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Cyclic Host Liquids for Facile and High-Yield Synthesis of [2]Rotaxanes

Tomoki Ogoshi,* Takamichi Aoki, Ryohei Shiga, Ryo Iizuka, Seita Ueda, Kazuki Demachi, Daiki Yamafuji, Hitoshi Kayama, and Tada-aki Yamagishi

Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan

Supporting Information

ABSTRACT: We developed "cyclic host liquids (CHLs)" as a new type of solvent. The CHLs are a nonvolatile liquid over a wide temperature range, are biocompatible and recyclable, have high thermal stability, and are miscible with many organic solvents. Compared with typical complexation systems, the CHL system is extremely efficient for maintaining host–guest complexation because an additional solvent is not required. Based on the efficient host–guest complexation in the CHL system, we demonstrated synthesis of [2]rotaxanes in pillar[5]arene-based CHL. High yields were obtained for [2]rotaxanes capped by cationization (yield 91%) and Huisgen reaction (yield 88%) between the axle and the stopper components in the CHL system, while the association constants between the axles and wheels were quite low (10–15 M^{-1}) in $CDCl_3$. The CHL system provides a new powerful approach for synthesis of mechanically interlocked molecules (MIMs) even with unfavorable statistical combinations of host–guest complexes.

Liquid media are commonly used for organic syntheses. Compared to a solid, molecules in a liquid have greater freedom of movement and can collide and react more easily with other molecules. Macrocyclic hosts, such as cyclodextrins (CDs),[1] calixarenes,[2] crown ethers,[3] cucurbiturils,[4] cyclobis(paraquat-*p*-phenylene)s (blue boxes),[5] and pillararenes,[6] have the ability to bind a variety of guests into their cavities. Using host–guest properties, position- and stereoselective organic and polymer synthesis[7] and construction of various mechanically interlocked molecules (MIMs), including rotaxanes,[1a−c,8] catenanes,[1a,9] polyrotaxanes,[1b−e] and polycatenanes[10] have been reported. However, these macrocyclic hosts are generally solids at room temperature. Therefore, the host and guest molecules have to be dissolved in a liquid to form the host–guest complexes. However, on a molecular level (Figure 1a), when solvating the host and guest, the liquid distances the guest molecules from the host. This decreases the stability of the host–guest complexes and reduces the efficiency of these chemical reactions. To overcome this problem, we developed cyclic host liquids (CHLs) by converting the host molecules from solids to liquids at room temperature by modification with triethylene oxide (TEO). The liquid CHLs can act as both host and solvent. Guest molecules will be directly surrounded by an excess of CHLs (Figure 1b). This will maintain inclusion of the guest molecule into the CHL cavity. In this study, we report the synthesis and physical properties of pillar[5]arene and CD-based CHLs, stable host–guest complexation, and facile and high-yield synthesis of [2]rotaxanes in pillar[5]arene-based CHL.

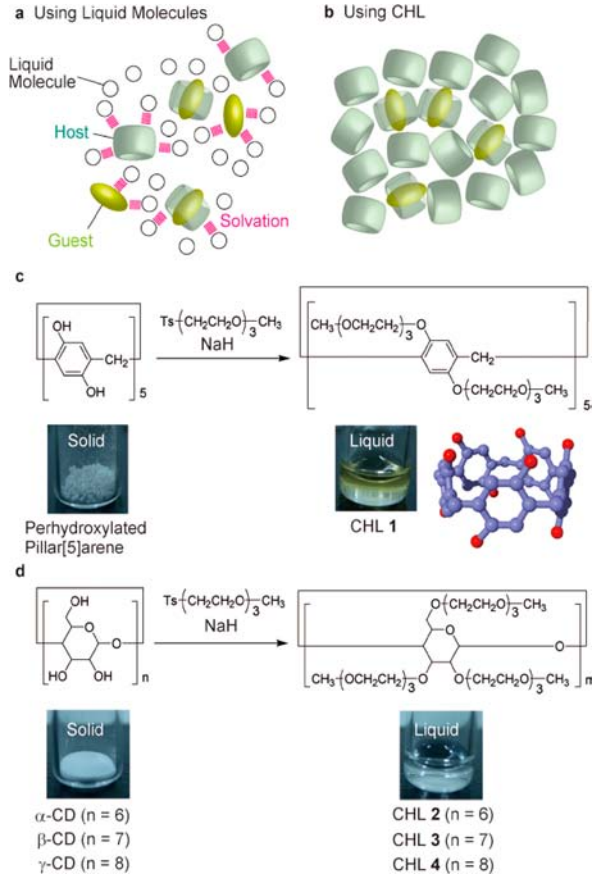

Figure 1. Concept and synthesis of CHLs. (a) Host–guest complexation using liquid molecules as solvents. (b) Host–guest complexation in CHLs. Synthesis and physical appearance of (c) pillar[5]arene-based CHL **1** and (d) CD-based CHLs **2**–**4**.

Pillar[5]arenes[6] (Figure 1c) are cyclic pentamers composed of electron-donating dialkoxybenzene units connected by methylene bridges at the para positions. Perhydroxylated pillar[5]arene has 10 reactive sites at its rims, and the presence

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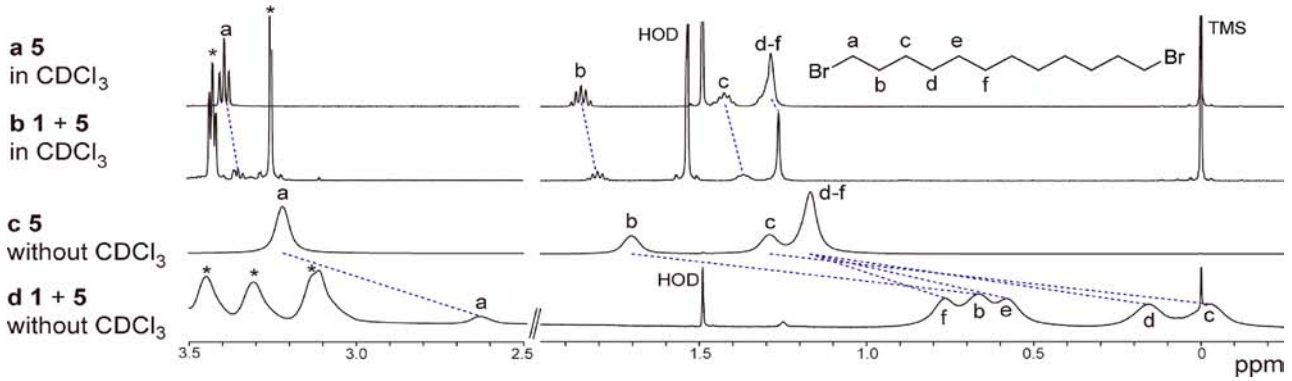

Figure 2. ^{1}H NMR spectra at 42 °C. (a) **5** (1 mM) in $CDCl_3$, (b) 1:1 mixture of **1** (1 mM) and **5** (1 mM) in $CDCl_3$, (c) **5** without $CDCl_3$, and (d) equimolar mixture of **1** and **5** without $CDCl_3$. Peaks with asterisk are proton resonances from **1**.

of functional groups at the reactive sites greatly affects its physical properties. While perhydroxylated pillar[5]arene is a solid at room temperature, we found that modification with TEO groups[6e] gave a liquid pillar[5]arene (Figure 1c, CHL **1**). Introduction of soft and flexible TEO chains would reduce the crystallinity of perhydroxylated pillar[5]arene and contributes to the liquid state. Because the TEO moiety is amphiphilic, CHL **1** was soluble in wide variety of solvents, including water, alcohols, acetone, chloroform, ethers, toluene, DMF, and DMSO and insoluble in hexane. This indicates that CHL **1** could be used as solvent for many compounds. We also synthesized TEO modified α-, β-, and γ-CDs (CHLs **2**–**4**) and found that modification converted the CDs from solids to liquids at room temperature (Figure 2d). CHLs **2**–**4** also showed similar high miscibility. Differential scanning calorimetry measurements showed that CHLs **1**–**4** were liquid even at −50 °C (Figure S9). Thermogravimetric analysis showed the compounds were stable up to 250 °C (Figure S10). These results indicate that CHLs **1**–**4** could be used as solvents for chemical reactions over a wide temperature range. The relative molecular masses of CHLs **1**–**4** were >1000, thus these compounds were nonvolatile and recyclable. Because of their high thermal stability, liquid state over a wide temperature range, and high miscibility, we used the CHLs as the solvent for complexation of guest molecules.

Pillar[5]arene derivatives formed stable host–guest complexes with protonated guests ($K > 10^4$ M^{-1}).[6f] By contrast, host–guest complexes of pillar[5]arene derivatives with linear neutral guest molecules were weak (K = 10–500 M^{-1}).[6g,h] Host–guest complexation between CHL **1** and these linear neutral guest molecules was investigated in the presence and absence of $CDCl_3$ by ^{1}H NMR (Figure 2). When 1,12-dibromododecane (**5**) was mixed with 1 equiv of CHL **1** in the presence of $CDCl_3$ (a typical complexation system using solvent), small upfield shifts of 0.0341, 0.0533, 0.0574, and 0.0232 ppm were observed for the H_a, H_b, H_c, and H_{d-f} protons of **5**, respectively, (Figure 2a,b). The small upfield shifts indicate weak complexation in $CDCl_3$. The stoichiometry of the complex determined from a Job plot was mainly 1:1 (Figure S11), and the association constant for the complex was 16.9 ± 1.0 M^{-1} (Figure S12), which is small and in the same range previously reported.[6g,h] Host–guest complexation in CHL **1** in the absence of $CDCl_3$ was investigated by ^{1}H NMR using a double NMR tube. The sample was placed in the inner tube and $CDCl_3$ in the external tube. The ^{1}H NMR spectra of **5** and an equimolar mixture of **5** and CHL **1**, both without $CDCl_3$, are shown in Figure 2c,d, respectively. When **5** was mixed with CHL **1** (Figure 2d), substantial upfield shifts of 0.585, 1.04, 1.32, 1.01, 0.588, and 0.403 ppm were observed for the H_{a-f} protons of **5**, respectively. These peak shifts were extremely large compared to those in the presence of $CDCl_3$ (Figure 2b), which indicates that the absence of $CDCl_3$ extremely enhanced the host–guest complexation. For weak host–guest complexes, such as 1,12-diazidododecane-**1** (Figures S13 and S14, K = 11.4 ± 8.1 M^{-1}) and dodecane-**1** (Figures S15 and S16, K = 16.4 ± 13.7 M^{-1}), large upfield shifts were also observed in the CHL system compared with the typical system in $CDCl_3$ (Figures S17 and S18). The CHL system is extremely efficient for maintaining host–guest complexation compared with a typical complexation system because of no addition of solvent.

Based on the efficient host–guest complexation in the CHL system, we synthesized [2]rotaxanes using CHL **1** (Figure 3).

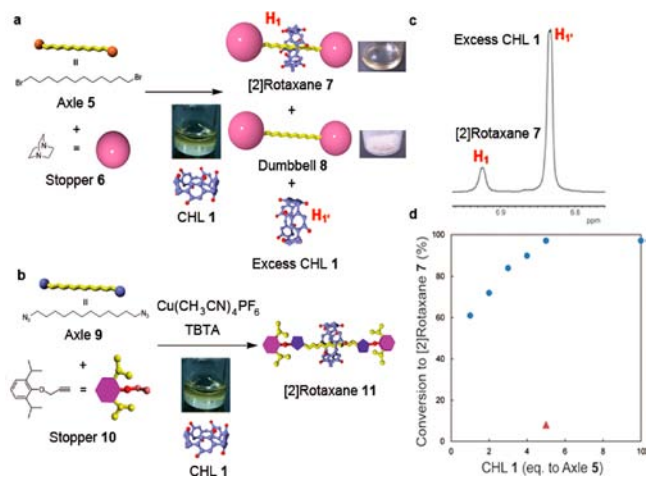

Figure 3. Synthesis of [2]rotaxanes by (a) cationization and (b) Huisgen reaction. (c) Partial ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of the mixture after the reaction of axle **5** and stopper **6** in CHL **1**. (d) Percentage conversion to [2]rotaxane **7** versus molar equivalents of CHL **1** compared to axle **5** in the CHL systems (blue circles) and in the typical solvent system (brown triangle).

Because 1,4-diazabicyclo[2.2.2]octane (**6**) is too large to fit in the cavity of **1**,[6i] it was used as a stopper (Figure 3a). The axle **5** (1 equiv) and stopper **6** (3 equiv) were dissolved CHL **1** (10 equiv), and the mixture was stirred for 24h at 25 °C. The resulting mixture was investigated by ^{1}H NMR (Figure 3c). Peaks for the phenyl protons of **1** were observed for CHL **1**

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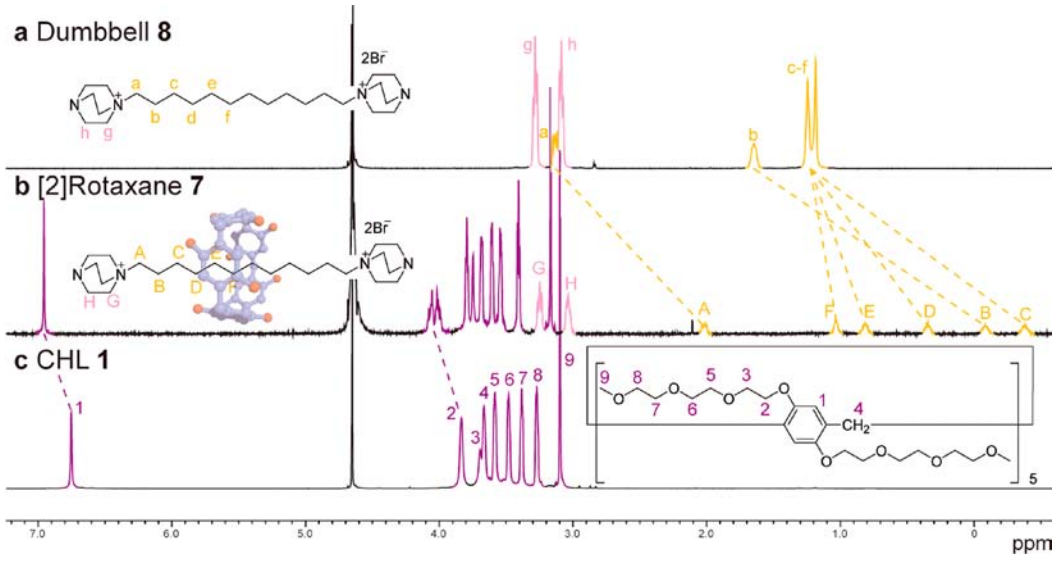

Figure 4. ^{1}H NMR spectra of (a) dumbbell **8**, (b) [2]rotaxane **7**, and (c) CHL **1** in $CDCl_3$ at 25 °C.

($H_{1'}$) and downfield for [2]rotaxane **7** (H_1). The downfield shift in this peak was caused by deshielding of the wheel segment of [2]rotaxane **7** by the guest. The ratio between these peaks was used to calculate the percentage of CHL **1** converted to [2]rotaxane **7**. The conversion was 97% (Figure 3d), which is very high. Peaks for protons in the axle molecule **5** were not detected (Figure S19), which suggests reaction between **5** and **6** reached completion to form the dumbbell-shaped molecule in the [2]rotaxane **7**. Any of this molecule that was not included in [2]rotaxane **7** was present as a free dumbbell-shaped molecule **8**. This was removed from [2]rotaxane **7** by washing with acetone because it was insoluble in acetone, while [2]rotaxane **7** was soluble. The isolated yield of [2]rotaxane **7** was 91%. The excess CHL **1** was easily removed by washing with diethyl ether and then recovered with high yield (>95%) by removing the diethyl ether under vacuum and washing with hexane. The recovered CHL **1** contained no reagents or reactants (Figure S20), thus the recovered CHL **1** could be reused. [2]Rotaxane **7** was liquid, while dumbbell **8** was solid (Figure 3a). Because the solid axle molecule was covered with the liquid wheel, the state of the axle changed. To the best of our knowledge, the liquid state of [2]rotaxane is the first example.

The effect of the amount of CHL **1** used in the reaction on the conversion to [2]rotaxane **7** was studied (Figure 3d). The conversion was 61% using 1.0 equiv of CHL **1** per equivalent of **5**. The conversion increased to 97% when the amount of CHL **1** was increased to 5 equiv. We also investigated synthesis of the [2]rotaxane **7** using $CDCl_3$ (0.3 mL) as a solvent, which is a typical complexation system using solvent and the same feed ratios as for the synthesis of the [2]rotaxane **7** in CHL **1**. The conversion was 8% even with small amount of $CDCl_3$ (Figure 3d, brown triangle). This low conversion could be attributed to the low association constant of the complexes **1**−**5** in the presence of $CDCl_3$ (K = 16.9 ± 1.0 M^{-1}). The rotaxanation in CHL **1** is far superior to that in $CDCl_3$. Axle **5** (1 equiv), stopper **6** (3 equiv), and pristine per hydroxylated pillar[5]-arene (1 equiv) were mixed in triethylene glycol (10 equiv) as a solvent and then stirred for 24h. However, the [2]rotaxane **7** was not formed, indicating that the presence of the solvent extremely decreased the conversion.

A [2]rotaxane in CHL **1** was synthesized using Huisgen 1,3-dipolar cycloaddition between a terminal alkyne and azide (Figure 3b). Axle **9** (1,12-diazidedodecane) and stopper **10** (1,3-bis(1-methylethyl)-2-(2-propyn-1-yloxy)benzene) were dissolved in CHL **1** with $[Cu(CH_3CN)_4PF_6]$ and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine. The mixture was stirred for 24 h at 25 °C. The percentage conversion to the [2]rotaxane (**11**) determined by the same method as for the [2]rotaxane **7** was 92%, which is again very high. Purification of the crude product from the reaction mixture by silica gel chromatography gave the [2]rotaxane **11** in high yield (88%). Even though the association constant of the complex between 1,12-diazidedodecane and **1** in $CDCl_3$ was weak (K = 11.4 ± 8.1 M^{-1}), the isolation yield of [2]rotaxane **11** was very high. This is because the complexation is efficiently maintained in the CHL system. Historically, rotaxanes have been synthesized by the "statistical" approach until 1981. In 1967, Harrison et al. first synthesized a [2]rotaxane by reacting the linear axle and a ring molecule attached to a solid support.[8a] However, the yield for a single reaction was limited to 0.08%, and repeating the reaction over 70 times only increased the yield to 6% because of the low association constant of the complex. In 1981, Ogino reported the first moderate yield synthesis of rotaxanes using favorable combinations of host−guest complexes with high association constants,[8b] and then extensive studies have been carried out by many scientists including the great pioneers Stoddart, Sauvage, Vögtle, and Leigh.[1a−c,8c−g] In this study, we used host−guest complexes with weak association constants in $CDCl_3$, and the rotaxane synthesis in $CDCl_3$ was unfavorable statistically (yield 8%). However, the CHL system enabled high-yield synthesis of [2]rotaxanes because of highly maintaining the host−guest complexation. This shows how the CHL system is a powerful approach for the synthesis of MIMs.

Comparison of the ^{1}H NMR spectra of [2]rotaxane **7** (Figure 4b) and dumbbell **8** (Figure 4a) was used to determine the location of the wheel segment in [2]rotaxane **7**. Upfield shifts of the proton signals from alkyl chains (yellow peaks, A−F) were observed because of aromatic shielding of **1** as the wheel in [2]rotaxane **7**. Signals from the phenyl (purple peak 1) and methylene (purple peak 2) protons of the wheel in the

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[2]rotaxane **7** showed downfield shifts because of deshielding caused by the axle. The two-dimensional NOESY study of [2]rotaxane **7** (Figure S21) showed correlations between the signals from the phenyl proton (purple peak 1) of the wheel and methylene protons (yellow peak E) of the axle and between the methylene group adjacent to the O atom of the wheel (purple peak 2) and methylene (yellow peaks D–F) of the axle. The results indicate that the wheel is located on the methylene linker. The same peak shifts and correlations were also observed in [2]rotaxane **11** (Figures S8 and S22). Proton peaks from the methylene adjacent to the O atoms (purple peak 2) were split into two groups in a 1:1 ratio by formation of the [2]rotaxane **7**. Because of the planar chirality of pillar[5]arene, the methylene protons are diastereomeric. This was also observed in pillar[5]arene-based rotaxanes[6f] and supports formation of [2]rotaxane **7**.

In conclusion, we developed CHLs as a new type of solvent. To the best of our knowledge, liquid-state macrocyclic hosts are little known, while liquid-state fullerene and π-conjugated molecules have been reported.[11] CHLs are a nonvolatile liquid over a wide temperature range, are biocompatible and recyclable, have high thermal stability, and are miscible with various organic compounds. The CHL system is excellent for maintenance of host–guest complexation. In this study, we demonstrated facile and high-yield synthesis of [2]rotaxanes in pillar[5]arene-based CHL even with unfavorable statistical combinations of host–guest complexes. We will synthesize [2]rotaxanes using CD-based CHLs **2**–**4**. The complexation in CHL is an intelligent system to maximize the concentration of host and guest species. The Huisgen reaction in CHLs will serve for various MIMs because this reaction has a high yield and is functional group tolerant and compatible with a wide range of substrates.[12] Future work will therefore focus on high-yield synthesis of MIMs using the Huisgen reaction in CHLs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section, characterization data, DSC, TGA, Job plots, ^{1}H NMR titrations, 2D NOESY NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ogoshi@t.kanazawa-u.ac.jp

Notes

The authors declare no competing financial interest.

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