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Synthesis of oligopyrrolic cluster bearing thiophene spacer as potential anion receptors

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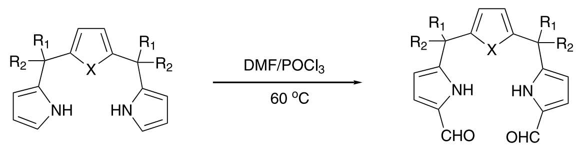
Abstract—The oligopyrrolic clusters and tripyrrylmethane have been synthesized and characterized by the utilization of 2-formylpyrroles and their derivatives as building blocks. Condensation of dialdehydes **9** with pyrrole in the presence of $BF_3(Et_2O)$ resulted in the formation of tripyrrlymethane **10**, while similar condensation performed in trifluoroacetic acid afforded oligopyrrolic cluster **11** on the other hand. The nature of substituents at *meso*-positions resulted in the formation of completely different products.

Polypyrrolic macrocycles have shown considerable interests since anion recognition properties have been discovered some years ago.[1] The conformational flexibility and H-bonding ability of calix[*n*]pyrroles enable to strongly hold guest species by multi-point, noncovalent interactions. Accordingly, many potential applications such as in the anionic sensors, neutral receptors and carriers have been explored recently.[2] In contrast to the cyclic oligopyrroles, the chemistry of linear oligopyrroles has not been explored and especially, the chemistry of oligopyrrolic clusters has been remained virtually unexplored except the quinoxaline based oligopyrroles reported by Sessler et al.[2f] The association constants for phosphate binding by those quinoxaline-based oligopyrroles showed improvement compared to those of closed systems. Simple mono atomic anions such as halogens easily fit or reside inside the cavity of calix[4]pyrroles while multi-atomic anions preferentially need H-bonding donors arranged three dimensionally in order to maximize the interactions. With these regards, the best model systems for multi-atomic anionic guests would be oligopyrrolic clusters having proper dimensions and binding sites. Thus, appropriately modified oligopyrrolic clusters may be a solution for these. Closed macrocycles such as calix[4]pyrroles have comparably smaller cavity sizes and multi-atomic anions such as phosphates or carboxylates are not accommodated well. Larger macrocycles than calix[4]pyrroles also did not show improved binding characteristics for larger anions.[3] Thus, the design and synthesis of a receptors displaying enhanced selectivity for larger anions would be challenging and here, we report the synthesis of pyrrolic acyclic clusters representing a new receptor system for rather larger anions.

Macrocyclic or acyclic oligopyrrolic compounds have shown various anion binding properties with diverse affinities. The synthesis of compounds **1**–**4** has been documented previously[4] and the bisformylation employing Vilsmeier–Haack reaction[5] afforded the desired products in good yields as shown in Scheme 1. The tripyrromethane (**4**) gave lowest yield (47%). Since our original intention was to synthesize various dimensional probes for the anion-binding oligopyrrylic clusters, we attempted to synthesize a cluster bearing thiophene spacer.

Treatment of **6** with excess pyrrole in the presence of acid catalyst (TFA) afforded desired cluster **11** in 52% yield. On the other hand, attempted reaction of **9** under the same condition as those of the synthesis of **11**



1 $X = S, R_1 = R_2 = CH_3$
2 $X = S, R_1 = R_2 = Ph$
3 $X = O, R_1 = R_2 = CH_3$
4 $X = NH, R_1 = H, R_2 = Ph(p\text{-}OMe)$

5 $X = S, R_1 = R_2 = CH_3$ (67 %)
6 $X = S, R_1 = R_2 = Ph$ (87 %)
7 $X = O, R_1 = R_2 = CH_3$ (72 %)
8 $X = NH, R_1 = H, R_2 = Ph(p\text{-}OMe)$ (47 %)

Scheme 1.

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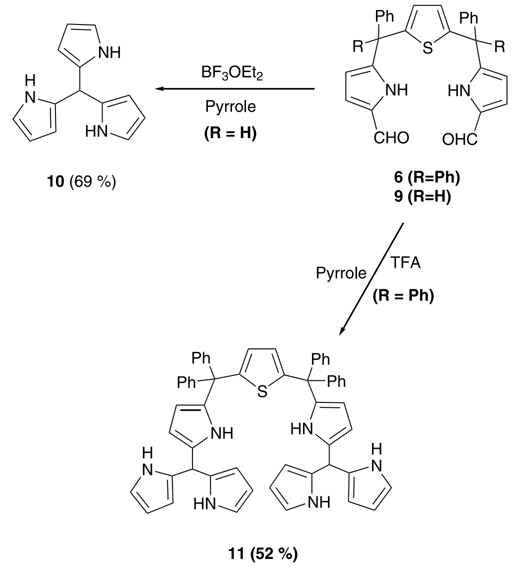
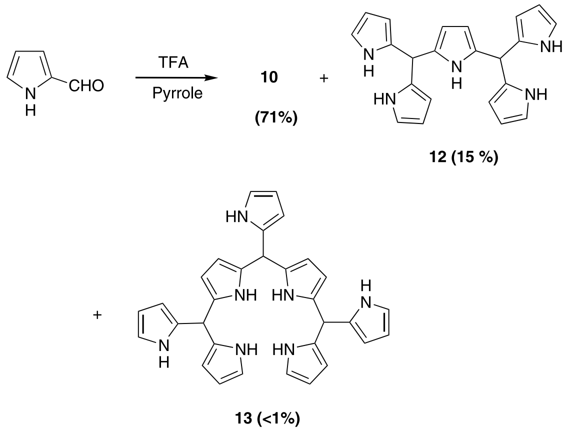


Scheme 2.



Scheme 3.

unexpectedly resulted in the formation of tripyrrylmethane (**10**) as single product. Attempted condensation of **9** with pyrrole in the presence of other acids such as BF_3 or arene sulfonic acid did not alter the outcome of the reaction. It is interesting to note that the existence of *meso*-hydrogen somehow enhance the cleavage of pyrrole-(*meso*-carbon) bond. The existence of two phenyl groups at *meso*-position may induce steric hindrance for initial protonation at 4-posion of pyrrole and subsequently the cleavage of pyrrole-(*meso*-carbon) bond is hampered. Any other thiophene derivatives were not detected except polymeric material in these reactions. Synthesis of **10** from acid-catalyzed reaction of orthoformate with pyrrole has been reported recently.[6] Although the facile cleavage of the pyrrole–carbon bond in **9** is not easy to rationalize at this point, the method provided here could be alternative method of the synthesis of tripyrrylmethane (**10**). The condensation of aromatic dialdehydes with furan or thiophene to give oligofuran (or oligothiophene) has been reported previously.[7]

The solvent-free condensation of 2-formylpyrrole in the presence of acid catalyst also afforded tripyrrylmethane (**10**) in high yield as shown in Scheme 3. Unlike the reaction shown in Scheme 2, 2,5-bis[(2,2′-dipyrryl)methyl]pyrrole (**12**) and higher oligomer (**13**) were also isolated in 15 and 1%, respectively, in this case.[9]

The solution phase anion binding properties of **11** was evaluated using proton NMR spectroscopic method. A tetrabutyl ammonium salt of $H_2PO_4^-$ was added to the solution of **11** (2.0 mM) in $CDCl_3$. The chemical shift changes of pyrrolic N–H in each addition of guest were plotted against molar equivalence of guest. The chemical shift was found to be a function of guest concentration and calculated binding constant using standard non-linear curve fitting was 65 mol^{-1} dm^3. These results confirm that the tripyrrylic clusters bearing thiophene spacer could recognize phosphate anion. The value obtained is far less than the one reported[2f] and this is probably due to the different geometric separation of the two binding units. The linear two-carbon spacer (quinoxaline) must be suitable for cooperative-binding. But the thiophene spacer makes the two binding units separated far apart and thus only inside two pyrrole units may participate the binding event. Indeed, the reported value is well match with the one of dipyrroquinoxaline.[2f] These results indicate that the proper dimensional separation and geometry of the binding subunits are important in recognition event of non-spherical anions.

In conclusion, we have demonstrated that the tripyrrylmethane (**10**) could be synthesized by several alternative methods with reasonable yield. This type of pyrrolic clusters could be applied to the synthesis of pyrrolic cage compounds.[8] The compounds reported here could be good models for the dimensional probes for anion-binding event. The preliminary anion binding studies of the titled compound shows mild phosphate affinity and currently complexation studies with other multi-atom anions are under progress.

Acknowledgements

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9. Spectroscopic data for the selected compounds: for **5**: Yield 0.54 g (67%), yellow solid; ^{1}H NMR ($CDCl_3$): δ 9.33 (s, 2H, aldehyde-H), 9.16 (brs, 2H, N-H), 6.92–6.91 (m, 2H, pyrrole-H), 6.66 (s, 2H, thiophene-H), 6.23–6.21 (m, 2H, pyrrole-H), 1.74 (s, 12H, CH_3). FAB MS calcd for $C_{20}H_{22}N_2SO_2$ 354.14, found 355.14 (M^++1). For **6**: Yield 0.57 g (87%); ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 2H, aldehyde-H), 8.87 (brs, 2H, N-H), 7.31–7.28 (m, 12H, Ar-H), 7.11–7.08 (m, 8H, Ar-H), 6.91 (d, 2H, $J=4.0$ Hz, pyrrole-H), 6.62 (s, 2H, thiophene-H), 6.18 (d, 2H, $J=4.0$ Hz, pyrrole-H). EI MS calcd for $C_{40}H_{30}N_2SO_2$ 602.20, found 602.19 (M^+). For **7**: Yield 0.26 g (72%); ^{1}H NMR ($CDCl_3$): δ 9.38 (brs, 4H, CHO and N-H), 6.88–6.86 (m, 2H, pyrrole-H), 6.14–6.13 (m, 2H, pyrrole-H), 6.00 (s, 2H, furan-H), 1.65 (s, 12H, CH_3). EI MS calcd for $C_{20}H_{22}N_2O_3$ 338.16, found 338.12 (M^+). For **8**: Yield 0.11 g (47%); ^{1}H NMR ($CDCl_3$): δ 9.26 (s, 2H, CHO), 9.25 (brs, 2H, N-H), 8.02 (brs, 1H, N-H), 7.06 (d, 4H, $J=7.3$ Hz, Ar-H), 6.86–6.85 (m, 2H, pyrrole-H), 6.83 (d, 4H, $J=6.7$ Hz, Ar-H), 6.07–6.05 (m, 2H, pyrrole-H), 5.80 (d, 2H, $J=2.5$ Hz, pyrrole-H), 5.37 (s, 2H, *meso*-H), 3.78 (s, 6H, OCH_3). EI MS calcd for $C_{30}H_{27}N_3O_4$ 493.20, found 493.16 (M^+). For **11**: Yield 0.11 g (52%); ^{1}H NMR ($CDCl_3$): δ 7.86 (brs, 4H, N-H), 7.75 (brs, 2H, N-H), 7.27–7.24 (m, 12H, Ar-H), 7.11–7.09 (m, 8H, Ar-H), 6.52–6.51 (m, 4H, pyrrole-H), 6.51 (s, 2H, thiophene-H), 6.05–6.02 (q, 4H, $J=2.8$ Hz, pyrrole-H), 5.92 (m, 4H, pyrrole-H), 5.87 (t, 2H, $J=3.0$ Hz, pyrrole-H), 5.79 (t, 2H, $J=3.0$ Hz, pyrrole-H), 5.42 (s, 2H, *meso*-H); FAB MS calcd for $C_{56}H_{46}N_6S$ 834.35, found 833.68. For **10**: ^{1}H NMR ($CDCl_3$): δ 7.98 (brs, 3H, N-H), 6.70–6.69 (m, 3H, pyrrole-H), 6.18 (q, 3H, $J=3.0$ Hz, pyrrole-H), 6.06 (m, 3H, pyrrole-H), 5.56 (s, 1H, *meso*-H); EI MS calcd for $C_{13}H_{13}N_3$ 211.11, found 211.12. For **12**: ^{1}H NMR ($CDCl_3$): δ 7.98 (brs, 4H, N-H), 7.89 (brs, 1H, N-H), 6.69–6.67 (m, 4H, pyrrole-H), 6.15 (q, 4H, $J=2.8$ Hz, pyrrole-H), 6.00–5.99 (m, 4H, pyrrole-H), 5.92 (d, 2H, $J=2.6$ Hz, pyrrole-H), 5.46 (s, 2H, *meso*-H). EI MS calcd for $C_{20}H_{21}N_5$ 355.18, found 355.16 (M^+).