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Crown Ether Appended Amidopyrrole Clefts

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Two new pyrrole amide–crown ether conjugates have been synthesised and their anion complexation properties studied in the absence and presence of stoichiometric quantities of sodium or caesium cations. Certain anions are sequestered by the metal cation in DMSO-d_6 (0.5% water), however, in one case a 4.7 fold increase in the fluoride affinity of the receptor was observed upon addition of caesium cations.

Keywords: Ion-pairing; Pyrrole; Ion-pair receptor; Anion recognition

The combination of a cation and anion binding site in the same receptor may result in the production of a receptor capable of coordinating an ion-pair with positive cooperativity of binding of one component of the pair when the other is present. This may lead to the production of receptors that can extract salts from aqueous solutions. A variety of ion-pair receptors have been synthesised in both the inorganic and organic arenas [1]. Reetz and co-workers have shown that crown ethers containing pendant boron atoms are capable of coordinating KF [2], whilst Beer *et al.* [3,4] and Reinhoudt and co-workers [5,6] have produced a variety of ion-pair receptors containing crown ether cation binding sites and amide or urea anion binding sites. Tasker and co-workers have shown that salen based receptors containing amine groups are efficient complexing agents for transition metal salts such as nickel sulphate [7], whilst Sessler and co-workers have appended crown ethers to calixpyrroles and shown that these compounds exhibit enhanced anion binding in the presence of stoichiometric amounts of sodium cations [1]. Smith and co-workers have combined anion-binding isophthalic amide clefts with crown ethers to produce receptors capable of binding a contact ion pair [8]. Recently, we have found that 2,5-diamidopyrroles are excellent neutral receptors for oxo-anions such as carboxylates and dihydrogen phosphate [9–14]. We decided to combine our 2-amido- and 2,5-diamidopyrrole anion binding groups with crown ether moieties and explore the coordination properties of these new materials by ^{1}H NMR titration techniques.

RESULTS AND DISCUSSION

Compound **1** was synthesised by reacting 5-methyl-3,4-diphenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester [15,16] with 4′-aminobenzo-15-crown-5-ether in the presence of $AlMe_3$ [17] (Scheme 1). The reaction mixture was quenched with 2 M HCl and after washing the organic phase with water, drying and removal of solvent, crystallization of the crude product from the minimum amount of acetonitrile led to the isolation of compound **1** in 28% yield.

Compound **2** was synthesised by reaction of 3,4-diphenyl-1*H*-pyrrole-2,5-dicarbonyl dichloride [18,19] with 4′-aminobenzo-15-crown-5 in dichloromethane in the presence of triethylamine and a catalytic amount of DMAP (Scheme 2) for 72 h with stirring under nitrogen. After reaction the reaction mixture was washed with water, dried with magnesium sulphate and the solvent then removed *in vacuo*. The desired compound was isolated in 33% yield by crystallization of the crude product from acetonitrile.

Slow evaporation of a dilute acetonitrile solution of compound **1** led to the formation of X-ray quality

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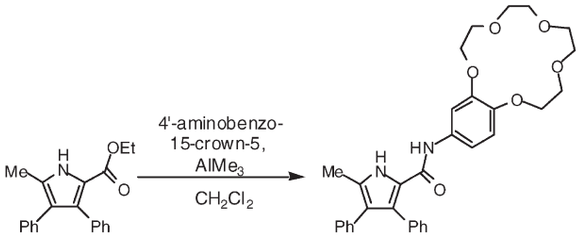
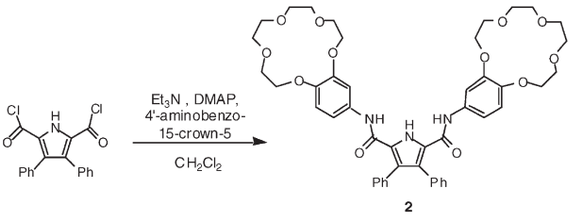


1

SCHEME 1



2

SCHEME 2

single crystals[†]. The crystal structure (Fig. 1) revealed the receptor forms a dimer via the formation of two hydrogen bonds between the pyrrolic NH group and the carbonyl group as has been observed previously in a variety of 2-amidopyrroles. The NH···OC distance was found to be 2.814(5) Å.

Proton NMR titration experiments in DMSO-d_6 (0.5% water) have been performed in order to investigate the anion coordination properties of receptors **1** and **2** (Table I) with the data fitted to a binding model using the EQNMR computer program[20]. All the titration curves (amide NH proton followed) were consistent with the formation of 1:1 complexes. As has been observed previously with 2,5-diamidopyrroles, receptor **2** proved to be selective for oxo-anions binding dihydrogenphosphate selectively and receptor **1** the mono-amide shows a considerably lower affinity for anions than the bis-amide analogue.

The same experiments were carried out in the presence of one equivalent of sodium or caesium cations for receptor **1** and two equivalents of both cations for receptor **2**. Interestingly, the presence of a cation did not enhance the anion coordination strength at all, instead a decrease of the association constant values was observed (Table II). Only fluoride was bound almost five times more strongly to receptor **2** in the presence of caesium cations in DMSO-d_6 (0.5% water) solution.

Interestingly, in some cases the metal ion seemed to compete with the anion binding site in the coordination of the anionic species. For example, upon addition of tetrabutylammonium fluoride to a DMSO solution containing **2** together with 2 equivalents of sodium tetraphenylborate, the first two equivalents of anion appear not to bind to the pyrrole anion-binding site. However, further addition of fluoride produced a "normal looking" curve (Fig. 2).

The same behaviour has been recently observed by Smith and co-workers during the investigation of the anion complexation properties of a simple urea based anion receptor in DMSO solution in the presence of a "non-innocent" metal cation such as sodium, potassium or caesium [21]. These authors attribute the unusual titration profile to the formation of an ion-pair resulting from anion sequesteration by the metal cation.

CONCLUSION

The results reported here confirm Smith's findings that metal cations can sequester anions from "ion-pair receptors" in that in these systems dihydrogen phosphate, and in some cases fluoride, are stoichiometrically sequestered by either sodium or caesium cations from compounds **1** or **2**. We are currently exploring other ways of constructing ion-pair receptors based on these motifs. The results of these studies will be published shortly [22].

EXPERIMENTAL SECTION

5-Methyl-3,4-diphenyl-1*H*-pyrrole-2-carboxylic Acid (Benzo-15-crown-5)-amide (1)

4′-Aminobenzo-15-crown-5 (835 mg, 2.9 mmol) was dissolved in CH_2Cl_2 (15 ml) and a 2 M hexane solution of $AlMe_3$ (1.47 ml, 2.9 mmol) was added dropwise. After stirring for 30 min

[†]*Crystallographic data for* $C_{32}H_{34}N_2O_6$: Monoclinic, space group $P2_1/n$, $a = 9.093(2)$, $b = 36.865(7)$, $c = 16.608(3)$ Å^3, $D_c = 1.296\,\mathrm{Mg\,m^{-3}}$, $\mu = 0.09\,\mathrm{mm^{-1}}$, $Z = 8$, $T = 120(2)$ K, colourless plate, $0.14 \times 0.10 \times 0.01\,\mathrm{mm^3}$. Data collection was carried out using an Enraf Nonius KappaCCD area detector and SHELXS-97 and SHELXL-97 (G.M. Sheldrick, 1997, University of Göttingen, Germany) programs were used for structure solution and refinement. 47013 reflections collected, 8960 independent [R(int) = 0.1535] which were used in all calculations. $R_1 = 0.0814$ for observed unique reflections [$F^2 > 2\sigma(F^2)$] and $wR_2 = 0.2251$ for all data. The macrocyclic crown ether moieties exhibit some conformational disorder which, combined with the poor data quality (maximum $2\theta = 25.03°$ and number reflections $F^2 > 2\sigma(F^2) = 3486$), are the causes of a slightly lower than normal accuracy of the structure. The maximum and minimum residual electron densities on the final difference Fourier map were 0.653 and $-0.471\,\mathrm{eÅ^{-3}}$, respectively. Supplementary data have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 187888).

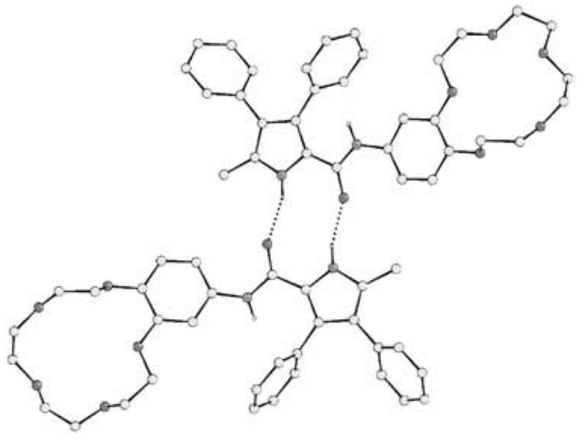


FIGURE 1 Crystal structure of receptor **1** showing the formation of a dimer in the solid state ($N_{pyrrole}\cdots OC = 2.814(5)$ Å).

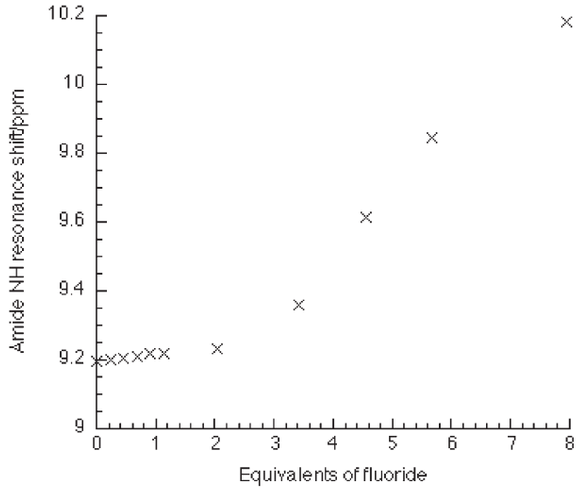


FIGURE 2 Proton NMR titration obtained by adding discrete amounts of fluoride anions to a DMSO solution of receptor **2** in the presence of two equivalents of sodium tetraphenylborate.

5-methyl-3,4-diphenyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (900 mg, 2.9 mmol) was added and the mixture stirred for 3 days. The solution was carefully quenched with 2 M HCl solution (20 ml) and the phases were separated. The water solution was extracted with CH_2Cl_2 (50 ml) and the organic phases were joined, dried on $MgSO_4$ and filtered off. The solvent was removed *in vacuo* and acetonitrile (5 ml) was added to the residue leading to the wanted compound as a white and crystalline sold (448 mg, 28%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.37 (s, 3H, CH_3), 3.75–4.09 (m, 16H, OCH_2), 6.37 (dd, 1H, $J_1 = 7.9$, $J_2 = 1.8$, Arom.), 6.72 (d, 1H, $J = 9$ Hz, Arom.), 7.06 (d, 1H, $J = 6.3$, Arom.), 7.12–7.43 (m, 10H, Arom), 9.70 (s, 1H, pyrr. NH) (amide NH hidden in the aromatic area). ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 12.47, 69.22, 69.86, 70.03, 70.77, 70.89, 71.29, 106.59, 111.80,115.18, 121.50, 126.43, 128.47, 128.62, 129.59, 130.02, 130.61, 131.80, 132.94, 135.70, 149.90, 159.56. MS (ES^+) 565 ($M + Na^+$), 1108 ($2M + Na^+$). HRMS (ES^+): 565.13 ($M + Na^+$), $\Delta = 1.6$ ppm. Anal. calcd for $C_{46}H_{51}N_3O_{12}$. $(1/3)H_2O\cdot(1/3)CH_2Cl_2$: C, 67.31; H, 6.17; N, 4.86. Found: C, 67.15; H, 5.67; N, 4.95.

TABLE I Association constant of receptors **1** and **2** (M^{-1}) with various anionic guests at 25°C in DMSO-d_6 (0.5% water)

Anion	Compound **1**	Compound **2**
Fluoride	*	67
Chloride	<10	16
Benzoate	70	895
Dihydrogen phosphate	307	1880

The anions were added as tetrabutylammonium salts. The errors were estimated to be <15%. *NH resonance disappears during titration.

3,4-Diphenyl-1*H*-pyrrole-2,5-dicarboxylic Acid Bis-(benzo-15-crown-5)-amide (2)

3,4-Diphenyl-1*H*-pyrrole-2,5-dicarboxylic acid (1.0 g, 3.3 mmol) was suspended in $SOCl_2$ (20 ml) and refluxed overnight. The reaction was allowed to cool and the excess of $SOCl_2$ was removed *in vacuo*. A brown solid formed that was dissolved in dichloromethane (30 ml) and Et_3N (0.74 g, 7.3 mmol) and DMAP (5 mg, 0.04 mmol) were added. After addition of 4′-aminobenzo-15-crown-5, the mixture was stirred at room temperature for 72 h.

TABLE II Association constant of receptors **1** in the presence of sodium ions, and **2** the presence of sodium and caesium ions (M^{-1}) with various anionic guests at 25°C in DMSO-d_6

Anion	Receptor **1** + 1 eq of Na^{+}*	Receptor **1** + 1 eq of Cs*	Receptor **2** + 2 eq. of Na^{+}*	Receptor **2** + 2 eq. of Cs^{+}*
Fluoride	†	†	†	307.5
Chloride	6.7	<10	16.6	1.8
Benzoate	29.7	87	296.7	816.4
Dihydrogen phosphate	‡	‡	‡	‡

The anions were added as tetrabutylammonium salts. The errors were estimated to be <15%. *Cation added as tetraphenylborate salt. †Sequestration behaviour: no shift up to one equivalent of anion followed by a shift NH resonance with broadening which dows not allow for an accurate determination of the chemical shift. ‡Sequestration behaviour.

The solution was then washed with water (3×50 ml), dried on $MgSO_4$, and filtered off. The solvent was removed *in vacuo* and the brown solid was recrystallized from acetonitrile (20 ml). A pale yellow solid was filtered off and washed with acetonitrile (2×20 ml) leading to the desired compound (yield: 0.89 g, 33%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.69–4.10 (m, 32H, OCH_2), 6.98 (d,2H, $J = 8.2$ Hz, Arom.), 7.03 (d, 2H, $J = 8.2$ Hz, Arom.), 7.22(s, 2H, Arom.), 7.26–7.36 (m, 10H, Arom.), 9.21 (s, 2H, CONH), 12.54 (s, 1H, NH). ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 69.20, 69.79, 69.94, 69.98, 70.72, 70.84, 71.32, 106.57, 111.89, 115.01, 125.31, 126.81, 129.09, 129.64, 131.71, 132.30, 133.66, 146.24, 149.83, 158.18. MS (ES^+) 442 ($M + 2Na^+$), 860 ($M + Na^+$). HRMS (ES^+): 860 ($M + Na^+$), $\Delta = 0.7$ ppm. Anal. calcd for $C_{46}H_{51}N_3O_{12}{\cdot}H_2O$: C, 64.55; H, 6.24; N, 4.91. Found: C, 64.40; H, 6.23; N, 4.91.

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