Convergent Access to Macrocycles via Reversible Transacetalation

Akihiro Yokoyama, Yuuki Nonaka, Daisuke Uchida, Shuichi Hiraoka, and Tsutomu Yokozawa*
Department of Applied Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686

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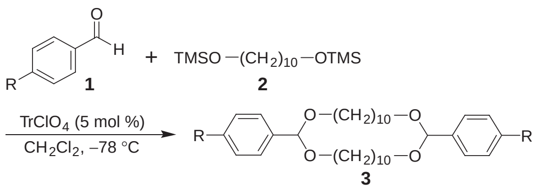
Acetalization of aromatic aldehydes **1** with bis(trimethylsilyl ether)s **2** or **4** in the presence of a Lewis-acid catalyst was investigated. Under the optimized conditions, this reaction initially gave a mixture of oligomers, which converged to a [2 + 2] macrocycle in high yield via reversible transacetalation.

Construction of molecular architecture via self-assembly generally requires reversible bond formation. When the process involves covalent bond formation, and the distribution of the products is controlled thermodynamically, it is classified as dynamic covalent chemistry.[1] Synthesis of macrocycles by means of thermodynamically controlled reactions has received increasing attention in recent years, and several kinds of reactions have been reported, such as reversible formation of ester,[2] imine,[3] disulfide,[4] hydrazone,[5] and acetal[6] linkages, and ring-closing metathesis.[7] In the course of our research on polyether synthesis using three-component polycondensation involving acetalization reaction,[8] we became interested in the synthesis of macrocycles by means of reversible transacetalation under thermodynamically controlled conditions. Recently, Stoddart et al. have reported the thermodynamically controlled formation of cyclic acetals in the reaction of a diacetonide of threitol with a diacetal compound under acidic conditions.[6a] Further, Mandolini et al. have demonstrated the acid-catalyzed transacetalation of formaldehyde acetals.[6b] In these reactions, it is necessary to use cationic templates, such as cesium[6a] or silver[6b] cation, in order to obtain single macrocycles in high yields. Here, we describe Lewis acid-catalyzed acetalization reactions between aromatic aldehydes and bis(trimethylsilyl ether)s without the use of cationic templates. The reactions initially give a mixture of oligomers, but reversible transacetalation then takes place to afford exclusively, in high yield, a [2 + 2] macrocycle, which might not be obtained via kinetically controlled reactions.

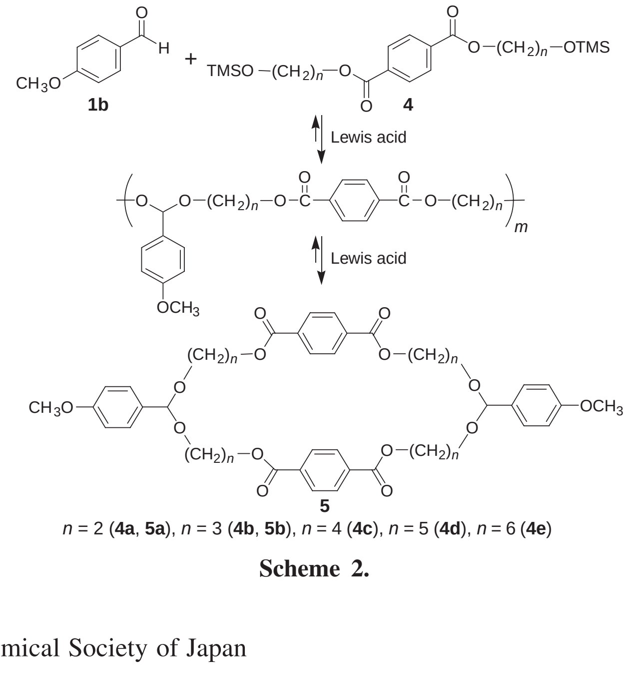
We first examined the reaction between benzaldehyde **1a** and 1,10-decanediol bis(trimethylsilyl ether) (**2**) (Scheme 1). Triphenylmethyl perchlorate ($TrClO_4$) was used as a Lewis-acid catalyst, because it has been reported to be a good catalyst for three-component polycondensation involving acetalization reaction.[9] When the reaction of **1a** with an equimolar amount of **2** was carried out in the presence of 5 mol % of $TrClO_4$ in CH_2Cl_2 ($[\mathbf{1a}]_0 = [\mathbf{2}]_0 = 0.29\,M$) at $-78\,°C$ for 12 h, a colorless solid was obtained as the product. The ^1H NMR spectrum of the product showed the presence of phenyl and decamethylene units, as well as the acetal group at the benzyl position, in equimolar amounts. Surprisingly, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra measured in the presence of silver trifluoromethanesulfonate as a cationization agent indicated that this product is not a [1 + 1] cyclic acetal, but a [2 + 2] cycle isolated yield being 74%. It is noteworthy that a 26-membered ring was easily obtained in high yield, not by a high dilution method. Benzaldehyde dimethyl acetal also reacted with **2**, but the yield of **3a** was decreased to 35%. On the other hand, *p*-anisaldehyde **1b** reacted with **2** faster than **1a** did under similar conditions, and the reaction for 5 h afforded **3b** in 77% yield. It is considered that the reaction was accelerated by the electron-donating ability of the methoxy group of **1b**, which would stabilize the carbocation intermediate formed at the carbonyl carbon of **1** in the transacetalation process. This is consistent with the result that the reaction of *p*-nitrobenzaldehyde **1c** with **2** did not give the cyclized product **3c** at all. The effect of reaction temperature was examined in the reaction of **1b** with **2** in CH_2Cl_2. When the reaction was carried out at $-20\,°C$, the yield of **3b** was decreased to 38%. Further, the reaction at room temperature did not give **3b**.



R = H (**1a**, **3a**), CH_3O (**1b**, **3b**), NO_2 (**1c**, **3c**)

Scheme 1.

We next investigated the reaction of **1b** with another bis(trimethylsilyl) ether **4a**, which contains terephthalic acid ester as a spacer between two trimethylsilyl ethers (Scheme 2). Since the terephthalic acid ester moiety would adopt a planar structure due to the conjugation between the aromatic unit and the ester linkages, we expected that the macrocycle would be formed more efficiently due to a decrease of the entropy. When the reaction of **4a** with **1b** was carried out under the optimized condi-



n = 2 (**4a**, **5a**), *n* = 3 (**4b**, **5b**), *n* = 4 (**4c**), *n* = 5 (**4d**), *n* = 6 (**4e**)

Scheme 2.

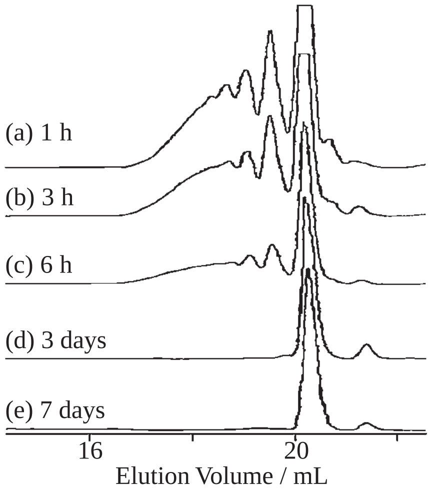


Figure 1. SEC profiles of the crude product obtained from the reaction between **1b** and **4a** in the presence of 10 mol % of TMSOTf in CH_2Cl_2/toluene (1/1, v/v) at −78 °C ($[\mathbf{1b}]_0 = [\mathbf{4a}]_0 = 0.083$ M).

tions for the acetalization between **1b** and **2** (using 5 mol % of $TrClO_4$ in CH_2Cl_2 at −78 °C), a complex mixture of oligomers was obtained. Therefore, we examined the effects of Lewis-acid catalysts and solvents, and found that the reaction with 10 mol % of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[10] in a 1/1 (v/v) mixture of CH_2Cl_2 and toluene at −78 °C gave a single product. The progress of the reaction was followed with size exclusion chromatography (SEC) using THF as the eluent. As shown in Figure 1a, SEC analysis of the reaction product at 1 h afforded a broad elution profile, indicating that the product was a complex mixture of oligomers. However, the elution profile converged with time (Figures 1b–1d), and finally, a single peak was obtained (Figure 1e). The product corresponding to the single peak was isolated by means of preparative HPLC (eluent: $CHCl_3$). Its ^{1}H and ^{13}C NMR spectra, as well as MALDI-TOF mass spectrum, revealed that the product was a [2 + 2] macrocycle **5a**. When the reaction was carried out under more diluted conditions ($[\mathbf{1b}]_0 = [\mathbf{4a}]_0 = 0.033$ M), **5a** was obtained in 71% yield. A CPK model study indicated that the cyclic structure of **5a** possesses an internal space large enough to take in one benzene ring between the two terephthalic acid ester moieties. Since terephthalic acid esters can serve as an acceptor, we speculate that toluene, which was used as the solvent along with CH_2Cl_2, might serve as a guest molecule of **5a** owing to a donor–acceptor interaction, thereby improving the efficiency of the convergent formation of **5a**.

The effect of the number of methylene units between the silyl ether moiety and the ester moiety in **4** on the transacetalation reaction was investigated by using **4b**–**4e** under the same conditions as those used for the isolation of **5a** (Scheme 2). When the reaction of **4b** ($n = 3$) with **1b** was carried out, the products converged to a single compound in 72 h (Figure 2a). Spectroscopic analyses after isolation by means of preparative HPLC revealed that the product was **5b**, and the isolated yield was 80%. The reaction of **4c** ($n = 4$) also afforded a single product (Figure 2b), but it could not be isolated due to decomposition during preparative HPLC. On the other hand, a further increase of the number of methylene units in **4** prevented the transacetalation from converging. As shown in Figures 2c and 2d, transacetalation reactions of **4d** ($n = 5$) or **4e** ($n = 6$) with **1b** gave a complex mixture of oligomers. These results might be explained in terms of a decrease in the entropy. As the number of methylene units in the bis(trimethylsilyl ether) **4** becomes larger, decrease of entropy arising from the cyclization would overcome the gain of entropy derived from the increase in the number of molecules in the reaction system. On the other hand, the reaction of **1** with **2** or **4a**–**4c** would initially proceed via the kinetically controlled process to give a mixture of oligomers, which might converge to a [2 + 2] macrocycle via thermodynamically controlled transacetalation promoted by the increase of entropy due to the increase in the number of molecules.

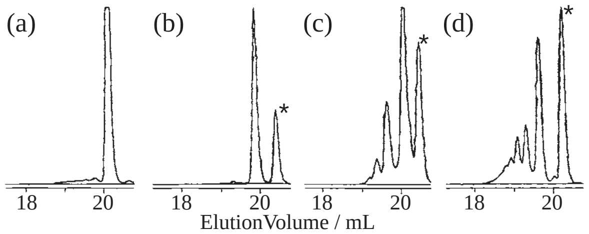


Figure 2. SEC profiles of the crude product formed in the transacetalation reaction of **1b** with (a) **4b**, (b) **4c**, (c) **4d**, or (d) **4e** in the presence of 10 mol % of TMSOTf in CH_2Cl_2/toluene (1/1, v/v) at −78 °C in 72 h ($[\mathbf{1b}]_0 = [\mathbf{4}]_0 = 0.033$ M). The peaks marked with an asterisk ($*$) correspond to the low-molecular-weight reagents.

In conclusion, the acetalization reaction of bis(trimethylsilyl ether) **2** or **4a**–**4c** with **1** affords [2 + 2] macrocycles in high yields. SEC analysis indicates that the reactions initially give a mixture of oligomers, which converges to a single product via transacetalation. Studies to construct three-dimensional compounds by means of transacetalation-based self-assembly are in progress.

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