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Anion Recognition in Water with Use of a Neutral Uranyl-salophen Receptor

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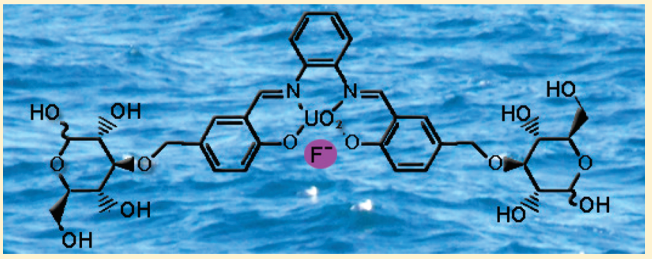
Supporting Information

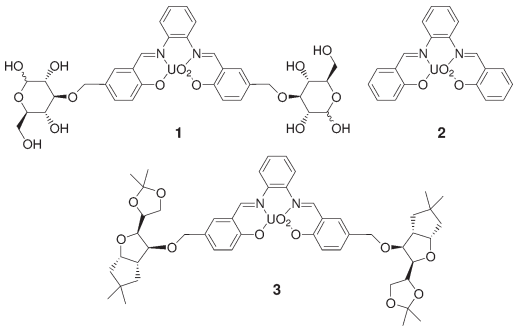
ABSTRACT: A new water-soluble uranyl-salophen complex incorporating two glucose units has been synthesized. This neutral derivative shows noteworthy binding affinity for fluoride in water thanks to the Lewis acid−base interaction occurring between the metal and the anion. Such interaction is strong enough to overcome the high hydration enthalpy of fluoride. Moreover this complex effectively binds hydrogen phosphate and exhibits remarkably strong association for nucleotide polyanions ADP^{3-} and ATP^{4-}.



Anions are ubiquitous in both the organic and mineral worlds. They play different key roles in biology and cause dramatic effects as environmental pollutants. Consequently, the development of synthetic anion receptors that work in water represents an area of significant current interest in supramolecular chemistry,[1] nurtured by the potential practical applications of the investigated systems to the detection and quantification of these species. The assignment is quite challenging for many reasons. Water is a highly competitive solvent, and anions are effectively hydrated so that any complexation process involving anion dehydration has to pay a strong energetic penalty. Moreover, anions are relatively large with wide range of geometries and charge-delocalized forms and often pH-sensitive too, since they can be involved in protonation equilibria. Hence their recognition requires boosting the affinity of the synthetic receptors through higher design complexity to supply reversible host−guest interactions able to survive in water. In general, several weak interactions have to be combined to achieve a strong and selective binding under such competitive conditions ("Gulliver effect").[2] It was thought at the beginning that only positively charged receptors[3] could compete with anion solvation, but lately it has been shown that also neutral hosts that rely on hydrogen bond formation[4] and/or on Lewis acidity[5] can show considerable anion affinity in water solutions.

On this premise we report here about the newly synthesized uranyl-salophen receptor **1**, soluble in water, which is able to display good affinity toward fluoride and hydrogen phosphate anions and to exhibit remarkably strong association for nucleotide polyanions ADP^{3-} and ATP^{4-}. The receptor makes use of an immobilized UO_2^{2+} dication as binding site for anions through a Lewis acid−base interaction.

It is well established that, when complexed with the tetradentate $N_2O_2^{2-}$ unit of the salophen ligand, the uranyl dication uses its fifth equatorial coordination site to bind strongly to hard Lewis bases, as witnessed by studies in organic solvents and in the solid state[6] and confirmed by DFT calculations (Figure 1). Here we show that this interaction is sufficiently strong to guarantee the recognition of selected anions in water without the use of additional structural binding motifs.



For the synthesis of **1**, 2 mol of 3-*O*-(3-formyl-4-hydroxybenzyl)-D-glucose, **4**, prepared as previously described,[7] was reacted in methanol at room temperature with 1 mol of 1,2-diaminobenzene in the presence of uranyl acetate, $UO_2(AcO)_2 \cdot 2H_2O$. The metal complex **1** precipitates from the reaction mixture upon slow addition of excess diethyl ether, Scheme 1. While the parent uranyl-salophen derivative **2** is completely unsoluble in water, the presence of the two glucose units provides fair solubility in this solvent.

The optical properties of complex **1** were investigated by UV−vis spectroscopy. The absorption spectrum for **1** exhibits the same fine structure that is commonly observed for analogous

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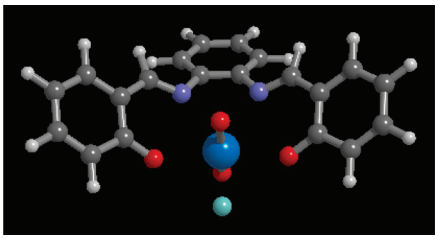
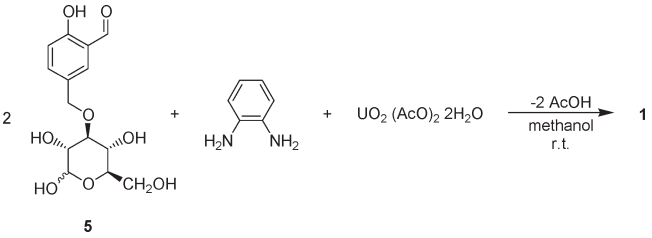


Figure 1. Calculated structure of the complex between the parent uranyl-salophen compound and F^-. See Supporting Information for computational details.

Scheme 1. Synthesis of Complex 1



uranyl-salophen complexes in organic solvents. A monotonic increase of absorbance in the region 280−550 nm on lowering the wavelength and a shoulder at 350 nm are observed (Supporting Information, Figure S5). If compared with the spectra of similar compounds in chloroform, absorbance intensities are slightly reduced by about 15%. The close adherence of optical data to the Lambert−Beer law at different wavelengths (Supporting Information, Figure S6) indicates the absence of significant dimerization[8] and aggregation phenomena of the receptor within the explored range of concentrations.

At the beginning, the interaction of the uranyl-salophen complex **1** with anions was investigated through spectrophotometric titrations, by adding increasing amounts of a standard aqueous solution of the given anion salt to a solution of **1** in bidistilled water. A typical titration experiment is reported in Figure 2. The addition of increasing amounts of sodium fluoride at 25 °C causes reproducible absorbance changes in the 280−450 nm region, where absorption of the added salt is negligible. Absorbance values at 330 nm fit to the binding isotherm for 1:1 complexation, described by eq 1, where [S] is the total anion concentration in each point, A is the corresponding experimental absorbance, $[R]_o$ is the analytical concentration of the receptor, A_o is the absorbance of the receptor alone, and ΔA_∞ is the limiting variation of the absorbance, Figure 2 inset.

$$A = A_o + \Delta A_\infty \frac{[R]_o + K^{-1} + [S] - \sqrt{([R]_o + K^{-1} + [S])^2 - 4[S][R]_o}}{2[R]_o} \quad (1)$$

The close adherence of titration data to the binding isotherm, combined with the presence of sharp isosbestic points, clearly suggests the occurrence of a clean 1:1 complexation phenomenon. Least-squares fitting of the data lead to calculated values of the association constants reported in Table 1.

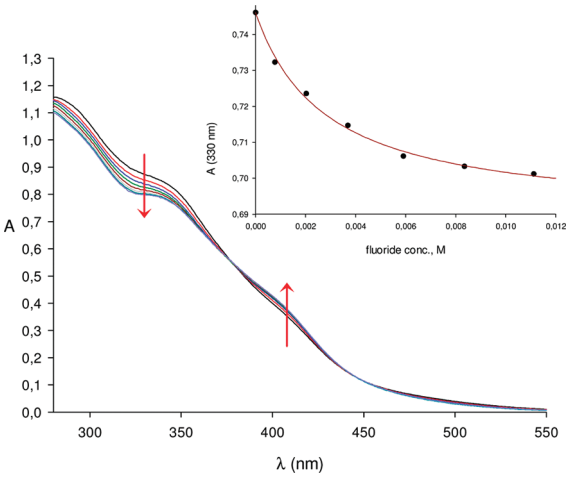


Figure 2. UV−vis absorption spectra of **1** upon addition of increasing amounts of sodium fluoride. The inset shows the titration plot at 330 nm of a 4.81 × 10^{-5} M solution of compound **1** with fluoride at 25 °C in bidistilled water. The points are experimental, the line is calculated using eq 1.

Table 1. Association Constants, K_a, for Complexes between 1 and Anions in Water at 25°C

anion	K_a (M^{-1})[a]
F^-	115 ± 6[b]
Cl^-	<5
CH_3COO^-	17 ± 4
SO_4^{2-}	<5
CN^-	<5[b]
NO_3^-	<5
N_3^-	<5
HPO_4^{2-}	480 ± 35[b]
AMP^{2-}	83 ± 8[b]
ADP^{3-}	>10^4[b]
ATP^{4-}	>10^4[b]
$P_2O_7^{4-}$	>10^4[b]

[a] Errors are calculated as ±2σ. [b] Obtained in MOPS buffer at pH 7.5.

The affinity of complex **1** toward fluoride anion, K_a = 115 M^{-1}, is quite notable although moderate, in view of the extremely high hydration enthalpy of the small fluoride anion ($\Delta H°$ = −504 kJ mol^{-1}). An inspection of the literature shows that very few neutral receptors able to achieve anion binding in water have been developed so far and that even more rare are those that bind fluoride. A number of examples are reported in which receptors work in organic solvent−water mixtures where the increase of the water content lowers the affinity toward fluoride to such an extent that the association, if it survives, can be hardly detected.[1,3a,9] In our case the strong interaction with the Lewis center (in DMSO K_a >10^6 M^{-1})[10] still persists in water, allowing quantitative binding measurements.

Given that recognition motifs that work for fluoride anion are generally also effective for cyanide, we investigated the affinity of **1** toward this analyte, whose detection in water represents an extremely important task due to its severe toxicity.[11] Preliminary UV−vis spectrophotometric titrations of **1** with an aqueous solution of NaCN led to puzzling results. The adherence of

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experimental data points to the binding isotherm was poor at low cyanide concentrations, and an abnormally high value of 1.6×10^4 M^{-1} for the association constant was obtained by nonlinear curve fitting. On the other hand, in anhydrous methanol no significant binding was observed between the anion and the structurally related uranyl complex **3**. This led us to conclude that no interaction takes place between **1** and cyanide in water and that the observed absorbance changes are attributable to the basicity of the anion. The addition of the titrating agent increases the pH, and the produced hydroxide anion associates to the metal. Unfortunately, it was not possible to quantify the strength of this association since the data, obtained by adding increasing amounts of NaOH to a solution of **1**, show the presence of inflection points, suggesting that multiple binding is probably involved. To prevent complications, we decided to adopt a protocol implying the use of a buffer. On the basis of the finding that sulfate does not associate to **1** (Table 1) and that no significant interactions between uranyl-salophen complexes and tertiary amines take place even in organic solvents,[12] the MOPS [3-(*N*-morpholino)propanesulfonic acid]/NaOH system was chosen as a suitable noninterfering species that provides an almost physiological pH. So we prepared a 10 mM solution of the buffer by dissolving MOPS in water and by adjusting the pH to 7.5 with a solution of NaOH. In order to verify the absence of significant interactions, we repeated a selected number of titration experiments in MOPS solutions, first of all that with fluoride (see Table 1 and Figures S7 and S8 in Supporting Information), obtaining association values comparable to those found in unbuffered solutions. In particular we repeated the titration of **1** with cyanide, and under these conditions, we did not observe any significant interactions. Since at pH = 7.5 cyanide is protonated by about 98%, this result does not exclude a possible interaction between cyanide and uranyl-salophen complexes but indicates that such interaction would only take place at higher pH values, where cyanide suffers the competition of OH^-.

The same protocol was also applied to the study of association between **1** and inorganic and organic phosphates, which require careful pH control. At pH = 7.5, phosphate exists mainly in the form of dianion HPO_4^{2-} and the measured binding constant with **1** is 480 M^{-1} (Table 1). Hence phosphate is definitely the inorganic anion that displays the strongest interaction with **1** in water, having only F^- as potential competing species. Years ago Reinhoudt et al. reported that uranyl-salophen complexes can selectively bind $H_2PO_4^-$ ions in organic solutions.[13] Obviously in water at pH = 7.5 the concentration of this species is negligible. Attempts to titrate complex **1** with an unbuffered water solution of $H_2PO_4^-$ led to the degradation of the receptor. The acidity of $H_2PO_4^-$ promotes the hydrolysis of the imine bond of the salophen ligand, and the absorbance band of the salycilaldehyde soon appears in the UV−vis spectrum.

In addition we also investigated the possibility of **1** to bind the biologically relevant anions AMP^{2-}, ADP^{3-}, and ATP^{4-} in water under physiological pH conditions. Association constants between **1** and adenosine nucleotides in MOPS buffer at pH = 7.5 are reported in Table 1 (Figures S9 and S12 in Supporting Information). The first remarkable result is that the association constants of adenosine monophosphate, AMP^{2-}, with **1** is about six times weaker than that with HPO_4^{2-}. A likely explanation for the relatively good affinity shown by the inorganic phosphate can be the formation of an intracomplex hydrogen bond between the hydroxyl group of the anion and one of the uranyl apical oxygens, "yl" oxygens, acting as hydrogen bond acceptors.[14] The occurrence of this binding motif in uranyl protein complexes suggests that this can be considered a common feature in uranyl structures.[15] Obviously a similar interaction can be ruled out in the case of AMP^{2-}. The binding constants between **1** and ADP^{3-} and ATP^{4-} are estimated to be higher than 10^4 M^{-1} since the intrinsic limitations of the spectrophotometric method allow only to fix a lower value limit.[16] However such values are quite different from the modest association constants found for AMP^{2-}. The occurrence of an additional interaction could be the reason for such a result. We have recently reported that the zinc-salophen complex prepared from 1,2-naphthalendiamine and 2-isopropylsalicylaldehyde binds nucleotides AMP^{2-}, ADP^{3-}, and ATP^{4-} in ethanol. The observed selectivity ($ADP^{3-} > ATP^{4-} > AMP^{2-}$) was correlated to the distance between the donor group and the adenosine moiety that leads to the simultaneous occurrence of a metal phosphate interaction and of $\pi-\pi$ stacking interactions between the adenine unit and the receptor.[17] In the present case, the addition of increasing amounts of a solution of adenosine to a solution of **1** did not cause any change in the absorption spectrum. So the only conclusion that we can draw is that, in the absence of any additional binding motif, the association with polyphosphates is stronger than that with the monophosphate derivative.

This has been verified by carrying out the titration of **1** with a solution of sodium pyrophosphate ($P_2O_7^{4-}$, PPi). As in the cases of ADP^{3-} and ATP^{4-}, pyrophosphate displays a very high association constant (Supporting Information, Figure S11) for which we were able to estimate only a lower limit of 10^4 M^{-1}.

In summary, we have reported the synthesis and anion binding capabilities in water of a novel uranyl-salophen derived receptor. Compound **1**, which is neutral, shows noteworthy binding affinity for fluoride. The Lewis acid−base interaction is strong enough to overcome the extremely high hydration enthalpy of the anion. Although the binding constant is modest, to the best of our knowledge it is one of the highest ever reported in pure water for a neutral receptor with no additional binding sites. Moreover, the good affinity for inorganic phosphate and for biologically relevant anions can provide helpful hints for the design of sensors based on metal-salophen units.

EXPERIMENTAL SECTION

Materials. All chemicals were used as obtained, without any further purification. Compound **4** was prepared according to a previously reported procedure.[7]

Complex 1. A solution of 3-*O*-(3-formyl-4-hydroxy-benzyl)-D-glucose **4** (0.073 g, 0.232 mmol), 1,2-diaminobenzene (0.013 g, 0.117 mmol), and $UO_2(OAc)_2$ $2H_2O$ (0.051 g, 0.12 mmol) in MeOH (8 mL) was stirred for 16 h. The complex was precipitated by slow addition of excess diethyl ether to the reaction mixture. After filtration, compound **1** was isolated as a red-orange solid (0.078 g, yield 35%). ^{1}H NMR (300 MHz, methanol-d_4): δ 9.54 (s, 2H), 7.82−7.52 (m, 2H), 7.07 (d, 2H, J = 8.41 Hz), 5.07 (d, 0.5H, J = 3.73 Hz), 4.46 (d, 0.5H, J = 7.79 Hz), 3.84−3.59 (m, 6H), 3.47−3.30 (m, overlapped with the solvent signal) ppm. ^{13}C NMR (75 MHz, methanol-d_4): δ 167.6, 164.6, 145.3, 135.0, 133.6, 127.3, 127.1, 126.9, 122.1, 118.7, 117.9, 95.3, 91.1, 83.1, 80.3, 75.0, 73.5, 72.9, 72.5, 72.3, 71.0, 70.1, 68.7, 68.6, 59.8, 59.7 ppm. HRMS (ESI-TOF) m/z M calcd for $C_{34}H_{38}N_2O_{16}NaU^+$ 991.2627, found 991.2643. The elemental analysis was not satisfactory even though NMR spectra and HPLC analysis confirmed purity (see Supporting Information). The formation of stable metal carbides might be the reason for the poor analysis.[18]

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■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR, ESI-HRMS, HPLC trace for complex **1**, UV−vis absorption spectra, titration plots together with computational details for the calculated structure of Figure 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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