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L-Lysine-linked anthracenophane derived from thermodynamically controlled intermediates

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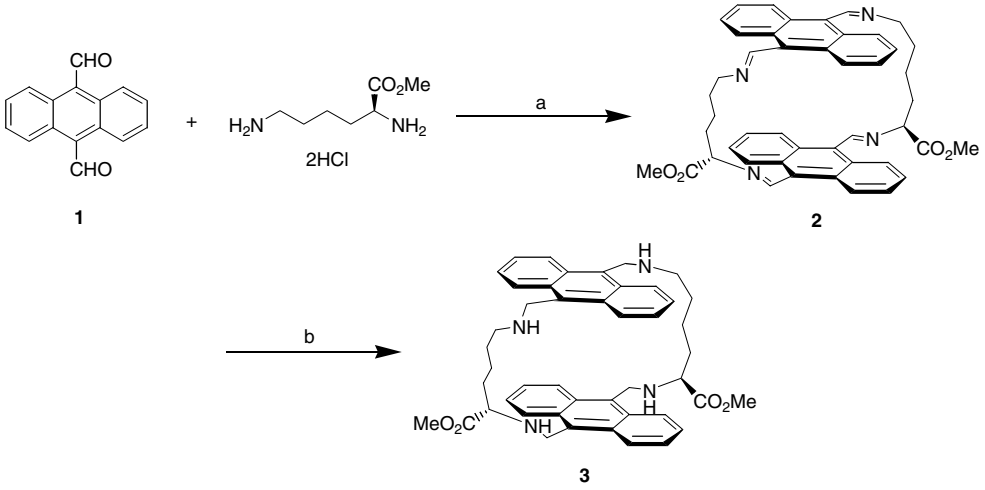
Abstract—We easily and simply synthesized L-lysine-linked anthracenophane from [2+2] macrocyclization between anthracene-9,10-dicarboxaldehyde and L-lysine methyl ester by thermodynamically controlled process. The structure was characterized by single crystal X-ray resolution and ^{1}H NMR. Circular dichroism spectrum showed induced-CDs including exciton-coupled CD, suggesting that intramolecular anthracene moieties exist in chiral arrangement. The resultant anthracenophane can form a 1:1 complex with a silver(I) ion in its cavity via NH-metal coordination and cation–π interaction ($K_a = 2.62 \times 10^5$ M^{-1}).

The development and application of macrocycles have been attracted greatly in modern chemistry in terms of their host–guest complexes and molecular recognition.[1] Inspired by the prevalence of cyclic macromolecules in nature, chemists have been fascinated by the physical properties of macrocycles and by effective synthetic methods such as high-dilution and self-assembly processes involving hydrogen bonding,[2] metal coordination,[3] and dynamic covalent chemistry.[4] Cyclophane, which is a class of macrocycles, is of considerable interest because variable functionalities could be introduced easily by the choice of arenes, bridges, and substituents.[5] Herein we describe simple and easy preparation of a novel cyclophane **3** containing two anthracene groups with two amino acid linkers, L-lysine methyl ester (Lys-OMe), by thermodynamic controlled processes (Scheme 1). This dynamic covalent bonding system produced cyclophane **3**, called anthracenophane **3**, in good yields.



Scheme 1. (a) Reagents and conditions: Et_3N, MeOH/CH_2Cl_2 (1:1, v/v), reflux, 18 h. (b) $NaBH_4$, THF/MeOH (2:1, v/v), 0 °C, 20 min, rt, 20 min.

Keywords: Macrocycles; Anthracene; Cation–π interaction; Silver ion; Host–guest system.
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In this work, we used an amino acid as a bridge, which may contribute to develop additional functionality such as introduction of chirality[6] and to perform further derivatization easily. We also examined the cavity's property of anthracenophane **3** by the titration of Ag^+ guest ion which is a typical cation–π interacting agent.[7]

We synthesized anthracenophane **3** in one-pot two-step synthesis via thermodynamically controlled intermediates from anthracene-9,10-dicarboxaldehyde (**1**)[8] and L-lysine methyl ester dihydrochloride (Scheme 1). The first step is the imine condensation and the second step is reduction of four imine bonds by $NaBH_4$. The [2+2] macrocyclization and reduction gave anthracenophane **3** as an only macrocyclic compound in 53% yield.[9] To resolve the reason why these reactions produce [2+2] macrocycles **3** principally, we monitored the first step reaction, imine condensation, by MALDI-TOF-MS (Fig. 1).[10] Indeed, the early stage (after 5 h in Fig. 1) of this reaction produced various compounds, such as cyclic 2+2 *mer* (*m/z*: 717.9), open chain 2+2 *mer* (735.8), 3+3 *mer* (1093.5), and longer linear oligomers (3+2 *mer*, 4+3 *mer*, 5+4 *mer*, 951.6, 1310.2, 1667.8, respectively). With the passage of the reaction time (after 28 h in Fig. 1), the products converged into a cyclic compound **2**, anthracene unit:lysine unit = 2:2. We assume that long chain linear oligomers are produced kinetically, and the transformation of cyclic 2:2 is controlled thermodynamically. Currently, it is not clear that why the cyclic structure of anthracene unit:lysine unit = 2:2 is more stable than others, however, it is interesting that self-assembly of anthracene moiety and L-lysine, which exists as variable conformations in solution, derives the specific simple cyclic structure.

The structure of anthracenophane **3** was characterized by single crystal X-ray resolution and ^1H NMR. Figure 2 shows the X-ray structure of anthracenophane **3**.[11] It

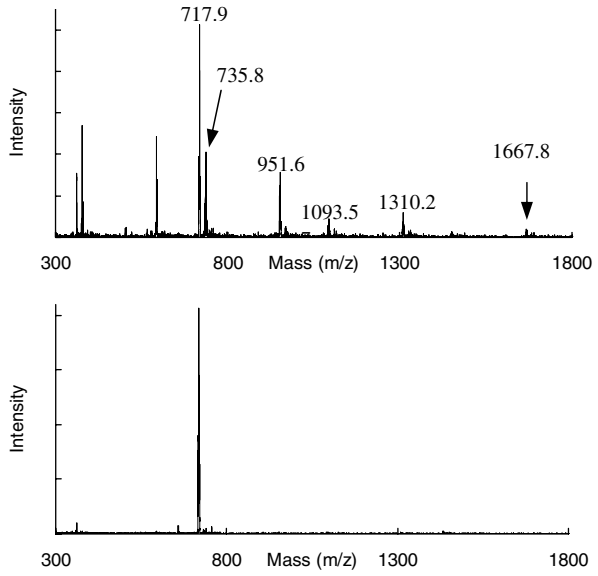

Figure 1. MALDI-TOF-MS spectra of the reaction mixture after 5 h (up) and 28 h (down). Conditions: [**1**] = [Lys-OMe] = 2.42 mM, [Et_3N] = 4.84 mM in MeOH/CH_2Cl_2 (1:1, v/v), rt.

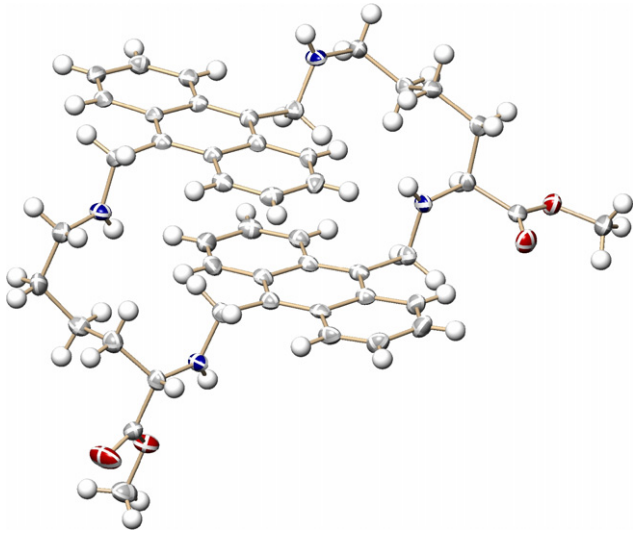

Figure 2. X-ray crystal structure of anthracenophane **3**.

revealed that **3** is not head-to-tail structure but head-to-head structure. ^1H–^1H COSY spectrum of **3** also indicated only two proton–proton couplings (H^a–H^b, H^c–H^d) showing head-to-head structure (see Supplementary data). In crystal, the distance between two anthracene rings is about 3.4 Å, which is the typical distance for *face-to-face* stacking. Figure 3 shows the aromatic region of ROESY spectrum of **3** in CD_3OD/DMSO-d_6 solution at 263 K. The spectrum exhibited NOE signals along the entire range of anthracene resonances indicating contacts between two anthracene rings (H^a–H^c, H^a–H^d, H^b–H^c, and H^b–H^d). 2D NMR indicates that the two anthracene rings are close to each other in solution.

We also investigated the chirality of anthracenophane **3** by circular dichroism (CD) spectra (Fig. 4). Anthracenophane **3** showed stronger CDs in the absorptive region of the anthracene moieties, including exciton-coupled CD, while the reference compound **4**[12] which has a non-cyclic structure, showed weaker CDs. The CDs of **3** induced from L-lysine suggest that the intramolecular anthracene moieties exist in chiral arrangement and the development of the chirality could be controlled by the linkers used.

From these structural analyses, we expected the chemical environment inside the cavity could be distinctive,

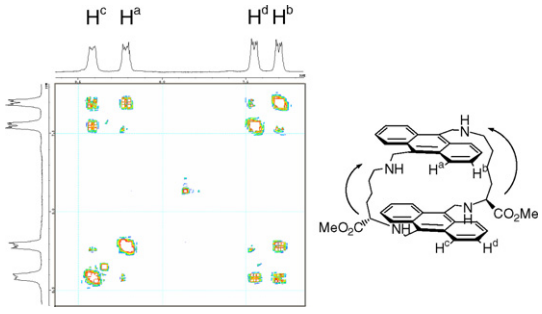

Figure 3. Aromatic region of the ROESY spectrum of anthracenophane **3** (3.9×10^{-3} M in CD_3OD/DMSO-d_6 (12:1, v/v), 263 K).

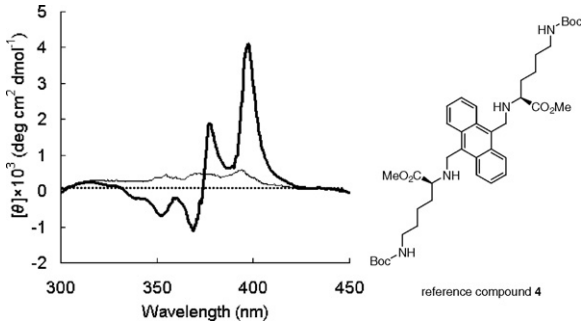

Figure 4. CD spectra of compound **3** (thick line) and **4** (thin line). Conditions: $[\mathbf{3}] = [\mathbf{4}] = 2.0 \times 10^{-4}$ M in DMSO/MeOH (1:9, v/v), rt.

because anthracene has wide π clouds; the nature of the cavity between two anthracene rings is considered to be π electron rich. To reveal the property of the cavity, silver ions were titrated to **3**. Ag^+ is widely known to interact with aromatic molecules through cation–π interaction. Figure 5 shows UV–vis absorbance changes of **3** (5.0×10^{-5} M) upon the addition of CF_3SO_3Ag in MeOH. With increasing the concentration of CF_3SO_3Ag, absorption maximum of **3** showed a bathochromic shift from 374 nm to 378 nm with distinct isosbestic point (376 nm). The results imply that the reaction involves only two species in a single equilibrium. To evaluate the binding constants with Ag^+, we confirmed the stoichiometry from continuous-variation plots (Job's plot).[13] The plots showed a maximum value at about 0.5, suggesting that the one-to-one complex was formed (Fig. 5 inset). From curve fit of 1:1 binding stoichiometry, the association constant K_a is 2.62×10^5 M^{-1} in MeOH solution.[14] On the other hand, the reference compound **4** weakly interacted with Ag^+ ion in MeOH solution ($K_a = 5.48 \times 10^3$ M^{-1}). These results suggest that an Ag^+ ion could exist within the inner cavity constructed by the two anthracene rings via NH-metal coordination and cation–π interaction.

In conclusion, we have demonstrated the synthesis and characterization of the L-lysine-linked anthracenophane. Anthracenophane **3** is easily and principally synthesized by self-assembly of Lys-OMe and anthracene-9,10-dicarboxaldehyde, followed by the condensation and reduction of the imine bonds. The time course of MALDI-TOF-MS spectra revealed [2+2] macrocycle is controlled thermodynamically. We have also demonstrated that anthracenophane **3** strongly binds an Ag^+ ion inside the cavity in MeOH solution via NH-metal coordination and up and down cation–π interactions. It is confirmed that the cavity has a space enough to accommodate small molecules. Moreover, a novel hydrophilic macrocycle could be obtained when the methyl ester groups in anthracenophane **3** were hydrolyzed, which may show distinct properties form **3** in aqueous solution, therefore, such investigation is ongoing.

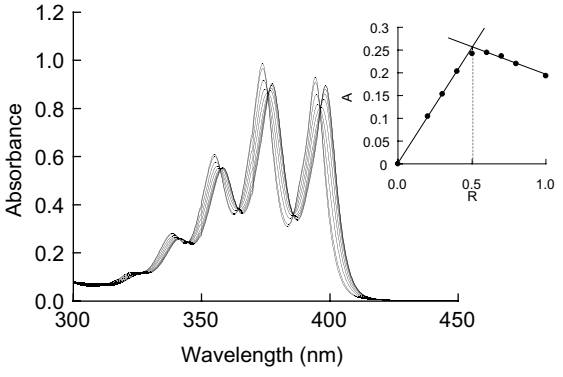

Figure 5. UV–vis titration of **3** (5.0×10^{-5} M) with CF_3SO_3Ag (0–6.9 equiv) in MeOH solution at 25 °C. (inset) Job's plot of mixtures of **3** and CF_3SO_3Ag recorded in MeOH solution. A = absorbance at $\lambda = 403$ nm; $R = [\mathbf{3}]/([\mathbf{3}]+[CF_3SO_3Ag])$, $[\mathbf{3}]+[CF_3SO_3Ag] = 5.0 \times 10^{-5}$ M.

Acknowledgment

We thank Dr. Kenji Yoza (Bruker AXS K.K.) for analyzing X-ray crystallography diffraction.

Supplementary data

Supplementary data associated with this article contain spectral data for **3** and **4**. This can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.028.

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9. *Anthracenophane* **3**: Compound **1** (341 mg, 1.46 mmol) and L-lysine methyl ester dihydrochloride (339 mg, 1.46 mmol) were suspended in a mixture of CH_2Cl_2 (20 mL) and MeOH (20 mL), and Et_3N (294 mg, 2.92 mmol) was added subsequently. The mixture was stirred at reflux for 18 h, and cooled at rt. After evaporation, the residue was diluted with brine and extracted with CH_2Cl_2. The organic solvent was evaporated under reduced pressure, and then the residue was dissolved in a mixture of MeOH (200 mL) and THF (100 mL) that was placed in an ice bath at nitrogen atmosphere. $NaBH_4$ (275 mg, 7.27 mmol) was then added slowly and the solution was stirred at 0 °C for 20 min and at rt for 20 min. The reaction was quenched by water, and the solvent was evaporated under reduced pressure. The residue was diluted with brine and extracted with CH_2Cl_2. The organic solvent was concentrated and purified by column chromatography (silica gel; CH_2Cl_2/MeOH (9.5:1)) to give **3** as an yellow solid (280 mg, 53%). IR (KBr): $\nu = 3329$ (N–H), 1728 cm^{-1} (C=O); ^1H NMR (300 MHz, acetonitrile-d_3, 25 °C, TMS): $\delta = 8.40$–8.37 (m, 4H), 8.22–8.19 (m, 4H), 7.41–7.37 (m, 4H), 7.20–7.17 (m, 4H), 4.64–4.38 (m, 8H), 3.83 (s, 6H), 3.61–3.57 (m, 2H), 2.92– 2.76 (m, 4H), 1.80–1.27 (m, 12H); MS (MALDI) calcd for $C_{46}H_{53}N_4O_4$ $[M+H]^+$ 725.9376, found 725.7119.
10. MALDI-TOF-MS instrument settings; matrix: No-matrix, Polarity: Positive.
11. Crystallographic data for structure **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 624280. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **3**: $C_{46}H_{52}N_4O_4$, $M_r = 724.92$, crystal size $0.13 \times 0.10 \times 0.08$ mm^3, $Z = 2$, monoclinic, space group $P2(1)$, $a = 9.165(3)$ Å, $b = 8.761(2)$ Å, $c = 22.854(6)$ Å, $\beta = 93.506(4)°$, $V = 1831.6(9)$ $Å^3$, $\rho_{calcd} = 1.314$ $Mg\ m^{-3}$, $T = 100$ K, $\theta_{min} = 0.89°$, $\theta_{max} = 27.10°$, $\lambda = 0.71073$, $\mu = 0.084$ mm^{-1}, $T_{min} = 0.9892$, $T_{max} = 0.9933$, final $R_1 = 0.0631$ and $wR_2 = 0.1092$ $[I > 2\sigma(I)]$.
12. *Compound* **4**: Compound **1** (234 mg, 1.00 mmol) and Nε-Boc-L-lysine methyl ester hydrochloride (888 mg, 2.99 mmol) were suspended in a mixture of CH_2Cl_2 (20 mL) and MeOH (20 mL), and Et_3N (303 mg, 2.99 mmol) was added subsequently. The mixture was stirred at reflux for 10 h, and cooled at rt. After evaporation, the residue was diluted with brine and extracted with CH_2Cl_2. The organic solvent was evaporated under reduced pressure, and then the residue was dissolved in MeOH (40 mL) that was placed in an ice bath at nitrogen atmosphere. $NaBH_4$ (227 mg, 6.00 mmol) was then added slowly and the solution was stirred at 0 °C for 20 min and at rt for 20 min. The reaction was quenched by water, and the solvent was evaporated under reduced pressure. The residue was diluted with brine and extracted with CH_2Cl_2. The organic solvent was concentrated and purified by column chromatography (silica gel; CH_2Cl_2/MeOH (35:1–30:1)) to give **4** as an yellow solid (560 mg, 77.6%). IR (KBr): $\nu = 3387$ (N–H), 1733, 1683 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.43$–8.40 (m, 4H), 7.57–7.53 (m, 4H), 4.73 (d, $J = 12.0$ Hz, 2H), 4.52 (d, $J = 12.0$ Hz, 2H), 4.46 (br, N–H), 3.84 (s, 6H), 3.52–3.47 (m, 2H), 3.07–3.01 (m, 4H), 1.76–1.31 (m, 12H), 1.42 ppm (s, 18H); MS (ESI) calcd for $C_{40}H_{59}N_4O_8$ $[M+H]^+$ 723.9186, found 723.7119.
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14. The binding isotherms were shown in Supplementary data.