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Convenient Route to Super-Expanded Calixpyrroles: Synthesis of Calix[*n*]furano[*m*]pyrroles ($n = 3, 4, 6, 8$ and $m = 2, 4$)

Nagarajan Arumugam, Yong-Sung Jang, and Chang-Hee Lee*

Department of Chemistry, Kangwon National University, Chun-chon 200-701, Korea

chhlee@kangwon.ac.kr

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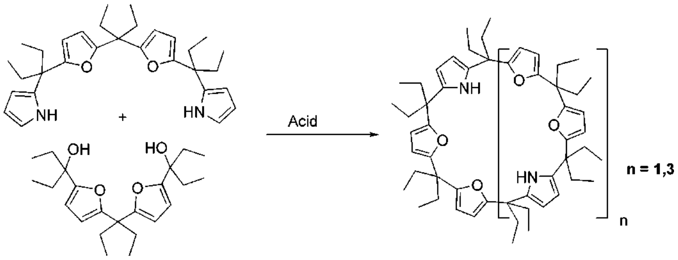
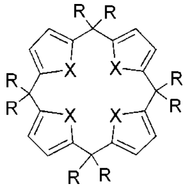
ABSTRACT



***meso*-Alkylporphyrinogen-like cyclic oligomers containing furans and pyrroles have been synthesized by “3 + 2” and “4 + 2” approaches. Condensation of 5,5,10,10,15,15-hexaethyl-21,22-dioxatetrapyrromethane with 2,5-bis[(α-hydroxy-α,α-dimethyl)furan] resulted in the formation of cyclic hexamer and cyclic dodcamer. Effects of catalysts, temperature, inorganic additives, solvent, and reaction concentration were examined.**

Anion binding chemistry is one of the key areas in the field of molecular recognition since anions play essential roles in biological processes, i.e., enzymatic reactions.[1] The trapping of smaller molecules such as nitric oxide by hosts is very important in medicinal chemistry, and recently the conformationally mobile calix[4]arene methyl ether (1-OMe) was found to capture nitric oxide (NO) with unprecedented efficiency ($K > 5 \times 10^8$ M^{-1}) upon oxidative activation.[2] The greater difficulties in binding anions compared to cations[3,4] and the key role of these receptors in ion selective electrodes, fluorescence sensors, and electrochemical signaling devices warrant the synthesis of newer and object-oriented macromolecules. Calix[4]pyrroles, the *meso*-octaalkylporphyrinogen skeleton, e.g., (**1**), have proved to be efficient receptors for the selective binding of anions[5] and cations.[6,7]



1. (X=NH)
2. (X=O)

These macrocycles manifested recognition and selectivity in binding with different anions and their subsequent release

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(1) Gale, P. A.; Sessler, J. L.; Kral, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140−5141.

(2) Rathore, R.; Lindeman, S. V.; Rao, K. S. S. P.; Sun, D.; Kochi, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 809−812.

(3) Sessler, J. L.; Gebauer, A.; Gale, P. A. *Gazz Chim. Ital.* **1997**, *127*, 723−726.

(4) Sessler, J. L.; Anzenbacher, P.; Jursikova, K.; Miyaji, H.; Genge, J. W.; Tvermoes, N. A.; Allen, W. E.; Shriver, J. A. *Pure Appl. Chem.* **1998**, *70*, 2401−2408.

(5) (a) Gale, P. A.; Genge, J. W.; Kral, V.; McKervey, M. A.; Sessler, J. L.; Walker, A. *Tetrahedron Lett.* **1997**, *38*, 8443−8444. (b) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777−1780. (c) Sessler, J. L.; Gale, P. A.; Genge, J. W. *Chem. Eur. J.* **1998**, *4*, 1095−1099. (d) Anzenbacher, P.; Jursikova, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020−11021. (e) Sessler, J. L.; Andrievsky, A.; Gale, P. A.; Lynch, V. M. *Angew. Chem., Int. Ed.* **1997**, *35*, 2782−2785.

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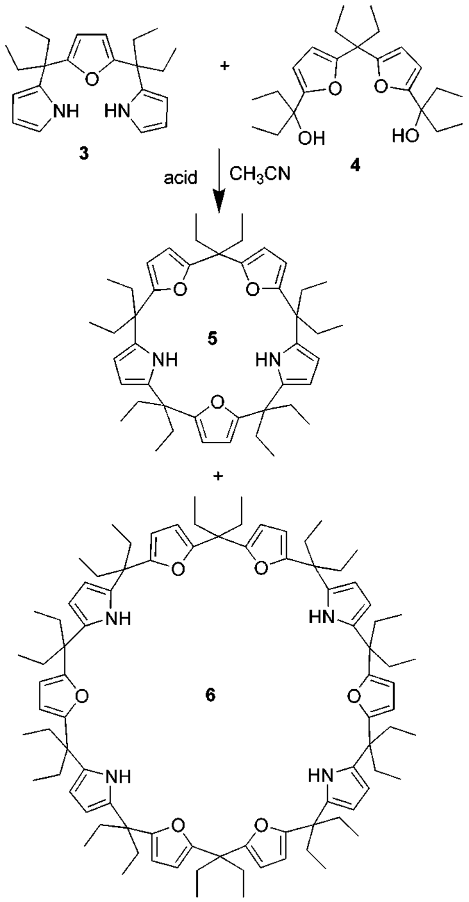
on chemical transformations.[8] Syntheses of calix[6]furan[9] and calixphyrin[10] have also been reported. Kohnke et al. recently reported the synthesis of calix[n]furano[m]pyrroles (where $n = 3$, $m = 3$; $n = 2$, $m = 4$; $n = 0$, $m = 6$) from calix[6]furans through oxidative opening of some or all of the furan rings followed by ring closure.[11] *meso*-Dialkyl or diaryl calix[6]pyrroles were found to possess alternate conformations.

Synthesis and binding effects of the mixed porphyrinogens containing furan rings are reported.[13] Though the first synthesis[14] of octamethyl tetraoxaquaterene (**2**) dates back to 1958, selective synthesis of larger oligomers is still a challenging task. The inherent advantages of these synthetic models include the variation in charge densities as well as cavity size of the macrocycles.

The ring size and the arrangement of heteroatoms can be manipulated by combinatorial condensation of different oligopyrromethane precursors. The syntheses of oligomeric macrocycles consisting of furan, pyrrole, or thiophene connected with methylene linkers have been previously reported.[10,13]

We also reported the syntheses of furan-pyrrole hybrid cyclic oligomers recently.[15] To demonstrate that larger macrocycles bearing more than 10 heterocycles can be synthesized by the same method, we attempted the syntheses of decameric and dodecameric hybrid calixpyrroles bearing *meso*-dialkyl substituents. Our synthetic route involves the condensation of oligopyrryl or oligofuryl units (**3**) with 5,5-diethyl-1,9-bis[(α-hydroxy-α,α-diethyl)methyl]furan (**4**) in the presence of acid catalyst under nonscrambling conditions (Scheme 1).[16] The condensation gave cyclic pentamer (**5**) in 54.5% yield and the cyclic decamer (**6**) in 15%. Higher reactant concentration (∼100 mM) gave lower overall yields of the cyclic oligomers.[17]

Scheme 1



Since the results shown in Scheme 1 indicate that even larger cyclic oligomers could be synthesized by condensing suitable precursors, we synthesized **7** from **4** and excess pyrrole in the presence of acid catalyst. The subsequent acid-catalyzed condensation of **7** with **4** resulted, as expected, in the formation of larger macrocycles as shown in Scheme 2. The reaction afforded **8** and **9** in 53% and 11% yields, respectively.[17] The full characterization of each oligomer was possible by mass spectrometry and proton NMR and carbon NMR spectra.

In the proton NMR spectra of the oligomers, all the pyrrolic and furanyl protons displayed similar chemical shifts regardless of their core size. The carbon spectra of **5** and **6** were almost identical. The resonance of pyrrolic N−H in proton NMR was observed at 7.90 ppm for **5** and 7.60 ppm for **6**. The slight downfield shift of the N−H resonance in **5** indicates its less flexible nature rendered by intramolecular hydrogen bonding. Clear distinction of each compound was possible by mass spectra due to their large difference in molecular weight. Various acids such as *p*-TSA, trifluoroacetic acid, and H$_3$PO$_4$ were applied in the condensation in order to assess the effect of acid catalysts. But no appreciable

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(6) Crescenzi, R.; Solari, E.; Floriani, C.; Villa-C. A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35*, 2413−2414.

(7) Kretz, C. M.; Gallo, E.; Solari, E.; Floriani, C.; Villa-C.; A.; Rizzoli, C. *J. Am. Chem. Soc.* **1994**, *116*, 10775−10776.

(8) Nation, D. A.; Reibenspies, J.; Martell, E. *Inorg. Chem.* **1996**, 4597−4603.

(9) Musau, M. R.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881−2888.

(10) Kral, V.; Sessler, J. L.; Zimmerman, R. S.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1055−1058.

(11) Cafeo, G.; Kohnke, F. H.; La-Torre, G. L.; White, J. P. A.; Williams, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1496−1498.

(12) Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2475−2478.

(13) Kohnke, F. H.; La Torre, G. L.; Paisi, M. F.; Menzer, S.; Williams, D. J. *Tetrahedron Lett.* **1996**, *37*, 4593−4596.

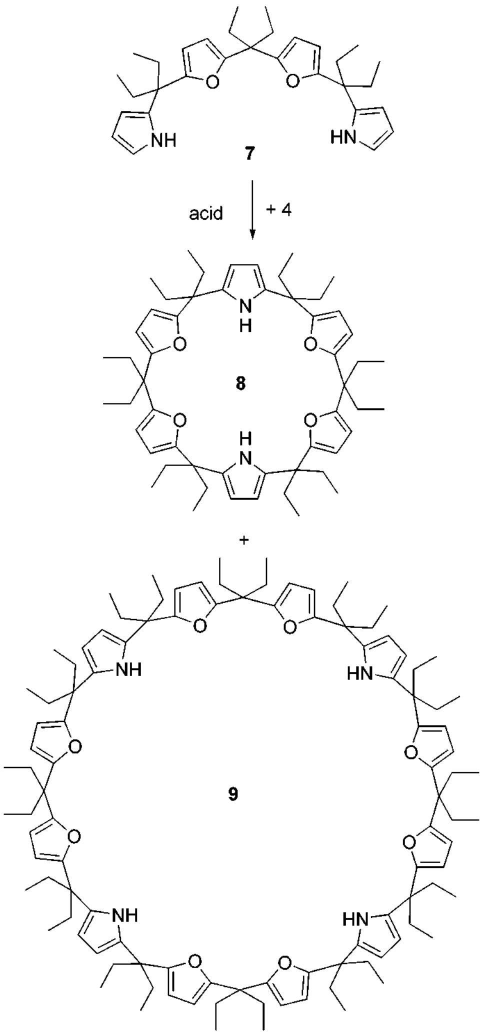
(14) Brown, W. H.; French, W. N. *Can. J. Chem.* **1958**, *36*, 371−377.

(15) Jang, Y. S.; Kim, H. J.; Lee, P. H.; Lee, C. H. *Tetrahedron Lett.* **2000**, *40*, 2919−2923.

(16) (a) Cho, W. S.; Kim, H. J.; Littler, B. J.; Miller, M.; Lindsey, J. S.; Lee, C. H. *J. Org. Chem.* **1999**, *64*, 7890−7901. (b) Littler, B. J.; Cringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864−2872.

(17) **General method of synthesis of 5, 6, 8, and 9:** A solution of the 1,9-di[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (**4**) (0.038 g, 0.1 mmol) and 5,5,10,10-tetraethyl-16-oxatripyrromethane (**3**) (0.033 g, 0.1 mmol) in acetonitrile (20 mL) was stirred under an N$_2$ atmosphere at 0 °C for 20 min, and then BF$_3$·Et$_2$O (1.2 μL, 0.01 mmol) was added. The mixture was stirred at 0 °C for 30 min and diluted with CH$_2$Cl$_2$ (20 mL), washed with 0.1 N NaOH (5 mL), and then with water (2 × 10 mL). The organic layer was dried over anhydrous NaHCO$_3$ and concentrated in vacuo. Flash chromatography on silica with hexanes/CH$_2$Cl$_2$ (1/1) afforded two products. Compound **5** was eluted first followed by **6**. Yield of **5**: 0.038 g (54.5%). Yield of **6**: 0.01 g, 15%. Compounds **8** and **9**: The mixture of 5,5,10,10,15,15-hexaethyl-21,22-dioxatetrapyrromethane **7** (0.048 g, 0.1 mmol) and 1,9-di[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (**4**) (0.038 g, 0.1 mmol) was treated in the same manner as for the synthesis of **5** and **6**. Column chromatography on silica (hexanes/CH$_2$Cl$_2$, 1/1) gave pure products. Yield of **8**: 0.043 g (53%). Yield of **9**: 0.018 g (11%).

Scheme 2



effect was observed, and all the acids were found to show catalytic activity and gave identical products distribution. We were further interested in assessing the role of inorganic additives as potential templates. Since calix[4]pyrroles have been considered as good receptors for cations and anions, we tested the utility of several salts as templates in “3 + 2” and “4 + 2” condensations. The reaction carried out in the presence of additives such as NH_4Cl, NaCl, Na_2HPO_4, $NaHPO_4$, 1,2,4,5-benzenetetracarboxylic acid, EDTA, $CdCl_2$, and $CsCO_3$ gave no significant improvement in the yields of either compounds.

All the reactions shown in Schemes 1 and 2 gave directly coupled (diol/pyrromethane) adducts (**5** and **8**) as the major product while 2/2 adducts (**6** and **9**) resulting from termolecular condensation were the minor products. The failure to observe any template effect and the similar activity of the various acid catalysts suggested that entropic factors are dominant. Attempts to selectively form the larger macrocycles by varying the temperature from −15 to 50 °C did not alter the product distribution. Though the present method affords larger ring systems for the first time, the yields of larger ring systems such as decamer and dodecamer need to be improved further. Compound **8** possesses different arrangement of heterocycles compared with the one reported by Kohnke et al.[11] The resonance of N−H signal in **8** was observed at 7.81 ppm while N−H signal in **9** appeared at 7.78 and 7.60 ppm as two distinctive signals. This observation may suggest compound **9** to adopt a twisted conformation through intramolecular hydrogen bonding similar to the one reported.[11]

Kohnke et al. suggested that the calix[6]pyrroles are able to distinguish different anions through size-selective trapping. This is contrary and advantageous over the hydrogen bonding interaction between the pyrrolic N−H and anion observed in the relatively smaller molecules such as calix[4]pyrroles.[2] Therefore, the larger macrocycles described in this Letter may be far more efficient in trapping unusually big guest molecules/ions and may bind with more than one guest. In view of the various new applications of calixpyrroles, the facile synthesis of modified calix[*n*]furano[*m*]pyrroles will widen their scope in ion-binding chemistry and material science. Work is in progress toward the synthesis of even larger macrocycles and evaluation of binding properties of these newer systems.

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Supporting Information Available: Spectroscopic data of the super-expanded calixpyrroles. This material is available free of charge via the Internet at http://pubs.acs.org.

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