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# Urea/thiourea derivatives and Zn(II)-DPA complex as receptors for anionic recognition—A brief account

PRIYADIP DAS, PRASENJIT MAHATO, AMRITA GHOSH, AMAL K MANDAL, TANMAY BANERJEE, SUKDEB SAHA and AMITAVA DAS*

Central Salt and Marine Chemicals Research Institute (CSIR), Bhavnagar 364 002, Gujarat, India
e-mail: amitava@csmcri.org

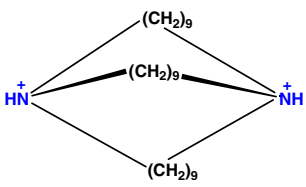
**Abstract.** This review covers few examples of anion complexation chemistry, with a special focus on urea/thiourea-based receptors and Zn(II)-dipicolyl amine-based receptors. This article specially focuses on structural aspects of the receptors and the anions for obtaining the desire specificity along with an efficient receptor–anion interaction. Two types of receptors have been described in this brief account; first one being the strong hydrogen bond donor urea/thiourea derivatives, which binds the anionic analytes through hydrogen bonded interactions; while, the second type of receptors are coordination complexes, where the coordination of the anion to the metal centre. In both the cases the anion binding modulate the energy gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and thereby the spectroscopic response. Appropriate choice of the signalling unit may allow probing the anion binding phenomena through visual detection.

**Keywords.** Anion receptor; supramolecular chemistry; colorimetric sensor; biological phosphate; urea/thiourea-based receptors.

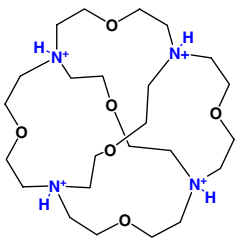
## 1. Introduction

A fluorescent or colorimetric chemosensor is defined as a chemical compound that complexes to an analyte with concomitant fluorescent or colorimetric signal transduction. Since 1970s, the coordination chemistry of group I and II metals and ammonium cations attracted more interest and consequently cation recognition is now a well-developed and matured area of chemistry. Compared to this, *anion receptors* did not receive much attention of the researchers; though the first report on a synthetic receptor for inorganic anions appeared in 1968, when size selective binding of $Cl^-$ ion was demonstrated with diprotonated form of 1,11-diazabicyclo-[9.9.9]nonacosane (**A**).[1] The field gained the necessary impetus in 1976 when Graf and Lehn reported that the protonated cryptate (**B**) could encapsulate $F^-$, $Br^-$ and $Cl^-$ anions.[2] Since then innumerable reports on various receptors have been developed and *anion receptors* as a research area has become more enriched.[3]

Anions play a major role in many biological processes and in structures like amino acids, neurotransmitters, enzyme substrates, co-factors and nucleic acid, etc. They are also important ingredients for a variety of industries related to agricultural fertilizers, food additives and water. Along with these, recent emphasis on environmental concern — both industrially and environmentally — necessitate the development of highly selective anion sensors. Recently, there has been a considerable surge of interest in developing neutral organic receptor molecules, which are capable of binding specific anionic guests selectively. However, in most cases, thermodynamic affinity of these receptors for a specific anionic analyte has been evaluated either through $^1$H NMR titration technique or through analyte binding induced changes in fluorescence or redox potential values.[4] Examples on the selective binding and sensing of anionic analytes showing optical output signals are rather limited and currently is increasingly




[A]



[B]

*For correspondence

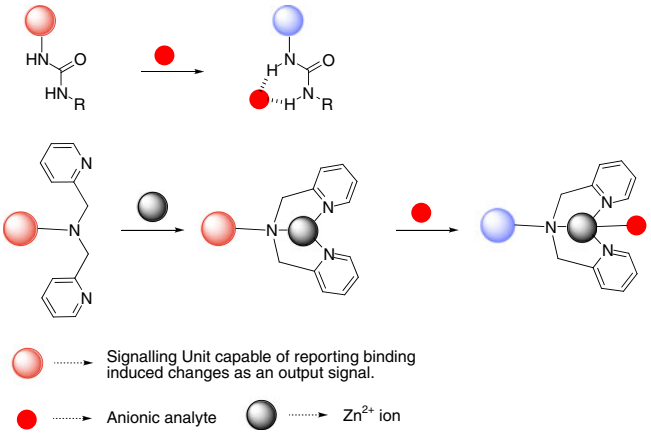
appreciated; as naked eye detection can offer instant qualitative and quantitative information. Further, a systematic approach to understand the relative affinity of the various anions towards a receptor molecule is still at a primitive level. Many reviews dealing with the subject of anion recognition have appeared in the literature in the last few years.[4,5] In this short account, a brief description of two types of receptors that could bind anionic analytes of biological importance in non-aqueous and aqueous solvents are to be discussed along with probable rationalization for the observed selectivity towards an anion by a specific receptor.

The most popular approach for design of the sensor molecules involves covalently introducing binding sites and signalling subunits to the chemosensors. Signalling unit is the one that reports the binding-induced changes in the output signal. The choice of receptor functionality in this design aspect is crucial and widely different methodologies could be adopted for achieving selectivity and the sensitivity of the targeted anion.

## 2. Key factors that affect the molecular recognition phenomena

Among two types of receptors that we are going to discuss here, first one being the strong H-bond donor urea and thiourea derivatives, which bind the anionic analytes through H-bonded interactions; while, the second type of receptors are coordination complexes, where the coordination of the anion to the metal centre modulate the energy gap of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and thereby the spectroscopic behaviour of the indicator (scheme 1).

In both approaches, the change in fluorescence or colour is reversible in principle to qualify as a chemosensor. The urea group possesses a *bis*-amide [–HN–C(O)–NH–] moiety with two acidic –N(H) hydrogens, which can be envisaged as good binding sites for anions. Urea generally acts as a bidentate ligand which forms a six-membered chelate ring when bound to a spherical anion owing to the presence of two H-bond donor groups. The exchange of the urea oxygen for a sulphur atom (thiourea) does not change the general geometry of the system; while it enhances the acidity of the amidic protons,[6] which in turn influences the anion binding event and there by the specificity and selectivity. Further, it is possible to modulate the acidity of the $–N(H)_{Urea/Thiourea}$ hydrogen by incorporating certain substituents or electron withdrawing group(s) and

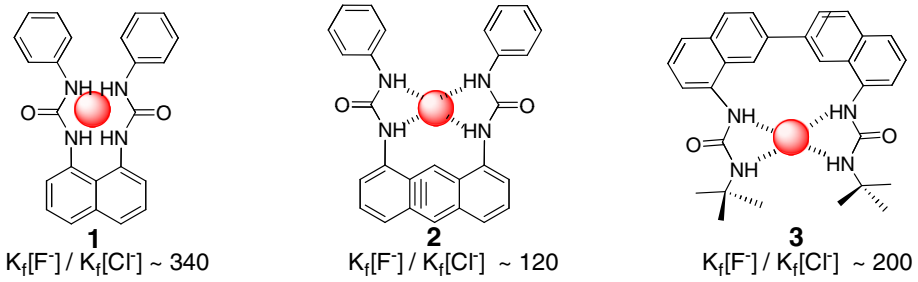



**Scheme 1.**

thereby the binding affinity towards a specific anionic analyte. A suitably substituted Urea/Thiourea derivative may also participate in deprotonation equilibrium in presence of strongly basic anion(s), which has interesting and useful consequences for colorimetric anion sensing.[7]

One of the earlier reports on the fluorosensor for $F^-$ describes *bis*-urea functionality (1,8-*bis* (N-phenylureido)naphthalene) (**1**) (scheme 2) as the receptor unit and naphthalene as the signalling group.[8] Association constant value ($K_f$) of this receptor for $F^-$, obtained through fluorescence titration studies, was found to be $\sim 10^5$ and more importantly the selectivity for $F^-$ has been found to be 340 times more than that of $Cl^-$. Similar studies with an analogous derivative derived from 1,8-anthracenedimethylamine (**2**) (scheme 2) reveal that $K_f$ for $F^-$ binding was $7.12 \times 10^5$ — while its selectivity compared to $Cl^-$ was only 120.[9]

For another closely related urea derivative (**3**), the selectivity for $F^-$ compared to $Cl^-$ was reported to be $\sim 200$.[10] Closer examination into the structural aspect of these two derivatives revealed that the varying separation distance between the two urea functionality could account for the observed change in selectivity in the latter case and was demonstrated in a more recent report.[11] This study revealed that the distance between urea functionalities could be optimized to achieve almost a specific binding to $F^-$, as compared to $Cl^-$ and $I^-$.[11] More interestingly, higher acidity of the thiourea derivative (**4**), as compared to that of the corresponding $–N(H)_{urea}$ in the urea derivative (**5**) was reflected in its higher binding affinity ($8.25 \times 10^5$ $M^{-1}$) towards $F^-$ than the urea one ($4.38 \times 10^5$ $M^{-1}$) and binding of fluoride ion to both receptors was strong enough to




**Scheme 2.**

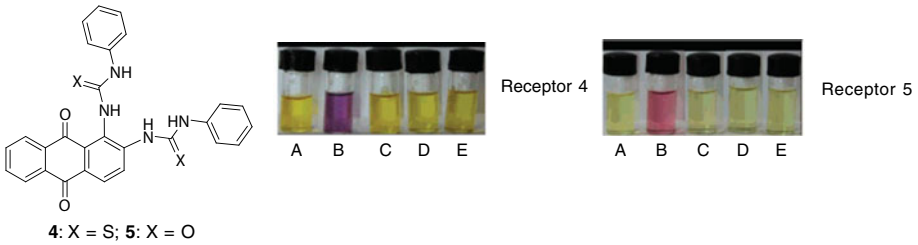



**Figure 1.** Change in colour of receptor **4** and receptor **5** in presence of different anions; [A = free receptor, B = $F^-$, C = $Cl^-$, D = $Br^-$, E = $I^-$]; [ref. 11a].

induce significant colour change in the visible region, which could easily be detected in naked eyes (figure 1).

The observed difference of selectivity for receptors **4** and **5** for $F^-$ was also explained on the basis of the RHF/6-31G* optimized structures for the complexes of receptors **4** and **5** with halides ($F^-$, $Cl^-$, $Br^-$) are shown in figure 2. Single point interaction energies calculated at B3LYP/6-31G* level using RHF/6-31G* optimized geometries without basis set superposition error correction were −120.2, −49.0 and −52.9 kcal/mol for $F^-$, $Cl^-$, and $Br^-$ respectively with receptor **1** and −127.8, −53.1 and −58.1 kcal/mol with receptor **2**.[12] In all cases, the halide ions were found to sit asymmetrically in receptor **4** and **5** and all four amide/thioamide protons participate in hydrogen bonding with anions (figure 2). Being smaller in size, fluoride ion approaches much closer to the cavity and could interact much strongly with the amide/thioamide protons.

Calculated binding energies for respective halide and receptor (**4/5**) further revealed that binding energies for receptor **4** are relatively larger than that of receptor **5**. This result supported the observed trend in association constant for receptor **4** and **5** with fluoride ion (table 1). It has been argued that the degree of charge transfer from nitrogen to sulfur in thioamide is significantly more than that of nitrogen to oxygen in amides and hence the N–H bonds are better acceptor in the former case.[13] Thus, the anathraquinone moiety not only acts as a colorimetric reporter group, but also provides an effective template with appropriate distance of separation between the urea/thiourea groups for selective binding of the fluoride ion. However, no deprotonation at either of the above discussed urea/thiourea complexes was reported. These same receptors (**4** and **5**) were also used for recognition and colorimetric detection of acetate and phosphate in presence of all other oxyanions. *ab initio* calculations predicted tweezers like binding modes of the receptors **4** and **5** with these anions and the higher affinity towards $H_2PO_4^-$ was predicted in acetonitrile and this matched well with the data obtained experimentally (tables 1 and 2). However, affinity constant for $H_2PO_4^-$ is two-fold lower as compared to that for fluoride ion.

Fabbrizi *et al*. and others have shown that through the insertion onto the molecular framework of electron-withdrawing substituents (e.g., $–NO_2$, $CF_3$) or positively charged groups (e.g., alkylpyridinium) the –N–H fragment of $–N(H)_{urea/thiourea}$ hydrogen can be further

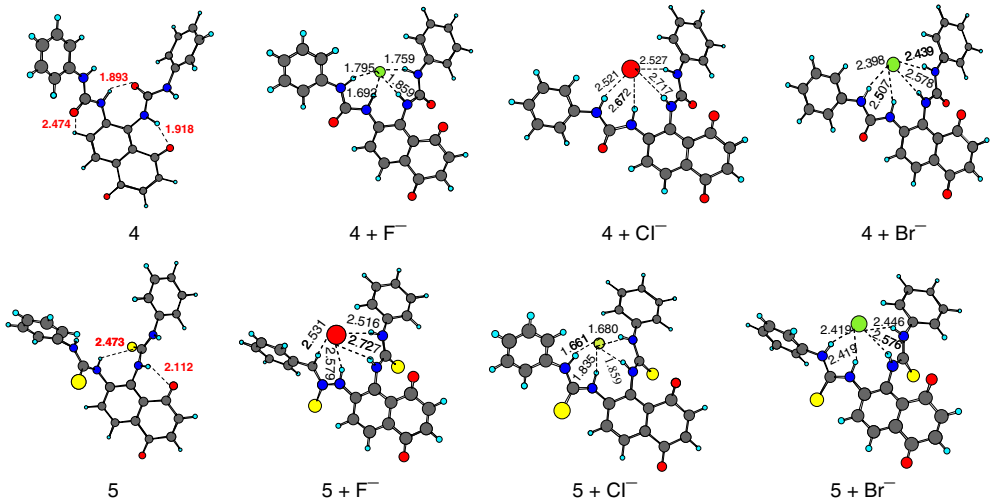
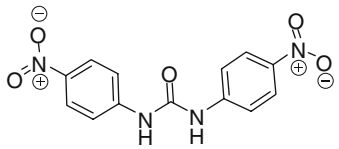



**Figure 2.** RHF/6-31G* optimized geometries for the free and halide ($F^-$, $Cl^-$ and $Br^-$) bound receptors **4** and **5**; (colour key: red (oxygen), blue (nitrogen), yellow (sulfur), purple (phosphorous); [ref. 11a].

polarized and thereby its H-bond donating efficiency.[7,14] However, this extreme polarization may lead to the occurrence of a definitive proton transfer from the receptor to an especially basic anion, a feature that pushes the anion out of the supramolecular control of the receptor. This process extrudes the operator from the discipline of supramolecular chemistry and leads classical Brønsted acid-base chemistry. However solvents used for such studies also plays an important role. For example HF in water has a $pK_a$ of 3.2 and in DMSO of 15. Therefore, in DMSO fluoride ion is a relatively strong base.

One of the initial urea derivative with the two appended $NO_2$ groups in the structurally simple 1,3-*bis*(4-nitrophenyl)urea (**6**) was studied in detail to reveal the influence on the acidity of the –N(H) hydrogens and its consequence on the spectral response.[15]



**6**

The formation of 1:1 complexes was observed with a variety of oxyanions, and corresponding association constants were determined through spectrophotometric titration experiments. This particular receptor did not show any selectivity for commonly used anions and respective binding constants, evaluated through spectroscopic titrations, are summarized in the (table 3) and the highest binding affinity was observed for $F^-$. For 1:1 adduct formation, the sequence of the log K values ($CH_3COO^- > C_6H_5COO^- > H_2PO_4^- > NO_2^- > HSO_4^- > NO_3^-$) reflect the decreasing intrinsic basicity of the anion. However, in presence of large excess of $F^-$, monodeprotonated form ($\mathbf{6}_{-\mathbf{H}}$) was formed. Authors have proposed a reasonably linear correlation between logK (K is affinity constant for 1:1 adduct formation) and the average negative charge on the oxygen atoms of each oxyanion based on the *ab initio* method of calculation. It was predicated that the presence of the 4-nitrophenyl substituents increases the Brønsted acidity of the receptor and favours the deprotonation of one urea N–H fragment.

The first added $F^-$ interacts with **6** through hydrogen bonding, while the second $F^-$ induces the deprotonation of one $–N(H)_{urea}$ fragment, with formation of

**Table 1.** Binding constants of various oxyanions towards receptor **4** and **5** in acetonitrile.

| Anion | $K_4$ ($M^{-1}$) | $K_5$ ($M^{-1}$) |
|---|---|---|
| Acetate | $(1.5 \pm 0.1)10^5$ | $(7.9 \pm 0.3)10^3$ |
| Phosphate | $(1.0 \pm 0.05)10^6$ | $(1.3 \pm 0.1)10^4$ |
| Benzoate | $(2.2 \pm 0.04)10^5$ | $(1.3 \pm 0.06)10^3$ |
| $OH^-$ | $(4.8 \pm 0.05)10^5$ | $(3.4 \pm 0.07)10^3$ |

[a]Tertiary butyl salt of the respective anions were used for the studies;
[b]K value reported ($K_5$ for receptor **5** and $K_4$ for receptor **4**), is the average of the 11 independent data evaluated from each individual Uv-vis titration data for the respective receptor and anion. Confidence limits for the respective K values are also shown; [reference 11b].

**Table 2.** Calculated interaction energies* for receptor **4** and **5** with various anions in kcal/mol (energies calculated in acetonitrile are given in parentheses).

| **4** | Basis set | $OH^-$ | $CH_3CO_2^-$ | $H_2PO_4^-$ | **5** | $OH^-$ | $CH_3CO_2^-$ | $H_2PO_4^-$ |
|---|---|---|---|---|---|---|---|---|
| | RHF/6-31G* | −94.8 (−30.0) | −54.1 (−14.7) | −49.2 (−16.4) | | −92.0 (−26.8) | −54.1 (−13.1) | −48.5 (−18.6) |
| | RHF/631+G* | −71.6 (−5.3) | −46.1 (−5.9) | −45.2 (−12.0) | | −70.6 (−5.3) | −47.6 (−5.0) | −44.9 (−14.7) |
| | RHF/6-31G* | | | | | | | |

Data taken from reference 11b.

the $[HF_2]^-$ ion. FH...$F^-$ complex has a large binding energy ($\Delta H_{298}$) of 191.6 kJ $mol^{-1}$ and is believed to the driving force for the $HF_2^-$ formation. A detailed study reported separately by McAllister and Maiya and their co-workers revealed that results of the DFT calculations using hybrid functional, such as B3LYP, were in good agreement with the *ab initio* methods B3LYP/6-311+G**//B3LYP/6-31G* and the calculated binding energy ($\Delta H_{298}$) in FH...$F^-$ was found to be 197.0 kJ $mol^{-1}$;[16] which was in good agreement with the experimental estimate. Thus, it is generally proposed that the higher stability of the polynuclear aggregate like $HF_2^-$ contribute favourably to facilitate the deprotonation in the receptor unit.[16] However, the Brønsted acid–base reaction can be triggered also by other anions such as acetate, phosphate or cyanide. Therefore, the colorimetric response due to deprotonation is not always a prerogative of fluoride.[17]

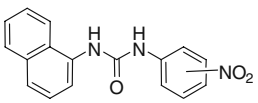
However, a more recent DFT study predicted a trend for the interaction of anions of different shapes with urea (**7**)/thiourea (**8**) receptor molecules, which do not always follow the basicity scale of anions.[6b] The selectivity trend for halides, tetrahedral oxyanions (like $H_2PO_4^-$, $ClO_4^-$ and $NO_3^-$) with urea/thiourea units was found to be in good agreement with experimental results for mono- and *bis*-urea/thiourea-based receptors. The order of selectivity predicted at B3LYP/6-311+G** level with urea/thiourea are: $F^- > CH_3COO^- > H_2PO_4^- > Cl^- \sim NO_3^- > B^- > ClO_4^-$. Further calculations performed at Hartree–Fock and MP2 levels using the 6-311+G** basis set revealed that similar selectivity trend was observed experimentally for these anions with mono-urea/thiourea receptors (figure 3).[6b] These results revealed that the interactions are electrostatic in nature, but cannot be related solely to the intrinsic basicity of anions. Thus, it has been argued that the selectivity trend might not necessarily follow the basicity scale for the studied anions. Authors concluded that the charge density pattern may not necessarily be a sole deciding factor for the preferential interaction with the receptors, optimal geometric arrangement of –N(H) donors and acceptors is also important to achieve the maximum stability.

**Table 3.** Constants of the complex formation equilibrium.[a]

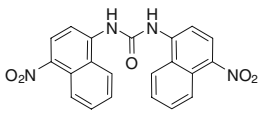
| Anions | Log K[b] | $\varepsilon$ ($M^{-1}$ $cm^{-1}$) |
|---|---|---|
| $CH_3COO^-$ | 6.61 (1) | 42172 (370 nm) |
| $C_5H_6COO^-$ | 6.42 (1) | 38249 (370 nm) |
| $H_2PO_4^-$ | 5.37 (1) | 39406 (370 nm) |
| $F^{-c}$ | log $K_1$ = 7.38 (9) | 20712 (370 nm) |
| | log $K_2$ = 6.37 (12) | 19324 (470 nm) |
| $NO_2^-$ | 4.33 (1) | 27200 (370 nm) |
| $HSO_4^-$ | 4.26 (1) | 28600 (370 nm) |
| $NO_3^-$ | 3.65 (5) | 23300 (370 nm) |
| $Cl^-$ | 4.55 (1) | 28700 (370 nm) |

[a]In an MeCN solution at 25°C: **6** + $A^-$ ⇌ [**6**.A]$^-$, and molar absorbances ($\varepsilon$) of the [**6**.A] $^-$, Hydrogen bonded complexes. [b]The value in parentheses is the uncertainty of the last figure. [c]The value of log $K_1$ refers to the H-bond complex formation; log $K_2$ refers to the receptor's deprotonation equilibrium: $[LH.F]^- + F^- \rightleftharpoons L^- + [HF_2]^-$ (ref. 15).

Structurally related compounds **9a–c**[18] and **10**[19] have been studied in more polar solvent mixtures, but they behave in a similar way. Three urea-based positional isomers (**9a–c**) showed a strong affinity for $F^-$, $CH_3COO^-$ and $H_2PO_4^-$ with an appreciable colour change in the presence of the excess $F^-$.[18]




**9**: a = Ortho, b=Meta, c=para




**10**

However, significant variation in spectral response for these receptors was observed for fluoride ion (figure 4). Detailed spectra and time resolved emission studies revealed that the position of the nitro-group in the urea derivative influences the acidity of the $–N(H)_{urea}$ and thereby the relative affinity towards respective anionic analytes. Spectral and *ab initio* studies showed the difference in the deprotonation sites for the ortho- and meta-/para-isomers in these cases (figure 5). Interestingly, of the two –N(H) hydrogens,

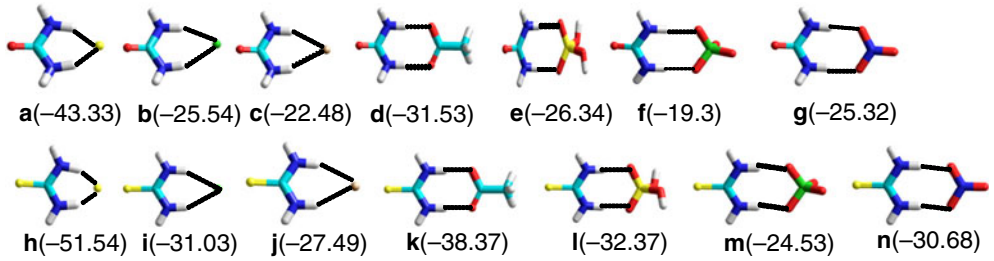



**Figure 3.** Optimized geometries of the complexes and their binding energy values (kcal/mol) at B3LYP/6- 311+G** level of theory. Urea: (**a**) **7**.$F^-$, (**b**) **7**.$Cl^-$, (**c**) **7**.$Br^-$, (**d**) **7**.$CH_3COO^-$, (**e**) **7**.$H_2PO_4^-$, (**f**) **7**.$ClO_4^-$, (**g**) **7**.$NO_3^-$; Thiourea: (**h**) **8**.$F^-$, (**i**) **8**.$Cl^-$, (**j**) **8**.$Br^-$, (**k**) **8**.$CH_3COO^-$, (**l**) **8**.$H_2PO_4^-$, (**m**) **8**.$ClO_4^-$, (**n**) **8**.$NO_3^-$. The calculated binding energy is the energy difference {E(complex) – E(anion) – E (urea/thiourea)}. (ref. 6b).

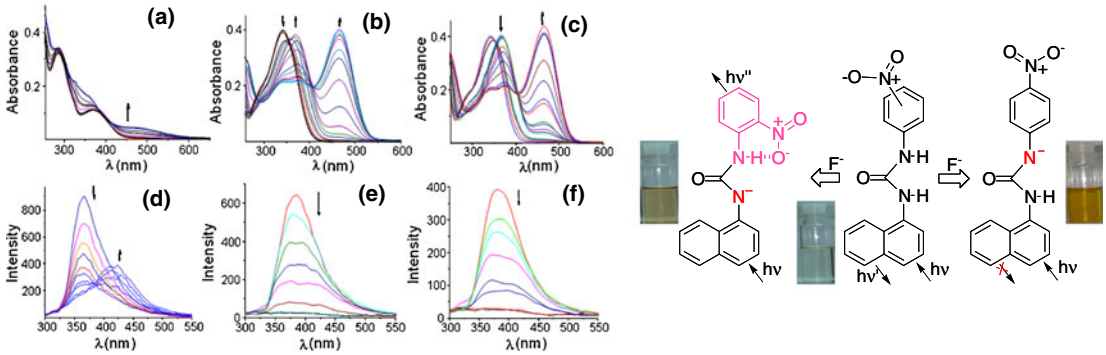



**Figure 4.** Change in electronic (**a**–**c**) and emission spectra (**d**–**f**) for $2.0 \times 10^{-5}$ M [in 1:9 (v/v) DMSO-$CH_3CN$] of **9a** (**a** and **d**); **9b** (**b** and **e**); **9c** (**c** and **f**) on addition of varying [($^t$Bu$_4$N)F] ($5.0 \times 10^{-6}$ – $2.0 \times 10^{-4}$ M) (ref. 18).

the one on the $NO_2$ phenyl moiety deprotonates in the case of **9b** and **9c**, but the converse occurs in the case of **9a**. The role of intramolecular H-bonding was envisaged by theoretical calculations. Photophysical studies confirmed the resonance energy transfer in the case of the *ortho*-isomer, which was not observable for other two isomers owing to the difference in the deprotonation sites in these dissymmetric derivatives. The *ortho*-isomer can act as a dual emission probe for $F^-$. In MeCN–DMSO (9:1), the isomer **9c** shows the highest affinity for fluoride within the series (log K = 3.83). While in case of **10**, similar binding affinity with anticipated decrease in luminescence quenching was observed.[19]

Fabbrizzi and co-workers, have shown that double-deprotonation by $F^-$ can be reasonably achieved in any system with sufficiently acidic –N(H) hydrogens, provided the solvent is polar enough. Three carbolinium fragments were introduced on a 1,3,5-trimethylbenzene platform, to yield a trifurcate receptor $\mathbf{11}^{3+}$.[20] This scaffold has the cavity to envelop spherical halide ions and

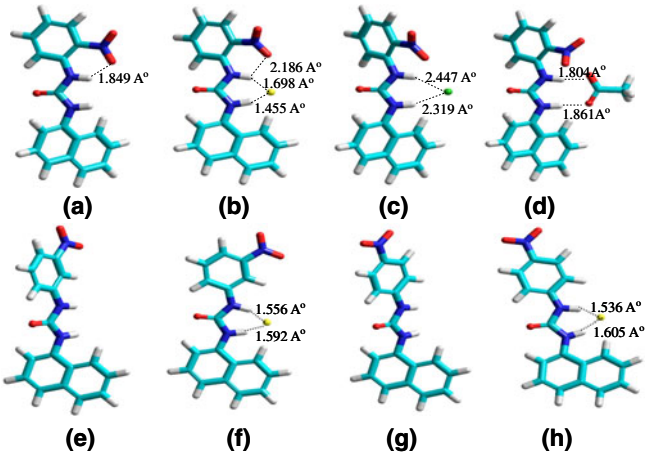
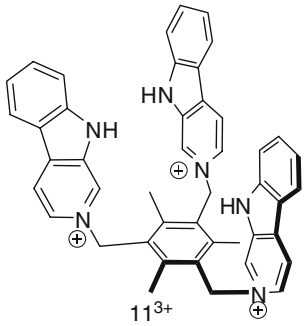
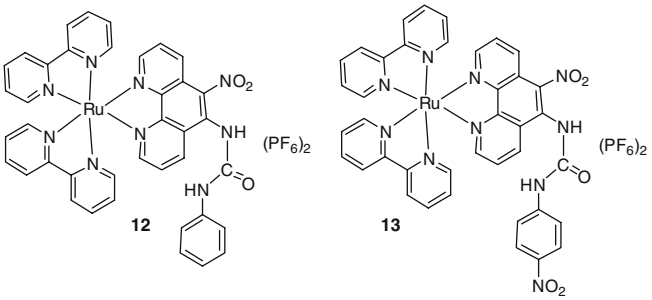



**Figure 5.** RHF/6-31G* optimized geometries for the free receptors and selected adducts: (**a**) **9a**; (**b**) **9a.**$F^-$; (**c**) **9a.**$Cl^-$; (**d**) **9a.**$CH_3COO^-$;(**e**) **9b**; (**f**) **9b.**$F^-$; (**g**) **9c**; (**h**) **9c.**$F^-$. (Colour code: red (oxygen), dark blue (nitrogen), gray (hydrogen), yellow (fluoride); [ref. 18].

formation of a 1:1 complexes was ascertained for $Cl^-$, $Br^-$, and $I^-$.




Efficient coordination of the envelop anion accounts for the extremely large stability of the $[\mathbf{11H}_3.\mathbf{X}]^{2+}$ complexes. However, $F^-$ gave a more intricate behaviour: **11** undergoes double deprotonation to yield $[\mathbf{11H}.2F]^+$.




Ruthenium(II)-polypyridyl complexes (**12** and **13**), could also be used as a receptor for $F^-$, $CH_3COO^-$ and $H_2PO_4^-$ in acetonitrile solution.[21,22] Binding of these anions caused an appreciable change in the colour of the acetonitrile solution, which could be detected by the naked eye.

At relatively lower concentration of anions, 1:1 H-boned adduct was formed,[21,22] however, at higher fluoride ion concentration, classical Brønsted acid-base type reaction prevailed for all three anions mentioned for derivatives (**13**) substituted with electron withdrawing nitro functionality.[21] To rationalize the relative affinity of the receptor **12** and **13** towards various anionic analytes, *ab initio* quantum chemical calculations have been performed. Authors have used only the active phen component ($\mathbf{L_{Phen}}^{\mathbf{13}}$) for simulation studies. Here, the optimized structure of **13** and its complex with $F^-$, $Cl^-$, $Br^-$, $CH_3COO^-$, $H_2PO_4^-$ and $HSO_4^-$ were optimized at the Hartree–Fock RHF/6-31G* level of theory (figure 6).[6a–c,g]

For computational simplicity, receptor **13** was modelled as the phen moiety only (figure 6). Optimized structures for $\mathbf{L_{Phen}}^{\mathbf{13}}$ and the corresponding complex with anions reveal that a C–H...O type interaction exists (figure 6). The distance between the one of the phen protons and one of the O-atoms of the two $–NO_2$ groups decreases on interaction with these anions and that results in a stronger C–H...O type interaction in the complexed state. Similarly, the C–H...$A^-$ distance follows the order $F^- > CH_3COO^- > H_2PO_4^-$ and thereby the interaction with the *phen* proton (figure 6). The calculated binding energies (ΔE) support the observed trend that fluoride binds preferentially in comparison to other anions studied here. Higher acidity of the

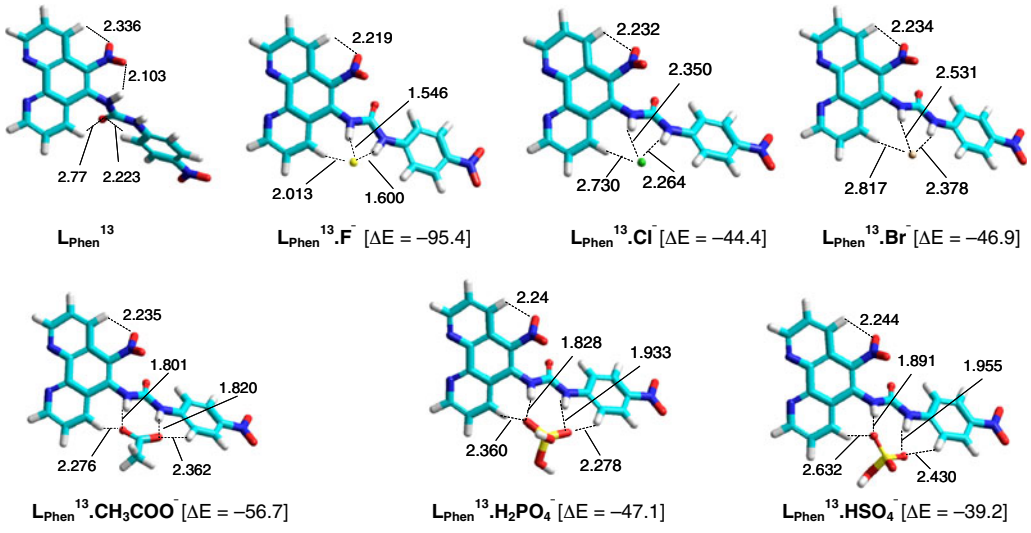



**Figure 6.** The RHF/6-31G* optimized geometries for $\mathbf{L_{Phen}}^{\mathbf{13}}$ and its complexes with $F^-$, $Cl^-$, $Br^-$, $CH_3COO^-$, $H_2PO_4^-$ and $HSO_4^-$ anions with the corresponding binding energies. Colour code: $F^-$ (yellow), $Cl^-$ (green), $Br^-$ (brown); [ref. 21].

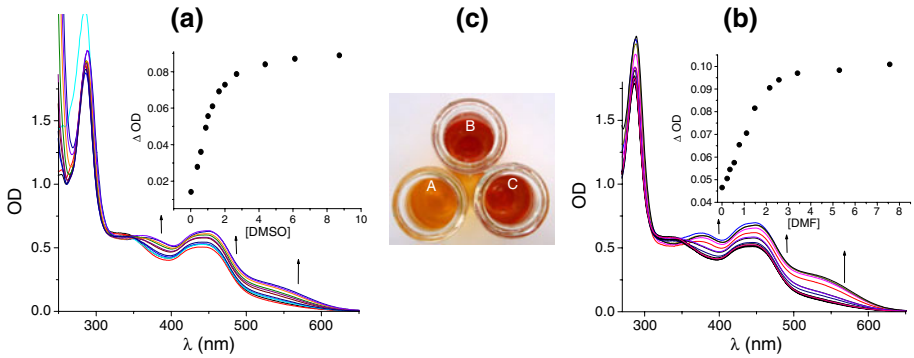
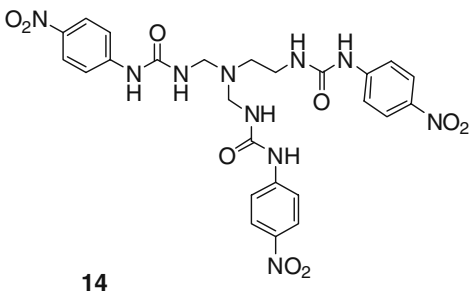



**Figure 7.** Absorption titration of receptor **13** ($2.0 \times 10^{-5}$ M) with varying DMSO ($1.3 \times 10^{-2}$ M – 0.6 M) (**a**) and with varying [DMF]: ($1.2 \times 10^{-2}$ M – 1.2 M) (**b**); while, (**c**) shows the corresponding colour changes for receptors **13**, **(A)**; DMSO, (**B**), DMF, (**C**) for each compound. Insets: Corresponding titration profile for each titration. (ref. 22).

–$N(H)_{urea}$ was evident in the detectable colour change of the solution of **13** in presence of neutral molecule like DMF and DMSO (figure 7). Thus, this complex also was found to act as a colorimetric sensor for neutral molecules like DMSO and DMF (table 4) — though respective binding affinity of the two receptors towards these neutral molecules are much weaker as compared to the anions. An amide-based receptor was reported by Smith *et al.*, where the receptor was synthesized in several steps and was used for binding studies using $^1$H NMR titration.[23]

To rationalize the relative affinities of $\mathbf{L_{Phen}}^{12}/\mathbf{L_{Phen}}^{13}$ towards DMSO or DMF and to have a better insight about the binding modes and geometries, structures for the respective adducts were optimized with RHF/6-31G* level of theory using $\mathbf{L_{Phen}}^{12}/\mathbf{L_{Phen}}^{13}$ as model for $Ru(bpy)_2L^{2+}$ (figure 8). It is reported that these binding affinity values are comparable to the one reported earlier by the urea functionality of parent structure for both receptors ($\mathbf{L_{Phen}}^{12}/\mathbf{L_{Phen}}^{13}$) rotates when bound to different anions (figure 8). However, in case of H-bonded adduct with DMSO or DMF, no such rotation was observed and entirely different geometry for the respective adduct was obtained (figure 8).

Binding energy for DMSO/DMF is also found to be much lower as compared to those for halides/oxyanions and agrees well with the lower binding affinities that we have obtained experimentally (table 4). Calculated binding energies further confirm stronger interaction with DMSO, compared to DMF, with these receptors (figure 8).



**14**

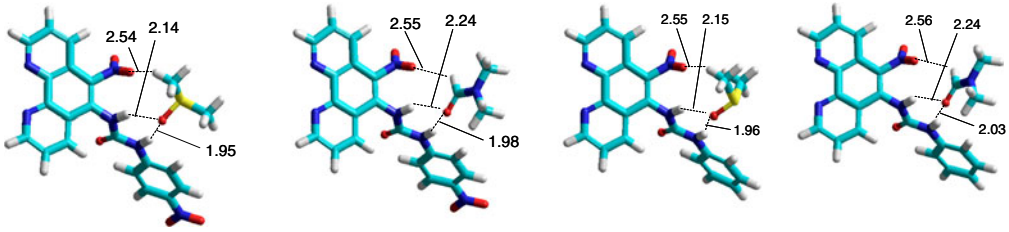
Another *tris* urea derivative (**14**) was used to develop an envelope type receptor for anionic analytes, where three urea functionalities of the tren-based *tris*–urea receptor molecule may encapsulate a spherical anion.[24] This showed the preferential binding with sulfate/phosphate anions. Single crystal X-ray structure for the sulphate adduct revealed that this receptor acted as a neutral molecular capsule within which a unique sulfate–$(H_2O)_3$–sulfate adduct is encapsulated (figure 9).

However, authors have reported a higher binding affinity for this receptor towards sulphate ion than the phosphate ion, though charge density is known to be higher on the oxygen atoms of the phosphate

**Table 4.** Binding constant values for DMSO and DMF evaluated from Uv-vis titration.[a]

| Complex.X<br>X is DMSO/DMF | $\mathbf{K}_a$ ($M^{-1}$) [$10^2$] |
|---|---|
| **2.** DMSO | 1.86 ( ± 0.2) |
| **2.** DMF | 1.43 ( ± 0.1) |
| **3.** DMSO | 1.59 ( ± 0.2) |
| **3.** DMF | 1.04 ( ± 0.1) |

[a]K value reported is the average of the six independent data evaluated from each individual Uv-vis titration data for the respective receptor and anion. Confidence limits for the respective K values are also shown.




**$L_{Phen}^{13}$.DMSO**[ΔE=–17.0] **$L_{Phen}^{13}$.DMF** [ΔE=–14.5] **$L_{Phen}^{12}$.DMSO** [ΔE=–16.2] **$L_{Phen}^{12}$.DMF** [ΔE=–12.6]

**Figure 8.** The RHF/6-31G* optimized geometries for **12** and **13** and its complexes with DMSO and DMF respectively with the corresponding binding energies given below each structure. Binding energies (ΔE) in kcal/mol. [Colour code: oxygen (red), nitrogen (blue), cyan (carbon), hydrogen (white)]; [ref. 22].

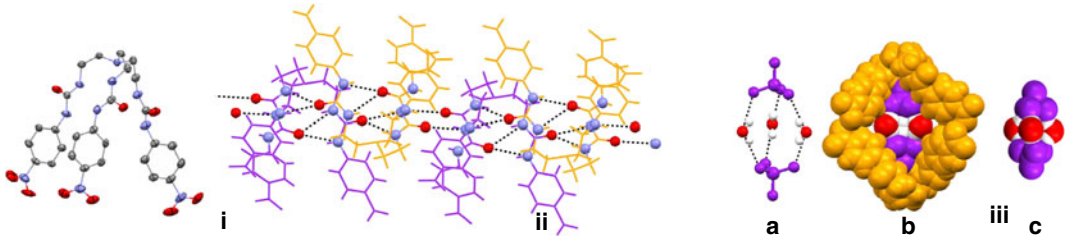
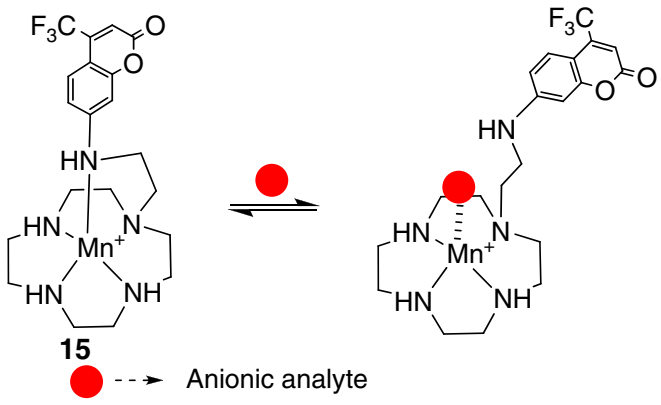



**Figure 9.** (**i**). Thermal ellipsoidal plot of **14**; Colour Code: oxygen (red), nitrogen (blue), carbon (grey). (**ii**). Complementary H-bonding of urea moiety forming 1 D network in **14**, alternate molecules are shown in purple and orange colour and the nitrogen (blue) and oxygen (red) atoms of urea are shown in ball and stick model]. (**iii**). (**a**) Ball and stick model of the sulfate–water adduct displaying hydrogen bonding (dotted lines), (**b**) space filling model of the adduct trapped inside the cavity of tren urea; tetra butyl ammonium cation and disordered water molecules are omitted for clarity, (**c**) Rugby ball shaped architecture of the adduct; [ref. 24].

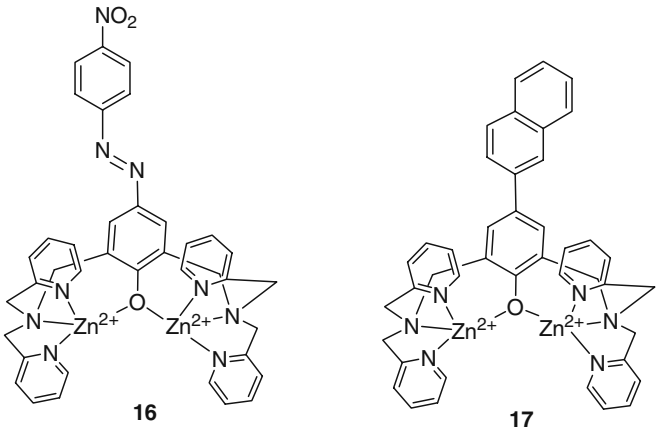
ion. Presumably, the geometry of the sulphate ion is more favourable for an efficient H-bonded interactions. Receptors based on hydrogen-bonding interactions are generally not suitable for application in biological samples. One of the essential criteria of the receptor molecule for such application is that it must perform in physiological conditions and thus it should be able to detect anion in aqueous or aqueous buffer solution. This makes things very challenging to the researcher, primarily due to the very high energy of hydration of anions like fluoride, phosphate, acetate, etc. To get around this problem, researchers have adopted different methodologies — use of weak metal-anion coordination is one of these where the binding induced changes in the output signal can be probed either through spectroscopy or change(s) in redox potential data.




**Scheme 3.**

Most popular example in this regard is recognition of phosphates, pyrophosphates (Ppi) and other biological phosphates like AMP (Adenosine monophosphate), ADP (Adenosine diphosphate), ATP (Adenosine triphosphate), CTP (cytisine triphosphate) because of the strong binding affinity between metal ions and these phosphate ions allow their detection in aqueous medium. However, successful design of the appropriate receptor functionality depends on several factors like binding affinity between metal centre and the targeted anionic analyte, hydration energy, as well as the ability to convert anion recognition into an output signal.

One of such earlier example was reported by Kikuchi *et al.*[25] They designed a $Cd^{2+}$-cyclen-coumarin system as a fluorescent chemosensor (**15**) for PPi ions. Here the




**Scheme 4.**

preferential binding of the $Cd^{2+}$ centre and PPi as compared to that between $Cd^{2+}$ centre and aromatic amine (scheme 3) accounts for the recognition and sensing.

Though, this receptor (**15**) did not show adequate selectivity (table 5), it showed preference for PPi over other inorganic phosphate in physiological condition.

It was observed that phosphate showed weaker affinity than PPi. It was argued that presumably the protonated forms, $HPO_4^{2-}$ and $H_2PO_4^-$, are dominant species in aqueous solution of pH 7.4 and their lower effective charge density is reflected in their weaker interactions than PPi. Authors could also demonstrate that the activity of phosphodiesterase, which hydrolyses the phosphodiester bond of cyclic nucleotides and AMP, could be monitored by using the chemosensor **15**.

**Table 5.** Apparent Dissociation Constants ($K_d$) of Sensor **15** with different anions in 100 mM HEPES Buffer (pH 7.4).[a]

| Anion | $K_d$ (M) | anion | $K_d$ (M) |
|---|---|---|---|
| pyrophosphate | $7.5 \times 10^{-5}$ | ATP | $1.4 \times 10^{-5}$ |
| Citrate | $9.0 \times 10^{-5}$ | ADP | $2.6 \times 10^{-5}$ |
| $I^-$ | $9.2 \times 10^{-3}$ | GMP | $4.8 \times 10^{-5}$[c] |
| Phosphate | $1.5 \times 10^{-2}$ | AMP | $4.4 \times 10^{-4}$ |
| $Br^-$ | $3.2 \times 10^{-2}$ | UMP | $1.7 \times 10^{-3}$ |
| $Cl^-$ | $9.0 \times 10^{-2}$ | CMP | $1.9 \times 10^{-3}$ |
| $F^-$ | b | cAMP | b |
| $ClO_4^-$ | b | | |

[a]All anions were added as sodium or potassium salts;
[b]$K_d$ was too large to be calculated.
[c]This value is smaller than the real $K_d$, because dynamic quenching was observed besides static quenching; [reference 25].

Among the metal ion complex based sensors, $Zn^{2+}$ complexes with a *bis*(2-pyridylmethyl)amine (DPA) unit have attracted considerable attention.[26] Hong and his co-workers have reported an azophenol-based colorimetric sensor **16**, which could selectively recognize PPi $\left(K_a = 6.6 \times 10^8 M^{-1}\right)$ among the various anions in water (scheme 4).[27] A shift of about 60 nm in electronic spectra was observed on binding to PPi. This particular sensor could bind PPi approximately 1000 times more tightly than Pi and be used over a wide range of pH (6.5–8.3). However, use of naphthalene moiety in **17** (scheme 4), instead of azo benzene functionality, allowed probing the PPi binding by changes in fluorescence spectra.

The association constant for PPi was very high ($2.9 \times 10^8$ $M^{-1}$) and this allowed detection of PPi in water at nanomolar concentrations. This was the first example of a complex that can discriminate PPi from ATP in aqueous solution. It was arguzzed that the total anionic charge density of the four O–P oxygen atoms involved in the complexation of ATP with Zn(II)-centre on the complex **17** is smaller than that of the four O–P oxygen atoms of PPi, which actually reduces the binding affinity of ATP significantly. Complex **17** could also be used to detect the PPi released from the dNTPs, which occurs stoichiometrically when DNA is synthesized by the action of DNA polymerase. Thus, this complex could be used for quick, one-step, homogeneous phase detection method to confirm DNA amplification after polymerase chain reactions (PCR).[28] The success of this method relied on the preferential binding of **17** to PPi in the presence of a large excess of ATP.

Very recent report revealed that a chromogenic complex **18** showed high affinity towards phosphate ion in tetra butyl ammonioum phosphate (TBAP) in acetonitrile solution and could preferentially bind to the ATP reversibly in aqueous solution at the physiological pH.[29]

This binding caused visual change in colour; while no such change was noticed with other related anions (AMP, ADP, PPi and Phosphate) of biological significance (figure 10). Thus **18**.**Zn** could be used either as the colorimetric sensor for ATP or as a staining agent for different biological cells (figure 11) through binding to the ATP, generated *in situ*. These stained cells could be viewed under normal light microscope and it was possible to distinguish the *Gram +ve* and the *Gram −ve* bacteria (*prokaryotes*) based on differential staining. Further experiments revealed that this reagent was non-toxic to the living cells and could be used for evaluating the cell growth dynamics. It has been argued that

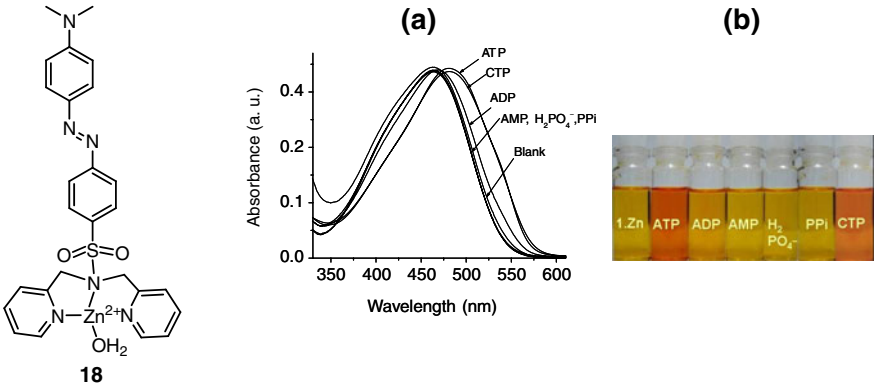



**Figure 10.** (**a**) Absorbance spectra of **18** (25 $\mu$M) in HEPES buffer solution (pH $\sim$7.2) at 25°C in the presence of various anions (250 $\mu$M) and (**b**) change in colour of **18** in aqueous solution from left to right: Blank, with ATP, ADP, AMP, PPi, $H_2PO_4^-$ (anion concentration 100 $\mu$M) and CTP (125 $\mu$M).

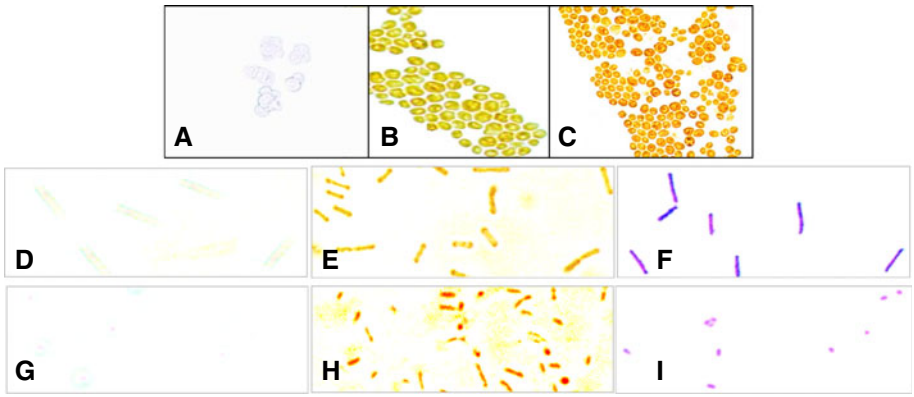



**Figure 11.** Light microscopic images (100 x) of (**A**) Blank Yeast cells, (**B**) Yeast cells with **18**, (**C**) after washing the stained cells with a water/ethanol (70/30, v/v) mixture. *Gram +ve Bacillus sp.* (**D**) without any staining agent, (**E**) when treated with **18**, (**F**) when treated with Gentian Violet dye; *Gram –ve Pseudomonas sp*. (**G**) without any staining agents, (**H**) when treated with **18**, (**I**) when treated with Safranin dye; [ref. 29b].

among ATP/CTP and PPi, where anions carry identical charges, interaction of PPi with **18** is very weak in nature and cannot induce any detectable spectral change. Earlier studies reveal that PPi prefers to act as a bridging ligand in related binuclear complexes rather than forming a stable six-member chelate complex. Further, much higher solvation energy for PPi in water, compared to ATP, might also contribute to the weaker binding of the effectively solvated PPi to Zn(II)-center in **18**.

## 3. Conclusions

In this brief review, we have tried to present a brief account of the different influences that play crucial roles in effecting the analyte–receptor interaction. We have discussed how geometry of the analyte or receptor and their relative spatial arrangements, charge density, media polarity and remote substitution on the receptor, along with the change(s) in structure of the analyte or receptor on formation of the receptor–analyte adduct could actually control the binding process. We have also discussed with specific example how computational studies could help in developing a better insight in understanding the anion recognition process.

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