Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3181–3184
Tetrahedron Letters

Synergistic effects of a specific metal template and H-bonds in controlling macrocyclization: a simple, selective, and effective cyclization from *N*,*N*-bis(2-hydroxybenzyl)alkylamine derivatives

Suwabun Chirachanchai *, Suttinun Phongtamrug, Thitiporn Rungsimanon

The Petroleum and Petrochemical College, Chulalongkorn University, Bangkok 10330, Thailand

Received 15 August 2007; revised 20 February 2008; accepted 28 February 2008
Available online 2 March 2008

Abstract

A macrocyclic compound obtained from a simple, selective, and effective reaction between *N*,*N*-bis(2-hydroxybenzyl)alkylamine derivatives and 1,3-bis(tosyloxy)propane is a good example of a cyclization controlled by synergistic effects of a metal template and hydrogen bonds.

Keywords: Macrocyclic compound; Metal template; Hydrogen bond; Azacrown ether

As macrocyclization is a random reaction between two backbone molecules, a dilute system[1,2] is the basic requirement to initiate the reaction between these two different molecules. In general, following reaction, purification such as column chromatography, extraction, or recrystallization is needed and this lowers the yield. Alignment of the molecules using a metal template is a good approach for selective cyclization,[1–4] however, in most cases, the yield is limited to about 30–40%. When the backbone molecules are in a H-bond network, the non-template macrocyclic synthesis via condensation, conjugation, and coupling reactions is also an effective pathway.[5] Therefore, it should be ideal if we could design the reaction in which both a metal template and H-bonds synergistically function in macrocyclization. Herein, we demonstrate a model in which the macrocyclization can be initiated by not only the effects of a specific metal template but also a H-bond network. As a result, a single step reaction between *N*,*N*-bis(2-hydroxybenzyl)alkylamine and 1,3-bis(tosyloxy)propane to produce a dibenzomonoazacrown ether in high yield without multi-step purification suggests the synergistic effects of the metal template and the hydrogen bonds in controlling the macrocyclization.

The simple reaction conditions produce the macrocyclic compounds in high yield without the use of a catalyst and multi-step purifications.

N,*N*-Bis(2-hydroxybenzyl)alkylamines are good model compounds as they possess both inter- and intramolecular hydrogen bonds in a dimeric system as clarified in our previous work (Fig. 1).[6] Considering the reaction between *N*,*N*-bis(2-hydroxybenzyl)alkylamines and 1,3-bis(tosyloxy)propane,[7] one may recognize the feasible possibilities of linear polymerization and macrocyclization, either [1+1] and/or [2+2], as shown in Scheme 1.

To answer the question of which compound in Scheme 1 was obtained, the structural characterizations were carried out as follows.[8] From FTIR, compound **1** gave absorptions at 3240 cm^{-1} (intermolecular H-bonds), 3200–2600 cm^{-1} (intramolecular H-bonds), 1612 cm^{-1} (trisubstituted benzene), 1350 cm^{-1} (C–N–C stretching), and 1242 cm^{-1}

* Corresponding author. Tel.: +66 2218 4134; fax: +66 2215 4459.
E-mail address: csuwabun@chula.ac.th (S. Chirachanchai).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.153

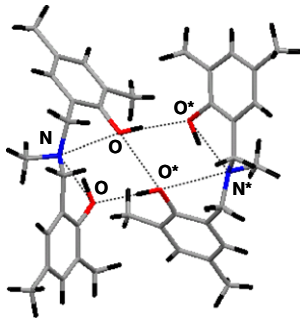
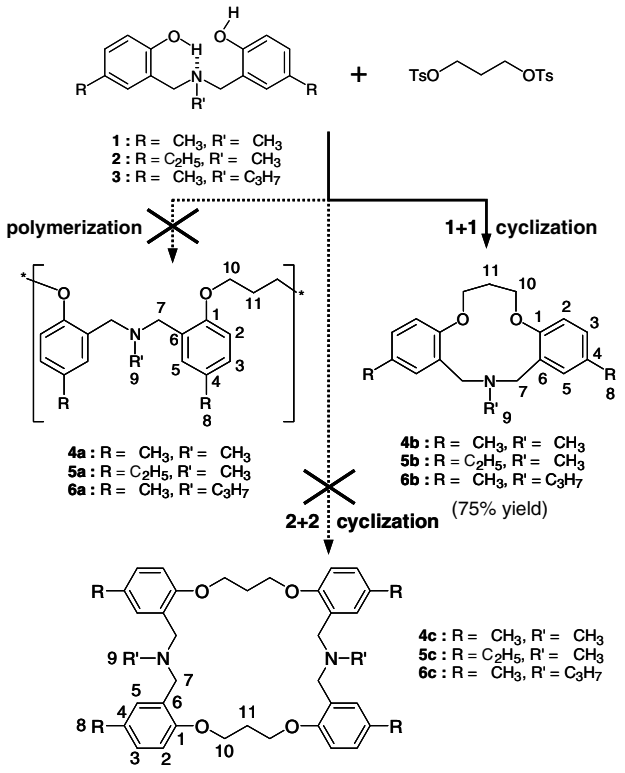


Fig. 1. Crystal structure of **1**.

(C–N stretching). After reaction with 1,3-bis(tosyloxy)propane, a new peak at 1065 cm^{-1} due to Ar-O–CH_2 stretching was observed while the broad OH peak disappeared implying successful etherification. Peak shifts, especially the 1350 to 1327 cm^{-1} and 1242 to 1250 cm^{-1} shifts, referring to the changes in the vibrational modes of C–N–C and C–N stretching were also observed. The results implied that the cyclization of **1** might result in **4a**, **4b**, or **4c** as detailed in Scheme 1. The ^1H NMR spectrum of **4** exhibits the protons at positions 2, 3, 5, 7, 8, and 9 (as indicated in Scheme 1) and those of the propyl chain (positions 10 and 11). In addition, ^1H–^{13}C HMBC indicated a significant interaction between C1 and H10. The ^1H–^1H NOESY spectrum demonstrated the strong interaction of H7 with H10 and H11.[9] Taking these results into consideration, the most probable mode of cyclization was [1+1].



Scheme 1. Feasible products of the reaction of *N*,*N*-bis(2-hydroxybenzyl)alkylamines and 1,3-bis(tosyloxy)propane.

The matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) revealed a single peak at $m/z = 312.6$ which corresponds to the [1+1] adduct **4b**.

Further analysis was performed by recrystallizing the compound from methanol, and colorless cubic crystals were obtained. Single crystal analysis using a Rigaku RAXIS-RAPID imaging plate with TEXSAN software was carried out. The orthorhombic space group *Pnma* with the R_1 value of 4.7% clearly indicated that the product from the reaction of **1** with 1,3-bis(tosyloxy)propane was **4b** with a [1+1] symmetrical structure.[10] Figure 2 shows an ORTEP view representing the 12-membered macrocycle **4b**. As there might be a possibility of mixtures of [1+1] and [2+2] macrocycles, we repeated the single crystal X-ray analysis using various crystals and found that all of the crystals had the structure of **4b** without any by-products (**4a** and **4c**).

Acetonitrile was the solvent of choice leading to the formation of **4b** in good yield compared to other solvents such as methanol, dioxane, and toluene. This implies that acetonitrile might maintain the H-bonded dimeric system as in the crystal state to favor selective macrocyclization. It is possible that **1** forms a H-bonded monomeric system in acetonitrile and this also favors the same macrocyclization. Apart from the role of the H-bond, the use of KOH as base was also important. We found that the reaction with other bases such as NaOH and triethylamine hardly gave any of product **4** (either **4a**, **4b**, or **4c**). This suggested that only K^+ functions as a specific metal template.

From the above, the mechanism for the macrocyclization can be explained as follows: (i) weakening of the intermolecular hydrogen bond of the dimeric system of **1** by K^+ resulting in a phenoxide ion at a single phenol group (the other phenol group maintains its intramolecular hydrogen bond with the aza-methylene unit in acetonitrile), (ii) nucleophilic substitution of a single tosyl group from the ditosylated compound at the phenoxide position, and (iii) nucleophilic addition between the terminal tosylated group and the other phenol group resulting in controlled macrocyclization. In the case of 2,2′-dihydroxydiphenylamine with no H-bond network, the nucleophilic addition of the ditosylated compound might occur randomly on the two phenoxide groups and lead to various by-products and a low yield.

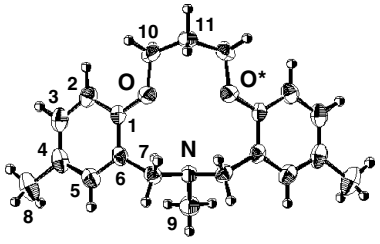


Fig. 2. ORTEP view of **4b**.

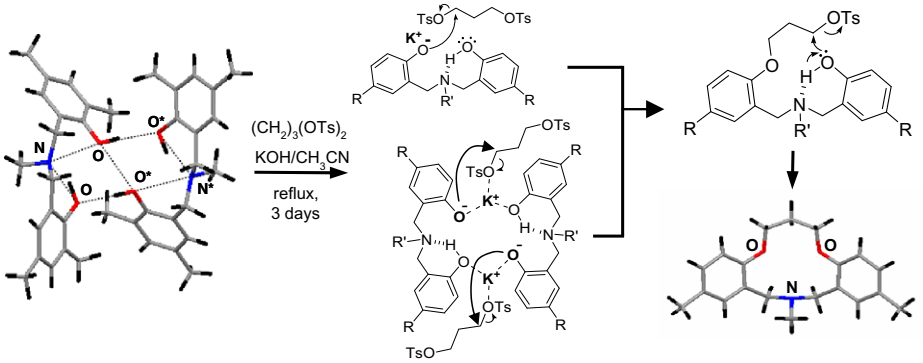


Fig. 3. Proposed mechanism of the formation of **4b**.

A series of *N*,*N*-bis(2-hydroxybenzyl)alkylamine derivatives, that is, *N*,*N*-bis(2-hydroxy-5-ethylbenzyl)methylamine, **2**, and *N*,*N*-bis(2-hydroxy-5-methylbenzyl)propylamine, **3**, were reacted under similar conditions to give compounds **5b**[11] and **6b**[12] in yields above 75% without any complicated purification. It should be noted that the remaining 25% might be the remaining dimeric species. For example, in the case of **1**, the crude product showed two spots on the TLC with $R_f = 0.24$ and 0.08 (5% CH_3OH in $CHCl_3$), referring to **1** and **4b**.

By comparing our results with those reported by Agai et al.[13] and Owston and coworkers,[14] we were able to confirm that our mechanism proceeds under synergistic effects involving a metal template and H-bond network. Agai et al. reported that the cyclization between 2,2′-dihydroxydiphenylamine and dichlorooxaalkane derivatives was achieved via a multi-step reaction using an alkylating agent, K_2CO_3, and KI to yield 7–40% of the desired products after column chromatography. They proposed a coordinate intermediate between K^+ and the bisphenol backbone molecules in forming the monoaza-12-crown-4. Owston et al. showed that the 'N_4' macrocyclic imine compounds were obtained from condensation involving the favorable intramolecular hydrogen bond between a dialdehyde and diamine derivatives. Taking all the above into consideration, the fact that (i) **1**–**3** possess dimeric H-bond network structures and (ii) the cyclization between **1**–**3** and a bistosyloxyalkane derivative selectively gives a [1+1] macrocycle with >75% yield without by-product formation only when we used KOH, leads us to conclude that the reaction proceeds under the synergistic effects of H-bonds and a metal template. The question might arise whether **1**–**3** in solution are in hydrogen-bond networks. The fact that the ESI-MS of, for example, **2** showed a spectrum with peaks (M+H) at m/z ~300, 600, and 899 referring to an assembly structure of two and three molecules leads us to suspect that **1**–**3** are not only in monomeric form but also in an assembly network of hydrogen bonds in solution.[15] This supports our speculation as mentioned in (i) above. To confirm the potassium-specific effects, reactions using other hydroxide bases are in progress.

We conclude that we can obtain a single type of macrocycle in high yield when only the backbone macromolecule is favored by a H-bond network, whereas the metal ion is involved specifically in coordination or initiates charge formation on the molecules to induce the macrocyclization. These synergistic effects allow us to prepare simple macrocyclic compounds. The proposed mechanism, either from monomers or dimers of **1**–**3**, to obtain [1+1] macrocycle is shown in Figure 3.

Acknowledgements

This work was financially supported by the Thailand Research Fund (Royal Golden Jubilee Ph.D. Program, Grant No. PHD/0068/2548 and Research Scholar Award, Grant No. RSA4680025). The acknowledgement is extended to Professor Mikiji Miyata (Osaka University, Japan) for his help in single crystal X-ray analysis and Professor Kohji Tashiro (Toyota Technological Institute, Japan) for valuable discussions.

References and notes

1. Dietrich, B. In *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: New York, 2004; Vol. 1, pp 830–844.
2. Dietrich, B.; Viout, P.; Lehn, J.-M. In *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH: New York, 1992; pp 65–71.
3. Reinholdt, D. N.; Gray, R. T.; Smit, C. J.; Veenstra, Ms. I. *Tetrahedron* **1976**, *32*, 1161.
4. Busch, D. H. *J. Inclus. Phenom. Macrocycl. Chem.* **1992**, *12*, 389.
5. Xing, L.; Ziener, U.; Sutherland, T. C.; Cuccia, L. A. *Chem. Commun.* **2005**, 5751.
6. Laobuthee, A.; Chirachanchai, S.; Ishida, H.; Tashiro, K. *J. Am. Chem. Soc.* **2001**, *123*, 9947.
7. *N*,*N*-Bis(2-hydroxy-5-methylbenzyl)methylamine,[15] **1** (0.27 g, 1 mmol) was refluxed in acetonitrile (150 mL) with potassium hydroxide (0.11 g, 2 mmol) for 1 h. A solution of 1,3-bis(tosyloxy)propane (0.38 g, 1 mmol) in acetonitrile (70 mL) was added dropwise and the reaction refluxed for 3 days before removing the solvent. The crude product was dissolved in dichloromethane and washed several times with water, before drying over anhydrous sodium sulfate. The solvent was removed to obtain a white solid product in 75% yield.
8. The characterization for **4b**: $C_{20}H_{25}NO_2$: 75% yield; mp = 203 °C; FTIR (KBr, cm^{-1}): 1504 (vs, trisubstituted benzene), 1327 (vs, C–N–C stretching), 1250 (vs, C–N stretching), 1065 (s, Ar-O–CH_2); ^1H NMR (600 MHz, $CDCl_3$): δ 2.13 (s, 3H, N–CH_3), 2.21 (q, 2H,

C–CH_2–C, $J_1 = 4.86$ Hz), 2.25 (s, 6H, Ar-CH_3), 3.61 (s, 4H, N–CH_2-Ar), 4.20 (t, 4H, CH_2–O, $J_2 = 5.02$ Hz), 6.73 (d, 2H, Ar-H, $J_3 = 7.90$ Hz), 6.97 (s, 2H, Ar-H), 6.98 (d, 2H, Ar-H, $J_4 = 8.56$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.4, 28.5, 40.9, 58.2, 67.7, 111.6, 128.1, 128.3, 128.8, 131.9, 155.5; MALDI-TOF MS: m/z 312.6 ($M+H^+$); Anal. Calcd for $C_{20}H_{25}O_2N$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.38; H, 7.69; N, 4.46.

9. ^1H–^{13}C HMBC for **4** (150 MHz, $CDCl_3$); H2:C1,C3,C4,C5,C6; H3:C1,C2,C4,C5,C6; H5:C1,C2,C3,C4,C6; H7:C1,C5,C6,C9; H8:C1,C2,C3,C4,C5,C6; H9:C7; H10:C1,C11; H11:C10. ^1H–^1H NOESY; H2:H3,H10; H3:H2,H8; H5:H7,H8,H9; H7:H5,H9,H10; H8:H3,H5; H9:H5,H7; H10:H2,H7,H11; H11:H10.
10. Crystal data for **4b**: $C_{10}H_{12.5}N_{0.5}O$, $M = 155.71$, orthorhombic, $a = 9.3556(7)$, $b = 15.341(1)$, $c = 11.8139(8)$ Å, $V = 1695.6(4)$ Å^3, $T = 296$ K, space group *Pnma* (no. 62), $Z = 8$, μ(Mo Kα) = 0.78 cm^{-1}, 12579 reflections measured, 1616 unique ($R_{int} = 0.032$) which were used in all calculations. The final $R_1 = 0.047$ and $Rw = 0.121$. X-ray data for compound **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258583. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033. e-mail: deposit@ccdc.cam.ac.uk).
11. The characterization for **5b**: $C_{22}H_{29}NO_2$: 75% yield; FTIR (KBr, cm^{-1}): 1503 (vs, trisubstituted benzene), 1248 (vs, C–N stretching), 1057 (s, Ar-O–CH_2); ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (6H, t, Ar-C–CH_3, $J_1 = 7.62$ Hz), 2.06 (3H, s, N–CH_3), 2.17 (2H, q, C–CH_2–C, $J_2 = 4.83$ Hz), 2.48 (4H, q, Ar-CH_2–C, $J_3 = 7.62$ Hz), 3.57 (s, 4H, N–CH_2-Ar), 4.14 (t, 4H, CH_2-O, $J_4 = 4.98$ Hz), 6.67 (d, 2H, Ar-H, $J_5 = 8.20$ Hz), 6.91 (s, 2H, Ar-H), 6.93 (d, 2H, Ar-H, $J_6 = 8.20$ Hz); MALDI-TOF MS: m/z 338.85.
12. The characterization for **6b**: $C_{22}H_{29}NO_2$: 75% yield; FTIR (KBr, cm^{-1}): 1505 (vs, trisubstituted benzene), 1253 (vs, C–N stretching), 1054 (s, Ar-O–CH_2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, CH_3–C–C–N, $J_1 = 7.32$ Hz), 1.44 (2H, m, C–CH_2–C–N), 2.02 (qu, 2H, C–CH_2–C, $J_3 = 4.98$ Hz), 2.22 (6H, s, Ar-CH_3), 2.34 (2H, t, C–C–CH_2–N, $J_4 = 7.32$ Hz), 3.55 (s, 4H, N–CH_2-Ar), 4.16 (t, 4H, CH_2–O, $J_5 = 4.98$ Hz), 6.71 (d, 2H, Ar-H, $J_6 = 8.20$ Hz), 6.92 (d, 2H, Ar-H, $J_7 = 8.20$ Hz), 7.07 (s, 2H, Ar-H); MALDI-TOF MS: m/z 340.75.
13. Agai, B.; Nemeth, V.; Bocskei, Z.; Simon, K.; Bitter, I.; Toke, L. *Tetrahedron* **1996**, *52*, 6713.
14. Owston, P. G.; Peters, R.; Ramsammy, E.; Tasker, P. A.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1980**, *24*, 1218.
15. Phongtamrug, S.; Pulpoka, B.; Chirachanchai, S. *Supramol. Chem.* **2004**, *16*, 269.