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Synthesis of calix[*n*]furano[*n*]pyrroles and calix[*n*]thieno[*n*]pyrroles (*n*=2,3,4) by '3+1' approach

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Abstract

Condensation of 5,5,10,10-tetramethyl-16-oxa-tripyrromethane and 2,5-bis[(α-hydroxy-α,α-dimethyl)methyl]furan or 2,5-bis[(α-hydroxy-α,α-dimethyl)methyl]thiophene resulted in cyclic, alternating oligomers of furan(thiophene) and pyrrole. The product distribution is independent of the reaction conditions, the presence of inorganic additives and temperature. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: hybrid calix[*n*]pyrrole; 3+1 condensation; anion binding.

Recently, *meso*-octaalkylporphyrinogens (so called calix[4]pyrroles) have been documented as the molecular recognition hosts of anionic guests.[1] Anion binding chemistry is an underdeveloped area but an important part of supramolecular chemistry especially in the field of fluorescence sensors, ion-selective electrodes and medicinal applications.[2] Among various anion binding receptors, calix[4]pyrroles have been studied extensively due to their easy availability.[2] The synthesis and properties of furan or pyrrole-containing macrocycles has been known for many years. Since octamethylquaterene was synthesized in 1958,[3] many higher oligomeric furans have been reported and solid-state structures have been elucidated. Most of the known oligomeric units have direct α–α connection regardless of their order of arrangement.[4] Polymers of furan, pyrrole and thiophene have also been investigated for their potential applications to new material since they possess interesting electrical, optical and electrochemical properties.[5] The synthesis of oligo-macrocycles containing furan, pyrrole or thiophene with a *meso*-linking carbon unit has also been reported.[5] The calix[4]pyrroles have also been exploited in their tetra-anionic form as strong binder of late transition metals[6] and *trans*-N_2O_2-porphyrinogen has been studied for the coordination of unsaturated metal ions.[7] As a part of our effort on the synthesis of calix[*n*]pyrroles hybridized with furans and thiophenes, we here report the synthesis and characterization of furan-pyrrole or thiophene-pyrrole alternating cyclic oligomers. To the best of our knowledge, the synthesis of furan-pyrrole hybrid cyclic oligomers connected with methylene bridge have not been well reported in the literature. The effects of the inorganic additives on the product composition and conditions for the selec-

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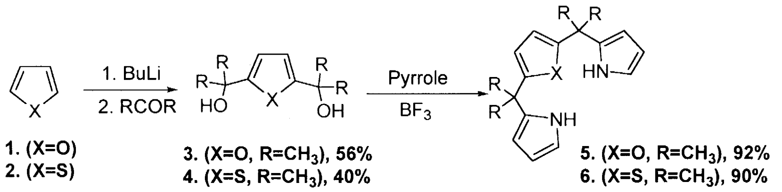
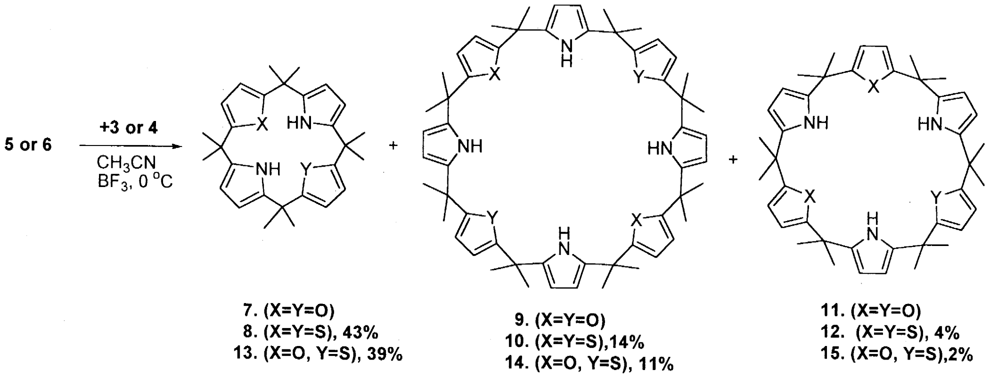
tive formation of higher cyclicoligomers were investigated. Our synthetic route involves the synthesis of 2,5-bis[(α-pyrryl-α,α-dimethyl)methyl]furan or 2,5-bis[(α-pyrryl-α,α-dimethyl)methyl]thiophene via acid-catalyzed condensation of 2,5-bis[(α-hydroxy-α,α-dimethyl)methyl]furan in the presence of excess pyrrole. The 3+1 condensation of these two afforded the macrocycles bearing alternating furan (thiophene) and pyrrole.

Bis-α,α′-alkylhydroxylation of furan **1** or thiophene **2** were carried out as shown in Scheme 1. Treatment of furan or thiophene with *n*-butyllithium (2 equiv.) followed by adding acetone afforded the corresponding diols in reasonable yields.[8] Based on the reactions previously employed for the formation of dipyrromethanes,[9] the diols **3** or **4** were treated with excess pyrrole in the presence of $BF_3 \cdot OEt_2$ (1 mol equiv.) to afford oxa- or thia-tripyrromethane **5** or **6** in good yields.



Scheme 1.

Since low scrambling conditions have been established for the '2+2' condensation of dipyrromethane and dipyrromethane-diol,[10] we applied those conditions in the condensations. As shown in Scheme 2, treatment of **5** or **6** with diol **3** or **4** in acetonitrile (10 mM, 0°C) in the presence of $BF_3 \cdot OEt_2$ (1 mM) afforded cyclictetramers **7** or **8**, respectively, in 40–60% yields as the major products. The less polar components **9** and **10** were also isolated in 10–20%. The trace amount of cyclic hexamer was isolated when furan containing **5** were condensed with diols **3** indicating the slow cleavage of pyrryl group during the condensation.



Scheme 2.

The separation of each component was possible by repeated column chromatography on silica. Initial column eluted with hexanes/methylene chloride (1/1) gave clear separation of the three components from the rest of the polar material. Then the mixture was eluted with chloroform to separate the most polar compound **7**. The other two compounds were separated by eluting hexanes/methylene chloride (1/1).

Condensation of thiophene containing **6** (X=S, $R=CH_3$) with diol **4** afforded cyclic tetramer in 45% yield and 14% of cyclic octamer. No cyclichexamer was isolated in this case but N-confused cyclictetramer was isolated in 4% instead. Condensation of *meso*-diphenyl analogue of **6** (X=S, R=Ph) with dipenyl analogue of diol **4** (X=S, R=Ph) gave only cyclictetramer in 30% yield. Small amounts of other components were observed on TLC but further isolation was not attempted due to their limited solubility in organic solvent. The thiophene containing cyclicoligomers **8, 10** and **12** were also synthesized similarly. The condensation carried out under standard condition gave **8** (43%), **10** (4%) and **12** (14%). The condensation of **5** (X=O, R=CH_3) with diol **4** (X=S, R=CH_3) also gave similar results. Cyclictetramer **13** was the major product (39%). Cyclicoctamer **14** (11%) and trace amount of hexamer **15** (2%) were isolated. Mass spectral analysis of compound **15** indicates that there are two oxygens in the core indicating a slow acid-catalyzed cleavage between *meso*-carbon and pyrrole in **5**.

Attempted condensation in the presence of inorganic salts gave almost identical products distribution and ratios with those without salts (Table 1). The overall yields were independent of the additives and temperature. These observations correspond to the previously recognized results of no templating effect of inorganic salts that were observed in the case of the condensation of furan with acetone.[4] TLC analysis showed that the reaction is basically completed within a few min of the reaction time and the yield remained unchanged. The condensation always gave tetramer as the major product under any attempted conditions. The cyclichexamer was formed in small amount and cyclicoctamer was a second major at low temperature. The ratio of tetramer/octamer is almost constant regardless of the reaction conditions.

Table 1

Dependence of yields on the condensation of **5** with **3** and the effect of added inorganic salts and reactant concentrations at 0°C. The reaction time was 30 min

Reaction conc.	BF_3	Added Salts	Yield (%)		
			7	**11**	**9**
100 mM	1 mM	None	30	1	9
		NH_4Cl	29	1	11
		NaCl	31	2	11
		LiCl	21	2	8
10 mM	1 mM	None	43	4	14
		NH_4Cl	42	3	15
		NaCl	44	3	11
		LiCl	44	5	8
1 mM	1 mM	None	56	5	17
		NH_4Cl	54	4	18
		NaCl	55	3	17

Change of reactant concentration (1 mM to 100 mM) also did not affect the yield and the product distribution. Higher reactant concentration (100 mM) gave much lower yields of the three oligomers (Table 1). Cyclic hexamer could be obtained up to 16% yield by direct condensation of pyrrole and diol **3** or **4**. As shown in Table 2, direct condensation of diol **3** or **4** with pyrrole gave mixture of cyclic oligomers consisting of lower yields of both cyclicoctamer and cyclictetramer but higher yields of cyclic hexamer compared with those of the '3+1' condensation shown in Scheme 2. Table 2 also shows product distribution at different temperatures. The overall yields of the three oligomers decrease with decreasing temperature. Obviously, it is advantageous to use the '3+1' approach to obtain a larger fraction of cyclicoctamer. Increasing the amount of acid to 5 mM and elevated temperature (25°C) in '3+1' condensation gave mixture of products (**7**/**11**/**9**=46%/9%/11%)[11] including N-confused cyclic tetramer (8% yield).

The full characterization of each oligomer was possible by mass spectrometry, proton NMR and carbon NMR spectra. The product distribution was determined from the ^1H NMR spectra of the three mixtures obtained from the crude column chromatography. The ratio of each product was determined from the integration of the distinctive resonances of β-pyrrolic or β-furanyl protons in each compound. The β-pyrrolic and β-furanyl signals of cyclic tetramer **7** were shown at 5.84, 6.04 ppm respectively and

Table 2

Dependence of yields on different combinations of reactants. The catalyst was $BF_3 \cdot OEt_2$ (1 mM). *8% of N-confused cyclictetramer was isolated at higher acid concentration (0.5 M)

Reactants	Reaction temp (°C)	Yield (%)		
		7	**11**	**9**
5 + 3	25*	52	5	18
	0	43	4	14
	-30	37	1	14
Pyrrole + **3**	25	22	11	8
	0	25	16	11
	-30	12	9	5

those of cyclic hexamer **11** appeared at 5.72 and 5.85 ppm respectively. The corresponding signals in cyclic octamer **9** were observed at 5.78 and 5.75 ppm respectively. The ratio was calculated from the area of 6.04 ppm for **7**, 5.72 ppm for **11** and 5.78 ppm for **9**. The proton NMR spectra of the three oligomers showed that the compound is symmetrical and all the pyrrolic and furanyl protons display similar chemical shifts regardless of their core-size. No conformational isomerization was observed at room temperature. Compound **9** also showed its symmetric character in ^{1}H NMR. The carbon spectra of **7**, **11** and **9** were almost identical and the distinction was only possible by mass spectral analysis. The molecular ion peak of **7** was shown at 430.14 (M^+) while that of **9** was observed at 860.83 (M^+). The single crystals of cyclic tetramer **7** was obtained by slow diffusion of hexanes to methylene chloride at room temperature and the X-ray analysis indicates the C_2 symmetry of the compound and alternating conformation (Fig. 1).

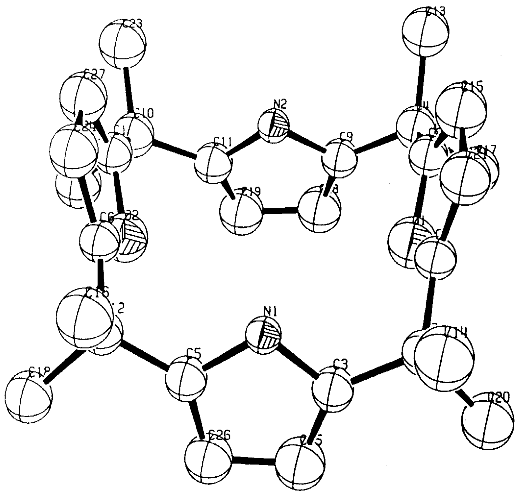


Fig. 1. ORTEP view of the X-ray structure of **7** showing alternating configuration

The various new applications of calixpyrroles and the easy construction of modified calixpyrroles with predesignated core-size and ligand-location will widen the scope of applicability. The hybrid calixpyrroles might be quite useful in biological applications such as anion sensing and antiviral drug delivery due to their amphiphilic binding characteristics. Currently, library-like construction of the modified calix[*n*]furano[*n*]pyrroles and calix[*n*]thieno[*n*]pyrroles is undergoing.

Acknowledgements

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References

1. (a) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc*. **1996**, *118*, 5140. (b) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun*. **1997**, 665. (c) Sessler, J. L.; Gebauer, A.; Gale, P. *Gazzetta Chimica Italiana* **1997**, *127*, 723. (d) Sessler, J. L.; Antrievsky, A.; Gale, P. A.; Lynch, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2782. (e) Sessler, J. L.; Burrell, A. K. *Top. Curr. Chem*. **1991**, *161*, 177.
2. Sessler, J. L.; Anzenbacher Jr., P.; Jursikova, K.; Miyaji, H.; Genge, J. W.; Tvermoes, N. A.; Allen, W. E.; Shriver, J. A. *Pure Appl. Chem*. **1998**, *70*, 2401.
3. Brown, W. H.; French, W. N. *Can. J. Chem*. **1958**, *36*, 371.
4. Hucke, A.; Cava, M. P. *J. Org. Chem*. **1998**, *63*, 7413 and references cited therein.
5. (a) Kohnke, F. H.; La Torre, G. L.; Parisi, M. F. *Tetrahedron Lett.* **1996**, *37*, 4593. (b) Musau, M. R.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881.
6. (a) Villa, A. C.; Rizzoli, C. *J. Chem. Soc., Chem. Commun*. **1991**, 790. (b) Chiesi-Villa, A. C.; Rizzoli, C. *J. Am. Chem. Soc*. **1993**, *115*, 3595. (c) Jacoby, D.; Isoz, S.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Am. Chem. Soc*. **1995**, *117*, 2793. (d) Jacoby, D.; Isoz, S.; Schenk, K.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1995**, *14*, 4816.
7. Crescenzi, R.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35*, 2413.
8. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887.
9. Lee, C. H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427.
10. Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem*. **1999**, *64*, 2864.
11. ^{1}H NMR ($CDCl_3$): For (**7**) δ 7.17 (bs, 2H, N-H), 6.04 (s, 4H, furan-H), 5.85–5.84 (d, 4H, pyrrole-H), 1.53 (s, 24H, -CH_3); ^{13}C NMR ($CDCl_3$) δ 159.40, 136.50, 103.71, 101.87, 35.38, 27.35. FAB MS calcd for $C_{28}H_{34}N_2O_2$: 430.26, found: 430.14 (M^+). For (**11**) δ 7.95 (bs, 3H, N–H), 5.85 (s, 6H, furan-H), 5.73–5.72 (d, 6H, pyrrole-H), 1.50 (s, 36H, -CH_3); ^{13}C NMR ($CDCl_3$) δ 160.29, 137.32, 104.15, 102.95, 36.52, 28.08. FAB MS calcd for $C_{42}H_{51}N_3O_3$: 645.39, found: 645.18 (M^+). For (**9**) δ 7.95 (bs, 4H, N-H), 5.78–5.77 (d, 8H, pyrrole-H), 5.75 (s, 8H, furan-H), 1.50 (s, 48H, -CH_3); ^{13}C NMR ($CDCl_3$) δ 160.31, 137.21, 104.35, 103.28, 36.60, 28.17. FAB MS calcd for $C_{56}H_{68}N_4O_4$: 860.52, found: 860.83 (M^+).