Efficient synthesis of novel macrocyclic tetraamide compounds: a unique reaction process involving both self-assembling and folding of intermediates

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A macrocycle having two isobutenyl and four amide moieties was successfully formed *via* two kinds of acyclic intermediates. These key intermediates possess the ability to self-organize due to intra- or intermolecular hydrogen-bonding interactions. In both intermediates, preorganized structures were favorably subject to nucleophilic attack at the carbonyl group by a terminal amino group, and preorganization made it possible to form the macrocycle under mild conditions.

Much attention has recently been paid to macrocyclic compounds containing amide groups.[1] These compounds not only can act as hydrogen-bonding host molecules but also can form macrocyclic rotors, as exemplified by catenanes[2] and rotaxanes.[3] Furthermore, acyclic amide compounds are also useful for the construction of well-defined structures *via* self-organization processes by inter- or intramolecular hydrogen bonding interactions. Recently, Lehn and Meijer and their coworkers demonstrated that artificial amideoligomers, which are designed to form intramolecular hydrogen bonds, undergo self-organization to afford helical structures.[4]

We have reported the syntheses of various macrocyclic compounds having isobutenyl groups and their tandem Claisen rearrangement to macrocycles with phenolic hydroxy groups.[5] In general, it is difficult to obtain macrocyclic compounds in good yields due to the competitive formation of acyclic oligomers. To avoid the undesired reactions, several synthetic techniques such as the metal-template effect or high dilution method have been utilized.

Here, we report the efficient synthesis of the novel macrocyclic amide compound **4** *via* self-organization processes of acyclic amide intermediates, and wish to highlight some unique properties of the intermediates, which play an important role in the formation of **4** (Scheme 1).[6]

Initially, we intended to prepare macrocycle **4** by reacting equimolar amounts of di(acid chloride) **1** and *p*-phenylenediamine (PDA) in THF at room temperature. However, under these conditions, we obtained only a trace amount of **4**; the main reaction products were acyclic oligoamide compounds. Thus, we planned at first to isolate the acyclic intermediate diamine **2** as the predominant product in the reaction of **1** with excess PDA. Then, we expected isolated acyclic diamine **2** to react with an equimolar amount of **1** under high-dilution conditions to give the macrocyclic amide **4**. Unexpectedly, the one-pot reaction of **1** with excess PDA yielded macrocycle **4** as the main product. This result was surprising because we expected the acyclic compound **2**, not the macrocycle **4**, to be formed predominantly under such conditions.

To study this unusual reaction in more detail, we carried out experiments under several different conditions.[7] As shown in Table 1, the yield of macrocycle **4** was influenced by the amount of *p*-phenylenediamine in the initial reaction mixture. The yield was maximal (61%) with 4 equiv. of PDA. When less than or more than 4 equiv. of PDA was used, the yield of macrocycle was less than maximal. Additionally, the formation of macrocycle **4** was strongly influenced by the concentration of starting materials. We note two important points from these results: (1) the formation of acyclic intermediate **2** is necessary in the initial stage of the reaction and (2) the reaction is promoted by acid; when 4 equiv. of *p*-phenylenediamine are used, 2 equiv. of the unreacted *p*-phenylenediamine acts as a base in the reaction solution to form *p*-phenylenediamine hydrochloride.

To investigate whether acyclic compound **2** was a key intermediate in the reaction, we isolated **2** and dissolved it in THF. We found that **2** did not change at all after the THF solution was allowed to stir overnight at room temperature. However, as expected, when 2 equiv. of *p*-phenylenediamine hydrochloride was added as an acid source to the solution, macrocycle **4** was formed in 69% yield after 24 h at room temperature, accompanied with the elimination of PDA. These results indicate that acyclic compound **2** is a key intermediate and that intermolecular aminolysis takes place in the presence of an acid source to give **4**. Interestingly, acyclic compound **3** was also formed in the reaction of acyclic compound **2**. When isolated acyclic compound **3** was retreated with *p*-phenylenediamine hydrochloride, macrocycle **4** was also obtained (yield 70%). This means that acyclic compound **3** is also an intermediate in the next step of the reaction and undergoes intramolecular aminolysis to give macrocycle **4**. From these results, it is suggested that the formation of macrocycle **4** takes place *via* key intermediates **2** and **3** yielded by acid (Scheme 1).

Several questions remain. First, it is well known that aminolysis proceeds more smoothly in polar solvents such as DMF. However, when DMF was used as solvent, aminolysis of **2** and **3** did not proceed. Secondly, the formation of

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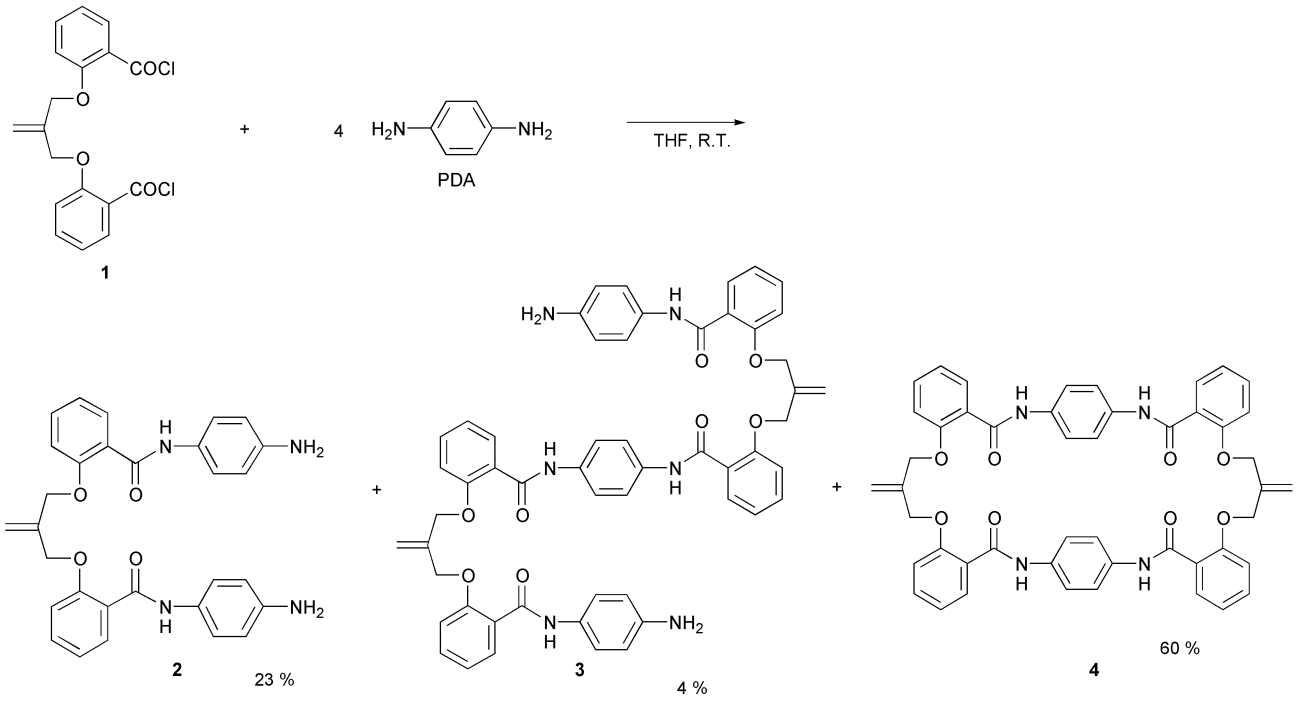
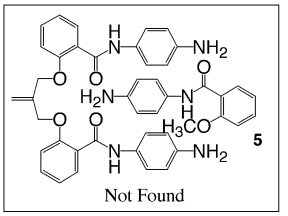


Scheme 1

Table 1 Effect of the amount of *p*-PDA on the yield of **4**

p-PDA/equiv.	Yield of **4**(%)
1.0	32
2.0	58
4.0	61
6.0	56
10.0	25



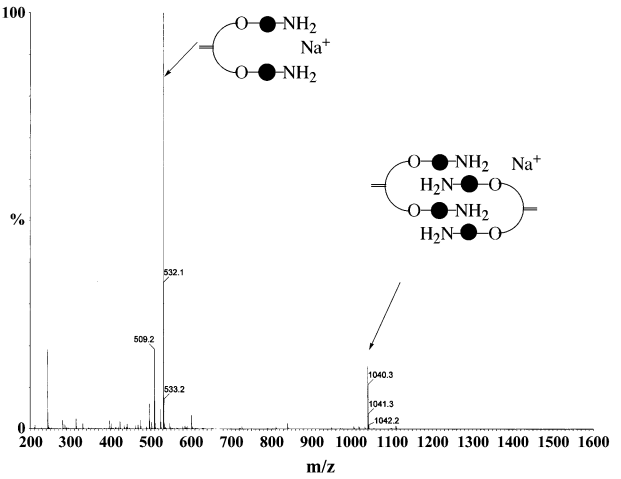


Fig. 1 ESI-mass spectrum of **2**.

macrocycle **4** was strongly influenced by the concentration of **2**. Thirdly, the reaction proceeds under mild conditions without formation of any other cyclic or linear oligomers: if an intermolecular aminolysis reaction of **3** takes place, linear oligomers should be obtained. These facts led us to wonder if self-organized structures of **2** and **3** involving hydrogen-bonding interactions might play an important role in the formation of macrocycle **4**. In addition, these intermediates have both amine and carbonyl groups, which could form hydrogen bonds under acidic conditions and interact intra- and intermolecularly with the carbonyl groups. Protonation of the terminal amine might play an important role not only in intra- or intermolecular hydrogen bonding between the amino and amide carbonyl groups but also in the activation of the amide carbonyl groups attached by an adjacent amino group.

We carried out the ESI-mass spectroscopic studies to investigate the self-assembling abilities of **2**. The result is shown in Fig. 1. The parent peak in the ESI-mass spectrum of **2** corresponds to the dimer of **2**. This result suggests that **2** self-assembles into a dimer complex through favorable intermolecular hydrogen-bonding interactions. In contrast, both for **2** + PDA and **2** + amine **5** mixtures, which can form a hydrogen bond at only one point, we observed no peak corresponding to the complex. These results indicate that hydrogen-bonding interactions at two points at least are necessary for complexation in solution.

To obtain further evidence for the intermolecular interaction of **2** and the formation of a self-assembled dimer, we measured the NOESY spectrum of **2**.[8] In THF-d_8 at 223 K, we observed cross-peaks between the amine and aromatic protons of neighboring amide groups (Fig. 2). An intramolecular interaction cannot result in such cross-peaks. This fact suggests intermolecular hydrogen-bonding interactions between the amide carbonyl and amine groups and formation of the dimer complex.

The NOESY spectrum was also helpful in investigating the structural features of acyclic compound **3**. We measured the NOESY spectrum of **3** in the presence of trifluoroacetic acid in THF-d_8 at 223 K. We observed cross-peaks between the amide protons and aromatic protons of neighboring amide groups (Fig. 3). These results indicate that intramolecular hydrogen-bonding interactions between terminal amino groups and

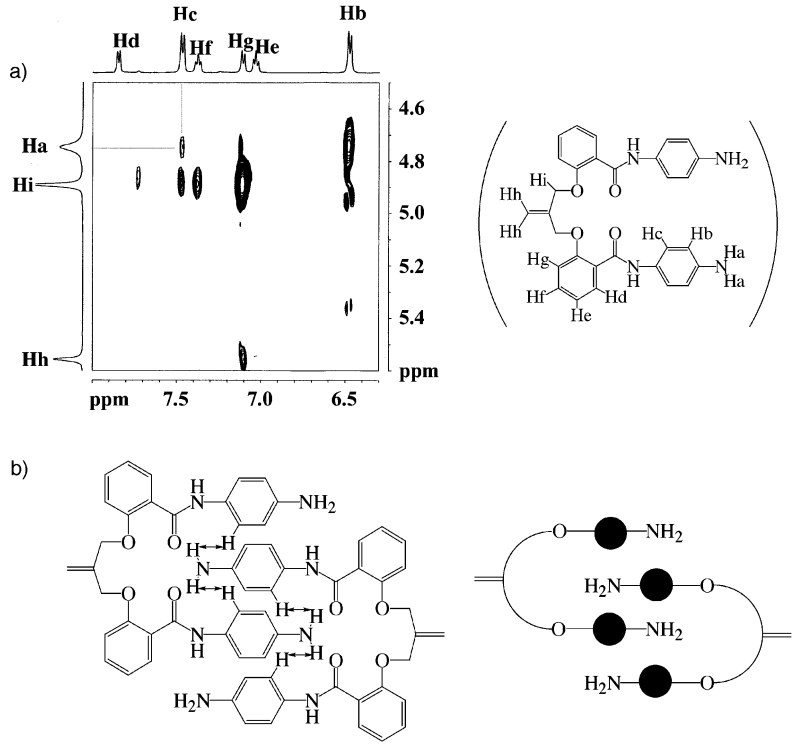


Fig. 2 (a) NOESY spectroscopic result of **2** (40 mM, 500 MHz, −50 °C, THF-d_8); (b) $H_{amine}\cdots H_{aromatic}$ interaction in **2** (shown as arrows) and schematic illustration of the self-assembled dimer of **2**.

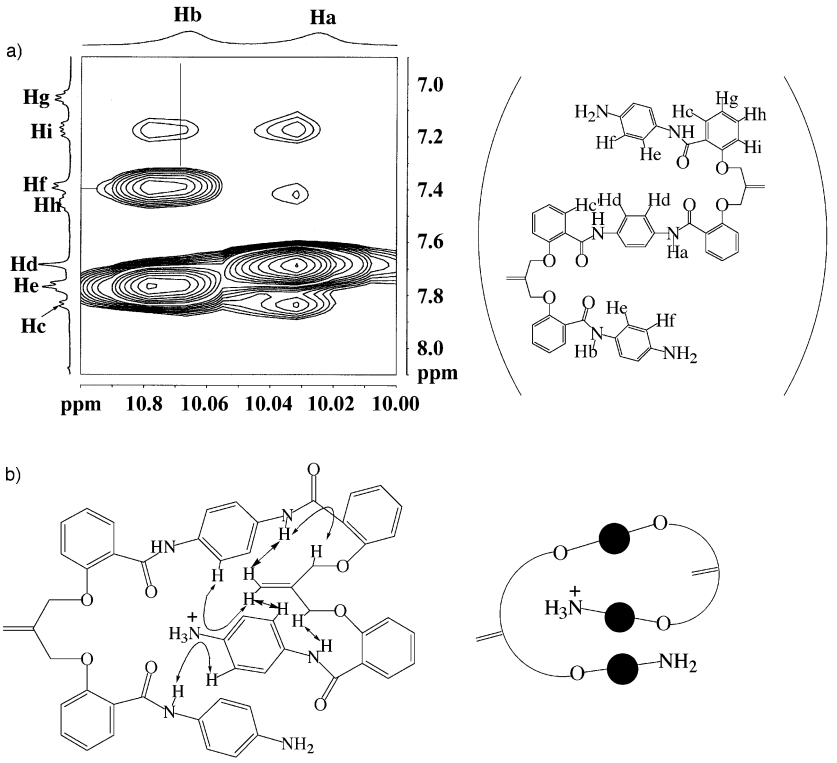
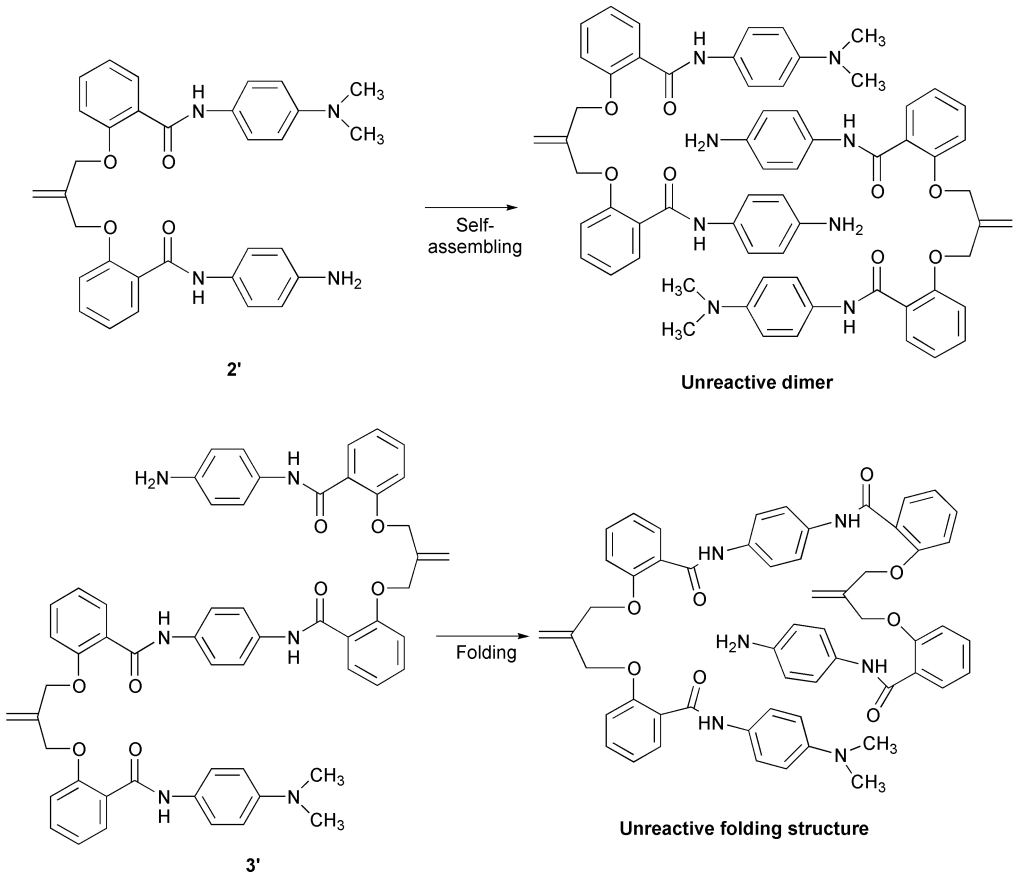


Fig. 3 (a) NOESY spectroscopic result of **3** (10 mM, in the presence of 10 mM CF_3COOH, 500 MHz, −50 °C, THF-d_8); (b) $H_{amide}\cdots H_{aromatic}$ interaction in **3** (shown as arrows) and schematic illustration of the folded structure of **3**.

amide carbonyl groups exist.[9] These interactions lead to the incorporation of the terminal amine moiety into the molecule. This results in a folded structure for **3** (Fig. 3).

From the foregoing results, it is suggested that self-assembly of **2** followed by folding to form **3** might play an important role in the formation of macrocycle **4**. In both the dimeric self-assembled structure **2** and folded structure **3**, amino groups could favorably attack the adjacent amide carbonyl carbon. Adoption of a folded structure **3** might suppress the formation of oligomers because intramolecular aminolysis in such a folded structure takes place faster than intermolecular aminolysis.



Scheme 2

Unambiguous evidence for the necessity of the dimeric self-assembled structure **2** and folded structure **3** was obtained from reactions using their analog **2′** and **3′**, each of which has one *N*,*N*-dimethyl-*p*-phenylenediamine moiety. These moieties are not able to hydrogen bond with carbonyl groups. When another amine end group (NH_2) in **2′** and **3′** utilized for hydrogen-bonding interactions, nucleophilic attack at the carbonyl carbon by the *N*,*N*-dimethylamino group would not occur. With both **2′** and **3′**, aminolysis reactions were not observed (Scheme 2). These results strongly support the presumption that the dimeric self-assembled structure **2** and folded structure **3** are indispensable for the formation of macrocycle **4**.

In this study, the formation of macrocycle **4**, containing two isobutenyl and four amide moieties, successfully proceeds *via* formation of an acyclic intermediate **2** followed by formation of **3**. These key intermediates possess the ability to self-organize due to intra- or intermolecular hydrogen-bonding interactions. After acyclic compound **2** self-assembles to form a dimer, intermolecular aminolysis occurs to afford acyclic compound **3** accompanied by elimination of *p*-phenylenediamine. In both intermediates, preorganized structures are favorably subject to nucleophilic attack on the carbonyl group by a terminal amino group, making it possible for macrocycle **4** to form under mild conditions. To examine whether this procedure is a generalized one or not, we carried out the reaction using *o*,*m*-phenylenediamine and 1,4-cyclohexyldiamine. In every case, however, macrocyclic compounds like **4** were scarcely obtained; for *o*-phenylenediamine and 1,4-cyclohexyldiamine, the 1 : 1 cyclic compound and for *m*-phenylenediamine the 1 : 2 acyclic diamine were obtained as the main product. These results indicate that the geometry of the diamines is an important factor in both stages, that is the formation of the 1 : 2 intermediate and its self-assembly process. Accordingly, the formation of macrocycles *via* unique self-organized processes is restricted to rigid and linear diamines.

We plan to apply the reaction described here to the synthesis of new macrocyclic amide compounds, catenanes and rotaxanes, and believe that unique properties of **2** and **3** are available for construction of self-assembling nanostructures.

Experimental

General procedure for the synthesis of macrocycle 4

The di(acid chloride) **1** (0.90 g, 2.5 mmol), in 10 mL of tetrahydrofuran (THF), was immediately added, with stirring, to a solution of either 0.5 g (5.0 mmol) or 1.1 g (10 mmol) of *p*-phenylenediamine in 40 mL of THF. The solution was stirred overnight at room temperature, during which time a white precipitate accumulated. After 12 h, the precipitate was filtered off. THF was separated from the filtrate and water was added to the residue to give a solid. The solid was combined with the precipitate, the mixture was washed first with water and then with a small amount of THF. The macrocycle **4** was obtained in 60% yield and was recrystallized from DMF and $CHCl_3$. Intermediates **2** and **3** were obtained as by-products and purified by using preparative gel permeation chromatography (GPC) ($CHCl_3$ as eluent).

Intermediate analogs 2′ and 3′

A solution of the di(acid chloride) **1** (0.19 g, 0.52 mmol) and an equimolar amount of *N*,*N*-dimethyl-1,4-phenylenediamine (0.071 g, 0.52 mmol) was stirred for 1 h in THF at room temperature. To the resulting solution, an equimolar amount of *p*-phenylenediamine (0.056 g, 0.52 mmol) was added and the

mixture stirred for 2 h. After removal of THF, the residue was washed with water and purified by GPC to afford **2′** (30%). Using **2** instead of *p*-phenylenediamine, **3′** was obtained in 20% yield.

2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.77 (s, Ar–O–CH_2–), 4.89 (br, Ar–NH_2), 5.39 [s, –C(=CH_2)–], 6.49 (d, CONH–*Ar*–NH_2), 7.02–7.07 (m, –O–*Ar*–CONH–), 7.33 (d, CONH–*Ar*–NH_2), 7.35–7.38 (m, –O–*Ar*–CONH–), 7.54–7.56 (m, –O–*Ar*–CONH–), 9.77 (s, Ar–CON*H*–Ar–NH_2). ESI-MS: m/z 532 ($M + Na^+$) (calcd $M + Na^+$ 509 + 23).

2′. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.85 (s, Ar–NCH_3), 4.77 (s, Ar–O–CH_2–), 4.92 (br, Ar–NH_2), 5.40 [s, –C(=CH_2)–], 6.50 (d, CONH–*Ar*–NH_2), 6.66 (d, CONH–*Ar*– NCH_3), 7.02–7.08 (m, –O–*Ar*–CONH–), 7.34 (d, CONH–*Ar*–NH_2), 7.37–7.40 (m, –O–*Ar*–CONH–), 7.50 (d, CONH–*Ar*–NCH_3), 7.55–7.58 (m, –O–*Ar*–CONH–), 9.77 (s, Ar–CON*H*–Ar–NH_2), 9.88 (s, Ar–CON*H*–Ar– NCH_3). ESI-MS: m/z 538 ($M + H^+$) (calcd $M + H^+$ 537 + 1).

3. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.76 (s, Ar–O–CH_2–), 4.78 (s, Ar–O–CH_2–), 5.08 (br, Ar–NH_2), 5.38 [s, –C(=CH_2)–], 6.52 (d, CONH–*Ar*–NH_2), 7.00–7.08 (m, –O–*Ar*–CONH–), 7.35 (d, CONH–*Ar*–NH_2), 7.38–7.41 (m, –O–*Ar*–CONH–), 7.53–7.57 (m, –O–*Ar*–CONH–), 7.64 (s, –CONH–*Ar*–CONH–), 9.78 (s, –O–Ar–CON*H*–Ar–NH_2), 10.16 (s, –O–Ar–CON*H*–Ar–CON*H*–Ar–O–). ESI-MS: m/z 931 ($M + Na^+$) (calcd $M + Na^+$ 909 + 23).

3′. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.85 (s, Ar–NCH_3), 4.83 (br, Ar–O–CH_2–), 545 [s, –C(=CH_2)–], 6.55 (d, CONH–*Ar*–NH_2), 6.72 (d, CONH–*Ar*–NCH_3), 7.09–7.12 (m, –O–*Ar*–CONH–), 7.40 (d, CONH–*Ar*–NH_2), 7.42–7.44 (m, –O–*Ar*–CONH–), 7.56 (d, CONH–*Ar*–NCH_3), 7.59–7.62 (m, –O–*Ar*–CONH–), 7.69 (s, –CONH–*Ar*–CONH–), 9.83 (s, –O–Ar–CON*H*–Ar–NH_2), 9.94 (s, –O–Ar–CON*H*–Ar–NCH_3), 10.22 (s, –O–Ar–CON*H*–Ar–CON*H*–Ar–O–). ESI-MS: m/z 960 ($M + Na^+$) (calcd $M + Na^+$ 937 + 23).

4. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.76 (s, Ar–O–CH_2–), 5.37 [s, –C(=CH_2)–], 7.01–7.04 (m, –O–*Ar*–CONH–), 7.21 (d, –O–*Ar*–CONH–), 7.33 (t, –O–*Ar*–CONH–), 7.64 (s, –CONH–*Ar*–CONH–), 10.15 (s, –O–Ar–CON*H*–Ar–CON*H*–Ar–O–). ESI-MS: m/z 824 ($M + Na^+$) (calcd $M + Na^+$ 801 + 23).

NOESY experimental conditions

^{1}H NMR spectral data were obtained on a Bruker AVANCE-500 spectrometer at 500.13 MHz. The 2D nuclear Overhauser effect spectroscopy (NOESY) were measured in the phase-sensitive mode. Spectra were obtained using a sweep width of 6000 Hz and 256 complex $t1$ values. A total of 1024 data points were collected along the $t2$ axis and the mixing time was 500 ms. The time-domain data matrix was expanded by zero filling to 1024 data points.

Notes and references

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6 Recently, we reported similar reactions involving self-assembly of intermediates as a key step: (*a*) H. Houjou, S.-K. Lee, Y. Hishikawa, Y. Nagawa and K. Hiratani, *Chem. Commun.*, 2000, 2197–2198; (*b*) H. Houjou, Y. Nagawa and K. Hiratani, *Tetrahedron Lett.*, 2001, **42**, 3861–3863.

7 We carried out the reaction in $CHCl_3$, CH_3CN, THF, and DMF. The highest macrocycle yield was obtained when we used THF solvent.

8 We expected that the addition of acid as trifluoroacetic acid would promote the formation of the dimer of **2**. Under such conditions, however, we could not observe cross-peaks between the amine and aromatic protons because of the broadening of the amine proton peaks.

9 The large downfield shifts were observed for both amide protons H_a and H_b with decreasing temperature. These results suggest that intramolecular hydrogen bonding interactions between amide protons and ether oxygen atoms also would exist.