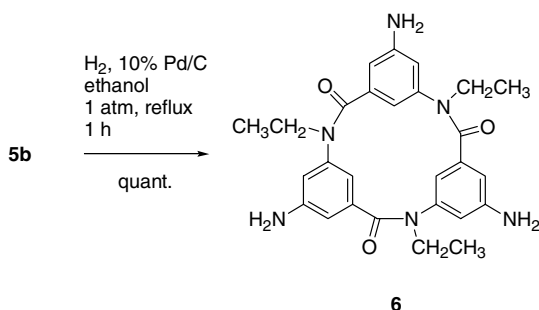
Figure 3. Schematic representation of relative position of two benzene rings, where each substituent ($-X$) is grabbed by a cavity of the other molecule.

two benzene rings (distance B) is 5.268 Å. Compound **5a**, which has an *N*-methyl group instead of the *N*-ethyl group of compound **5b**, shows intrinsically the same crystal structure and packing features including the dimeric assemble (see Supplementary data).

The calix[3]amide **5b** was easily converted to the corresponding amine **6** by catalytic reduction under a hydrogen atmosphere in a quantitative yield (Scheme 2). Single X-ray crystallographic analysis was carried out for the crystals obtained from CH_3OH .¹¹ The conformer of cyclic trimer **6** also formed a dimeric structure constructed by enantiomeric conformers (Fig. 4).

The crystal structure and dimeric feature of compound **6** is shown in Figure 4. Hydrogen atoms of an amino group, which is grabbed in a cavity is interacted with two out of three amino groups of the cavity through hydrogen bondings, where the distances between the nitrogen atoms are 3.569 and 3.945 Å. The distance between two aromatic planes (distance A in Fig. 3) is 3.282 Å that is longer than that of **5b**, and the horizontal distance between the centers of two benzene rings (distance B) is 4.843 Å, which is shorter than that of **5b**, which might be due to the hydrogen bondings between the amino groups.

^1H NMR measurements of **5a–d** and **6** at ambient temperature showed that the equilibrium between the *syn* and *anti* conformations, which includes racemization process, is fast as that of compound **1** reported before.⁶ Preliminary dynamic ^1H NMR measurement in $\text{DMF-}d_7$ of **5a–d** and **6** revealed that the energy barrier between the *syn* and *anti* conformations is not significantly affected by the substituents at the meta position (data not shown). The self-complementary dimeric feature of



Scheme 2.

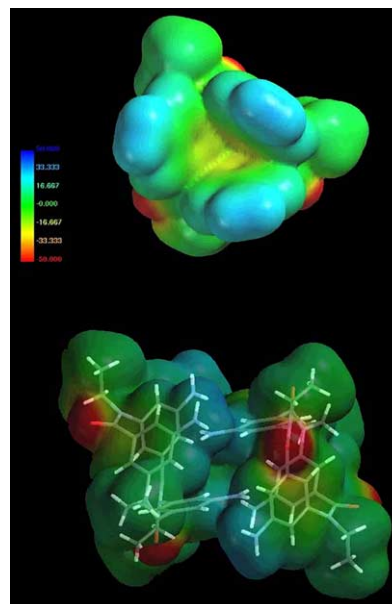


Figure 4. Static potential map⁹ of compound **6** based on the crystal structure and the dimeric feature.

these compounds cannot be observed in solution under various conditions (solvent, temperature and concentration). Therefore, the formation of the dimeric assemble in the crystals is caused by the crystal packing assisted by aromatic–aromatic interactions (and hydrogen bondings for **6**), and is weakened by the dynamic feature, the fast equilibrium between *syn* and *anti* conformations.

In conclusion, substituted cyclic trimers can be easily synthesized in high yields in just a few steps from a commercially available starting material. These macrocyclic compounds have a small cavity, which grabs a substituent of another molecule and results in the dimeric complementary assemble in the crystals. The macrocycle with amino groups can be converted for various analogues such as amide, urea, and carbamate. We believe that these macrocyclic skeletons can be used as the scaffold for various host molecules, especially anion receptors because those functional groups will work as binding sites.¹² We are now exploring diversification and recognition abilities of three-dimensionally tridentate anion receptors based on the cyclic triamide skeletons.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.082.

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- 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; though, ordinarily, 'cis-amide' and 'trans-amide' should be named (*E*)- and (*Z*)-amide, respectively.
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- Calculations on compounds **5b** and **6** were carried out using the Spartan '04 software packages. The crystal structure for each compound was used as a starting point; that is, no geometry optimization was performed.
- Crystal data of **5a**: C₂₅H₁₉Cl₃N₆O₉, *M* = 653.81, triclinic, *P*-1, *a* = 9.326(2), *b* = 11.689(3), *c* = 13.557(3) Å, α = 100.258(4), β = 97.600(4), γ = 92.500(4)°, *V* = 1438.0 (6) Å³, *Z* = 2, *D*_c = 1.510 Mg m⁻³, *T* = 173 K, crystal size 0.50 × 0.30 × 0.10 mm³, *R* = 0.0510, *wR*₂ = 0.139 [*I* > 2σ(*I*)], GOF on *F*² = 1.047, μ = 0.382 mm⁻¹, *T*_{min} = 0.8321, *T*_{max} = 0.9628. CCDC-280333. Crystal data of **5b**: C₂₇H₂₄N₆O₉, *M* = 576.52, monoclinic, *P*₂₁/*n*, *a* = 9.4900(4), *b* = 16.0952(7), *c* = 17.6257(8) Å, α = 98.8950(10)°, *V* = 2659.8(2) Å³, *Z* = 4, *D*_c = 1.440 Mg m⁻³, *T* = 150 K, crystal size 0.15 × 0.15 × 0.10 mm³, *R* = 0.393, *wR*₂ = 0.0544 [*I* > 2σ(*I*)], GOF on *F*² = 1.706, μ = 0.111 mm⁻¹, *T*_{min} = 0.9836, *T*_{max} = 0.9890. CCDC-280334.
- Crystal data of **6**: C₂₇H₃₀N₆O₃, *M* = 486.57, triclinic, *P*-1, *a* = 9.602(4), *b* = 10.329(2), *c* = 13.845(4) Å, α = 74.489(20), β = 77.38(3), γ = 72.99(2)°, *V* = 1250.4(7) Å³, *Z* = 2, *D*_c = 1.292 Mg m⁻³, *T* = 296 K, crystal size 0.20 × 0.10 × 0.10 mm³, *R* = 0.751 [*I* > 2σ(*I*)], GOF on *F*² = 1.000, μ = 0.070 mm⁻¹. CCDC-280335.
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