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Cosmosen: Octa-Armed 24-Membered Cyclic Octaamine Synthesized from a Byproduct in the Preparation of 4-Benzyl-2,6-dioxocyclen

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ABSTRACT: The synthesis of an octa-armed 24-membered cyclic octaamine (**1**) is reported. When 4-benzyl-1,4,7,10-tetraazacyclododecane-2,6-dione (**3a**) was prepared by the reaction of diethylenetriamine with diethyl *N*-benzyliminodiacetate (**2**), a dimeric macrocycle (**3b**) was obtained as a byproduct in a 5% yield. An octa-armed 24-membered cyclic octaamine (**1**), named *Cosmosen*, was prepared via the reductive amination and reduction of **3b**. The binding constants for the 1:1 and 2:1 (Ag^+/**1**) complexation of **1** were estimated to be ca. 7.9 and 13.9, respectively, by titration experiments using UV−vis spectrometry in methanol and chloroform (v/v, 9:1) solutions at 298 K.

The macrocyclic polyamines of the series [3*m*]aneN$_m$ ($m > 6$) have attracted substantial attention not only because of the possibility to bind more than one metal ion within the macrocyclic cavity[1−17] but also because of the development of anion coordination chemistry.[18,19] In the case of 12-membered macrocyclic polyamines, the formation of mononuclear complexes is preferred. Unlike 12-membered macrocyclic polyamines, as the size of these macrocycles increases, their flexibility increases, and the coordination features of their metal complexes depend on the metal ions.[8−17] Additionally, the stabilities of the binuclear complexes increase in the case of large macrocyclic polyamines. The crystal structures of dinuclear complexes of [24]aneN$_8$ and [30]aneN$_{10}$ with Cu(II), Zn(II), Pd(II), and Ni(II) have already been reported.[11−17]

The general method for synthesizing large macrocyclic polyamines has been reported to include the cyclization of the appropriate polyamine, as described by Atkins.[20] The reported synthetic reactions have a large number of steps and occur under vigorous reaction conditions. Additionally, the overall yield seriously decreases as the size of the macrocycle increases. Another proposed synthetic method for a large macrocycle is 2:2 cyclization. The syntheses of Schiff and non-Schiff base-type large macrocycles based on 2:2 cyclization have been abundantly reported.[21−29] Usually, the synthesis of macrocyclic compounds is carried out under high-dilution conditions to increase the yield of the cyclic compounds and decrease the formation of polymers.[27−34]

Our group has synthesized tetra-armed cyclens with aromatic side arms and their silver(I) complexes. When silver(I) complexes were formed, the aromatic side arms in the armed cyclens covered the Ag^+ incorporated into the cyclen cavities via $Ag^+−\pi$ and CH−π interactions, similar to an insectivorous plant (Venus flytrap).[35−41] We called the armed cyclens argentivorous molecules.[42] We also reported that a silver(I) complex of a double-armed 24-membered macrocycle, which consisted of two nitrogen atoms and six sulfur atoms, formed a 2:1 (Ag^+:ligand) complex.[27] In the silver(I) complex, each aromatic side arm encapsulated the silver(I) ion from the opposite side. Therefore, we were interested in the conformation of the aromatic side arms in an octa-armed 24-membered macrocyclic octaamine when they formed complexes with multiple silver ions. In addition, we thought that the analysis of these conformational changes of the aromatic side arms would provide helpful information for the development of a new argentivorous molecule.

During the preparation of 4-benzyl-2,6-dioxocyclen (**3a** in Scheme 1), we accidentally found a benzyl-substituted 24-membered macrocyclic byproduct. Following our previous works on tetra-armed cyclens, we started to prepare an octa-armed 24-membered cyclic octaamine. A tetra-armed 24-membered macrocyclic tetraoxooctaamine[43] and an octa-armed 24-membered octameric cyclic peptoid[44] have been

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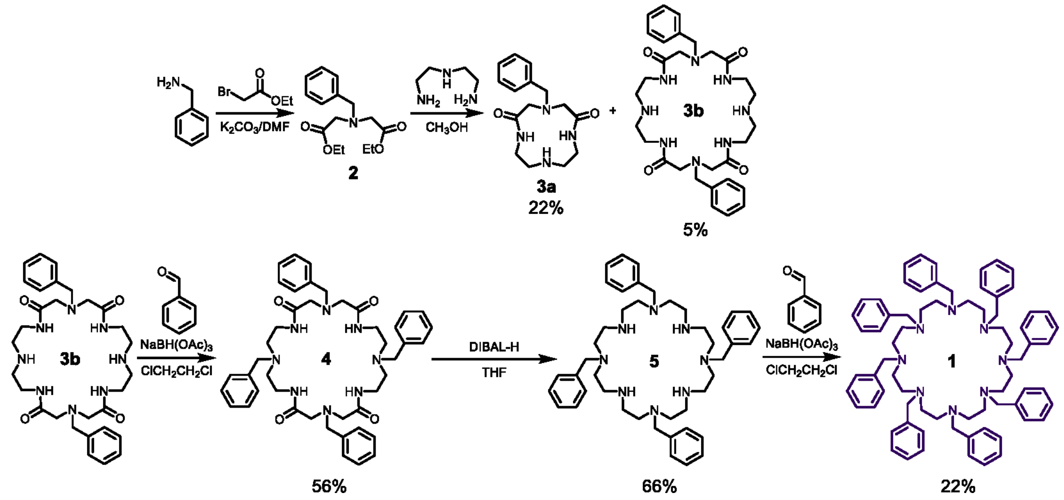
Scheme 1. Synthesis of *Cosmosen* (1)



reported (Figure 1). However, there is no example of an octa-armed 24-membered cyclic octaamine. Since *Cosmos* has eight flower petals, we named the octa-armed cyclic octaamine *Cosmosen*. We also report the binding constants for 1:1 and 1:2 complexes ($1/Ag^+$), which were measured by UV−vis titration experiments.

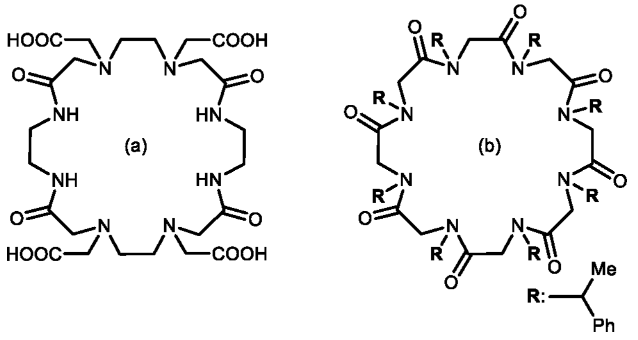


Figure 1. Examples of previously reported armed 24-membered cyclic tetraoxo and octaoxo macrocyclic octaamines.

The five-step synthesis of target compound **1**, an octa-armed cyclen with benzyl groups, starting from benzylamine is shown in Scheme 1. The *N*-benzyl cyclen is an important starting material to adopt two or more aromatic rings in the side arms. Although Tweedle and co-workers have reported the synthesis of **3a** under high-dilution conditions in ethanol,[45] the 2:2 cyclization product (**3b**) has not been reported. In this paper, we attempted to synthesize compound **3b** as a key precursor, which was expected to be obtained as a byproduct. A mixture of **3a** and **3b** was obtained by 1:1 and 2:2 reactions of **2** with diethylenetriamine under high-dilution conditions at 70 °C for 7 days. The majority of **3a** in the reaction mixture was obtained by recrystallization from methanol. After the crystals were filtered, the filtrate was concentrated, and the remaining reddish-yellow oil was separated by silica gel column chromatography. The second fraction was collected and concentrated. The oily substance was recrystallized from methanol to obtain **3b** as a white powder in a 5% yield. It is important to note that the 2:2 cyclization product was obtained in a 10% yield when it was converted to the 1:1 cyclization product. The resulting products **3a** and **3b** were characterized by ^1H and $^{13}C\{^1H\}$ NMR spectra, fast atom bombardment (FAB) mass spectrometry, and elemental analysis (Figures S1 and S2). The ^1H NMR spectra of **3a** and **3b** clearly show the successful separation of the mixture's two components (Figures S1 and S2, respectively). When the ^1H NMR spectrum of **3b** was compared with that of **3a** (Figure 2), the H_3 proton signal of **3b** was shifted downfield (+0.2 ppm) because the H_3 protons in **3a** were located in the shielding region of the neighboring C═O groups;[39] on the other hand, the H_3 protons in **3b** were not. As we mentioned above, **3a** has already been reported without **3b**.[45] Finally, the FAB mass spectra of **3a** and **3b** are m/z 291 ($M + H^+$) and m/z 581 ($M + H^+$), respectively, confirming that they are the 1:1 and 2:2 cyclization products. Our result is the first instance of a 2:2 cyclization by the reaction of diethylenetriamine with a diethyl iminodiacetate derivative.

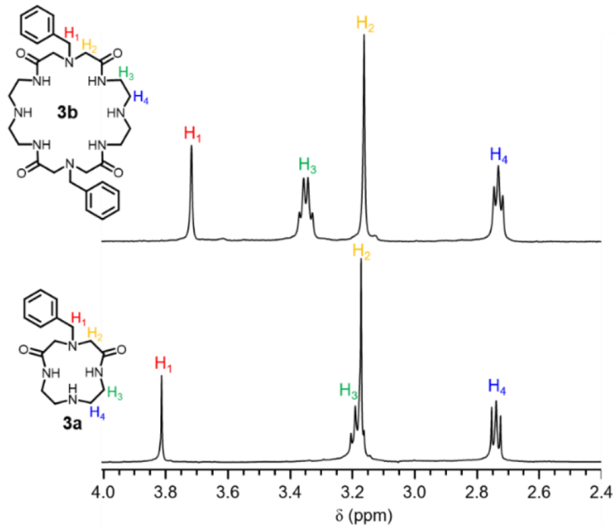


Figure 2. Comparison between the ^1H NMR spectra (aliphatic region) of **3a** and **3b** in CD_2Cl_2.

The benzyl side arms were attached to the tetraoxo 24-membered cyclic octaamine **3b** by reductive amination. The reaction of **3b**, benzaldehyde, and sodium triacetoxyborohydride ($NaBH(OAc)_3$) in 1,2-dichloroethane for seven days gave compound **4**. The purification of **4** was conducted via recrystallization from methanol instead of column chromatography. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **4** are shown in Figure S3. The structure of **4** was also characterized by single-crystal X-ray analysis (Figures 3 and S4). The colorless single crystal of **4** suitable for X-ray analysis was obtained by recrystallization from methanol. Compound **4** crystallizes in the triclinic space group $P\bar{1}$ (Table S1). In the crystal structure, two crystallographically different macrocycles with similar conformations are arranged side by side with an adjacent macrocycle. The cyclen unit of **4** is quite planar and elongated, and the four benzyl arms show a 1,2-alternate conformation. It was confirmed by NMR and mass spectra as well as single-crystal X-ray diffraction data that the 2:2 cyclization reaction was again accomplished. As we expected, the H_3 protons in **4** were not located in the shielding area of the neighboring C═O groups (Figure S3a).

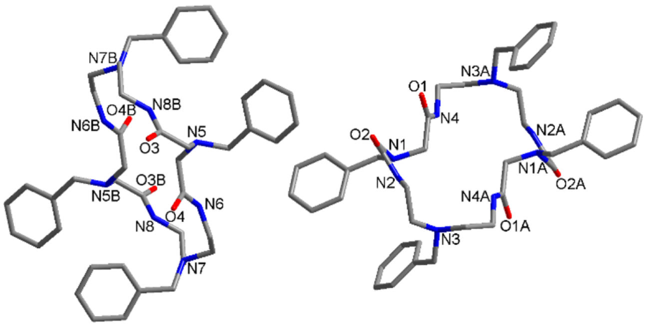


Figure 3. Crystal structure of the precursor macrocycle **4**. Hydrogen atoms are omitted.

The reduction of **4** by diisobutylaluminum hydride (DIBAL-H) gave the reduction product **5**. The isolation of **5** was performed by silica gel column chromatography (chloroform/methanol/ammonia = 5:1:0.5) as a reddish yellow oil in a 66% yield. Compound **5** was characterized by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, FAB-MS, and elemental analysis (Figure S5).

Ag^{+} ion-induced cold ESI mass and UV−vis spectral changes were carried out to investigate the complexation behavior toward Ag^{+} ions. We performed cold electrospray ionization mass spectrometry (CSI-MS) experiments by varying the Ag^{+} content (0.0−3.0 equiv) in the presence of **5**, and the formation of complexes with different stoichiometries was confirmed (Figure S6). The mass spectrum of **5** with 1.0 equiv of Ag^{+} was dominated by fragment ion peaks for the 1:1 complex at m/z 811, indicating that the species present was $[\mathbf{5} + Ag^{+}]^{+}$. When 2.0 equiv of Ag^{+} was added, a new fragment ion peak arising from the 1:2 species, $[\mathbf{5} + 2Ag^{+} + OTf^{-}]^{+}$, was observed at m/z 1067.

To estimate the binding constants between **5** and the Ag^{+} ions, a UV−vis titration experiment was performed by varying the silver(I) content (0.0−2.5 equiv) in the presence of **5** (8.0×10^{-4} M) in a mixture of methanol and chloroform (v/v, 9:1) (Figure S7a). The stability constants ($\log\beta_1$ and $\log\beta_2$) for the 1:1 and 1:2 ($\mathbf{5}/Ag^{+}$) complexations were calculated by HyperSpec software[46] to afford 6.5(3) and 13.0(5), respectively, suggesting the formation of the stable 1:2 complex (Figure S7b).

The octabenzyl-armed 24-membered cyclic octaamine (**1**) was prepared by the reductive amination of **5** with benzaldehyde in the presence of $NaBH(OAc)_3$ in 1,2-dichloroethane. The reaction mixture was separated and purified by silica gel column, affording **1** as a pale yellow oil in a 22% yield. The structure of **1** was confirmed by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, CSI-MS, and elemental analysis (Figures 4 and S8). To the best of our knowledge, the compound is the first example of an octa-armed cyclic octaamine. Structural information on the Ag^{+} complex with **1** in a solution was obtained by Ag^{+} ion-induced CSI-MS and UV−vis titration experiments (Figures 5 and S9 and S10, respectively).

A CSI-MS titration experiment was performed by varying the Ag^{+} content (0−3.0 equiv) in the presence of **1** (Figures 5 and S9). When 0.5 equiv of Ag^{+} was added to **1**, a fragment ion peak for $[\mathbf{1} + Ag^{+}]^{+}$ appeared at m/z 1172. The mass spectrum of **1** with 1.0 equiv of Ag^{+} was monopolized by peaks for the 1:2 ($\mathbf{1}/Ag^{+}$) complex at m/z 639 and 1427, indicating that the species were $[\mathbf{1} + 2Ag^{+}]^{2+}$ and $[\mathbf{1} + 2Ag^{+} + OTf^{-}]^{+}$, respectively. The addition of over 1.5 equiv of Ag^{+} led to a new set of multi-silver(I) complexes. In particular, as more excess Ag^{+} was added, the peak intensity of high equivalents of the silver complex increased (Figure 5) because these high

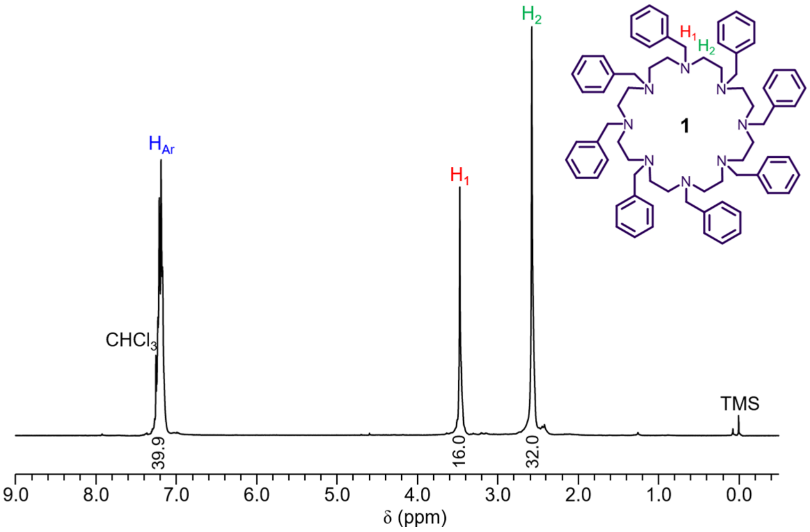


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1**.

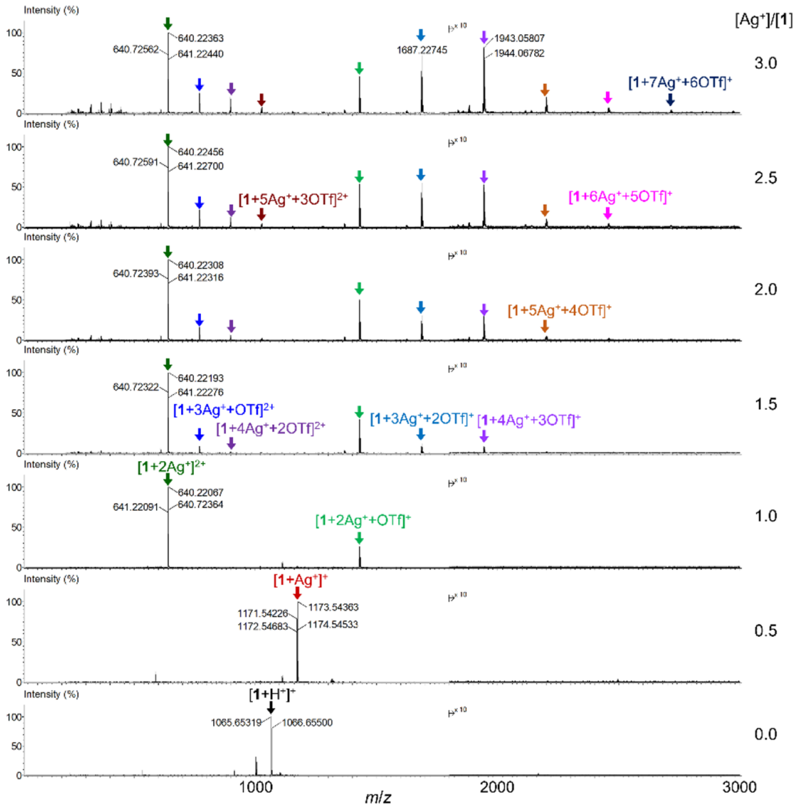


Figure 5. CSI mass spectra of **1** (9.2×10^{-4} M) in the presence of different molar ratios of AgOTf in a mixture of $CHCl_3$ and CH_3OH (1:19) at 298 K.

equivalents of silver complexes would form clusters under the ESI mass conditions.

A UV−vis titration experiment was performed by varying the silver(I) content (0.0−2.5 equiv) in the presence of **1** (4.1×10^{-5} M) in a methanol and chloroform (v/v, 9:1) solution at 298 K. According to the addition of AgOTf, the absorption increased (Figure S10a) due to the complexation of the cyclen ring with Ag^+. As shown in the titration curve at 229 nm (Figure S10a), the absorbance of **1** gradually increased between 0.0 and 2.0 equiv of silver(I). Above 2.0 equiv., the absorbance shows a much smaller increase, suggesting the formation of a stable 1:2 (ligand-to-metal) complex as a primary product. From the titration data, the stability constants for the 1:1 and 1:2 (**1**/Ag^+) complexation between silver(I) and **1** were obtained using HyperSpec software,[46] and the $\log\beta_1$ and $\log\beta_2$ values were estimated to be 7.9(2) and 13.9(3), respectively (Figure S10b). The binding constants suggest the formation of 1:2 complex that was more stable than the **5**/Ag^+ complex due to the Ag^+−π interactions between the silver(I) ions incorporated in the cyclic amine and the aromatic side arms.

In conclusion, we have developed a synthetic method for the preparation of an octa-armed 24-membered cyclen (*Cosmosen*, **1**). In the case of the key precursor **3b**, we successfully obtained it as a byproduct via a 2:2 cyclization reaction. The synthetic reaction process of the 24-membered cyclen is mild and short compared to the reported method for [24]aneN_8. The intermediates and final compound were obtained at reasonable yields. We believe that **1** can be used as a key pseudo-rotaxane compound, which consists of a cationic macrocyclic wheel molecule and an anionic axial molecule. The study of rotaxane with a cationic wheel and an anionic axis is now in progress.

■ EXPERIMENTAL SECTION

General. All reagents were of standard analytical grade and were used without further purification. Melting points were obtained with a Mel-Temp capillary apparatus and were not corrected. The FAB mass spectra were obtained using a JEOL 600 H mass spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectra were measured on a JEOL ECP400 spectrometer (400 MHz). UV−vis spectra were recorded on a JASCO V-650 spectrophotometer. Stability constants were calculated using HyperSpec ver. 1.1.33.[46] Cold ESI mass spectra were recorded on a JEOL JMST100CS mass spectrometer. The elemental analysis was carried out on a Yanako MT-6 CHN microcorder.

Synthesis of 4-Benzyl-1,4,7,10-tetraazacyclododecane-2,6-dione (3a) and 4,16-Dibenzyl-1,4,7,10,13,16,19,22-octaazacyclotetracosane-2,6,14,18-tetraone (3b). Compound **2** (16.7 g, 60.0 mmol) and diethylenetriamine (9.69 g, 93.9 mmol) were dissolved in MeOH (1.9 L). Then, the mixture was stirred and refluxed at 70 °C (in a heating mantle) under a nitrogen atmosphere for seven days. Then, the solvent was evaporated, and white macrocycle **3a** was afforded as a white powder by recrystallization from methanol. The residue was finally purified by column chromatography (chloroform/methanol/aqueous ammonia = 5:1:0.06) to obtain **3a** and **3b**. Flash column chromatography afforded products **3a** and **3b** as white solids in a 22% yield (3.91 g) and pale yellow solids in a 5% yield (0.93 g), respectively.

3a. mp: 155.4−156.0 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ 7.39−7.27 (m, 7H), 3.81 (s, 2H), 3.20−3.16 (m, 8H), 2.74 (t, J = 5.7 Hz, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.7, 137.7, 129.3, 129.1, 128.3, 62.9, 60.8, 45.4, 38.1. FAB-MS (matrix DTT/TG = 1:1) m/z 291 ($[M + H]^+$, 100%). Anal. Calcd for $[C_{15}H_{22}N_4O_2{+}0.5H_2O]$: C, 60.18; H, 7.74; N, 18.71. Found: C, 60.22; H, 7.64; N, 18.96.

3b. mp: 181.6−182.9 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ 7.46 (t, J = 5.1 Hz, 4H), 7.38−7.27 (m, 10H), 3.72 (s, 4H), 3.36 (q, J = 5.6

Hz, 8H), 3.16 (s, 8H), 2.73 (t, *J* = 5.5 Hz, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 137.7, 129.5, 129.1, 128.4, 60.9, 59.2, 48.9, 39.2. FAB-MS (matrix DTT/TG = 1:1) *m*/*z* 581 ([M + H]$^+$, 30%). Anal. Calcd for $C_{30}H_{44}N_8O_4$+0.25H_2O: C, 61.57; H, 7.66; N, 19.15. Found: C, 61.43; H, 7.67; N, 19.04.

Synthesis of 4,10,16,22-Tetrabenzyl-1,4,7,10,13,16,19,22-octaazacyclotetracosane-2,6,14,18-tetraone (4). Compound **3b** (0.17 g, 0.295 mmol) and benzaldehyde (0.430 g, 4.05 mmol) were added to 1,2-dichloroethane (25 mL), and the mixture was stirred for six days at room temperature under a nitrogen atmosphere. Then, sodium triacetoxyborohydride (1.40 g, 6.62 mmol) was added to the reaction mixture, and the mixture was stirred for one day at room temperature under a nitrogen atmosphere. A saturated sodium hydrogen carbonate solution (10 mL) was added, and the mixture was extracted with chloroform (20 mL, three times). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography (chloroform/methanol = 10:1) to remove impurities. Silica gel column chromatography (chloroform/methanol/aqueous ammonia = 5:1:0.2) was performed to produce purified **4**. Yield: 56% (0.126 g). mp: 153.8−154.2 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ 7.32−7.22 (m, 20H), 7.11 (t, *J* = 5.0 Hz, 4H), 3.70 (s, 4H), 3.58 (s, 4H), 3.28 (q, *J* = 5.6 Hz, 8H), 3.10 (s, 8H), 2.55 (t, *J* = 5.7 Hz 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 138.7, 137.5, 129.2, 129.1, 128.5, 128.4, 127.7, 127.4, 59.7, 59.0, 57.8, 53.8, 37.4. FAB-MS (matrix Glycerin) *m*/*z* 761 ([M + H]$^+$, 20%). Anal. Calcd for $C_{44}H_{56}N_8O_4$+0.5H_2O: C, 68.64; H, 7.46; N, 14.55. Found: C, 68.83; H, 7.41; N, 14.47.

Synthesis of 1,7,13,19-Tetrabenzyl-1,4,7,10,13,16,19,22-octaazacyclotetracosane (5). Ten milliliters of a diisobutylaluminum hydride solution in THF (1 M) was slowly added to compound **4** (0.113 g, 0.148 mmol) at 0 °C. Then, the mixture was stirred for one day at room temperature under an argon atmosphere. The reaction mixture was cooled to 0 °C. Benzene (27 mL) and sodium fluoride (1.47 g, 35.1 mmol) were added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was cooled again to 0 °C, and 4 mL of water was added to the reaction mixture. The reaction mixture was stirred for one day at room temperature and then evaporated with chloroform (30 mL, three times). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography (chloroform/methanol/aqueous ammonia = 5:1:0.5) to obtain **5** in a reddish yellow oil state. Yield: 66% (0.068 g). mp: 153.8−154.2 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ 7.31−7.19 (m, 20H), 3.57 (s, 8H), 2.61−2.53 (m, 32H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.1, 129.0, 128.3, 127.1, 59.6, 53.3, 47.1. FAB-MS (matrix Glycerin) *m*/*z* 707 ([M + H]$^+$, 15%). Anal. Calcd for $C_{44}H_{64}N_8$+0.3 $CHCl_3$: C, 71.82; H, 8.75; N, 15.12. Found: C, 71.65; H, 8.70; N, 14.86.

Synthesis of 1,4,7,10,13,16,19,22-Octabenzyl-1,4,7,10,13,16,19,22-octaazacyclotetracosane (1). Compound **5** (0.61 g, 0.087 mmol), benzaldehyde (0.10 g, 0.96 mmol), and sodium triacetoxyborohydride (0.21 g, 0.98 mmol) were added to 1,2-dichloroethane (25 mL), and the mixture was stirred for eight days at room temperature under a nitrogen atmosphere. Saturated sodium hydrogen carbonate solution (40 mL) was added, and the mixture was extracted with chloroform (20 mL, three times). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography (chloroform/methanol/aqueous ammonia = 10:1:0.06) to remove impurities. After silica gel column chromatography (chloroform/methanol = 40:1) was performed, compound **1** was obtained as a pale yellow oil. Yield: 22% (0.020 g). ^1H NMR (400 MHz, CD_2Cl_2): δ 7.23−7.17 (m, 40H), 3.47 (s, 16H), 2.57 (m, 32H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 128.8, 128.1, 126.7, 59.4, 52.6. CSI-MS *m*/*z* 1065.88 ([M + H]$^+$). Anal. Calcd for $C_{72}H_{88}N_8\cdot0.6CHCl_3$: C, 76.68; H, 7.85; N, 9.85. Found: C, 76.57; H, 7.64; N, 9.72.

X-ray Crystallographic Analysis. X-ray data were collected on a Bruker SMART APEX II ULTRA diffractometer equipped with graphite monochromated Mo K_α radiation (λ = 0.71073 Å) generated by a rotating anode. The cell parameters for the compounds were obtained from a least-squares refinement of the spot. Data collection, data reduction, and semiempirical absorption correction were carried out using the software package APEX2.[47] All of the calculations for the structure determination were carried out using the SHELXTL package.[48] In all cases, nonhydrogen atoms were refined anisotropically, and hydrogen atoms were placed in idealized positions and refined isotropically in a riding manner along with their respective parent atoms. The relevant collected crystal data and refinement data for the crystal structures are summarized in Table S1. CCDC 2071938 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00737.

NMR spectra, systal structure, CSI-MS data, and UV−vis spectra (PDF)

Accession Codes

CCDC 2071938 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Bianchi, A.; Micheloni, M.; Paoletti, P. Large polyazacycloalkanes: ligational properties and anion coordination chemistry. *Pure Appl. Chem.* **1988**, *60*, 525−532.

(2) Bencini, A.; Bianchi, A.; Micheloni, M.; Paoletti, P.; Garcia-España, E.; Niño, M. A. Coordination Tendency of [3*k*]aneN_k Polyazacycloalkanes. Thermodynamic Study of Solution Equilibria. *J. Chem. Soc., Dalton Trans.* **1991**, 1171−1174.

(3) Micheloni, M. Large Polyazacycloalkanes and Small Macrocyclic Cages. *Comments Inorg. Chem.* **1988**, *8*, 79−100.

(4) Micheloni, M.; Paoletti, P.; Bianchi, A. 1,4,7,10,13,16,19-Heptaazacycloheneicosane. A Large, Potentially Dinucleating Polyazacycloalkane. Synthesis and Equilibria between Hydrogen and Copper(II) Ions. *Inorg. Chem.* **1985**, *24*, 3702−3706.

(5) Bencini, A.; Bianchi, A.; Garcia-España, E.; Giusti, M.; Micheloni, M.; Paoletti, P. Solution Chemistry of Macrocycles. 5.[1] Synthesis and Ligational Behavior toward Hydrogen and Copper(II) Ions of the Large Polyazacycloalkane 1,4,7,10,13,16,19,22,25-Nonaazacycloheptacosane ([27]aneN_9). *Inorg. Chem.* **1987**, *26*, 681−684.

(6) Bencini, A.; Bianchi, A.; Garcia-España, E.; Micheloni, M.; Paoletti, P. Synthesis and Ligational Properties of the Two Very Large Polyazacycloalkanes [33]aneN_{11} and [36]aneN_{12} Forming Trinuclear Copper(II) Complexes. *Inorg. Chem.* **1988**, *27*, 176−180.

(7) Bencini, A.; Bianchi, A.; Garcia-España, E.; Micheloni, M.; Paoletti, P. Anaerobic Complexation of Cobalt(II) by [3*k*]aneN_k (k = 7−12) Polyazacycloalkanes. *Inorg. Chem.* **1989**, *28*, 2480−2482.

(8) Bencini, A.; Bianchi, A.; Garcia-España, E.; Giusti, M.; Mangani, S.; Micheloni, M.; Orioli, P.; Paoletti, P. Synthesis and Complexing Properties of the Large Polyazacycloalkane 1,4,7,10,13,16,19,22,25,28-Decaazacyclotriacontane (L). Crystal Structure of the Monoprotonated Dicopper(II) Complex $[Cu_2(L)HCl_2](ClO_4)_3\cdot 4H_2O$. *Inorg. Chem.* **1987**, *26*, 1243−1247.

(9) Bencini, A.; Bianchi, A.; Garcia-España, E.; Mangani, S.; Micheloni, M.; Orioli, P.; Paoletti, P. Polynuclear Zinc(II) Complexes with Large Polyazacycloalkanés. Equilibrium Studies and Crystal Structure of the Binuclear $[Zn_2([30]aneN_{10})(NCS)](ClO_4)_3$ Complex. *Inorg. Chem.* **1988**, *27*, 1104−1107.

(10) Bencini, A.; Bianchi, A.; Dapporto, P.; Garcia-España, E.; Marcelino, V.; Micheloni, M.; Paoletti, P.; Paoli, P. Heptacoordination of Manganese(II) by the Polyazacycloalkane [21]aneN_7. Crystal Structure of the $[Mn([21]aneN_7)](ClO_4)_2$ Solid Compound and Thermodynamics of Complexation in Water Solution. *Inorg. Chem.* **1990**, *29*, 1716−1718.

(11) Bianchi, A.; Mangani, S.; Micheloni, M.; Nanini, V.; Orioli, P.; Paoletti, P.; Seghi, B. Dicopper(II) Complex of the Large Polyazacycloalkane 1,4,7,10,13,16,19,22-Octaazacyclotetracosane (bistrien). Synthesis, Crystal Structure, Electrochemistry, and Thermodynamics of Formation. *Inorg. Chem.* **1985**, *24*, 1182−1187.

(12) Bencini, A.; Bianchi, A.; Dapporto, P.; Garcia-España, E.; Micheloni, M.; Paoletti, P. Polynuclear Zinc(II) Complexes with Large Polyazacycloalkanes. 2.[1] Equilibrium Studies and Crystal Structure of the Binuclear Complex $[Zn_2LCl_2](Cl)ClO_4\cdot 4H_2O$ (L = 1,4,7,10,13,16,19,22-Octaazacyclotetracosane). *Inorg. Chem.* **1989**, *28*, 1188−1191.

(13) Bencini, A.; Bianchi, A.; Castelló, M.; Di Vaira, M.; Faus, J.; Garcia-España, E.; Micheloni, M.; Paoletti, P. Thermodynamic Study of the Formation in Aqueous Solution of Cadmium(II) Complexes with Polyazacycloalkanes. Synthesis and Crystal Structure of the Dicadmium(II) Complex $Na[Cd_2(L)Cl_2](ClO_4)_3$ (L = 1,4,7,10,13,16,19,22,25,28-Decaazacyclotriacontane). *Inorg. Chem.* **1989**, *28*, 347−351.

(14) Bencini, A.; Bianchi, A.; Castelló, M.; Dapporto, P.; Faus, J.; Garcia-España, E.; Micheloni, M.; Paoletti, P.; Paoli, P. Nickel(II) Complexes of [3*k*]aneN_k Polyazacycloalkanes (k = 7−12) Solution and Solid-State Studies. *Inorg. Chem.* **1989**, *28*, 3175−3181.

(15) Bencini, A.; Bianchi, A.; Dapporto, P.; Garcia-España, E.; Paoletti, P.; Paoli, P.; Ramirez, J. A.; Rodriguez, A. Thermodynamic and Structural Properties of Palladium(II) Polynuclear Complexes of Azamacrocycles. Crystal Structure of the $[Pd_2([24]aneN_8)](ClO_4)_4$ Complex. *Inorg. Chem.* **1993**, *32*, 1204−1208.

(16) Andres, A.; Bencini, A.; Carachalios, A.; Bianchi, A.; Dapporto, P.; García-España, E.; Paoletti, P.; Paoli, P. Interaction of Lead(II) with Highly-Dentate Linear and Cyclic Polyamines. *J. Chem. Soc., Dalton Trans.* **1993**, 3507−3513.

(17) Schumann, H.; Bottgef, U. A.; Zietzke, K.; Hemling, H.; Kociok-Kohn, G.; Pickardt, J.; Ekkehardt Hahnb, F.; Zschunke, A.; Schiefnef, B.; Gries, H.; Radiichel, B.; Platzeke, J. 1,4,7,10,13,16,19,22-Octaazacyclotetracosane-1,4,7,10,13,16,19,22-octaacetic Acid (H_8OTEC) and 1,4,7,10,14,17,20,23-Octaazacyclohexacosane-1,4,7,10,14,17,20,23-octaacetic Acid (H_8OHEC): Synthesis and Characterization of Two Large Macrocyclic Polyamine Polycarboxylic Ligands and Some of Their Copper(II) and Lanthanide(III) Complexes. *Chem. Ber.* **1997**, *130*, 267−277.

(18) Dietrich, B.; Hosseini, M.; Lehn, J. M.; Sessions, R. B. Anion Receptor Molecules. Synthesis and Anion-Binding Properties of Polyammonium Macrocycles. *J. Am. Chem. Soc.* **1981**, *103*, 1282−1283.

(19) Kimura, E.; Sakonaka, A.; Kodama, M. A Carbonate Receptor Model by Macromonocyclic Polyamines and Its Physiological Implications. *J. Am. Chem. Soc.* **1982**, *104*, 4984−4985.

(20) Atkins, T. J.; Richman, J. E.; Oettle, J. E. MACROCYCLIC POLYAMINES: 1,4,7,10,13,16-HEXAÄZACYCLOÖCTADECANE. *Org. Synth.* **1978**, *58*, 86.

(21) Brooker, S. Complexes of thiophenolate-containing Schiff-base macrocycles and their amine Analogues. *Coord. Chem. Rev.* **2001**, *222*, 33−56.

(22) Pilkington, N. H.; Robson, R. COMPLEXES OF BINUCLEATING LIGANDS III. NOVEL CONPLEXES OF A MACROCYCLIC BINUCLEATING LIGAND. *Aust. J. Chem.* **1970**, *23*, 2225−2236.

(23) Menif, R.; Martell, A. E.; Squattrito, P. J.; Clearfield, A. New Hexaaza Macrocyclic Binucleating Ligands. Oxygen Insertion with a Dicopper(I) Schiff Base Macrocyclic Complex. *Inorg. Chem.* **1990**, *29*, 4723−4729.

(24) MacLachlan, M. J.; Park, M. K.; Thompson, L. K. Coordination Compounds of Schiff-Base Ligands Derived from Diaminomaleonitrile (DMN): Mononuclear, Dinuclear, and Macrocyclic Derivatives. *Inorg. Chem.* **1996**, *35*, 5492−5499.

(25) Kim, H.-S.; Kwon, I.-C.; Choi, J.-H. Synthesis of Crown Ethers Containing a Thiazole Subcyclic Unit. *J. Heterocycl. Chem.* **1999**, *36*, 1285−1289.

(26) Cameron, S. A.; Brooker, S. Metal-Free and Dicopper(II) Complexes of Schiff Base [2 + 2] Macrocycles Derived from 2,2′-Iminobisbenzaldehyde: Syntheses, Structures, and Electrochemistry. *Inorg. Chem.* **2011**, *50*, 3697−3706.

(27) Habata, Y.; Seo, J.; Otawa, S.; Osaka, F.; Noto, K.; Lee, S. S. Synthesis of diazahexathia-24-crown-8 derivatives and structures of Ag^+ Complexes. *Dalton Trans.* **2006**, 2202−2206.

(28) Xu, Z.; Huang, X.; Liang, J.; Zhang, S.; Zhou, S.; Chen, M.; Tang, M.; Jiang, L. Efficient Syntheses of Novel Cryptands Based on Bis(*m*-phenylene)-26-crown-8 and Their Complexation with Paraquat. *Eur. J. Org. Chem.* **2010**, *2010*, 1904−1911.

(29) Jung, D.; Chamura, R.; Habata, Y.; Lee, S. S. Extra Large Macrocycle: 40-Membered Macrocycle via 2:2 Cyclization and Its Dimercury(II) Complex. *Inorg. Chem.* **2011**, *50*, 8392−8396.

(30) Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. Metal-Free Methods in the Synthesis of Macrocyclic Schiff Bases. *Chem. Rev.* **2007**, *107*, 46−79.

(31) Pattenden, G.; Thompson, T. Design and synthesis of novel tubular and cage structures based on thiazole-containing macrolactams related to marine cyclopeptides. *Chem. Commun.* **2001**, 717–718.

(32) Hesford, M. J.; Levason, W.; Matthews, M. L.; Reid, G. Synthesis and complexation of the mixed tellurium-oxygen macrocycles 1-tellura-4,7-dioxacyclononane, [9]aneO_2Te, and 1,10-ditellura-4,7,13,16-tetraoxacyclooctadecane, [18]aneO_4Te_2 and their selenium analogues. *Dalton Trans.* **2003**, 2852–2858.

(33) Levason, W.; Manning, J. M.; Nirwan, M.; Ratnani, R.; Reid, G.; Smith, H. L.; Webster, M. Selenoether macrocyclic chemistry-syntheses and properties of new potentially tridentate and hexadentate Se/O-donor macrocycles. *Dalton Trans.* **2008**, 3486–3492.

(34) Shimizu, H.; Cojal González, J. D.; Hasegawa, M.; Nishinaga, T.; Haque, T.; Takase, M.; Otani, H.; Rabe, J. P.; Iyoda, M. Synthesis, Structures, and Photophysical Properties of π-Expanded Oligothiophene 8-mers and Their Saturn-Like C_{60} Complexes *J. J. Am. Chem. Soc.* **2015**, *137*, 3877–3885.

(35) Habata, Y.; Ikeda, M.; Yamada, S.; Takahashi, H.; Ueno, S.; Suzuki, T.; Kuwahara, S. Argentivorous Molecules: Structural Evidence for Ag^+-π Interactions in Solution. *Org. Lett.* **2012**, *14*, 4576–4579.

(36) Habata, Y.; Oyama, Y.; Ikeda, M.; Kuwahara, S. Argentivorous molecules with two kinds of aromatic side-arms: intramolecular competition between side-arms. *Dalton Trans.* **2013**, *42*, 8212–8217.

(37) Habata, Y.; Taniguchi, A.; Ikeda, M.; Hiraoka, T.; Matsuyama, N.; Otsuka, S.; Kuwahara, S. Argentivorous Molecules Bearing Two Aromatic Side-Arms: Ag^+–π and CH–π Interactions in the Solid State and in Solution. *Inorg. Chem.* **2013**, *52*, 2542–2549.

(38) Habata, Y.; Okeda, Y.; Ikeda, M.; Kuwahara, S. The water-soluble argentivorous molecule: Ag^+-π interactions in water. *Org. Biomol. Chem.* **2013**, *11*, 4265–4270.

(39) Habata, Y.; Kizaki, J.; Hosoi, Y.; Ikeda, M.; Kuwahara, S. Argentivorous molecules bearing three aromatic side arms: synthesis of triple-armed cyclens and their complexing property towards Ag^+. *Dalton Trans.* **2015**, *44*, 1170–1177.

(40) Ikeda, M.; Sah, A. K.; Iwase, M.; Murashige, R.; Kuwahara, S.; Habata, Y. Double-armed and tetra-armed cyclen-based cryptands. *Supramol. Chem.* **2017**, *29*, 370–377.

(41) Ju, H.; Tenma, H.; Iwase, M.; Lee, E.; Ikeda, M.; Kuwahara, S.; Habata, Y. Inclusion of alkyl nitriles by tetra-armed cyclens with styrylmethyl groups. *Dalton Trans.* **2020**, *49*, 3112–3119.

(42) "Argentivorous" is different from "argentophilic". "Argentophilic" is used in the sense of Ag^+–Ag^+ interactions. For example, see: Schmidbaur, H.; Schier, A. Argentophilic Interactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 746–784.

(43) Lohse, J.; Wernberg, O.; Yi-Min, H.; Bao-Yu, X.; Dou-Man, J.; Liao-Rong, C.; Bao-Sheng, L. A Convenient Route to 24-Membered Macrocycles Incorporating Two EDTA Units. *Acta Chem. Scand.* **1995**, *49*, 768–770.

(44) D'Amato, A.; Pierri, G.; Tedesco, C.; Della Sala, G.; Izzo, I.; Costabile, C.; De Riccardis, F. Reverse Turn and Loop Secondary Structures in Stereodefined Cyclic Peptoid Scaffolds. *J. Org. Chem.* **2019**, *84*, 10911–10928.

(45) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. Synthesis of Nonionic Gadolinium Chelates Useful as Contrast Agents for Magnetic Resonance Imaging. l,4,7-Tris(carboxymethyl)-10-substituted-l,4,7,10-tetraazacyclododecanes and Their Corresponding Gadolinium Chelates. *Inorg. Chem.* **1991**, *30*, 1265–1269. The synthesis of **3a** was mentioned in this paper, but no description on the characterization was reported.

(46) Gans, P.; Sabatini, A.; Vacca, A. Investigation of equilibria in solution. Determination of equilibrium constants with the HYPERQUAD suite of programs. *Talanta* **1996**, *43*, 1739–1753.

(47) *APEX2*; Bruker AXS Inc.: Madison, WI, 2008.

(48) Sheldrick, G. Crystal structure refinement with SHELXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3–8.