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Synthesis of expanded calix[*n*]pyrroles and their furan or thiophene analogues

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Abstract—*meso*-Dialkylporphyrinogen-like mixed cyclic oligomers containing furans, pyrroles and thiophenes have been synthesized by '3+1', '3+2' and '3+ketone' approaches. Condensation of 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-ethyl]furan with 2,5-bis[(α-hydroxy-α,α-dimethyl)furan or 2,5-bis[(α-hydroxy-α,α-dimethyl)thiophene resulted in the formation of the mixture of cyclic tetramer, cyclic octamer and cyclic hexamer possessing different numbers of furans (thiophenes) and pyrroles. The major product was found to be the cyclic tetramer in '3+1' condensation while cyclic pentamer was the major product in '3+2' condensation. Appreciable amounts of cyclic decamer was isolated in '3+2' condensation. The formation of furan–pyrrole alternating cyclic hexamer in '3+1' condensation indicates acid-catalyzed, reversible cleavage of the starting material during the reaction. In the same analogy, cyclic dodecamer was synthesized by '4+2' approach. Synthesis of cyclic dodecamer and cyclic pentadecamer was also achieved by condensing 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-ethyl]furan with ketones. The effect of catalysts, temperature, templates, solvent and concentration was examined and no appreciable changes in the product distribution were found.

1. Introduction

Selective sensing of anions is one of the key areas in the field of molecular recognition.[1] Of particular interests are the development of ion selective electrodes, fluorescent sensors, and electrochemical signaling devices. Considerable efforts have been devoted to the design and synthesis of new sensing systems and various anion receptors with different degree of affinity have been designed and synthesized as a result of those active studies.[2–6] Despite these effort receptors capable of recognizing simple anions with high affinity are rare. Halide ions have been known to play important roles in biological processes. For example, chloride ion is involved in respiration in erythrocytes.[7] Fluoride has been used for dental caries and treatment of osteoporosis.[3] Some hexaaza macrocycles have been shown to form a stable complex with ATP and possess a catalytic activity in the hydrolysis of ATP.[8] The interest toward the development of newer and functionalized halide ion receptors inspired us to study the chemistry of calix[*n*]pyrroles. Calix[4]pyrroles and calix[4]furans have proved to be efficient in selective binding with anions[9] and cations.[10,11] Since the pyrrole or furan based macrocycles manifest recognition and selectivity toward different anions, proper design of the host molecules would result in unique binding activities.[12] Anion binding is exclusively through hydrogen bonding interaction in most cases and therefore it is weak and thus more difficult to achieve than cation binding.[13,14]

The first synthesis of expanded calixpyrrole bearing six pyrrole rings have been reported recently by Kohnke et al.[15] Their synthesis was based on the partial or complete opening of the furan rings followed by ring closure to pyrrole. The solid state structure of *meso*-substituted calix[6]pyrroles were shown to possess 1,3,5-alternating conformation.[16,17] Although the first synthesis of hybrid calix[4]pyrroles dates back to 1958,[18] the synthesis of larger cyclic oligomers containing furans and thiophenes is still a challenging task. Since systematic variation of the core-atom or core-size would result in different recognition properties, the development of customized systems associated with the control of charge densities, conformational flexibility and cavity sizes is an urgent demand. The macrocycles possessing different cavity size can accommodate larger guest molecules and can function as multi-nuclear host by proper folding. With these considerations, herein we report the synthesis and characterization of larger cyclic oligomers containing up to total of fifteen furan and pyrrole rings.

2. Results and discussions

In order to manifest various types of interaction, the host molecules must have proper functionalities as well as in addition to meeting their proper geometrical constraint. The functionalities must be placed so as to maximize the non-covalent interactions such as electrostatic, hydrogen

Keywords: calixpyrrole; super expansion; multinuclear receptor; '3+1' condensation; '4+2' condensation.

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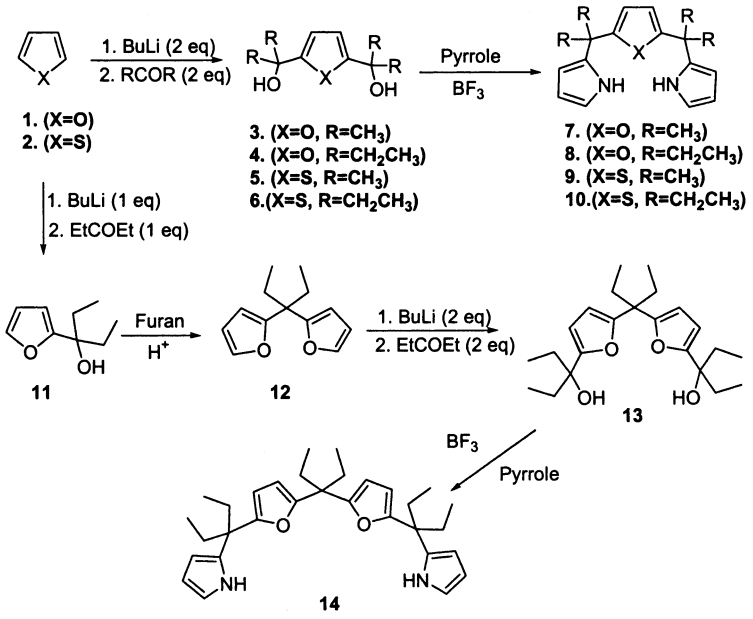
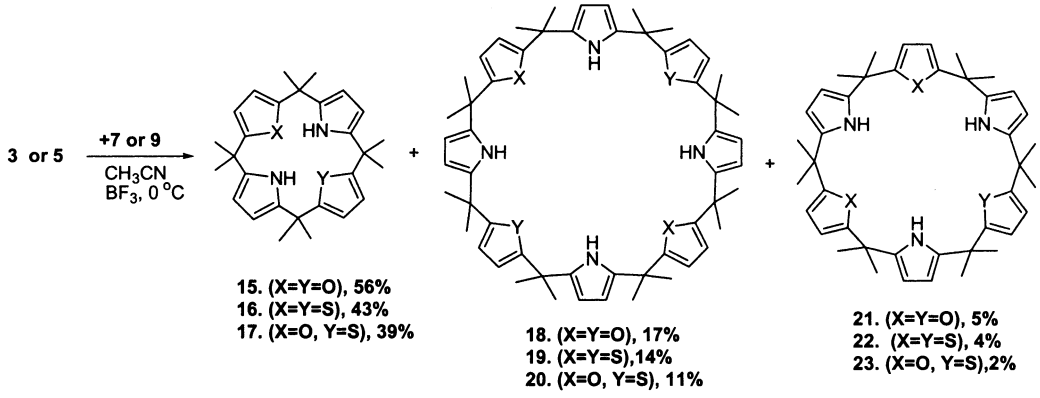


Scheme 1.

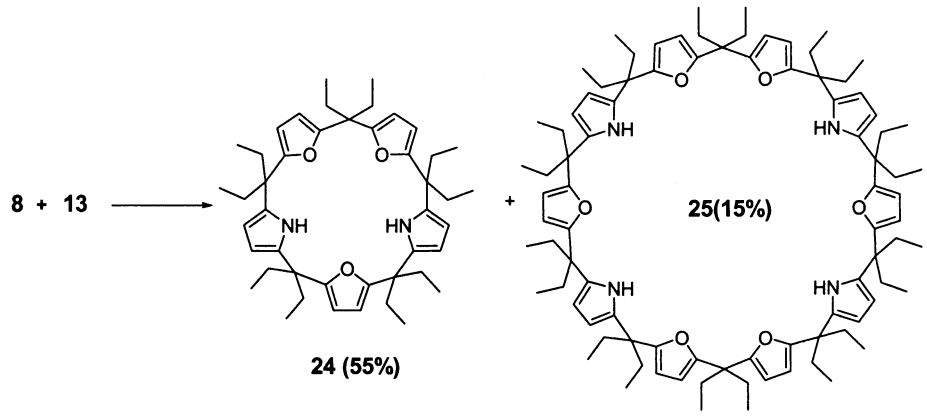
bonding, Van der Waals and metal–ligand interactions. Among them, we have been interested in developing neutral receptors and proposed to synthesize cyclic oligomers possessing large number of furan and pyrrole rings in order to enable them accommodate larger anions or multiple anions by winding–unwinding mode of action. The alternating array of furan and pyrrole rings in the molecule could be ideal for non-bonding interaction with guest molecules. Synthesis of macrocyclic oligomers containing furan, pyrrole or thiophene linked with one carbon unit has been reported.[19,20] *trans*-N_2O_2-porphyrinogen-like compounds have shown coordination of unsaturated metal ions.[21] We also reported the synthesis of furan–pyrrole hybrid cyclic oligomers connected with methylene bridge recently.[22]

Our synthetic route involves the condensation of oligopyrryl or oligofuryl units with 2,5-bis[(α-hydroxy-α,α-dialkyl)-methyl]furan or 1,9-bis[(α-hydroxy-α,α-dialkyl)methyl]-furan in the presence of acid-catalyst. α-Hydroxylation of furan or thiophene was carried out as shown in Scheme 1. Treatment of furan (**1**) or thiophene (**2**) with *n*-butyl lithium followed by adding acetone or 3-pentanone afforded the corresponding diols as reported earlier.[23] Treatment of diols (**3**, **4**, **5** or **6**) with excess pyrrole in the presence of $BF_3{\cdot}OEt_2$ (0.1 mol equiv.) afforded corresponding oligomers (**7**), (**8**), (**9**) and (**10**), respectively. The sequence shown in Scheme 1 was successfully employed for the synthesis of alternating oligomers of furan (or thiophene) and pyrrrole in their structure.

The hybrid tetramer (**14**) was synthesized by a sequence of reactions involving the condensation of alcohol (**11**) with furan to give difurylmethane (**12**). Then bis-α-hydroxylation of (**12**) to yield (**13**) followed by condensation with pyrrole gave dioxatetrapyrromethane (**14**). Treatment of (**7**) with diol (**3**) (10 mM in acetonitrile, 0°C) in the presence of catalytic amount of $BF_3{\cdot}OEt_2$ (1 mM) afforded cyclic-tetramer (**15**) in 56% yield as the major product (Scheme 2). The less polar components (**18**) and (**21**) were also isolated in 17 and 5%, respectively. The formation of small amount of cyclic hexamer (**21**) indicates the slow, acid-catalyzed cleavage of pyrryl group during the reaction. Condensation of thiophene-containing 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-ethyl]thiophene (**9**) with diol (**5**, R= methyl) also afforded cyclic tetramer (**16**), cyclic octamer (**19**) and cyclic hexamer (**22**) in 43,14 and 4% yield,



Scheme 2.



Scheme 3.

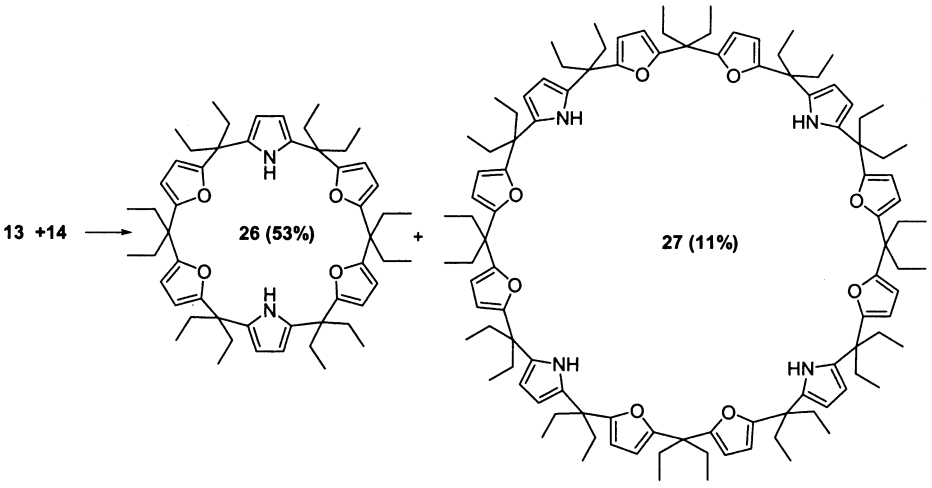
respectively. The formation of (**22**) indicates that the intermediary compound formed by the condensation of diol (**3**) with two molecules of (**7**) is susceptible for the cleavage of a pyrrolic moiety under acidic condition and subsequent cyclization will give cyclic hexamer (**21**). Other minor product identified from the condensation of (**9**) and (**5**) was a N-confused cyclic tetramer. Condensation of (**3**) with (**9**) also gave similar results. Cyclic tetramer (**17**) was isolated in 39% yield while (**20**) and (**23**) were isolated in 11 and 2%, respectively.

Condensation of (**8**) with (**13**) in the presence of acid catalyst afforded cyclic pentamer (**24**) as the major product and the cyclic decamer (**25**) as minor product (Scheme 3). The higher reactant concentration (from 1 to 100 mM) resulted in similar overall yields and the product distribution was not changed significantly. Encouraged by the success in synthesizing (**18**) and (**25**), we tried to synthesize even larger macrocycles. Condensation of (**14**) with (**13**) was attempted as shown in Scheme 4. The reaction also gave a mixture of the products (**26**) and (**27**) in 53 and 11% yield, respectively.

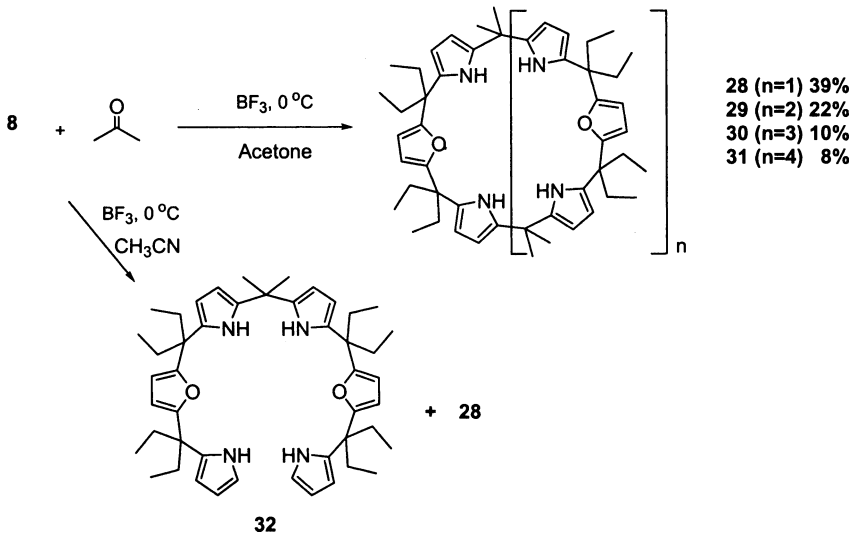
The full characterization of each oligomer was possible by mass spectrometry, proton NMR and carbon-13 NMR spectroscopy. The proton NMR spectra of the isolated oligomers showed symmetrical pattern and all the pyrrolic and furanyl protons displayed similar chemical shifts regardless of the size of the macrocycles. The carbon-13 NMR spectra of (**17**), (**20**) and (**23**) were almost identical and the distinction was only possible by mass spectral analysis due to the large differences in their molecular weight. Single crystal of the cyclictetramer (**15**) was obtained by slow diffusion of hexanes to methylene chloride at room temperature and the X-ray analysis indicated the C_2 symmetry of the compound and alternate conformation of furan and pyrrole.[22]

In order to improve the formation of the larger cyclic oligomers and to minimize the scrambling of the starting material and intermediates, we investigated the utility of different catalysts in the cyclo-condensation reactions. The results obtained from the '3+1' (Scheme 2), '3+2' (Scheme 3) and '4+2' (Scheme 4) condensations carried out with various catalysts indicate that *p*-toluene sulfonic acid, trifluoroacetic acid and phosphoric acid show some catalytic activity with unchanged product distribution. All the reactions were comparably clean and could be applied to the synthesis of thiophene containing analogues.

We were further interested in assessing the role of different templates, viz cationic as well as anionic templates since these oligomeric calixpyrroles are considered good cationic



Scheme 4.



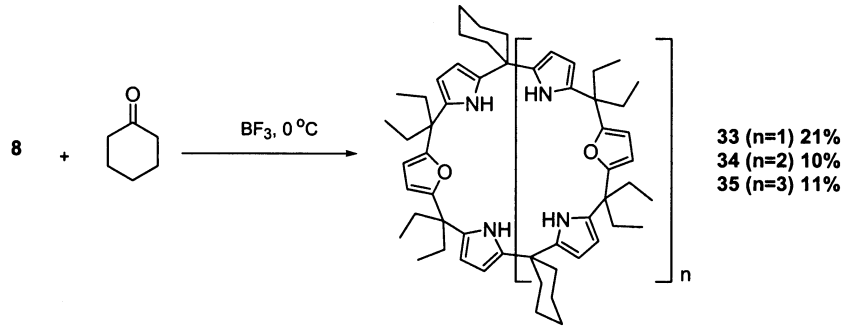
Scheme 5.

and anionic receptors depending on the nature of heteroatoms and the size of the macrocycle. We have tested the '3+1', '3+2' and '4+2' condensations by applying different templates such as NH_4Cl, NaCl, Na_2HPO_4, $NaHPO_4$ and observed no significant improvement in the yields. Other templates such as 1,2,4,5-benzene tetracarboxylic acid, EDTA, $CdCl_2$ or $CsCO_3$ which are expected to lead the selective formation of the higher oligomers, also gave negative effect in the '3+1' and '3+2' condensation. All the condensations shown in Schemes 2–4 gave smaller macrocycles (bimolecular condensation) as the major product while larger macrocycles resulting from termolecular condensation were formed as the minor product. Failure to observe any template effect and the similar activities of different acid catalysts suggested that entropic contribution might be a dominating factor in the condensation. Attempts to selectively form the larger cyclic oligomers by lowering the reaction temperature from 50 to −15°C did not alter the product distribution either.

Schemes 5 and 6 show another type of combination. Condensation of (**8**) with acetone resulted in a mixture of different cyclic oligomers. When (**8**) was treated with excess acetone (as a solvent), the mixture of hexamer (**28**), nanomer (**29**), dodecamer (**30**) and pentadecamer (**31**) were formed in 39, 22, 10 and 8%, respectively. All the components were easily separated by column chromatography except (**30**) and (**31**) which were further separated by size exclusion chromatography (Biobead 100X, THF).

Condensation of (**8**) with acetone carried out in the presence of solvents (such as chloroform or acetonitrile) resulted in the formation of cyclic hexamer in 13% as the only cyclic product and linear hexameric compound (**32**) was also isolated in 13% while most of the starting material was recovered. Different cyclic oligomers were obtained from the reaction of 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-ethyl]-furan (**7**), 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-propyl]furan (**8**) and 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-ethyl]thiophene (**9**) with acetone or cyclohexanone, but reaction with other ketones such as 3-pentanone or admantan-2-one failed to give any condensation products. The lower reactivity of latter carbonyl compounds may be due to the steric hinderance. It is interesting to note that only acetone and cyclohexanone lead to macrocyclic compounds and no other ketones gave similar reaction at this point. The product distribution remained almost the same regardless of different combination of the reactants.

Analysis of the proton NMR spectra of the isolated oligomers showed that the smaller macrocycles have weaker intramolecular hydrogen bonding than the larger ones. For example, tetramer (**15**) shows N–H resonance at 7.18 ppm while that of octamer (**18**) shows at 7.94 ppm.



Scheme 6.

Pyrrolic N–H resonance of larger oligomers appeared at lower field as sharp singlet, while the respective resonance of smaller ones showed rather broad signal at higher field. All the pyrrolic N–H resonances show single signals except the cyclic dodecamer (**27**) which shows two distinctive signals at 7.62 and 7.61 ppm. This observation may be associated with asymmetric conformational folding of the compound. The resonance of N–H signal for the two hexamers (**26**) and (**28**) appeared at 7.77 and 7.66 ppm, respectively. The analysis also indicates that less number of nitrogen in the core favors stronger intramolecular hydrogen bonding due to increased number of hydrogen bonding acceptors. The use of furan-containing building blocks in the '3+1' type condensation afforded varying amounts of the different oligomers and the condensation of thia-2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-propyl]thiophene (**9**) with thiophene diol (**5**) resulted in the formation of the higher percentage of the octameric compound on the other hand. Though the present methods would be a good synthetic route to the super expanded calixpyrroles, better selectivity for the formation of larger oligomers need to be developed. An alternative method for the larger cyclic oligomers would be the direct head-to-tail coupling of linear oligofuranopyrrole such as (**32**). The reaction of cyclohexanone with (**8**) also gave three different cyclic oligomers and the yields of each oligomers were comparably low (Scheme 6). The isolation of (**35**) was rather difficult due to its similar polarity with some unknown impurities.

The preliminary binding studies carried out with pentameric compound (**28**) in organic solvent with ^{1}H NMR spectroscopy did not show any indication of preferable binding. The inner pyrrolic N–Hs were not exchanged upon addition of methanol-d_4 or D_2O while those in larger oligomers (**29**–**31**) were exchanged rapidly. This observation indicates that the N–Hs in (**28**) are involved in stronger intramolecular H-bonding with the adjacent furan oxygen. This might be responsible for the failure to observe any change in the chemical shift.

In conclusion, we were able to synthesize and isolate super expanded calix[*n*]furano[*n*]pyrroles by the condensation of various oligofuranopyrroles. Considering the various applications of larger oligomeric calixpyrroles, the facile synthesis of the new calixpyrroles outlined in this article will widen their scope in ion-binding chemistry and materials science. The utility of calix[*n*]pyrroles as anion receptors will be probed in the fields of anion sensing and antiviral drug delivery. Work is in progress towards the synthesis and evaluation of binding properties of these and even larger calix[*n*]pyrroles.

3. Experimental

3.1. General

^{1}H NMR spectra (400 MHz, Bruker IFS 48) were recorded in $CDCl_3$ with TMS as the internal standard. FAB mass spectra were obtained on AUTO SPEC M-363 high-resolution mass spectrometer. Column chromatography was performed on silica (Merck, 230–400 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. CH_2Cl_2 (reagent grade) was distilled from K_2CO_3. All other reagents were obtained from Aldrich and used as received unless noted otherwise. Compounds (**3**–**6**) and (**11**) were prepared by reported procedure.[23]

3.1.1. 2,5-Bis-[1-methyl-1-(1*H*-pyrrol-2-yl)-ethyl]furan (7). To a stirred mixture of diol (**3**) (1.2 g, 6.51 mmol) and pyrrole (9.03 mL, 13.02 mmol) was added $BF_3{\cdot}OEt_2$ (82.5 μL, 0.65 mmol) in ice-bath under nitrogen. The mixture was stirred for 30 min in ice-bath then combined with CH_2Cl_2 (100 mL). The mixture was immediately washed with aqueous NaOH (0.1N, 20 mL) and water twice. The organic layer was dried ($NaHCO_3$) and the solvent including excess pyrrole was removed in vacuo. Resulting amorphous solid was purified by column chromatography on silica (hexanes/CH_2Cl_2, 1:1) to afford white solid. Yield 1.84 g (92%); ^{1}H NMR ($CDCl_3$) δ 7.91 (bs, 2H), 6.59–6.57 (m, 2H), 6.11–6.09 (m, 2H), 6.01–5.99 (m, 2H), 5.93 (s, 2H), 1.62 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 159.833, 138.096, 116.809, 107.630, 103.727, 103.149, 36.217, 27.541. FAB MS Calcd for $C_{18}H_{22}N_2O$ 282.17, Found 282.19 (M^+).

3.1.2. 2,5-Bis-[1-ethyl-1-(1*H*-pyrrol-2-yl)-propyl]furan (8). A solution of 2,5-bis[(α-hydroxy-α,α-diethyl)methyl]furan (**3**, 0.231 g, 1 mmol) in pyrrole (1.38 mL, 1.4 g, 20 mmol) was stirred at 0°C under N_2 atmosphere for 30 min. To this stirred solution $BF_3{\cdot}Et_2O$ (81 μL, 0.64 mmol) was added and stirred at 0°C for 30 min. The reaction mixture was diluted with dichloromethane (20 mL) and quenched with 0.1N NaOH (5 mL). The organic layer was washed with water (2×10 mL) and dried over anhyd. $NaHCO_3$. Column chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded the product in white solid. Yield 0.30 g (90%); R_f: 0.61 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.81 (bs, 2H), 6.57 (m, 2H), 6.11 (m, 2H), 6.0 (S, 2H), 5.97 (s, 2H), 1.96 (q, 8H), 0.82 (t, 12H); ^{13}C NMR ($CDCl_3$) δ 157.81, 135.67, 116.32, 107.49, 105.99, 105.01, 44.57, 28.86, 8.51. FAB MS Calcd for $C_{22}H_{30}N_2O$ 338.24, Found 338.23 (M^+).

3.1.3. 2,5-Bis-[1-methyl-1-(1*H*-pyrrol-2-yl)-ethyl]thiophene (9) and 2,5-bis-[1-methyl-1-(1*H*-pyrrol-2-yl)-propyl]thiophene (10). Compound (**5**) (1.4 g, 6.74 mmol), pyrrole (9.4 mL, 134 mmol) and $BF_3{\cdot}OEt_2$ (85 μL, 0.67 mmol) were treated identically as for the synthesis of **7**. Column chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded pure product (**9**) as white solid. Yield 1.8 g (90%); ^{1}H NMR ($CDCl_3$) δ 7.87 (bs, 2H, N–H), 6.67 and 6.65 (dd, 2H, pyrrole-H), 5.93 (s, 2H, thiophene-H), 6.14 and 6.12 (dd, 2H, pyrrole-H), 6.07–6.05 (m, 2H, pyrrole-H), 1.70 (s, 12H, $-CH_3$); ^{13}C NMR δ 152.597, 139.356, 122.072, 116.723, 107.516, 103.470, 37.704, 31.016. MS (EI) Calcd for $C_{18}H_{22}N_2S$ 298.15, Found 298.14 (M^+). Compound (**10**) was synthesized from (**6**) using the above procedure. Yield 2.18 g (90%); ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 2H), 6.68 (m, 2H), 6.65 (s, 2H), 6.11 (m, 2H), 6.07 (m, 2H), 2.0 (q, 8H), 0.71 (t, 12H); ^{13}C NMR ($CDCl_3$) δ 150.56, 137.19, 123.40, 116.54, 107.34, 105.58, 45.71, 31.25, 8.52. FAB MS Calcd for $C_{22}H_{30}N_2S$ 354.21, Found 355.18 (M^+).

3.1.4. 5,5-Diethyldifurylmethane (12). A solution of 2-(α,α-diethyl-α-hydroxy)methylfuran (**11**, 0.247 g, 1.6 mmol) in furan (2.33 mL, 2.18 g, 32 mmol) was stirred at

0°C under N_2. $BF_3{\cdot}Et_2O$ (0.081 mL, 0.09 g, 0.64 mmol) was added and stirred at 0°C for 30 min. The reaction mixture was combined with CH_2Cl_2 (20 mL) and then quenched with NaOH (0.1N, 5 mL). The organic layer was washed with water (2×10 mL) and dried over anhyd. $NaHCO_3$. Flash chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded difurylmethane (**12**) in white solid. Yield 2.69 g (70%); ^{1}H NMR ($CDCl_3$) δ 7.3 (bs, 2H), 6.3 (m, 2H), 6.13 (m, 2H), 2.07 (q, 4H), 0.7 (t, 6H); ^{13}C NMR ($CDCl_3$), δ 158.114, 141.034, 109.667, 106.154, 45.651, 27.661, 8.288. FAB MS Calcd for $C_{13}H_{16}O_2$ 204.12, Found 204.15 (M^+).

3.1.5. 1,9-Bis[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (13). To a three necked round bottomed flask provided with a magnetic stirrer and a reflux condenser was added hexanes (50 mL), TMEDA (0.756 mL, 0.582 g, 5 mmol) and *n*-BuLi (2 mL, 1.38 g, 5 mmol). To this stirred solution was added bis(5,5-diethyl)difurylmethane (**12**, 1.02 g, 5 mmol) and the mixture heated under reflux for 1 h. The lithium salt thus formed was added to a solution of pentan-3-one (1.06 mL, 10 mmol) in THF (50 mL) under N_2 atmosphere using a canula. The mixture was stirred for 30 min at room temperature, after which the reaction was quenched with saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2×25 mL). The organic layer was washed with water and dried ($NaHCO_3$). The solvent was removed under reduced pressure and compound **13** was separated by flash chromatography on silica (CH_2Cl_2) as white solid. Yield 1.22 g (65%); ^{1}H NMR ($CDCl_3$) δ 6.1 (d, 2H), 6.01 (d, 2H), 1.98 (q, 4H), 1.78 (q, 8H), 0.8 (t, 12H), 0.72 (t, 6H); ^{13}C NMR ($CDCl_3$) δ 157.76, 106.58, 105.55, 45.93, 32.07, 28.51, 8.54, 7.87. FAB MS Calcd for $C_{23}H_{36}O_4$ 376.26, Found 376.53 (M^+).

3.1.6. 5,5,10,10,15,15-Hexaethyl-21,22-dioxatetrapyrromethane (14). A solution of 1,9-bis[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (**13**, 0.386 g, 1 mmol) in pyrrole (1.38 mL, 1.4 g, 20 mmol) was stirred at 0°C under N_2. $BF_3{\cdot}Et_2O$ (0.081 mL, 0.09 g, 0.64 mmol) was added and stirred at 0°C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and quenched with NaOH (0.1N, 5 mL). The organic layer was washed with water (2×10 mL) and dried ($NaHCO_3$). Flash chromatogarphy on silica (hexanes/CH_2Cl_2 (1:1) afforded pure product as white solid. Yield 0.403 g (85%); R_f 0.48 (hexanes/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.9 (s, 2H), 6.6 (d, 2H), 6.1 (m, 2H), 6.0 (m, 8H), 2.0 (q, 12H), 0.7 (t, 18H); ^{13}C NMR ($CDCl_3$) δ 157.38, 156.65, 135.64, 115.98, 107.47, 106.39, 106.28, 105.01, 45.98, 44.77, 29.55, 28.26, 8.62, 8.48. FAB MS Calcd for $C_{31}H_{42}N_2O_2$ 474.32, Found 475.30 (M^++H).

3.1.7. Condensation of (7) with (3). To an ice-cooled solution of (**7**) (100 mg, 0.35 mmol), (**3**) (62 mg, 0.35 mmol) dissolved in acetonitrile (35 mL) was added $BF_3{\cdot}OEt_2$ (4.5 μL, 0.04 mmol). The whole mixture was stirred for 30 min and then combined with aqueous NaOH (0.1N, 10 mL) to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic layer was dried ($NaHCO_3$). Solvent was removed in vacuo and resulting solid was separated by column chromatography on silica. TLC analysis shows mainly three spots and some tailing component close to the origin. The initial column was performed using hexanes/CH_2Cl_2 (1:1) in order to separate the fast moving three components from the last of the tailing part. Then the second column performed in $CHCl_3$ gave clean separation of slow moving cyclic tetramer (**15**). The fast moving fraction (mixture of **18** and **21**) was further separated by repeating column chromatography (hexanes/CH_2Cl_2, 1:1). The cyclic hexamer (**21**) was eluted first and the slow moving fraction was identified as cyclic octamer (**18**). Yields for (**15**) 66 mg (56%); for (**21**) 3.5 mg (4%); for (**18**) 22 mg (14%); ^{1}H NMR ($CDCl_3$): For (**15**) δ 7.17 (bs, 2H), 6.04 (s, 4H), 5.85–5.84 (d, 4H), 1.53 (s, 24H); ^{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 (**18**) δ 7.95 (bs, 2H), 5.85 (s, 6H), 5.73–5.72 (d, 6H), 1.50 (s, 36H); ^{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 (**21**) δ 7.95 (bs, 4H), 5.78–5.77 (d, 8H), 5.75 (s, 8H), 1.50 (s, 48H); ^{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^+).

3.1.8. Condensation of (7) with (5). To the solution of (**7**) (450 mg, 1.59 mmol), (**5**) (320 mg, 1.59 mmol) dissolved in acetonitrile (160 mL) was added $BF_3{\cdot}OEt_2$ (20 μL, 0.16 mmol). The mixture was treated identically as for the condensation of (**7**) with (**3**). Resulting solid was separated by column chromatography on silica. TLC analysis shows mainly three spots and some tailing component close to the origin. The initial column was performed using hexanes/CH_2Cl_2 (1:1) in order to separate the fast moving three components from the last of the tailing part. Then the second column performed in hexanes/CH_2Cl_2 (3:1) gave clean separation of (**17**) and (**23**). The last moving band (**20**) was separated by successive elution with hexanes/CH_2Cl_2 (3:2). Yields for (**17**) 280 mg (39%); for (**23**) 10 mg (2%); for (**20**) 80 mg (11%); ^{1}H NMR ($CDCl_3$): For (**17**) δ 6.92 (bs, 2H), 6.66 (s, 2H), 6.08 (s, 2H), 5.88–5.87 (m, 2H), 5.84–5.82 (m, 2H), 1.62 (s, 12H), 1.54 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 159.68, 154.24, 138.89, 137.79, 120.39, 104.88, 102.76, 101.57, 37.69, 36.31, 30.33, 27.85. FAB MS Calcd for $C_{28}H_{34}N_2OS$ 446.24, Found 446.26 (M^+). For (**23**) δ 7.98 (bs, 2H), 7.77 (bs, 2H), 6.33 (s, 2H), 5.91–5.85 (m, 4H), 5.79–5.77 (m, 4H), 5.75–5.74 (d, 2H), 1.66 (s, 12H), 1.53 (s, 24H); ^{13}C NMR ($CDCl_3$) δ 160.39, 160.30, 153.54, 138.89, 137.35, 137.30, 122.40, 104.41, 104.20, 103.34, 102.97, 38.40, 36.67, 36.62, 31.50, 28.20. FAB MS Calcd for $C_{42}H_{51}N_3O_2S$ 661.37, Found 661.41 (M^+). For (**20**) δ 7.79 (bs, 4H), 6.37 (s, 4H), 5.89–5.88 (m, 4H), 5.85–5.83 (m, 4H), 5.74 (s, 4H), 1.62 (s, 24H), 1.50 (s, 24H); ^{13}C NMR ($CDCl_3$) δ 159.84, 153.04, 138.27, 136.90, 121.90, 103.97, 103.37, 102.86, 37.96, 36.26, 31.18, 27.84. FAB MS Calcd for $C_{56}H_{68}N_4O_2S_2$ 892.48, Found 892.51 (M^+).

3.1.9. Condensation of (9) with (5). To an ice-cooled solution of (**9**) (330 mg, 1.11 mmol), (**5**) (220 mg, 1.11 mmol) dissolved in acetonitrile (110 mL) was added $BF_3{\cdot}OEt_2$ (14 μL, 0.11 mmol). The whole mixture was stirred for 30 min and then combined with aqueous NaOH (0.1N, 10 mL) to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×80 mL) and the organic layer was dried

($NaHCO_3$). Solvent was removed in vacuo and resulting solid was separated by column chromatography on silica. TLC analysis shows mainly three spots. The gradient column chromatography afforded clean separation of each component. The fast moving N-confused calix[2]thieno[2]-pyrrole in 4% (15 mg) was eluted when hexanes/CH_3Cl (1:1) was applied. Then the second band identified as (**16**) was eluted when hexanes/CH_3Cl (3:1) was used as eluent. The slow moving cyclic octamer (**19**) and hexamer (**22**) was eluted by applying hexanes/$CHCl_3$ (3:2). Yields for (**16**) 230 mg (43%); ^{1}H NMR ($CDCl_3$) δ 7.10 (bs, 2H), 6.69 (s, 4H), 5.89–5.88 (d, 4H), 1.63 (s, 24H); ^{13}C NMR ($CDCl_3$) δ 154.57, 122.49, 103.90, 38.54, 31.84. FAB MS Calcd for $C_{28}H_{34}N_2S_2$, 462.22, Found 462.23 (M^+). Yield for (**19**) 70 mg (14%); ^{1}H NMR ($CDCl_3$) δ 7.59 (bs, 4H), 6.35 (s, 8H), 5.95–5.94 (d, 8H), 1.62 (s, 48H); ^{13}C NMR ($CDCl_3$) δ 154.16, 140.16, 121.33, 102.61, 38.21, 31.09. FAB MS Calcd for $C_{56}H_{68}N_4S_4$ 924.43, Found 924.56 (M^+). Yield for (**22**) 8 mg (2%); ^{1}H NMR ($CDCl_3$) δ 7.55 (bs, 3H, N–H), 6.37 (s, 6H, thiophene-H), 5.95–5.94 (d, 6H, pyrrole-H), 1.62 (s, 36H, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.60, 138.76, 122.34, 103.74, 38.50, 31.76.

3.2. Direct condensation of (3) with pyrrole

To an ice-cooled solution of (**3**) (200 mg, 1.09 mmol), pyrrole (75 μL, 1.09 mmol) and acetonitrile (109 mL) was added $BF_3{\cdot}OEt_2$ (10 μL, 0.08 mmol) under nitrogen. The mixture was stirred for 30 min at 0°C. Then the mixture was combined with aqueous NaOH (0.1N, 10 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried ($NaHCO_3$) and solvent was removed in vacuo. The resulting solid was separated by column chromatography on silica. The separation procedure was the same outlined for the separation and condensation of (**7**) and (**3**). Yields for (**15**) 29 mg (25%); for (**18**) 13 mg (11%); for (**21**) 19 mg (16%).

3.2.1. Synthesis of pentamer (24) and decamer (25). A solution of the 1,9-bis[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (**13**) (0.038 g, 0.1 mmol) and 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-propyl]furan (**8**) (0.033 g, 0.1 mmol) were dissolved in acetonitrile (20 mL) and stirred under N_2 at 0°C for 20 min and then $BF_3{\cdot}Et_2O$ (1.2 μL, 0.01 mmol) was added. The mixture was stirred for 30 min and then diluted with CH_2Cl_2 (20 mL), washed with aq. NaOH (0.1N, 5 mL) and with water (2×10 mL). The organic layer was dried ($NaHCO_3$) and concentrated in vacuo. Flash column chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded two products, (**24**) and (**25**). Pentamer (**24**): Yield 0.038 g (54.5%); R_f: 0.79 (hexanes/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.92 (bs, 2H), 6.0 (d, 2H), 5.9 (m, 6H), 5.81 (s, 2H), 1.8 (q, 20H), 0.7 (t, 30H); ^{13}C NMR ($CDCl_3$) δ 158.22, 157.65, 157.08, 134.65, 133.75, 106.39, 106.19, 105.85, 104.21, 103.40, 45.39, 44.4, 44.20, 30.43, 28.99, 27.47, 8.69, 8.56, 8.32; FAB MS Calcd for $C_{45}H_{62}N_2O_3$ 678.47, Found 679.43 (M^++H, 8%), 649.39 ($M^+-C_2H_6$, 100%). Decamer (**25**): Yield 0.01 g (15%); R_f: 0.53 (hexanes/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.62 (bs, 4H), 5.83 (s, 8H), 5.81 (m, 8H), 5.76 (s, 4H), 1.87 (q, 40H), 0.62 (t, 60H); ^{13}C NMR ($CDCl_3$) δ 157.92, 157.59, 156.19, 133.74, 133.28, 106.65, 106.30, 106.26, 104.82, 104.57, 46.41, 44.89, 44.73, 30.0, 29.81, 29.56, 8.94, 8.76, 8.62; FAB MS Calcd for $C_{90}H_{124}N_4O_6$ 1356.95, Found 1356.77 (M^+, 10%), 1327.78 ($M^+-C_2H_5$, 100%).

3.2.2. Synthesis of hexamer (26) and dodecamer (27). A solution of the 5,5,10,10,15,15-hexaethyl-21,22-dioxatetrapyrromethane (**14**) (0.048 g, 0.1 mmol) and 1,9-bis[(α,α-diethyl-α-hydroxy)methyl]-5,5-diethyldifurylmethane (**13**) (0.038 g, 0.1 mmol) were dissolved in acetonitrile (20 mL) and stirred under N_2 atmosphere at 0°C for 20 min and then $BF_3{\cdot}OEt_2$ (1.2 μL, 0.01 mmol) was added. The mixture was stirred at 0°C for 30 min and diluted with CH_2Cl_2 (20 mL), washed with aq. NaOH (0.1N, 5 mL) and then with water (2×20 mL). The organic layer was dried ($NaHCO_3$) and concentrated in vacuo. Flash chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded two products, (**26**) and (**27**). For (**26**): Yield 0.043 g (53%); R_f: 0.73 (hexanes/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.81 (bs, 2H), 5.9 (m, 12H), 1.9 (q, 24H), 0.7 (t, 36H); ^{13}C NMR ($CDCl_3$) δ 157.61, 156.44, 134.11, 106.36, 106.01, 104.11, 45.86, 44.46, 29.18, 28.91, 8.7, 8.55; FAB MS Calcd 814.56, Found 814.49 (M^+, 7%), 785.46 ($M-C_2H_6$, 100%). For (**27**): Yield 0.018 g (11%); R_f: 0.55 (hexanes/CH_2Cl_2, 2:1); ^{1}H NMR ($CDCl_3$) δ 7.62 and 7.61 (d, 2H), 5.89–5.84 (m, 24H, furan, pyrrole-Hs), 1.90 (m, 48H, methylene), 0.69 (m, 72H, methyl); ^{13}C NMR ($CDCl_3$) δ 157.92, 157.56, 156.17, 133.73, 133.61, 133.29, 106.63, 106.59, 106.27, 104.81, 104.56, 46.34, 44.88, 44.76, 44.72, 29.99, 29.71, 29.67, 29.54, 8.89, 8.75, 8.64, 8.61; FAB MS Calcd for $C_{108}H_{148}N_4O_8$ 1629.13, Found 1600.86 ($M^+-C_2H_5$, 36%), 1465 (41%), 1327 (100%).

3.2.3. Condensation of (8) with acetone. To a solution of 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-propyl]furan (**8**) (0.33 g, 0.1 mmol) and acetone (10 mmol) stirred at 0°C under N_2 was added $BF_3{\cdot}Et_2O$ (1.2 μL, 0.1 mmol). The mixture was stirred for 30 min and then quenched with aq. NaOH (0.1N, 10 mL) solution followed by extraction with CH_2Cl_2. The organic layer was washed with water and dried over anhyd. $NaHCO_3$. Column chromatography on silica (hexanes/CH_2Cl_2, 1:1) gave four bands. The fast moving band was identified as cyclic hexamer (**28**) followed by nanomer (**29**), dodecamer (**30**) and pentadecamer (**31**). For (**28**): Yield 0.03 g (39%); R_f: 0.80 (hexanes/CH_2Cl_2, 1:1); ^{1}H NMR ($CDCl_3$), δ 7.66 (s, 4H), 5.88 (m, 4H), 5.80 (s, 4H), 5.74 (m, 4H), 1.85 (q, 16H), 1.50 (s, 12H), 0.66 (t, 24H); ^{13}C NMR ($CDCl_3$), δ 157.69, 137.76, 134.8, 106.13, 104.73, 103.04, 44.6, 35.48, 29.48, 8.66; FAB MS Calcd for $C_{50}H_{68}N_4O_2$ 756.53, Found 756.50 (M^+, 36%), 727.43 ($M^+-C_2H_5$, 100%). For (**29**): Yield 0.017 g (22%); R_f: 0.76 (hexanes/CH_2Cl_2, 2:1); ^{1}H NMR ($CDCl_3$), δ 7.5 (s, 6H), 5.88 (m, 6H), 5.8 (m, 6H), 5.8 (s, 6H), 1.9 (q, 24H), 1.50 (s, 18H), 0.64 (t, 36H); ^{13}C NMR ($CDCl_3$), δ 171.19, 157.52, 137.58, 134.13, 106.48, 105.06, 102.99, 44.96, 35.38, 30.56, 30.26, 29.71, 29.34, 21.06, 14.21, 8.88, 8.59; FAB MS Calcd for $C_{75}H_{102}N_6O_3$ 1134.80, Found 1134.55 (M^+, 31%), 1105.51 ($M^+-C_2H_5$, 100%). For (**30**): Yield 0.014 g (10%); R_f: 0.71 (hexanes/CH_2Cl_2, 2:1); ^{1}H NMR ($CDCl_3$), δ 7.54 (s, 8H), 5.85 (m, 8H), 5.82 (m, 8H), 5.81 (s, 8H), 1.82 (q, 30H), 1.5 (s, 24H), 0.64 (t, 48H); ^{13}C NMR ($CDCl_3$), δ 157.92, 137.98, 134.54, 106.88, 106.80, 103.39, 45.36, 45.85, 35.78, 30.72, 30.65, 29.74, 9.28; FAB MS Calcd for $C_{100}H_{136}N_8O_4$ 1513.07, Found 1513.91 (M^+, 1%), 1484.89 ($M^+-C_2H_5$, 3.6%), 1105.60 (M^+, 100%).

For (**31**): Yield 0.014 g (8%); R_f: 0.69 (hexanes/CH_2Cl_2, 2:1); ^1H NMR ($CDCl_3$), δ 7.75 (s, 10H), 5.86 (m, 10H), 5.84 (m, 10H), 5.82 (s, 10H), 1.8 (q, 40H), 1.42 (s, 30H), 0.6 (t, 60H); ^{13}C NMR ($CDCl_3$), δ 157.53, 137.58, 134.16, 125.53, 106.39, 104.92, 102.92, 44.87, 35.328, 30.55, 30.32, 8.83; FAB MS Calcd for $C_{108}H_{148}N_4O_8$ 1891.34, Found 1862.05 ($M^+-C_2H_5$, 7.9%), 1484.83 (M^+, 100%).

3.2.4. Condensation of (8) with acetone in acetonitrile. To a solution of 2,5-bis[1-methyl-1(1*H*-pyrrol-2-yl)-propyl]-furan (**8**) (0.067 g, 0.2 mmol) and acetone (20 μL) in acetonitrile (20 mL) stirred at 0°C under N_2 atmosphere wad added $BF_3{\cdot}Et_2O$ (2.4 μL, 0.02 mmol). The mixture was stirred for 30 min and then worked up as described above. Column chromatography on silica (hexanes/CH_2Cl_2, 1:1) afforded 0.01 g (13%) of hexamer (**28**). R_f 0.69 (Hexanes/CH_2Cl_2, 1:1). Another minor product isolated from the column was identified as the linear furano-pyrrole (**32**). Yield 0.01 g (13%); R_f: 0.60 (hexanes/CH_2Cl_2, 1:1); ^1H NMR ($CDCl_3$) δ 7.84 (s, 2H), 7.46 (s, 2H), 6.56 (s, 2H), 6.09 (m, 2H), 5.95 (m, 2H), 5.92 (m, 2H), 5.88 (m, 4H), 5.84 (m, 2H), 1.9 (q, 16H), 1.48 (s, 6H), 0.62 (t, 24H); ^{13}C NMR ($CDCl_3$) δ 158.40, 139.02, 135.46, 106.94, 104.50, 103.23, 102.94, 44.28, 35.60, 30.10, 29.71, 27.33, 8.27; FAB MS Calcd for $C_{47}H_{64}N_4O_2$ 716.50, Found 716.30 (M^+, 11%), 688.33 ($M-C_2H_5$, 11%). The major component isolated was the unreacted starting material (**8**) (0.034 g, 45% recovery); R_f: 0.64 (hexanes/CH_2Cl_2, 1:1). The identity was confirmed by NMR.

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References

1. (a) Gale, P. A.; Sessler, J. L.; Kral, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140. (b) Purrello, R.; Gurrieri, S.; Lauceri, R. *Coord. Chem. Rev.* **1999**, *190–192*, 683. (c) Beer, P. D.; Cadman, J. *Coord. Chem. Rev.* **2000**, *205*, 131. (d) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
2. (a) Pflugrath, J. W.; Quiocho, F. A. *Nature* **1985**, *314*, 257. (b) Luecke, H.; Quiocho, F. A. *Nature* **1990**, *347*, 402.
3. Black, B. C.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438.
4. Iverson, B. L.; Shreder, K.; Kral, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 11022.
5. Jagessar, R. C.; Shang, W. M.; Scheidt, R.; Burns, D. H. *J. Am. Chem. Soc.* **1998**, *120*, 11684.
6. Sessler, J. L.; Andrievsky, A.; Genge, J. W. *Advanced Supramolecular Chemistry*; Lehn, J. M., Ed.; JAI: Greenwich, CT, 1997; Vol. 4, p. 97.
7. Stryer, L. *Biochemistry*; Freeman: New York, 1998, Chapter 37.
8. Hosseini, M. W.; Lehn, J.-M.; Maggiora, L.; Mertes, K. B.; Mertes, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 537.
9. Gale, P. A.; Genge, J. W.; Kral, V.; McKervey, M. A.; Sessler, J. L.; Walker, A. *Tetrahedron Lett.* **1997**, *38*, 8443.
10. Crescenzi, R.; Solari, E.; Floriani, C.; Villa, C. A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35*, 2413.
11. (a) Kretz, C. M.; Gallo, E.; Solari, E.; Floriani, C.; Villa, C. A.; Rizzoli, C. *J. Am. Chem. Soc.* **1994**, *116*, 10775. (b) Benech, J. M.; Bonomo, L.; Solari, E.; Scopelliti, R.; Floriani, C. *Angew. Chem., Int. Ed. Engl.* **1999**, *111*, 2107.
12. Nation, D. A.; Reibenspies, J.; Martell, E. *Inorg. Chem.* **1996**, *35*, 4597.
13. Sessler, J. L.; Gebauer, A.; Gale, P. A. *Gazz. Chim. Ital.* **1997**, *127*, 723.
14. 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.
15. Cafeo, G.; Kohnke, F. H.; Torre, L. G. L.; White, J. P. A.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1496.
16. Turner, B.; Botoshansky, M.; Eichen, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2475.
17. Kohnke, F. H.; Torre, L. G. L.; Paisi, M. F.; Menzer, S.; Williams, D. J. *Tetrahedron Lett.* **1996**, *37*, 4593.
18. Brown, W. H.; French, W. N. *Can. J. Chem.* **1958**, *36*, 371.
19. Nagarajan, A.; Jang, Y. S.; Lee, C. H. *Org. Lett.* **2000**, *2*, 3115.
20. Kral, V.; Sessler, J. L.; Zimmerman, S.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1055.
21. Crescenzi, R.; Solari, E.; Floriani, C.; Villa, C. A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35*, 2413.
22. Jang, Y. S.; Kim, H. J.; Lee, P. H.; Lee, C. H. *Tetrahedron Lett.* **2000**, *40*, 2919.
23. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887.