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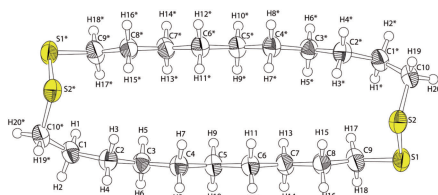
論題(和文)	
Title	Effective synthesis and crystal structure of a 24-membered cyclic decanedisulfide dimer
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出典 / Citation	Chem. Lett., Vol. 41, No. 12, p. 1678
Citation(English)	Chem. Lett., Vol. 41, No. 12, p. 1678
発行日 / Pub. date	2012, 12

Effective Synthesis and Crystal Structure of a 24-Membered Cyclic Decanedisulfide Dimer

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A 24-membered cyclic decanedisulfide dimer (1,2,13,14-tetrathiacyclotetracosane) was effectively synthesized by resin-supported cyclization of 1,10-decanedithiol. Despite the formation of a series of cyclic oligomers, no monomeric decanedisulfide resulted. The crystal structure of the dimeric macrocycle was reported.



REPRINTED FROM

**Chemistry
Letters**

Vol.41 No.12 2012 p.1678–1680

CMLTAG
December 5, 2012

The Chemical Society of Japan

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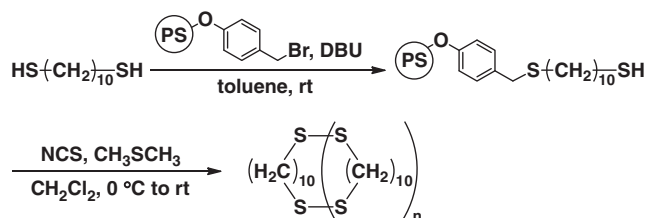
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A 24-membered cyclic decanedisulfide dimer (1,2,13,14-tetrathiacyclotetracosane) was effectively synthesized by resin-supported cyclization of 1,10-decanedithiol. Despite the formation of a series of cyclic oligomers, no monomeric decanedisulfide resulted. The crystal structure of the dimeric macrocycle was reported.

Macrocyclic molecules have recently drawn great interest due to the structural uniqueness to form noncovalently bound molecular architectures such as catenanes and rotaxanes, which show extraordinary properties unattainable by traditional covalently linked molecules.^{1–4} To construct such macrocyclic structures with a sufficient ring size, typically a 24-membered ring for threading of an oligomethylene or oligooxyethylene chain as well as dialkylammonium and bipyridinium units, appropriate end-to-end coupling of a linear molecule is essential. For this purpose, the reversible conversion of thiol to disulfide is considered suitable, and the properties of cyclic molecules with disulfide linkages have been extensively investigated.^{5–9} Moreover, rotaxane was recently constructed by “clipping” via a disulfide linkage to form a 22-membered ring.¹⁰ Therein, the optimized combination of the axle and wheel components is a crucial factor to assemble such supramolecular structures. As cyclic disulfide molecules including peptides are often prepared by solid-phase synthesis,¹¹ the dynamics to control the ring size of oligomers was studied.^{12,13} Here we report the effective synthesis of a macrocyclic decanedisulfide dimer (1,2,13,14-tetrathiacyclotetracosane) by resin-supported cyclization. Interestingly, a series of cyclic decanedisulfide oligomers formed with exception of the monomeric cycle contrasting the previous report.¹⁴ Furthermore, single crystals of the decanedisulfide dimer were successfully obtained, and the crystal structure was resolved to show a 24-membered macrocyclic molecular architecture.

Resin-supported cyclization of α,ω -alkanedithiol with various methylene chain lengths was previously reported to form monomeric cyclic alkanedisulfide of 6-, 7-, 9-, 11-, 12-, and 14-membered rings.¹⁴ This method allowed for a preferential intramolecular reaction via the pseudo-dilution effect as follows. One of the thiol groups of α,ω -alkanedithiol is first attached onto the resin. The resulting 1-alkanethiol-appended resin through a sulfide linkage is reacted with a complex of *N*-chlorosuccinimide (NCS) and dimethyl sulfide to induce cyclization by the reaction between the activated thiol group and internal sulfide linkage. In consequence, cyclic disulfide is liberated from the resin, while the unreacted linear starting material stays on the resin for easy separation. We therefore investigated the cyclization reaction in detail by using commercially available 1,10-decanedithiol with a bromo-Wang resin (Scheme 1).¹⁵ First, 1,10-decanedithiol was reacted with a



Scheme 1. Synthetic scheme of macrocyclic decanedisulfide oligomers by resin-supported cyclization.

bromo-Wang resin (0.5–1.5 mmol g^{−1} loading) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to immobilize one of the dithiol chain ends. A preformed complex of NCS and dimethyl sulfide was added to the resin to cause cyclization. The ¹H NMR spectra of the crude mixture of the cyclized products (Figure S1b)²⁷ in comparison with 1,10-decanedithiol (Figure S1a)²⁷ showed that the disappearance of a triplet signal from the thiol protons at 1.33 ppm and downfield shift of the methylene protons adjacent to the thiol groups from 2.52 (doublet of triplets) to 2.7 (triplets) ppm, indicating the formation of disulfide bonds. Size-exclusion chromatography (SEC) of the crude mixture showed a series of resolved peaks, where the peak area decreased with increasing molecular weight with a significant proportion of the smallest species, along with an unresolved broad hump at a much higher molecular weight region (Figure 1b). This indicated that the formation of smaller oligomers is favored, but the reaction was not selective for a single structure, suggesting the intermolecular disulfide exchange may also have taken place under the reaction conditions.^{16,17} The ratio of the smallest product (having turned out to be a dimer, vide infra):second smallest product (trimer):third smallest product (tetramer):fourth smallest product (pentamer):fifth smallest product (hexamer):sixth smallest product (heptamer) were 63%:20%:9%:4%:2%:1% determined by the peak areas. Polymeric species appeared as the broad hump likely formed irrelevant to the resin-supported reaction. Noteworthy, the smallest product formed had a higher peak molecular weight (*M*_p = 300 in Figure 1b), or a hydrodynamic volume, than the linear starting material (*M*_p = 260 in Figure 1a). Considering that a cyclic polymer has a smaller hydrodynamic volume than a linear counterpart,^{18,19} this result implied the absence of monomeric cyclic decanedisulfide despite a small ring strain energy (ca. 3 kcal mol^{−1}) of cyclododecane.²⁰ These suggested that the entropic effect to prefer the formation of smaller oligomers and the ring strain to circumvent the construction of the monomeric cycle are both in effect in the present reaction. Noteworthy, although the reaction conditions performed in the present study were essentially the same as those in the literature,¹⁴ in which monomeric cyclic disulfide

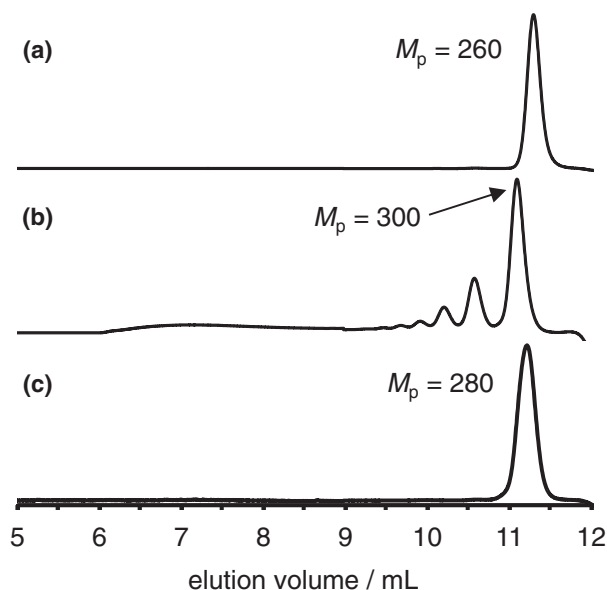


Figure 1. SEC traces of (a) 1,10-decanedithiol, (b) a crude mixture of cyclized decanedisulfide oligomers, and (c) a fractionated dimer.

molecules were reported to be selectively formed, we reproducibly obtained a mixture of oligomers.

For detailed analysis, each of the six smallest oligomers was fractionated by preparative SEC. The analytical SEC traces of these isolated oligomers showed M_p 's of 280, 510, 730, 960, 1200, and 1500 (Figure S2).²⁷ The ^1H NMR spectra showed that the chemical shifts of the signals from the methylene groups adjacent to the sulfur atoms (2.71–2.68 ppm) and those second adjacent (1.70–1.67 ppm) shifted upfield as the size of the oligomers increased (Figure S1).²⁷ Also, the peak at 1.25 ppm became relatively larger along with the ring size. The FAB mass spectra of the six smallest oligomers exactly matched calculated values for the dimer through heptamer of decanedisulfide with appropriate isotope distributions (Figure S3).²⁷ For example, the smallest oligomer had peaks at m/z 408, 409, and 410, which well-matched the calculated isotope distribution of the decanedisulfide dimer (Figure S3a).²⁷ Based on these results, the formation of the macrocyclic decanedisulfide oligomers without the presence of the monomeric form was confirmed.

X-ray diffraction studies are arguably the most important means to elaborate molecular structures, especially for nontraditional and unique structures owing to the visualization of an atomic arrangement. Among the series of the macrocyclic oligomeric products, single crystals of the decanedisulfide dimer were successfully obtained for crystal structure analysis. The dimer with high purity was dissolved in *n*-hexane, and the solution was cooled to -25°C to give single crystals with sufficient quality for X-ray diffraction, where the crystallographic studies even allowed for the determination of the positions of the hydrogen atoms. On the other hand, the trimer and larger oligomers did not show sufficient crystallinity to form single crystals likely due to the ring size.

The crystallographic data of the dimer are shown below.²¹ The space group is *Pccn* (#56) with lattice constants of $a = 8.6278(13) \text{ \AA}$, $b = 28.918(3) \text{ \AA}$, $c = 9.459(2) \text{ \AA}$, and $V =$

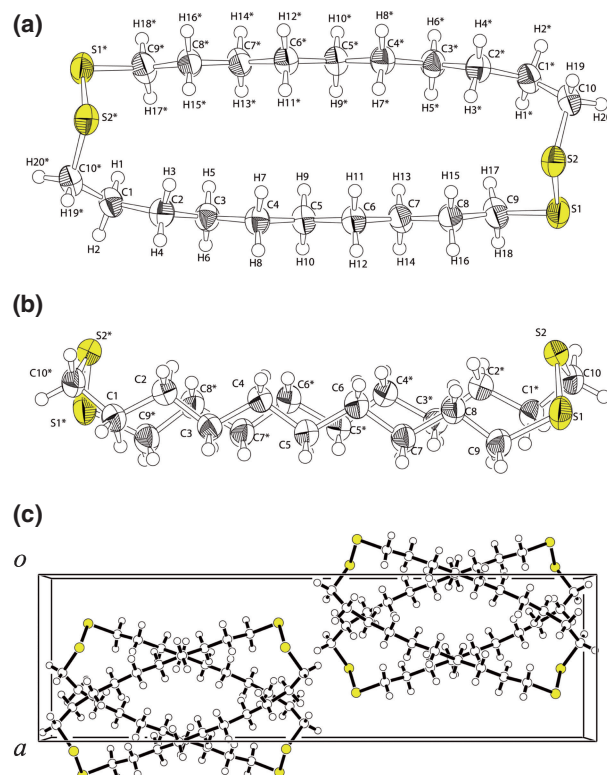


Figure 2. Crystal structure of a macrocyclic decanedisulfide dimer. ORTEP drawing and atomic numbering scheme of the (a) top and (b) side views.²² (c) Projection onto the *ab* plane.

$2360.0(7) \text{ \AA}^3$. A unit cell contains four molecules; a half of the molecule is crystallographically independent and located on a general position, and a twofold axis exists at the center of the macrocycle (Figure 2). The macrocycle is in a rectangle-like flattened form, where the structure is folded at around the disulfide bonds (Figure 2a).²² The long and short axes of the rectangular form of the macrocycle are 12.9 and 3.1 \AA , respectively. This conformation is similar to those of large cycloalkanes ($\text{C}_{24}\text{H}_{48}$,²³ $\text{C}_{26}\text{H}_{52}$,²³ and $\text{C}_{34}\text{H}_{68}$)²⁴ and uncomplexed 30-crown-10 ether,²⁵ suggesting that cyclic molecules consisting of long methylene or oxyethylene chains, which do not show any strong interactions, prefer to be packed in this manner to minimize the energy. On the other hand, the cavity of dibenzo-24-crown-8 ether, one of typical crown ethers used as the wheel component of rotaxane,^{1–4} is rather outspread by the rigid phenylene moieties.²⁶ The side view of the long axis of the present decanedisulfide macrocycle shows the zigzag conformation of the decylene chains similar to the aforementioned large cycloalkanes (Figure 2b).^{22–24} The macrocycles are stacked along the *c* axis, where adjacent macrocycles in the direction are staggered by approximately 40° (Figure 2c).

In conclusion, a cyclic decanedisulfide dimer was efficiently synthesized by resin-supported cyclization. Although a series of oligomers was produced, no formation of monomer was confirmed. The macrocyclic structure of the decanedisulfide dimer was revealed by crystal structure analysis. Since the size of a 24-membered cyclic structure is known to allow for threading, coupled with reversible disulfide bonding, the present

macrocyclic decanedisulfide dimer as well as other oligomers is expected to be a versatile component for the construction of physically entangled molecular architectures such as catenanes, rotaxanes, and knots.

We thank Ms. M. Ishikawa (Material Analysis Suzukake-dai Center, Technical Department, Tokyo Institute of Technology) for FAB mass spectrometry. The authors are grateful to Prof. M. Kakimoto and Prof. T. Hayakawa for access to measurement facilities. This work was supported by The Kurata Memorial Hitachi Science and Technology Foundation (T.Y.) and KAKENHI (Nos. 23685022 (T.Y.), 23106709 (T.Y.), and 23350050 (Y.T.)).

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- 15 The bromo-Wang resin (1.5 g) was immersed in toluene (21 mL), and the resulting suspension was stirred at ambient temperature for 1 h under nitrogen atmosphere. To the suspension of the swollen resin were added 1,10-decanedithiol (1.0 mL, 4.6 mmol) and DBU (1.0 mL, 6.7 mmol), and the mixture was stirred at ambient temperature for 64 h under nitrogen atmosphere. The decanethiol-appended Wang resin was collected by filtration, washed with CH₂Cl₂, and dried under reduced pressure. The yield was 1.6 g. Subsequently, the decanethiol-appended Wang resin (1.6 g) was immersed in CH₂Cl₂ (40 mL), and the resulting suspension was stirred at ambient temperature for 1 h under nitrogen atmosphere. Dimethyl sulfide (0.55 mL, 7.5 mmol) was added to a CH₂Cl₂ solution (35 mL) of NCS (806 mg, 6.0 mmol), and the mixture was stirred at 0 °C for 10 min under nitrogen atmosphere. The resulting suspension was added to the CH₂Cl₂ suspension of the swollen resin, and the mixture was stirred for 2 h at 0 °C and another 2 h at ambient temperature. The reaction mixture was filtered, and the filtrate was washed with water, dried over anhydrous Na₂SO₄, and evaporated to dryness under reduced pressure to give a crude mixture of macrocyclic decanedisulfide oligomers as pale brown oil (248 mg). Dimer, trimer, tetramer, pentamer, hexamer, and heptamer were separated by preparative SEC fractionation. The dimer was further purified by column chromatography (SiO₂, *n*-hexane) followed by recrystallization from *n*-hexane to yield colorless crystals (9.4 mg).
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- 21 Crystallographic data of the decanedisulfide dimer. C₂₀H₄₀S₄, *M*_r = 408.80, clear and colorless, size 0.40 × 0.36 × 0.14 mm³, orthorhombic, *Pccn* (#56), *a* = 8.6278(13) Å, *b* = 28.918(3) Å, *c* = 9.459(2) Å, *V* = 2360.0(7) Å³, *Z* = 4, *D*_{calcd} = 1.150 g cm^{−3}, *λ* (Mo Kα) = 0.71069 Å, *T* = 296 K, *μ* = 0.404 mm^{−1}. Refinement was performed using all observed reflections (3437 reflections). The final *R*₁ value is 0.0357 for 2142 [*F*² > 2.0σ(*F*²)] observed reflections. 2θ_{max} = 60°, GOF = 1.033. The crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-888603.
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- 27 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.