Synthesis, Characterisation and Preliminary Anion complexation studies of a nuetral novel 2,7-diacetamido fluorene molecular tweezer receptor

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Abstract: *A novel 2,7-diacetamido fluorene receptor has been synthesized and characterized via ^{1}H NMR, ^{13}C NMR, DEPT 135, ^{1}H-^{1}H COSY, HMQC, HMBC experiments. Preliminary anion binding studies via ^{1}H NMR indicate recognition and complexation of bromide anion. There are only a few neutral amide receptors reported to date*. [Nature and Science. 2008;6(2):80-89]. ISSN: 1545-0740.

Research in Anions coordination Chemistry is increasing, considering the versatile role anions play in nature, medicine, laboratory and industrial processes etc. Several concepts of anion binding motifs have been explored over the years. These include the synthesis of acyclic and macrocyclic ligands incorporating a positively charged centre or a Lewis acidic centre in close proximity and in tandem with amide hydrogen bonds[1-4]. For example, porphyrin (1) was shown spectrally and electrochemically to sense, Cl^-, Br^-, NO_3^-, HSO_4^- and $H_2PO_4^-$ anions with selectivity trend: $H_2PO_4^- > HSO_4^- > Cl^- > Br^- > NO_3^-$. A similar selectivity trend was noted for compound (2) [4]. Other receptors have use neutral urea motifs to complex anions with large binding constants and excellent selectivity[4-8]. For example, a series of highly potent and remarkably highly selective free base "Picket fence" porphyrin urea receptors (3)-(6) and their Zn(II) complexes (7)-(9) were synthesized, characterized[5-6] and anion binding studies investigated. The *Cis*-5,10,15,20-*tetrakis*(2-(arylurea)phenyl)porphyrins bind strongly (K (M^{-1}) > 10^3-10^5) to chloride anion in DMSO-d_6 and also in the more competitive solvent system DMSO-d_6/D_2O (88:12, v/v) as revealed by ^{1}H NMR titration studies. To the very best of knowledge, it is the largest stability constant reported to date for any anion receptors complexing chloride in a highly competitive DMSO-d_6 solvent and also the best chloride selective receptor reported. The selectivity trend $Cl^- > Br^- > H_2PO_4^- > HSO_4^- > NO_3^-$ is also novel for any neutral urea-anion binding system. Of great significance, X-ray crystallography revealed *Cis*-5,10,15,20-*tetrakis*(2-(4-chlorophenylurea)phenyl)porphyrin to be the first coordination complex of an anion (chloride and bromide) bound by a neutral free-base porphyrin. Still other anion binding motifs include the use of Lewis acid centres such as boron and mercury to complex anion such as fluoride[8]. The design and synthesis of neutral receptors is receiving increasing attention, considering the prevalence of amide hydrogen bond in nature[7-8]. There are only a few neutral amide receptors reported to date.

Anion binding and transport has a unique role in nature: In membrane transport for example, the selective flow of ions into and out of cells occurs via anion transport mechanisms. Such processes have been regulated by ion binding proteins whose main mechanism of transport rely on extensive hydrogen bonding in the binding sites complementary to the anion being transported. Phosphate chelation is said to involve the formation of twelve complementary hydrogen bonds with the protein, five from the main chain and seven from side chain residues. Amide hydrogen bonding are also involved in sulphate binding[9,10] with selectivity ratios of phosphate over sulphate or sulphate over phosphate greater than 10^5. Also, in nature, the selective binding for anion is achieved via the positional alignment of amide hydrogen bonds[4]. In Biochemistry, 70% of naturally occurring enzymes require an anion either as a substrate or as a cofactor[12]. For example, the enzyme carbonic anhydrase has as its cofactor Zn^{2+}, a Lewis acid which coordinates OH^-

and thus allowing it to perform its catalytic function. The genetic encoded material DNA and RNA, essential in cell replication and organism growth and ATP which provides the energy required for growth and metabolism are polyanions. Their negative charges are conferred by phosphate ester groups[13]. In the laboratory, anions act as nucleophiles (CN^-), redox active agents ($S_2O_8^{2-}$) in titrations, bases (^-OR) and as phase transfer catalysts. In pursuit of neutral receptors, exhibiting strong and selective complexation for anions in highly competitive solvents, receptor (11), 2,7-diacetamido fluorene was synthesized and characterised. Such a receptor present convergent amide binding sites to host anions, Fig. 2.0 i.e –CO-NH---- anion hydrogen bonds. In such a neutral system, it might also be possible that the positive induced carbonyl carbon may assist in some form of induced dipole---anion interaction, Fig.3.0. Compound (11) was synthesized via the addition of the requisite acid chloride, acetyl chloride to the amine: 2,7- diamino fluorene, dissolved in CH_2Cl_2 in the presence of ET_3N and stirred under nitrogen, Scheme 1.0. The crude sample after work up was purified via flash column silica gel chromatography to gave compound (11) as a white solid in 65 % yield . Compound (11) was characterized via ^{1}HNMR, ^{13}CNMR, , Dept 135, ^{1}H-^{1}H COSY, HMBC, HMQC, FAB MS spectra and IR spectroscopy and these are presented in the experimental sections.

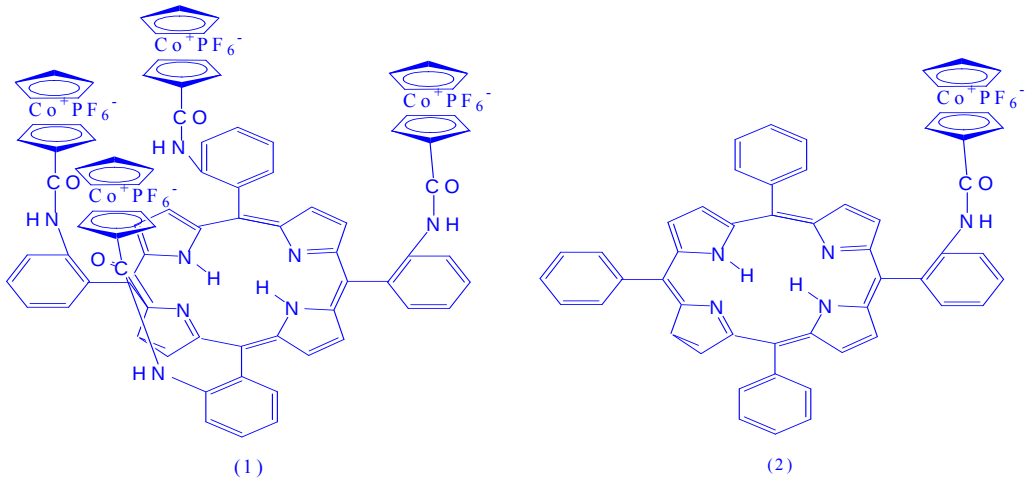
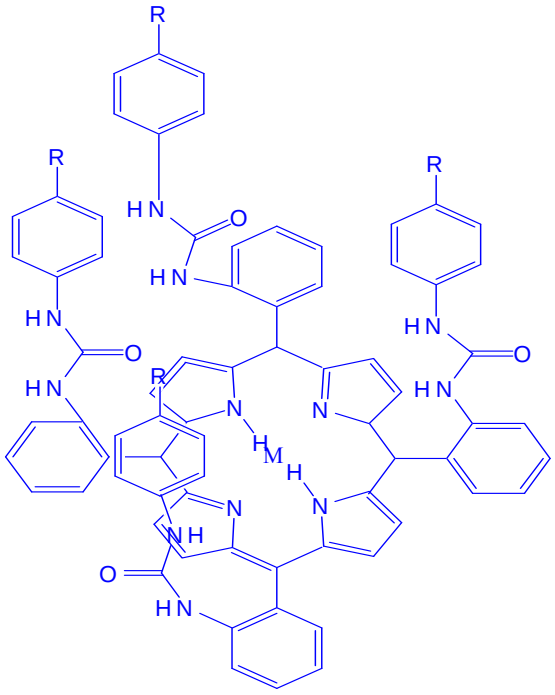


Fig. 1.0. Positively charged cobalticinium amido phenyl functionalised porphyrins: *Cis*-5,10,15,20-*meso tetrakis* (*ortho* cobaltocenium) amido phenyl porphyrin(1) and 5-(*ortho*-(cobaltocenium amido phenyl)-10,15,20-triphenyl porphyrin(2)



R = H, (3)

R = Cl, (4)

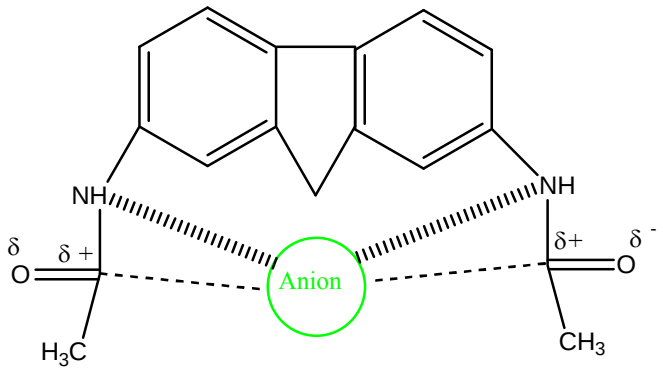
R = F, (5)

R = NO_2 (6)

M = Zn

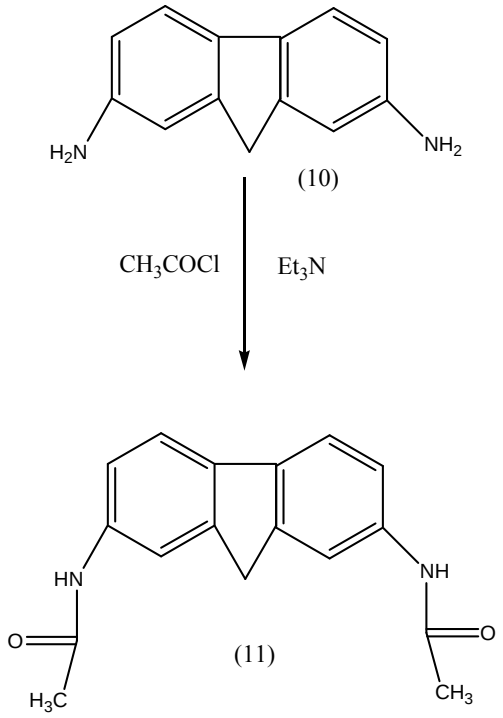
R =H (7), R=Cl (8), R = F (9)

Fig. 2.0. Neutral "Picket fence" Porphyrin urea anion receptors: (α,α,α,α)-5,10,15,20-*meso tetrakis*(2-(arylurea)phenyl) porphyrins.



(11)

Fig. 3.0. Proposed mode of anion binding by the molecular Tweezer (11)



Scheme 1.0. Synthesis of compound (11)

The ^{1}H NMR spectrum, Fig. 4.0, recorded in DMSO-d_6 indicates that the amide protons H-14 and H-17 resonate as a broad singlet downfield at 9.98 ppm. Aromatic protons resonate as a singlet, doublet and double of doublets in the region 7.47 to 7.86 ppm. The singlet at 7.86 ppm is due to H-1=H-8 protons. H-4 = H-5 protons couple with H-3 =H-6 protons. As such they resonate as a doublet at 7.69 ppm. However, H-3=H-6 protons are split into a doublet by H-4 protons which is further split by H-1(J=1.6Hz) resulting in a doublet of doublets. The CH_2 protons that bridge the two benzene rings resonate as a singlet at 3.85 ppm. The CH_3 protons of the acetyl group is seen as a conspicuous sharp singlet at 2.05 ppm, Fig. 4.0. The ^{13}C NMR spectrum indicates the presence of nine different signals due to nine different carbons of the structure. DEPT-135 experiments were used to differentiate the CH_3, CH and CH_2 protons. Accordingly, the only CH_3 proton resonate at 24.42 ppm, whereas the bridged methylene CH_2 protons resonate at 36.9 ppm. The CH aromatic carbons resonate at 119.76, 118.06 and 116.11 ppm. Quaternary carbons were seen at 136.46, 138.13, 143.79 ppm whereas the carbonyl carbons resonate at 168.48 ppm. The complete spectral assignment was furnished via ^{1}H NMR, ^{13}CNMR, ^{13}CNMR-DEPT -135, HMQC, HMBC and ^{1}H-^{1}H COSY experiments and are summarized in Table 1.0.

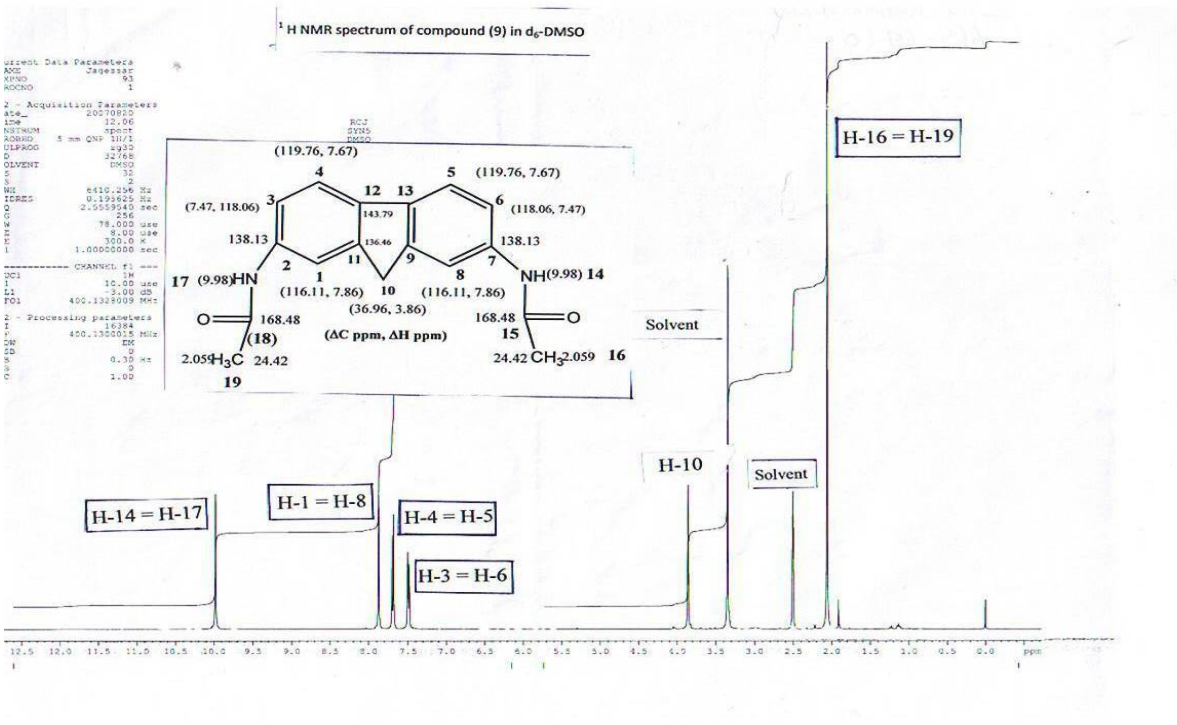


Fig. 4.0 [1] H NMR spectrum of compound (11) in DMSO-d_6

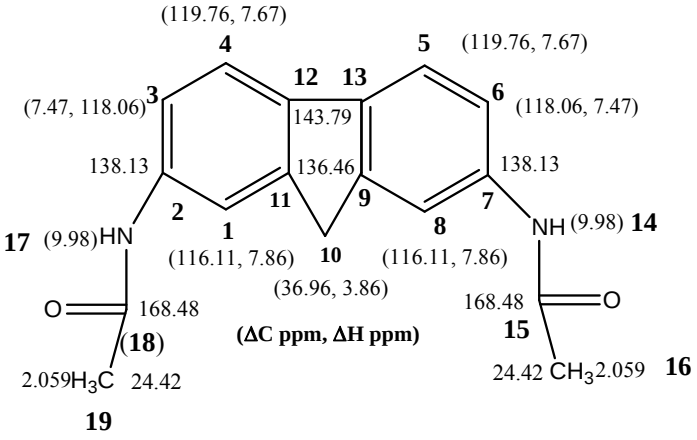


Fig. 5.0 ([13] CNMR and [1] H NMR chemical shifts for respective carbons and protons of compound (11)

Table 1. NMR DATA for compound 11 ($CDCl_3$) [a]

Position	δC	δH (jHH, HZ)	^{1}H-^{1}H COSY	HMBC
1 = 8	116.11	7.86 (s)	H-3, H-4, H-10	118.06(C-3), 136.46(C-11)
2 = 7	138.13	QC	QC	QC
3 = 6	118.06	7.47 (dd, J =1.6Hz)	H-1, H-4	116.11(C-1), 118.06(C-3), 119.76(C-5), 136.46(C-11)
4 = 5	119.76	7.67 (d, J =8.4 Hz)	H-3, H-1, H-10	118.06(C-3), 136.46(C-11), 143.79(C-12)
5 =4	119.76	7.67 (d, J =8.4 Hz)	H-1, H-3, H-10	118.06(C-3), 136.46(C-11), 143.79(C-12)
6 = 3	118.06	7.47 (dd, J=1.6Hz),	H-1, H-4	116.11(C-1), 118.06(C-3), 119.76(C-5), 136.46(C-11)
7 = 2	138.13	QC	QC	QC
8 = 1	116.11	7.86	H-3, H-4, H-10	118.06(C-3), 136.46(C-11)
9 = 11	136.46	----------	QC	
10	36.96	3.86	H-1, H-3, H-4	136.46(C-11), 116.11(C-1), 143.79(C-12)
11= 9	136.46	QC	QC	QC
12=13	143.79	QC	QC	QC
13=12	143.79	QC	QC	QC
14=17	---------	9.98 (s)	---------	116.11(C-1), 118.06(C-3), 168.48(C-15)
15=18	168.48	QC	QC	QC
16 = 19	24.42	2.059	---------	--------

17 =18	NH	9.98 (s)	---------	--------
18 =15	168.48	---------	---------	--------
19 =16	24.42	2.059 (s)	---------	168.48(C-15)

[a] 400 MHz for ^{1}H NMR and 100 MHz for ^{13} C NMR. All Chemical shifts (relative to TMS) are given in δ(ppm) and coupling constants expressed in Hertz.

QC: Quaternary carbon

Preliminary Anion complexation studies:

Preliminary anion binding studies for (11) were investigated via the stepwise addition of tetrabutylammonium halide to solution of compound (11) in deuterated DMSO- d_6 at room temperature. Before, any addition took place, the ^{1} H NMR spectrum of the free ligand was recorded . Addition of stepwise equivalents of anion resulted in significant shifts in the host protons. The ^{1} H NMR spectrum was recorded after each addition. For example, after the addition of 1 equivalent of bromide, the amide protons, -NH-CO- at 9.994 ppm exhibited downfield shift of δS = 0.13 ppm suggesting -CO-NH---Anion complexation. Aromatic protons have also responded to complexation. A new peak at 8.3 ppm is evident. The singlet resonance due to aromatic proton, H-1 shifted downfield from 7.86 to 7.98 ppm (δS = 0.12 ppm) after the addition of two equivalents. Also, the aromatic doublet at 7.64, H-5 exhibited an upfield shift of 0.07 ppm and remained broad. The other doublet at 7.496 exhibited a downfield shift of 0.06 ppm. However, the fluorene methylene protons, H-10 exhibited an insignificant downfield shift of 0.007 ppm.. These shifts are significant, considering that complexation was done in the polar DMSO-d_6 solvent. These results are summarized in the table below:

Table 2.0 ^{1} HNMR chemical shifts of ligand (10) protons after the addition of two equivalents

Protons	Chemical Shifts Free Ligand	Chemical Shifts After the addition of two equivalents of Br-	δS
Methyl protons, H-16 = H-19	2.061	2.088	0.027 ppm
Fluorene methylene protons, H-10	3.858	3.851	0.007 ppm
Aromatic doublet, H-6	7.496	7.56	0.06 ppm
Aromatic doublet, H-5	7.639	7.71	0.07 ppm
Aromatic singlet, H-1	7.862	7.98	0.12 ppm
Amide NH proton, H-14= H-17	9.994	10.13	0.13 ppm

Conclusions: A novel 2,7-diacetoamido fluorene receptor has been synthesized and characterized via ^{1}H NMR, ^{13} C NMR, DEPT 135, ^{1}H-^{1}H COSY, HMQC, HMBC experiments. Preliminary anion binding studies via ^{1} H NMR indicate recognition and complexation of bromide anion. There are only a few neutral amide receptors reported to date. Future work will investigate coordination with other anions.

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General: 2,7-diaminofluorene and acetyl chloride were purchased from Aldrich in the USA. Melting points were measured on a Geahaka model PF 1500 version 1.0 apparatus and are uncorrected. ^{1}H and ^{13}C NMR COSY, HMQC and HMBC spectra were recorded on a Bruker DRX-500 spectrophotometer, using $CDCl_3$ as the solvent. Chemical shifts are quoted in δ ppm and coupling constants expressed in Hertz (Hz). Silica gel 60A (70-230 mesh) was used for flash column chromatography. TLC analyses were done on precoated Kieselgel 60 F_{254} plates.

Experimental: 2,7-diamido fluorene receptors: The amine(0.22 g, 1.1 x 10^{-3} mol) was dissolved in dried CH_2Cl_2 and stirred for 15 minutes under nitrogen. This was followed with the addition of Et_3N, leaving a brown solution . To that solution was added acetyl chloride, CH_3COCl (0.19g, 2.4 x 10^{-3} mol)stepwise. The reaction mixture was left stirring for 24 hours under nitrogen. Solvents were removed in *vacuo*, yielding a brown crude product. After workup, a pale brown solid was obtained. The latter was purified via flash column chromatography on silica gel to yield compound (2) as the major product in yield of 65% (0.2g).

Compound (11) $C_{17}H_{16}O_2N_2$:M.P: 43.4-43.6˚C ^{1}H NMR ($CDCl_3$) δ: 9.978 (s, br; 2H; NH), 7.864 (s, 2H; ArH), 7.68 (d, 2H; J = 8.4Hz; ArH), 7.49 (dd, 1H; J =1.6Hz, ArH), 7.47(dd, J = 1.6Hz, 1H; ArH) 3.85 (s, 2H; CH_2), 2.06(s, 6H; CH_3); ^{13} CNMR ($CDCl_3$, 400MHz) □: 168.47, 143.79, 138.14, 136.48, 119.76, 118.05, 116.11, 38.95, 24.42. DEPT 135: C=O (168.48) QC: 143.75, 138.13, 136.46, ArH CH: (119.76, 118.05, 116.11), 36.958 (CH_2), 24.42(CH_3); COSY:H-1/H-3,H-4,H-10; H-3/H-1,H-4;H-4/H-3,H-1,H-10; H-5/H-1,H-3,H-10;H-6/H-1,H-4;H-8/H-3,H-4,H-10;H-10/H-1,H-3/H-4; HMBC correlations: H-1/C-3, C-11;H-3/C-1,C-3,C-5,C-11;H-4/C-3,C-11,C-12,H-5/C-3,C-11,C-12,H-6/C-1,C-3,C-5,C-11,H-8/C-3,C-11,H-10/C-11,C-1,C-12,H-14/C-1,C-3,C-15;H-19/168.48.

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