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Hydrogen-bonding pyrrolic amide cleft anion receptors

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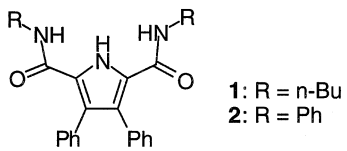
Abstract—The use of simple 2,5-diamidopyrrole derivatives as anion receptors has been investigated. Reaction of 3,4-diphenylpyrrole-2,5-dicarboxylic acid chloride with *n*-butylamine or aniline has produced two new amidic cleft anion receptors **1** and **2**. The anion-coordination ability of these species has been determined by ^{1}H NMR titration techniques. Crystal structures of **1** and **2** have been elucidated, revealing a continuous hydrogen bonding network formed by **1** and dimerization of **2** via NH···O and CH···O hydrogen bonds.

1. Introduction

The anion coordination ability of receptors containing pyrrole groups has been an area of increasing interest in the last decade. Recent developments in the area of anion recognition and sensing have produced a variety of new selective complexation agents for anionic guests.[1] However, the great variety of anionic species and their importance in the environment, in biological systems and potential medical applications presents a continuing challenge to design selective receptors.[2] The pioneering work of Sessler in the area of anion complexation by pyrrolic macrocycles,[3] of Beer[4] and Reinhoudt[5] on amidic hydrogen bond donating anion receptors, of Crabtree on anion coordination by amide cleft species[6] and the recent work of Schmuck on carboxylate recognition by guanidinium substituted pyrrole amides[7] led us to speculate whether simple pyrrole based amide cleft species would function as efficient anion receptor species.[8] In order to test this hypothesis, two new pyrrolic cleft species **1** and **2** were prepared from 3,4-diphenylpyrrole-2,5-dicarboxylic acid chloride and their anion binding abilities studied by ^{1}H NMR titration techniques.



1: R = n-Bu
2: R = Ph

2. Results and discussion

3,4-Diphenylpyrrole-2,5-dicarboxylic acid was prepared via literature methods.[9] The acid chloride was prepared by refluxing the bis acid in thionyl chloride overnight followed by rigorous drying under high vacuum. The

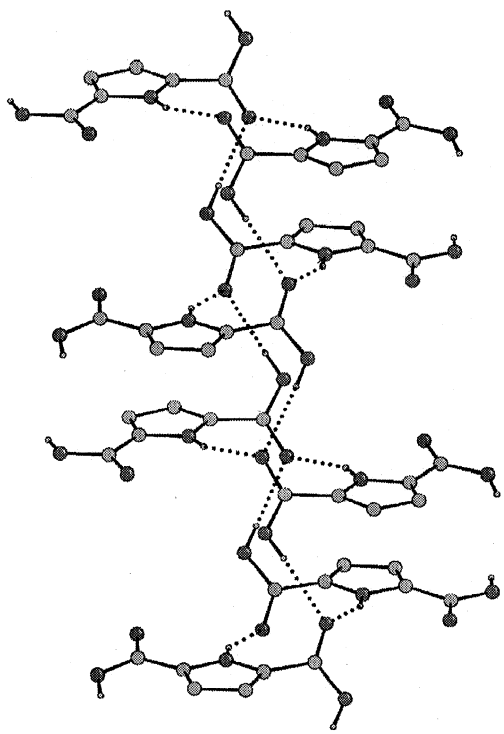


Figure 1. The X-ray crystal structure of **1** (butyl and phenyl groups omitted for clarity) displaying a hydrogen bonding network in the solid state.

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bis acid chloride was then dissolved in dry dichloromethane and 2.0 equiv. of either butylamine or aniline (to produce compounds **1** or **2**, respectively) added with excess triethylamine and the reaction stirred overnight. The resulting solution was reduced in vacuo and the residue purified by column chromatography to yield compounds **1**[10] and **2**[11] in 18 and 47% respective yields.[12]

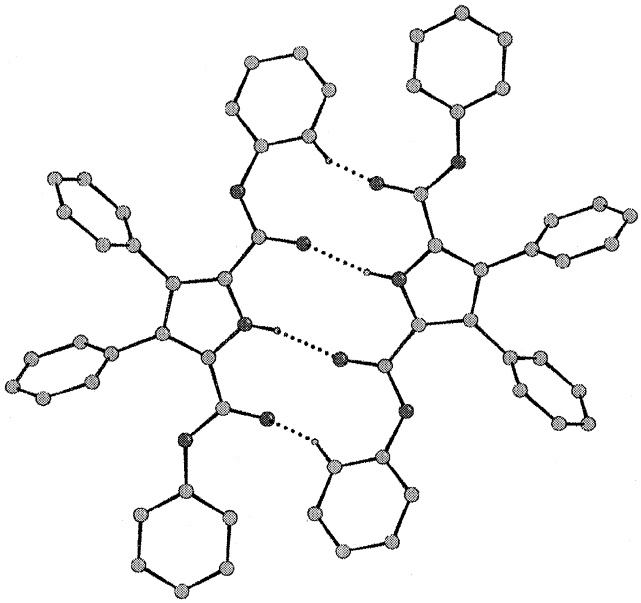

Figure 2. X-ray crystal structure of **2** showing dimerization via two NH···O and two CH···O hydrogen bonds in the solid state.

Table 1. Association constants of **1** and **2** (M^{-1}) with various anionic guest species at 25°C[a]

Compound	Anion[a]	Solvent	K_a (M^{-1})[b]
1	Fluoride[c]	CD_3CN	85
1	Chloride[c]	CD_3CN	138
1	Bromide	CD_3CN	<10
1	Dihydrogen phosphate	CD_3CN	357
1	Benzoate	CD_3CN	2500
2	Fluoride	DMSO/H_2O 0.5%	74
2	Chloride	DMSO/H_2O 0.5%	11
2	Bromide	DMSO/H_2O 0.5%	<10
2	Dihydrogen phosphate	DMSO/H_2O 0.5%	1450
2	Benzoate	DMSO/H_2O 0.5%	560

[a] Anions added as tetrabutylammonium salts dried under high vacuum with heating at 70°C for 24 h prior to use. Acetonitrile water content = 0.03%. Solubility problems prevented studies on compound **2** to be conducted in acetonitrile solution.

[b] Errors estimated to be <15%.

[c] The amount of water present in the acetonitrile can have a dramatic effect on fluoride/chloride selectivity. In the presence of 0.5% water, fluoride is bound with a stability constant of 37.5 M^{-1}, whereas chloride is bound more weakly (K = 12.5 M^{-1}).

Single crystals of compounds **1** and **2** were obtained from CH_2Cl_2/EtOH and acetonitrile, respectively.[13] Both compounds are involved in hydrogen bonding arrays in the solid state. The two independent molecules in crystals of **1** differ only in the conformation of the butyl chains and form pseudo centro-symmetric dimers via chemically equivalent hydrogen bonds. The oxygen atoms then each accept a second hydrogen bond to bridge the dimers into chains that extend along the *c* axis (Fig. 1). Both independent molecules in the crystal structure of **2** form centro-symmetric dimers via both N–H···O hydrogen bonds, and C–H···O hydrogen bonds (Fig. 2).

The association constants of compounds **1** and **2** with a variety of putative anionic guests were measured using ^{1}H NMR titration techniques by following shifts in the amide NH proton resonance.[14] In all cases the data was indicative of 1:1 receptor:anion complex formation, which was confirmed by Job plot analysis. The results are shown in Table 1 and reveal that both **1** and **2** selectively bind oxo-anions in preference to fluoride, chloride or bromide.

3. Conclusions

Receptors **1** and **2** are easy to make selective receptors for oxo-anions. We are currently working to incorporate these pyrrolic cleft systems into a variety of more complex anion receptor and sensor systems for selective complexation and detection of oxo-anions. The results of this work will be published in due course.

Acknowledgements

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8. Interestingly, *N*-unsubstituted pyrrole groups with amide moieties in the 2 and 4 positions are present in pyrronamycins, novel antitumor antibiotics: Asai, A.; Sakai, Y.; Ogawa, H.; Yamashita, Y.; Kakita, S.; Ochiai, K.; Ashizawa, T.; Mihara, A.; Mizukami, T.; Nakano, H. *J. Antibiot*. **2000**, *53*, 66–69.
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10. Spectroscopic data for compound **1**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.91 (t, 6H, $J=7.26$, CH_3), 1.23 (m, 4H, CH_2CH_3), 1.37 (m, 4H, CH_2), 3.20 (m, 4H, NCH_2), [7.10 (t, 2H, $J=5.46$, Ar), 7.18 (m, 4H, Ar), 7.30 (m, 4H, Ar), +obscured amide CONH, 2H], 12.03 (s, 1H, NH). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 13.7, 19.9, 31.2, 39.0, 124.1, 125.7, 128.1, 128.9, 130.9, 133.6, 160.4. +ve ESMS (857.6 2 M+ Na^+). Elemental analysis: **1**+1/2 H_2O: calcd: C, 73.21; H, 7.56; N, 9.85. Obs. C, 72.82; H, 7.37; N, 9.75.
11. Spectroscopic data for compound **2**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.15 (t, 2H, $J=7.29$, Ar), 7.34 (m, 14H, Ar), 7.55 (d, 4H, $J=8.19$, Ar), 9.37 (s, 2H, CONH), 12.67 (s, 1H, NH). ^{13}C NMR (75.48 MHz, DMSO-d_6): 119.3, 123.5, 124.7, 126.8, 127.2, 127.8, 128.7, 130.5, 133.7, 138.5, 158.6. +ve ESMS (937.4 2 M+ Na^+). Elemental analysis **2**+ 1/3 H_2O calcd C, 77.73; H, 5.15; N, 9.07. Obs. C, 77.90; H, 4.76; N, 8.80.
12. The moderate yields of these reactions are attributed to the formation of other species (see Boatman R. J.; Whitlock, H. W. *J. Org. Chem*. **1976**, *41*, 3050–3051). The crystal structure of a four-component condensation by-product was elucidated (see Ref. 13).
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 160246 (compound **1**), CCDC 160248 (compound **2**) and CCDC 160247 (by-product (see Ref. 12)). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. After the original submission of this manuscript, a similar hydrogen-bonding motif to that observed in compound **2** has been reported in a methyl 5-amidopyrrole-2-carboxylate (see: Schmuck, C.; Lex, J. *Eur. J. Org. Chem*. **2001**, 1519–1523).
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