

SYNTHESES AND CHARACTERISATION OF DIUREA MOLECULAR TWEESORS FOR THE RECOGNITION OF ANION

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(Received: March 13, 2013 - Accepted: June 25, 2013)

ABSTRACT

Two novel urea anion receptors (11) and (12) were synthesized from building block 3,3'-methylene diamine and was characterized via the techniques of ¹H NMR, ¹³C NMR, DEPT-135 ¹H-¹H COSY, HMQC and HMBC spectroscopy. The ¹H NMR profile of both compounds reveals diagnostic peaks. For compound (11), the urea NH protons resonate as two singlets downfield at 8.706 ppm and 8.635 ppm, whereas for compound (12) these two urea -NHCONH protons resonate together at 8.614 ppm. There seem to be no rotation of the structure on the NMR time scale as the bridged CH₂ protons resonate as a singlet. The integration pattern for the aromatic hydrogens for both compounds is: 2: 4: 2: 4: 4, consistent with the structure. ¹³C NMR spectrums reveal fourteen signals for both structures in accordance with fourteen different types of carbon. Dept-135 indicates eight different CH protons. Preliminary anion binding studies via ¹H NMR spectroscopy revealed complexation with dicarboxylate anions in the highly competitive solvent, d₆-DMSO.

Keywords: Novel urea receptors, 3,3'-methylene diamine scaffold, spectroscopic techniques, integration pattern, dicarboxylate anion

INTRODUCTION

The molecular recognition of anions is a current, active and difficult area of Supramolecular chemistry, considering the ubiquitous properties of anions¹⁻⁵. Anions play pivotal roles in biological, environmental and Supramolecular sciences¹⁻²⁸. Of great interest is the design, syntheses and use of neutral receptors for selective binding of anions⁶⁻²⁷. Also, such receptors present a balance between rigidity and flexibility, an important feature in designing a host for encapsulation of a substrate. In designing an anionic host, charge and shape complementarity between the host and anionic guest are of paramount importance¹⁻⁵. Most anion receptors reported to date are macrocyclic in nature^{1-5,6-28}.

Anion recognition by hydrogen bonding urea-based receptors is a relatively new motif of anion coordination Supramolecular Chemistry²⁵⁻²⁷. The efficiency of urea as an anion receptor subunit depends on the presence of two proximate polarised N-H moieties, capable of chelating a spherical anion and also donating two parallel H-bonds to the oxygen atoms of a carboxylate or of an inorganic oxoanion, a property which is also shared with other diamides such as squaramide. The urea functionality is usually synthesised via the reaction of a primary amine group with an isocyanate in significant yields²⁵⁻²⁷. Both symmetrical and unsymmetrically substituted derivatives can be synthesised. Neutral receptors of urea, thiourea and amides are of further significance because the transport of anions such as phosphate, PO₄³⁻ anion through cell membranes is regulated by neutral binding proteins⁹⁻¹⁵. Also, neutral anion receptors, especially those of the amido type exploit hydrogen bonding interactions with anions and are found in biological systems. Depending on their spatial orientation (geometry), neutral amides are expected to selectively complex guest substrates^{12-14,20-24}. There are several reports of anion recognition by urea receptors^{15-19,25-27}. For example, A *bis*-urea and a *bis*-thiourea host (1), both derived from 1,3-*bis*-(aminomethyl)benzene have been shown to bind dihydrogenphosphate selectively over various other anions according to the selectivity trend: H₂PO₄⁻ > CH₃COO⁻ > Cl⁻ > HSO₄⁻ > NO₃⁻ > ClO₄⁻. The much stronger binding of H₂PO₄⁻ by the *bis*-thiourea is due to the stronger H-bond donor strength of the thiourea groups, Figure 1.0. Binding selectivity is explained in terms of the complex geometry and the basicity of the guest anions. The lack of self-association was also an added advantage of this relatively novel class of receptor for dihydrogen phosphate.

Benzimidazolium urea anion based receptors have been designed and synthesised²⁶. On the basis of fluorescence, UV-Vis, ¹H NMR spectroscopic studies and X-ray single crystal structure analyses, it was confirmed that the receptor displays strong (C-H)⁺...X, N-H...X hydrogen bonds and charge-charge interactions with anions. More importantly, these investigations demonstrated that the charged (C-H)⁺ benzimidazolium and urea moieties play a synergistic role in anion recognition.

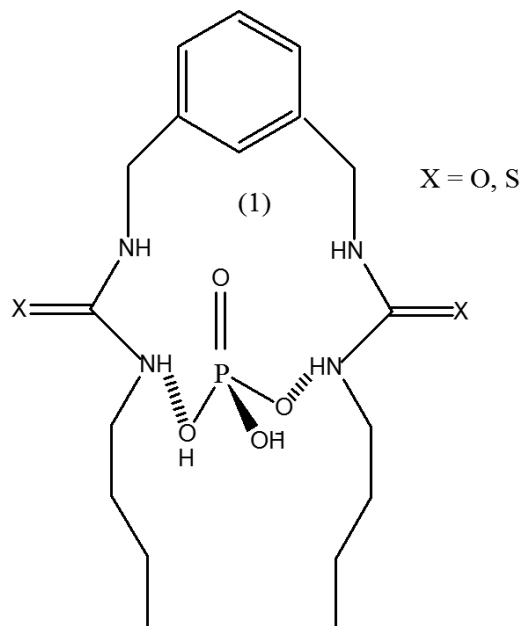


Figure 1. *bis* urea and *bis* thio urea anion receptors.

A neutral urea anion receptor (2) with a tripodal pseudocavity was synthesized in good yield²⁷ (Figure 2) The influence of preorganization and rigidity of the receptors towards anion recognition was evaluated using rigid and flexible unit receptors. Binding affinities were investigated using ¹H NMR and luminescence titration methods. Receptor (2) showed high binding affinities with 1:1 stoichiometry for aromatic carboxylate anions in polar solvents. No binding was observed with small anions, due to the large cavity and the rigidity of the receptor. The obtained results are explained based on the rigidity and preorganization of the receptor.

Neutral porphyrin urea anion receptors (3)-(6) and their corresponding zinc complexes (7-9), exploiting the neutral urea binding motif and in case of the zinc complexes, Lewis acid interactions have been reported¹⁶⁻¹⁷ (Figure 2). Significantly large association constants have been reported for these compounds binding to anion in highly competitive solvents such as d₆-DMSO. For example neutral free base porphyrin urea anion receptors (3) - (6) selectively complex halides anions over phosphate with association constant of 1 x 10⁵ M⁻¹ in d₆-DMSO¹⁶⁻¹⁷. The a,a,a,a-5,10,15, 20 *meso* tetrakis-(2-(aryluera)phenyl) porphyrins bind strongly (K(M⁻¹) > 10³-10⁵) to chloride and bromide anion in DMSO-d₆ and in DMSO-d₆/D₂O (88:12, v/v) as revealed by ¹H NMR titration

studies. These porphyrin derivatives exhibited significant binding selectivity since they complexed with the spherical Cl^- and Br^- to a much greater extent than with the tetrahedral H_2PO_4^- , HSO_4^- and trigonal NO_3^- anions in DMSO-d_6 binding systems. The corresponding zinc complexes also show a decrease in binding constant and selectivity.

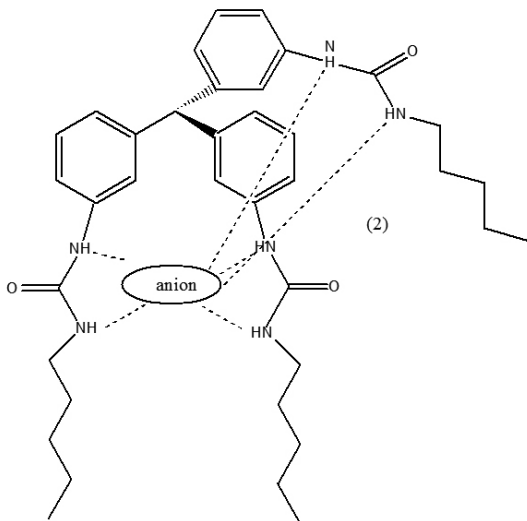
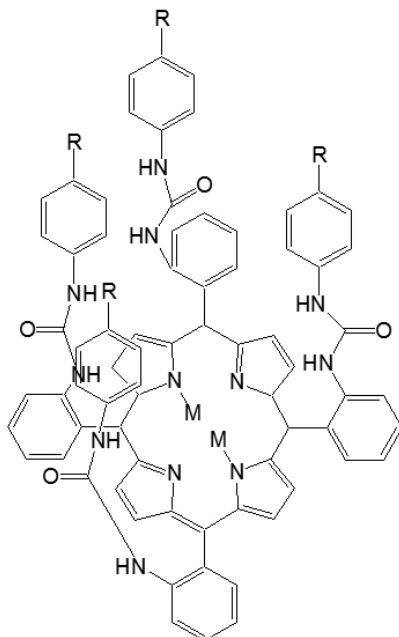


Figure 2. A tripod urea anion receptor.



M=M=H

R = H, (3)

R = Cl, (4)

R = F, (5)

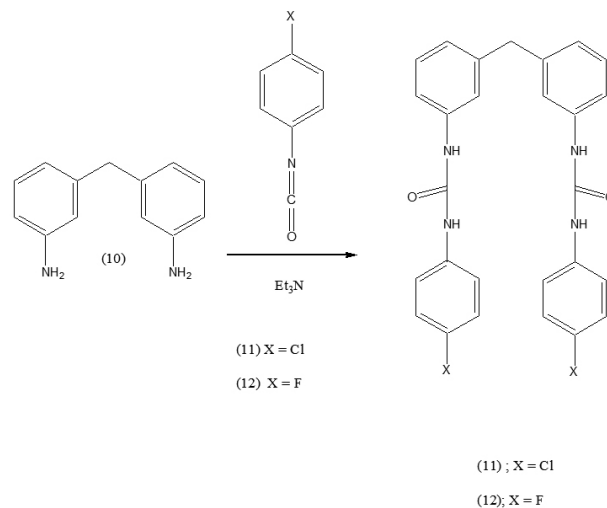
R = NO_2 (6)

M, M = Zn

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

Figure 3. Porphyrin Urea anion receptors and their corresponding metal complexes.

This paper focuses on the syntheses, characterization and preliminary anion binding studies of molecular clef type urea receptors (11) and (12) incorporating the urea, $-\text{HNCONH}-$ moieties. These receptors are built on the molecular scaffold of 3,3'-methylene diamine and present convergent binding sites to anionic substrates.



Scheme 1. synthesis of urea anion receptors

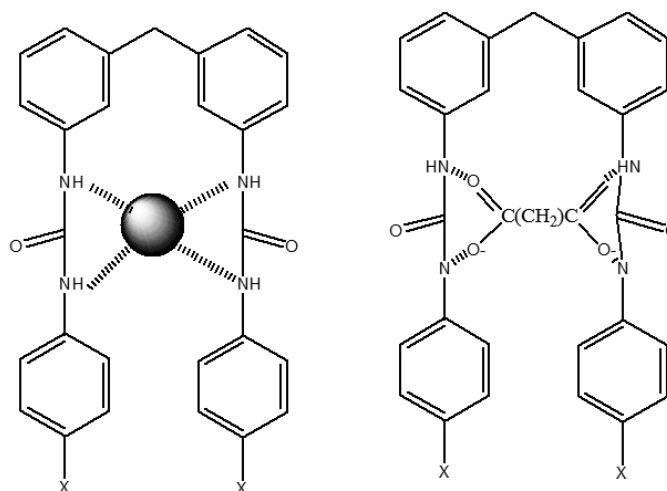


Figure 4. Proposed mode of anion binding for a spherical chloride ion and a dicarboxylate anion by urea anion receptors (11) and (12).

EXPERIMENTAL

Synthesis

(0.40g, 2.02×10^{-3} mol) of the diamine was dissolved in 50ml of CHCl_3 in a 100ml RB flask. The reaction mixture was left stirring for 15 minutes under nitrogen. To this solution was added the 4-chlorophenyl (0.59g, 3.883×10^{-3} mol) or 4-fluorophenyl isocyanate (0.0044, 0.68g). The reaction changed colour after 5 minutes to a white curdy nature. It was left stirring for 24 hrs after which the precipitate was filtered. The product was then taken up in H_2O , stirred and filtered. The yield of compound (3) and (4) were (0.94g, 92.19%) and (0.82g, 83.93%) respectively.

Characterisation:

Compound (3), $\text{C}_{27}\text{H}_{22}\text{O}_2\text{Cl}_2$; $^1\text{H NMR}$ (300MHz) d: 3.859 (s, CH_2), 6.865 (d; 2H; $J = 6.9$ Hz, ArH), 7.083-7.128 (m, 4H, ArH), 7.22-7.128 (m, 2H; ArH), 7.181-7.278 (m, 4H, ArH), 7.305-7.276 (m, 4H, ArH), 7.437-7.464 (d; 4H; $J = 8.1$ Hz, ArH), 8.61 (s, 4H; NHCONH); $^{13}\text{C NMR}$ (400 MHz) d: 155.06 (CO), 144.47 (ipso-C-Ar), 142.30 (ipso-C-Ar), 141.38 (ipso-C-Ar), 140.24, 131.52

(CH-Ar), 131.28 (CH-Ar), 128.03 (ipso-C-Ar), 125.23 (Ar-CH), 122.42 (Ar-CH), 121.24 (Ar-CH), 119.25 (Ar-CH), 118.76 (Ar-CH), 44.02 (CH₂); Dept 135: 131.53, 131.28, 125.22, 122.40, 121.22, 119.25, 118.74, 40.43 (CH₂); ¹H-¹H COSY: H-1/H-2, H-3; H-2/H-1, H-3; H-3/H-2/H-1; H-8/H-9; H-9/H-8; H-10/H-11; H-11/H-10; HMBC: H-1/C-3, C-4; H-2/C-4; H-3/C-1, C-4; H-5/C-1, C-4; H-8/C-10, H-9/C-11, H-10/C-8, H-11/C-9; FABMS: CALCD for C₂₇H₂₂O₂Cl₂N₄; 505.39; Found: 505.39

Compound (4): C₂₇H₂₂O₂F₂; ¹HNMR (400MHz) d: 3.859 (s; CH₂), 6.865-6.847 (d; 2H; J = 7.2 Hz, ArH), 7.106-7.083 (d; 2H; J = 9.2Hz, ArH), 7.128-7.106 (d; 2H; J = 8.8Hz, Ar-H), 7.220-7.201 (m, 2H; Ar-H), 7.320-7.278 (m, 4H; Ar-H), 7.462-7.428 (m, 4H; ArH), 8.635 (s, NH-CO-NH; 2H), 8.71 (s, 2H; NHCONH); ¹³CNMR (400MHz) d: 153.03 (CO), 142.23 (ipso-C-Ar), 140.24 (ipso-C-Ar) 136.48 (ipso-C-Ar), 136.45 (ipso-C-Ar), 129.27 (Ar-CH), 122.85 (Ar-CH), 120.48 (Ar-CH), 120.37 (Ar-CH), 118.93 (Ar-CH), 116.44 (Ar-CH), 115.85 (Ar-CH), 115.55 (Ar-CH) 41.80 (CH₂); DEPT (400MHz) d: 127.90 (Ar-CH), 121.47 (Ar-CH), 119.10(Ar-CH), 119(Ar-CH), 117.55(Ar-CH), 115.06 (Ar-CH), 114.47(Ar-CH), 114.18(Ar-CH), 44.01(CH₂); ¹H-¹H COSY: (H-1/H-2, H-3; H-2/H-1, H-3; H-3/H-2, H-1; H-4/H-3; H-8/H-9; H-10/H-11; HMQC: H-1/115.85, H-2/120.48; H-3/122.85; H-8/115.55; H-9/120.37; HMBC: H-1/C-2, C-3, C-4; H-2/C-1, C-3, C-4; H-3/C-2, C-1, C-4; H-4/C-2, C-1, C-5; H-8/C-10, H-9/C-10, C-11; FABMS: CALCD for C₂₇H₂₂O₂F₂N₄; 472.49; Found: 472.00

RESULTS AND DISCUSSION

Compounds (11) and (12), described as diurea molecular tweezers are built on the building block, 3,3' methylene diamine. Both compounds (11) and (12), spectroscopic integrity were established via ¹H NMR, ¹³C NMR, DEPT-135, ¹H-¹H COSY, HMQC and HMBC spectroscopic techniques. ¹H-¹H COSY shows protons/protons connectivity, HMQC shows the connectivity of individual protons to carbon and HMBC also shows the connectivity of protons to two or more carbon away. Using all these spectroscopic techniques, compounds (11) and (12) were characterized.

The ¹H NMR profile of both compounds reveals diagnostic peaks. The spectrum of both compounds can be compared. For compound (11), the urea NH protons resonate as two singlets downfield at 8.706 ppm and 8.635 ppm. For compound (12) these two urea -NHCONH protons resonate at 8.614 ppm. Urea protons for compound (11) seems to be more upfield than that for compound (12). Methylene CH₂ protons show singlet resonance at 3.873 ppm and 3.859 ppm for (11) and (12) respectively, suggesting that there is no conformational rotation about the CH₂ unit of the 3,3' methylene dianiline scaffold on the NMR timescale. For compound (11), aromatic protons resonate in the region 6.837 ppm to 7.464 ppm whereas for compound (12) this is seen at 6.847 to 7.462 ppm.

For compound (11), four sets of aromatic signals were obtained. The integration pattern for the aromatic hydrogens been 2: 2: 8: 4, consistent with the structure (16H). Aromatic protons H-4 on ring A and B resonate as a virtual doublet at 6.837 ppm (J = 6.9Hz) whereas H-2 and H-3 resonate together as a multiplet and this is seen at 7.28 ppm (4H). Protons H-1 (2H) are seen as a virtual triplet at 7.16 ppm (J = 7.2Hz), resulting from an AB type coupling. Protons on ring C and D, H-8 and H-9 resonate as a doublet (4H) and this is seen at 7.437 ppm (J = 8.1Hz). The doublet resonance for protons H-10 (2H) and H-11(2H) is seen at 7.276 ppm (J = 8.7Hz) and respectively. Urea -NHCONH- protons are seen as two doublets at 8.71 and 8.64 ppm. Urea, NHCONH protons for compound (11) seem to be more upfield than urea protons for compound (12).

For compound (12), five sets of aromatic resonances were seen. Protons on ring C and D, H-8 and H-9 are seen as two sets of doublets. The integration pattern for the aromatic hydrogens been 2: 4: 2: 4: 4 consistent with the number of aromatic hydrogens (16H) for the structure. One set of doublet (2H) is seen at peak 3, 7.18 ppm (J = 8Hz) for H-8 and the other couple proton (J = 8.0Hz) is seen at peak (4), 7.28 ppm for H-9 (2H). Likewise two sets of doublets are seen for protons H-10 and H-11. Each proton is split by one another to yield two doublets. One of these is seen at peak (2), 7.08 ppm, the other couple proton (J = 8.8Hz) is seen in peak (4) at 7.28 ppm. Protons H-1 and H-2 (4H) resonate together as two virtual triplets at 7.428 ppm (J = 4.8Hz; J = 5Hz). Proton H-3 (2H) also resonate as a virtual triplet at 7.128 ppm (J = 9.2 Hz) in peak 2. Aromatic protons H-4 shows a small coupling interaction and resonate as a virtual doublet (J = 7.2Hz) at 6.865 ppm.

¹³CNMR spectra reveal fourteen signals for structures (11) and (12), in accordance with fourteen different types of carbon. For compound (11) these resonate at (155.06, 144.47, 142.30, 141.38, 131.52, 131.28, 128.03, 125.23, 122.42, 121.24, 119.25, 118.76 and 44.02 ppm. Dept 135 indicates

aromatic CH protons at (131.53, 131.28, 128.03, 125.23, 122.40, 121.24, 119.25, 118.76 and CH₂ protons at 44.01 ppm). Ipso resonances are seen at (144.47, 142.30, 141.38 and 128.03) ppm. The carbonyl carbon resonate far downfield at 155.06 ppm. Compound (12) fourteen carbon signals are seen at (153.03, 142.23, 140.24, 136.48, 136.45, 129.27, 122.85, 120.48, 120.37, 118.93, 116.44, 115.85, 115.55 ppm. Dept 135 indicates aromatic CH protons at 129.27, 122.85, 120.48, 120.37, 118.93, 116.44, 115.85, 115.0. The CH₂ carbon is seen at 40.43 ppm.

¹H-¹H COSY experiments revealed ¹H-¹H connectivity. For example, H-1 proton (on ring A) couples with H-2 and H-3 protons i.e shows cross peaks which are in line with those for H-2 and H-3. H-8 couples with H-9 and H-10 couples with H-11 on ring C and D. Methylene, H-5 protons shows no ¹H-¹H connectivity and thus resonate as a singlet upfield. Urea -NHCONH- protons show no coupling interaction with aromatic protons of the phenyl ring.

HMBC shows the connectivity of protons to two or more carbon away and these are presented in the experimental section.

Preliminary anion complexation studies with dicarboxylate anion in d₆-DMSO revealed significant downfield shifts in the host urea- NHCONH- protons. Shifts greater than 1.2 ppm were observed after the addition of one equivalent of anion. This indicates significant urea -NHCONH- hydrogen bonding interactions amongst other non-covalent interactions contributing to the overall anion binding process (Figure 4 and 5).

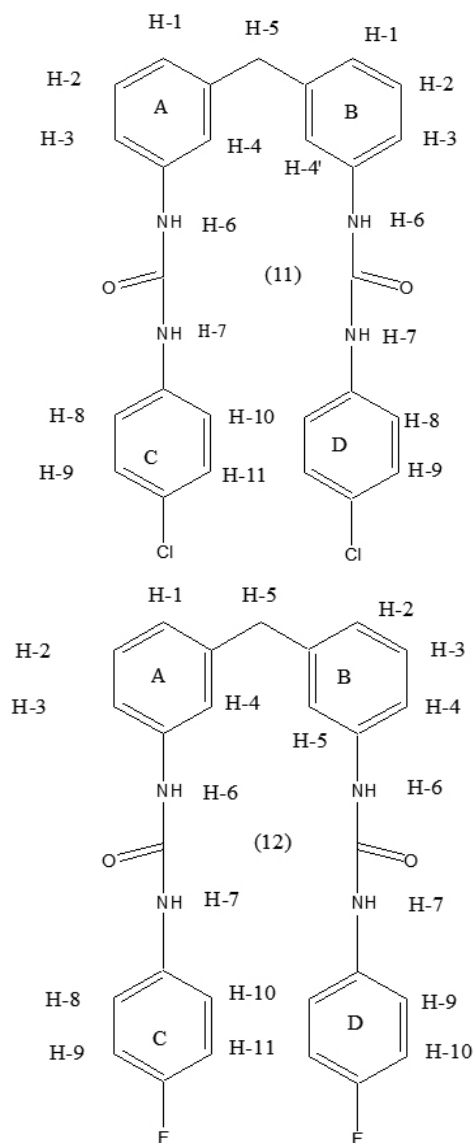


Figure 5. Shows the proposed mode of anion binding of receptor (11) and (12) to a dicarboxylate anion.

CONCLUSIONS

Two novel urea anion receptors based on the 3,3' methylene diamine molecular scaffold have been synthesized and characterized using conventional contemporary spectroscopic techniques. Preliminary anion binding studies revealed complexation to linear dicarboxylate anion in the highly competitive d_6 -DMSO solvent medium.

ACKNOWLEDGEMENTS

This project was finally supported by Dr. R.C. Jagessar. Spectroscopic data were collected overseas.

REFERENCES

- J.M, Lehn, *Supramolecular Chemistry: Concepts and Perspectives*. (1st ed.). New York, Wiley-VCH, (Chapter 3), (1995).
- Supramolecular Chemistry of Anions*; Wiley-VCH: New York, (1997).
- F.P. Schmidtchen, M. Berger, *Artificial Organic Host Molecules for Anions: Chem. Rev.* 97, 1609-1646, (1997).
- P.D. Beer, *Transition-Metal Receptor Systems for the Selective Recognition and Sensing of Anionic Guest Species., Acc. Chem. Res.* 31 (2), 71-80, (1998).
- K. Bowman-James, *The Coordination Chemistry of Anions, Acc. Chem. Res.* 38, 671-678, (2005).
- R. Martinez-Manez, F. Sancenon, *Fluorogenic and chromogenic chemosensors and reagents for anions, Chem. Rev.*, 103, 4419-4476, (2003).
- F. Sancenon, A.B. Descalze, M.A. Miranda, J. Sato, *A colorimetric ATP sensor based on 1,3,5-triarylpent-2-en-1,5-diones, Angew. Chem., Int. Ed.*, 40, 2640, (2001).
- T. Gunnlaugason, A.P. Davis, J.E. O'Brien, M. Glynn, (2002). *Fluorescent sensing of Pyrophosphate and Bis-carboxylates with charge neutral PET chemosensors., Org. Lett.* 4, 2449, (2002).
- G. Hennrich, H. Sonnennachein, L. Reach-Genger, *Tetrahedron Lett.*, 42, 2805, (2001).
- K. Choi, A.D. Hamilton, *Macrocyclic anion receptors based on directed hydrogen bonding interaction, Coordination Chem. Rev.* 240, 101-110, (2003).
- S.L. Wiskur, H. Ait-Hissou, J.J Lavigne, E.V. Anslyn, *Teaching Old Indicators New Tricks, Acc. Chem. Res.* 34, 963-972, (2001).
- L. Kuo, J.H. Liao, C.T. Chen, C.H. Huang, C.S. Chen, J.M. Fang, *Two Arm Ferrocene Amide Compounds: Synclinal Conformations for Selective Sensing of Dihydrogen Phosphate ion, Organic Letters*, 5 (11), 1821-1824, (2003).
- S. Kubic, R. Goddard, R. Kirchner, D. Nolting, Seidel., *Recognition of Anions, J. Angew. Chem. Int. Ed.*, 40, 2648, (2001).
- I.V. Korendovych, M. Cho, L.P. Butler, J.R. Staples, E.V.R. Rybak-Akimova, *Anion binding to monotopic and ditopic macrocyclic amides, Organic letters.* 8(15):3171-4, (2006).
- J. Schearder, J.F.J Engbersen, A. Casnati, R. Ungaro, D. N. Reinhoudt, *Complexation of halide Anions and Tricarboxylate anions by Neutral Urea Derivatives, p-tert-butylcalix[6]arene, J. Org. Chem.*, 60, 6448-6454, (1995).
- R.C Jagessar, M. Shang, W.R Scheidt, D. H Burns, *Neutral Ligands for selective Chloride Anion Complexation: (a,a,a,a) (Cis)-5,10,15,20 -Tetrakis (2-(arylurea) phenyl porphyrins: J. Am.Chem.Soc.*, 120 (45), 11684-11692, (1998).
- R.C Jagessar, D. H. Burns, (Cis)-5,10,15,20 -Tetrakis (2-(arylurea) phenyl porphyrins: *Novel neutral ligands for remarkably selective and exceptionally strong chloride anion complexation in (CD₃)₂SO, J. Chem. Soc., Chem. Commun.*, 1685 – 1686, (1997).
- S. Amemiya, P. Buhlmann, Y. Umezawa, R. C. Jagessar, D. H. Burns, *An ion-selective electrode for acetate based on a urea-functionalized porphyrin as a hydrogen bonding ionophore, Anal Chem.*, 71(5), 1049 – 1054, (1999).
- P. D Beer, A. R Graydon, L. R Sutton, *Luminescent anion recognition: selective induced emission by binding of dihydrogenphosphate. Polyhedron*, 15 (14), 2457-2461, (1996).
- Z. Chen, A.R. Graydon, P.D. Beer, *Electrochemical response to anions in acetonitrile by neutral molecular receptors containing ferrocene, amide and amine moieties., J. Chem. Soc., Faraday Trans.* 92(1), 97-102, (1996).
- P.D. Beer, M.G.B. Drew, D.K Smith, *Selective electrochemical recognition of bidentate anionic guests in competitive solvents using novel ferrocenyl thiourea and guanidinium receptors. J. Organomet. Chem.* 543 (1-2), 259-261, (1997).
- P.D. Beer, M.G.B. Drew, R. Jagessar, (1997). *Selective anion recognition by Novel 5, 10, 15, 20 - tetrakis (o-ferrocenyl carbonylaminophenyl - substituted) zinc metalloporphyrin receptors, J. Chem. Soc., Dalton Trans.*, 881 – 886, (1997).
- P.D. Beer, M.G.B Drew, D. Heseck, R. Jagessar, *Spectral and Electrochemical Anion Sensing by a novel 5,10,15,20-tetrakis(R-substituted)Porphyrin Receptor(R=C₆H₄NHC(O)C₅H₄CoC₅H₅⁺PF₆⁻), J. Chem. Soc., Chem. Commun.*, 1187-1189, (1995).
- V. Amendola, L. Fabbrizzi, L. Mosca, *Anion recognition by hydrogen bonding: urea-based receptors, Chem. Soc. Rev.*, 39, 3889-3915, (2010).
- S. Nishizawa, P. Bühlmann, M. Iwao, Y. Umezawa, *Anion Recognition by Urea and Thiourea Groups: Tetrahedron Lett.* 36, 6483-6486, (1995).
- A. Fan, H.K Hong, S. Valiyaveetil, J.V. Jagades, *A Urea-Incorporated Receptor for Aromatic Carboxylate Anion Recognition, Journal of Supramolecular Chemistry*, 2 (1-3), 247-254, (2002).
- Z.Y. Dong, G. H. Gao, *Recognition and sensing of anions through synergistic effects using simple benzimidazolium-urea receptors, Chinese Science Bulletin*, 57 (11), 1266-1274, (2012).