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Exclusive Macrocyclization through Multiple Si-O Bond Formations from Diol and Dichlorosilane

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This paper describes an exceptionally efficient macrocyclization method through multiple Si–O bond formations between diol and dichlorosilane. The square-shaped cyclic tetramer was exclusively obtained due to a hemilabile conformational lock of Ar–O–Si–O–Ar linkage. The synthetic method is significantly efficient, rapid, and feasible even under high concentration.

Macrocycles are important structural motifs in a wide range of research fields spanning from materials chemistry to biology. Owing to their distinctive molecular structure, macrocycles have found widespread applications such as chemical sensing,[1] platforms for supramolecular architectures[2] and molecular machines,[3] catalysis,[4] and drug discovery.[5] Therefore, macrocycles have been long-standing targets in synthetic chemistry, while an efficient and practical construction of a macrocyclic structure still remains a great challenge; many macrocyclizations encounter synthetic obstacles such as the need for extremely dilute reaction conditions (mM order) and low macrocyclization efficiency.[6]

A strategy of conformational lock has proved effective for facilitating macrocyclizations. An appropriate conformation locked by intramolecular interactions and/or steric effects promotes a short end-to-end distance of a specific oligomeric intermediate, that is favorable for size-selective cyclization. This strategy is often associated with successful syntheses of amide- or urea-based macorcycles.[6b,6c,7] However, design of a building block capable of the conformational lock is still limited, and most of the previous methods provide an unsatisfactory macrocyclization efficiency.

In this paper, we have achieved a highly efficient macrocyclization by using a commercially available dichlorosilane and an aromatic diol such as 1,4-dihydroxybenzene, 4,4'-dihydroxybiphenyl, and 4,4'-(ethyne-1,2-diyl)diphenol (Figure 1). The synthetic method was found to be nearly quantitative, rapid, and feasible even under dramatically high concentration (3.0 M concentration based on the monomer unit). Consequently, the macrocyclization efficiency index, defined by Emac = $\log_{10}$[yield³·concentration], reached an outstanding level.[9] Based on theoretical calculations, we proposed that a key to success of this transformation is inherent conformational preference of the Ar–O–Si–O–Ar linkage; an hemilabile conformational lock of the Ar–O–Si–O–Ar linkage weakly enforces a direction of linkers, resulting in shape-selective macrocycle formation (Figure 1, bottom).[8]

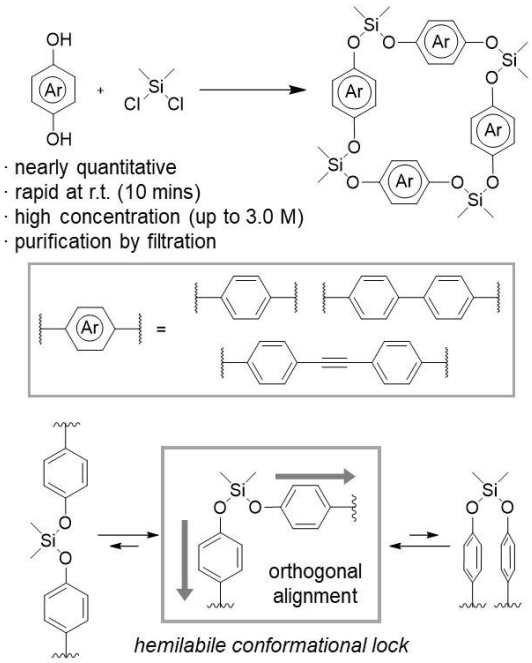

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Figure 1. The concept and molecular design for macrocyclization based on a hemilabile conformational lock.

Conformational preference of an Ar–O–Si–O–Ar unit was first evaluated by DFT calculations of a model compound, $Me_2Si(OPh)_2$. An energy landscape was calculated as a function of the torsion angles of C_{Ph}–O–Si–O′ (ϑ) and C_{Ph}′–O′–Si–O (ϑ'). Among 324 geometries calculated here, 17 conformers are classified as the most stable group with a relative energy of 0–1 kcal/mol, and 78 conformers fall within the next stable group (1–2 kcal/mol) (Figure S11). Figure 2a shows a cross section of the potential energy surface with ϑ value fixed to 60°. The most stable isomer with ϑ' of 300° is a global minimum in the calculations. This isomer adopts a nearly orthogonal conformation (86.1°) between the two phenyl groups (Figure 2b). The two dihedral angles (ϑ = 60° and ϑ' = 300°) correspond to nearly gauche-gauche conformations of the Ar–O–Si–O–Ar unit. In this isomer, one *o*-hydrogen atom of a phenoxy group is in close proximity to other oxygen atoms (H···O = 2.51 and 2.49 Å). A detailed analysis of weak intramolecular interactions by the NCI (non-covalent interaction) plot also supports the attractive CH···O hydrogen bonds (Figure 2c).[10] Although a basicity of Si–O bond is known to be weak,[8,11] we assume that the CH···O hydrogen bonds play a non-negligible role in the conformational preference. Additionally, the NCI plot suggests dispersion interactions between Si–Me groups and the aromatic rings. Overall, these results imply that the conformation of the Ar–O–Si–O–Ar unit is weakly locked to the orthogonal alignment, which is expected to contribute to selective formation of a macrocycle with the orthogonal silyl ether-based vertex.[12]

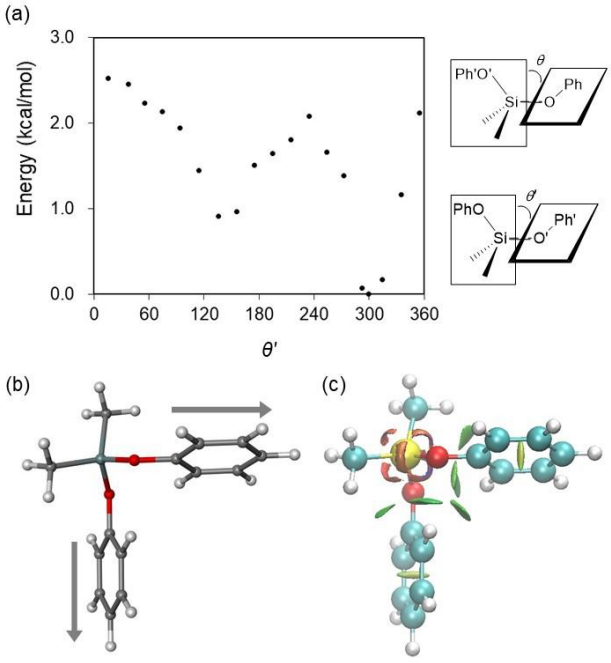
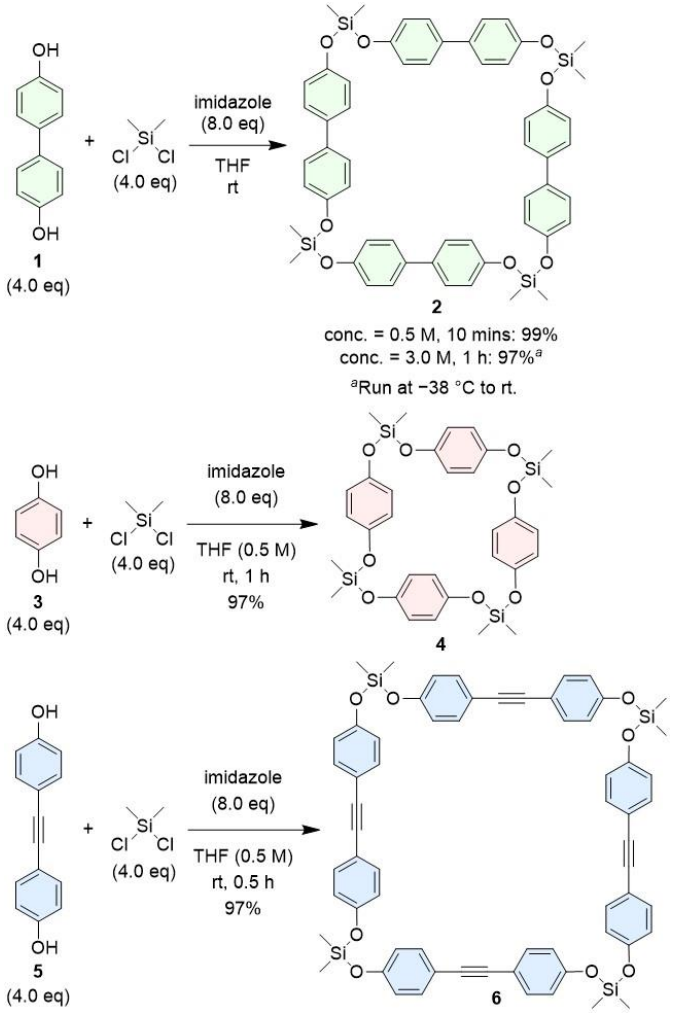


Figure 2. (a) A cross section of the potential energy surface, where a torsion angle of ϑ is fixed to 60°. Structure (b) and NCI plot (c) of the most stable isomer with ϑ' value of 300°.

Synthesis of macrocycle **2** was examined with 4,4'-dihydroxybiphenyl **1** and dichlorodimethylsilane (Scheme 1). Dichlorosilane was added dropwise to a solution of diol **1** (0.5 M) and imidazole in THF. During the addition (< 1 min), a white solid derived from imidazole hydrochloride formed, which clearly indicated the rapid progress of the Si–O bond formation. After removal of the solid by filtration and evaporation of the filtrate under vacuum, a macrocyclic compound was obtained nearly quantitatively. In ^{1}H, ^{13}C, and ^{29}Si NMR spectra of the product, a single set of aromatic and methyl signals was observed, indicating the formation of a single macrocyclic product. The selective formation was further supported by recycling preparative GPC analysis of the crude product. The macrocyclic structure was unambiguously determined by single crystal X-ray analysis to reveal that the obtained product was a macrocycle consisting of four diol and four silyl units (vide infra). Of interest, the present reaction exhibited prominent features compared with the previously reported macrocyclizations; the reaction completed within 10 mins, and surprisingly, the selective formation of **2** was observed even under high concentration (3.0 M based on the monomer unit). Thus, the ability to perform this reaction under high concentration conditions obviously highlights the unique feature of the present macrocyclization. The reaction at 3.0 M concentration gave a macrocyclization efficiency index (E_{mac} defined by $\log_{10}$[yield (%)^3·concentration (mM)]) of 9.44, which reaches an outstanding level among the previously reported macrocyclizations.[6,9] When used with hydroquinone (**3**) as aromatic linker units, macrocyclization also proceeded smoothly to afford macrocycle **4** in 97% yield (Scheme 1, middle). Moreover, this macrocyclization was found to be applied to the efficient synthesis of a larger macrocycle **6** consisting of diphenylacetylene linkers (Scheme 1, bottom). It is worth noting that a similar type of macrocyclic compounds with O–Si(*i*Pr)$_2$–O units at the vertexes have been previously synthesized via ring closing metathesis of $(i\text{Pr})_2\text{Si}(\text{OC}_6\text{H}_4\text{C}{\equiv}\text{CMe})_2$.[13] Despite the structural similarity of the product, this previous method requires dilute reaction conditions (0.0266 M), and the yield and selectivity are low (cyclic trimer: 14%, cyclic tetramer: 18%). Therefore, in addition to the structural features of the silyl ether bond, the unprecedentedly high efficiency of the present macrocyclization is attributed to the utilization of Si–O bond formation.



Scheme 1. Syntheses of macrocycles from aromatic diols and dichlorosilane.

The macrocyclic structures of **2** and **4** were determined by X-ray crystallographic analyses (Figure 3). In the crystalline state, both compounds **2** and **4** adopt a nearly square conformation, while that of **4** is slightly distorted as indicated by the varying distances between the macrocycle centroid and the center of each linker unit. These square shapes obviously reflect the orthogonal conformation expected by DFT calculations. In both macrocycles, the four silicon atoms are situated on the same plane, while the eight oxygen atoms significantly deviate from this plane, oriented either upward or downward (side views in Figure 3). In compound **2**, a completely alternate sequence of up and down conformations is observed, resulting in a C_4-symmetry axis. On the other hand, a less symmetric conformational sequence of down-down-up-down-up-up-down-up is observed in **4**. The varying up/down orientations are derived from the conformational changes of Ar–O–Si–O–Ar units. Macrocycle **2** exhibits nearly gauche conformations of Ar–O–Si–OAr, with dihedral angles of 60.5(2) or 61.2(2)° (Figure 3c). In contrast, compound **4** possesses two types of different conformations for the Ar–O–Si–OAr units; ϑ at the two diagonal corners with down/down or up/up conformations are 103.6(2) or 80.7(2)°, while the other type of conformations show the dihedral angles of 72.7(2) and 67.6(2)°. These angles correspond to intermediate values of the representative conformations shown in Figure 3c. This less symmetric structure reflects the shallow energy landscape regarding the dihedral angles ϑ and ϑ'. In the crystal packing of compound **2**, two disordered Et_2O molecules was encapsulated by an intrinsic cavity of **2** (for the detail, see the supporting information).[14] On the other hand, owing to a small cavity size, **4** encapsulates the methyl group on the neighboring macrocycles.

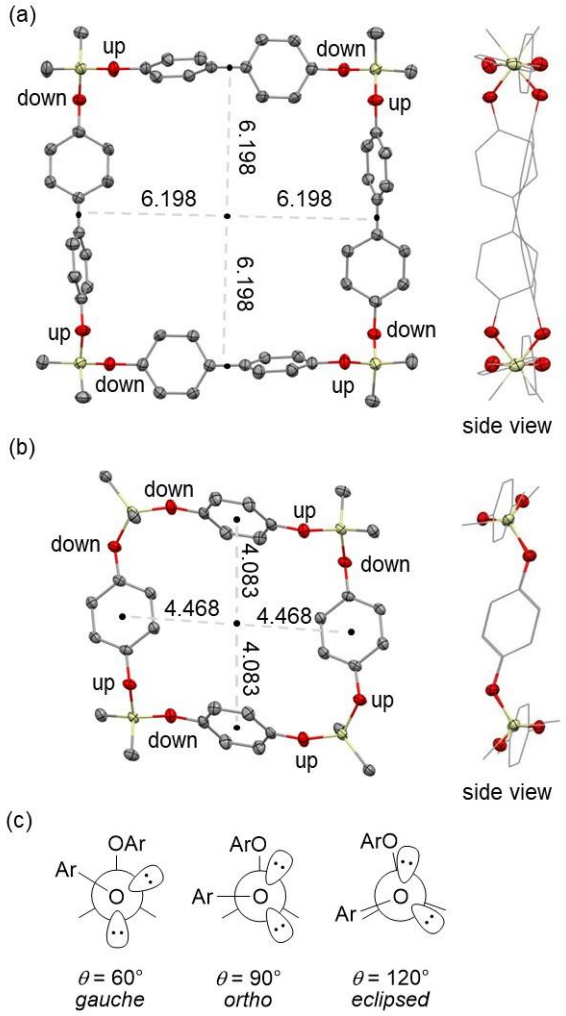


Figure 3. X-ray structures of **2** (a) and **4** (b). The solvent molecules and hydrogen atoms are omitted for clarity. Selected distances are shown in Å. (c) Conformations of Ar–O–Si–O–Ar with their notations.

We turned our attention to the exceptionally high efficiency and selectivity of the present macrocyclization. All macrocycles synthesized here are readily soluble in THF, and thus we can exclude that the high selectivity is derived from a precipitation-driven macrocyclization. Therefore, to obtain an insight into the high efficiency, several control experiments were conducted. When a reaction was performed using other solvents (dioxane and CH_2Cl_2) and bases (N-methylimidazole and NEt_3), macrocycle **2** was formed with excellent selectivity (>96%, Figure S1). Also, considering the efficient formations of different–sized macrocycles **2**, **4**, and **6** under similar conditions, template effect of solvent or base molecules can be excluded.[15]

We next examined dynamic behaviour of the Si–O bond under the macrocyclization conditions. Macrocycle **2** was treated with dibutyldichlorosilane or diol **3** at room temperature in THF for 4 h, macrocycle **2** was completely recovered in each case (Figure S2–S4). Furthermore, macrocycles **2** and **4** did not undergo Si–O bond metathesis even in the presence of imidazole hydrochloride or imidazole (Figure S5). Note that a Si–O bond formation between alcohol and chlorosilane with imidazole is known to proceed irreversibly.[16] Particularly in the present macrocyclization system, imidazole hydrochloride is completely insoluble in THF, which moreover results in inhibition of the reverse reaction of the Si–O bond formation, i.e., chlorination of Si–OR with imidazole hydro chloride. The same examinations with a model compound, $Me_2Si(OC_6H_4OMe)_2$, also resulted in complete recovery of the starting silyl ether (Figure S6–S9). Thus, the inertness toward these reactions is not derived from the macrocyclic structure. These results likely agree with the previous studies on Si–O bond metathesis and Si–OR/H–OR exchange, wherein much harsh reaction conditions are required to drive the reactions.[17] For instance, Jonson reported Si–O bond metathesis of $Et_2Si(O–allyl)_2$, in which the reaction temperature range was 60-180 °C and the reaction time required was several hours.[17f] More importantly, carboxylic acid is required as an additive to activate the Si–O bond. Therefore, although further studies are needed to obtain a conclusive insight into this high efficiency, the present system is unlikely to be governed by complete thermodynamic equilibrium via dynamic covalent bond recombination.

In conclusion, we have developed the remarkably efficient macrocyclization method via multiple Si–O bond formations. Owing to the hemilabile conformational lock of the Ar–O–Si–O–Ar units, this strategy enables the selective formation of the cyclic tetramers even under high concentrations. Moreover, the synthetic method offers notable advantages including a rapid reaction and nearly quantitative yields. Consequently, the macrocyclization efficiency reached an outstanding level. Organosilicon compounds, particularly those containing Si–O bonds, are ubiquitous and significantly important in chemical industries and material sciences. These practical advantages also offer fascinating possibilities for the development of new functional macrocycles. Further studies are currently ongoing in our laboratory with the aim of uncovering the underlying mechanisms and broadening its applicability.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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