Specific recognition of fluoride anion using a metallamacrocycle incorporating a uranyl-salen unit†‡

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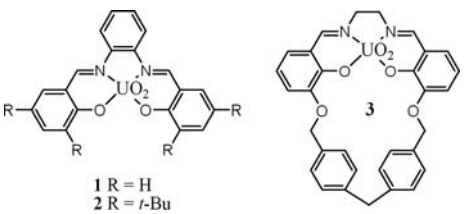
Received (in Montpellier, France) 11th April 2008, Accepted 25th April 2008
First published as an Advance Article on the web 19th May 2008
DOI: 10.1039/b806149a

The design and synthesis of a novel fluoride receptor that uses a salen-complexed Lewis acidic uranyl center as the sole binding site is reported here. This receptor binds fluoride anions in DMSO with a high affinity constant ($K > 10^6$ M^{-1}) and exhibits a negligible affinity ($K < 10$ M^{-1}) towards otherwise effective competitors, such as acetate, phosphate and cyanide anions.

The molecular recognition of fluoride anion is currently attracting great interest due to its chemical and biological importance, as witnessed by a host of papers on the subject published in the last few years.[1] The construction of specific chemosensors calls for the design and synthesis of receptors capable of binding fluoride anions with both high efficiency and selectivity. In the vast majority of reported systems, fluoride anion is coordinated using hydrogen bonding interactions.[2] Less numerous, yet still well documented, are receptors containing a Lewis acidic center, such as boron or silicon.[3] More rarely reported are those receptors based on a metal center, either alone or in combination with additional binding sites.[4] Here, we report a highly effective and selective neutral receptor that makes use of an immobilized UO_2^{2+} dication as the sole binding site for fluoride.



When complexed with the tetradentate $N_2O_2^{2-}$ unit of either salen or salophen ligands, the uranyl dication uses its fifth coordination site in the equatorial plane to bind strongly to hard anions, as shown by studies in solution and in the solid state.[5] The affinity of the parent uranyl-salophen compound, **1**, for fluoride is revealed by the orange to bright yellow color change induced by the addition of tetrabutylammonium fluoride (TBAF) to a 1 mM solution of **1** in DMSO. The reversible nature of the interaction was proved by the finding that the addition of water lead to the recovery of the original absorption spectrum of **1** (Fig. S1†). This is easily understood in terms of hydrogen bonding interactions between water and fluoride anions, and possibly by the coordination of an oxygen of a water molecule to the uranyl center. The spectroscopic changes observed when a very dilute solution of **1** was treated with increasing quantities of TBAF is shown in Fig. 1. There is a definite tendency for the sigmoid behaviour of the titration curves to become less pronounced upon increasing the analyte concentration (Fig. S2†). When the concentration approaches 1 mM, the titration profiles are sharp curves, reaching a plateau at 1 equiv. of added fluoride (Fig. 2). The same behavior is experienced in the ^{1}H NMR titration reported in Fig. S3.†

This finding, combined with the existence of sharp isosbestic points (Fig. 1), clearly indicates that during the titration, receptor **1** is a two state system, and that only one strong complex of 1 : 1 composition is formed with fluoride anions.[6] No spectral changes were observed upon adding 200 mol equiv. of the tetrabutylammonium (TBA) salts of chloride,

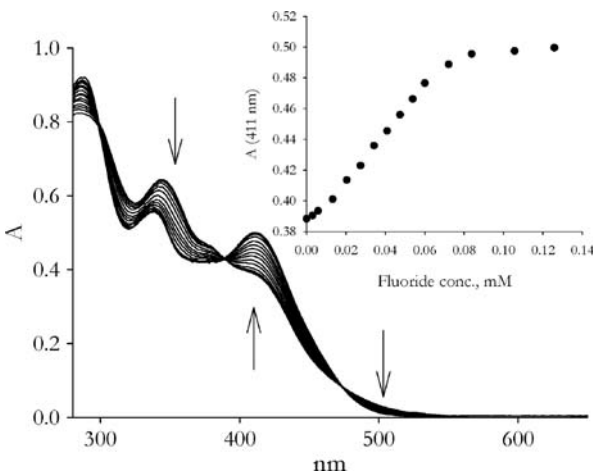


Fig. 1 UV-vis spectral changes of 3.9×10^{-5} M **1** (DMSO, 25 °C) upon addition of TBAF. The inset shows the spectral changes at 411 nm.

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† Electronic supplementary information (ESI) available: Typical UV-vis and NMR titrations; X-ray data; ^{1}H and ^{13}C NMR spectra of receptors **2** and **3**. See DOI: 10.1039/b806149a

‡ CCDC 670306. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b806149a

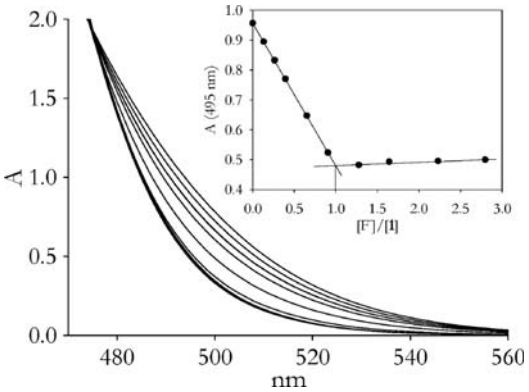


Fig. 2 UV-vis titration of 8.7×10^{-4} M **1** with TBAF in DMSO. The inset shows 1 : 1 complex formation.

bromide or iodide anions. This was also the case with weakly basic oxyanions, such as ClO_4^- and SO_4^{2-}. Although, because of the sigmoid-shaped titration curve (Fig. 1), the affinity of complex **1** towards fluoride anions could not be measured on the basis of the absorption titration, the above observations clearly highlight the high selectivity of **1** for fluoride anions over other halides and weakly basic anions. However, the situation with more basic anions, such as AcO^- and $H_2PO_4^-$, was different. Fig. 3 shows the spectroscopic changes experienced by **1** upon titration with tetramethylammonium acetate (TMAAcO). Unlike in Fig. 1, the titration plot in Fig. 3 has the expected shape for a 1 : 1 binding isotherm. Similar behaviors were observed for titrations with TBA H_2PO_4. The results of the titration experiments are listed in the first column of Table 1, including an estimate of the binding affinity towards fluoride ion based on competition experiments, in which **1** was titrated with TBAF in the presence of a large excess of TMAAcO (Fig. S4†).

While the parent uranyl-salophen complex appears to bind fluoride ion significantly more strongly than the other basic anions, with a selectivity that compares well with, or even exceeds, those experienced by more structured receptors,[1] even higher selectivities are considered desirable for many applications. As a first effort to develop a more selective fluoride receptor based on the uranyl-salophen unit, we considered the *tert*-butylated derivative, **2**, which easily prepared by the condensation of 3,5-di-*tert*-butyl-salicylaldehyde with 1,2-diaminobenzene in the presence of $UO_2(AcO)_2{\cdot}2H_2O$ in methanol. The introduction of bulky *tert*-butyl groups was meant to promote steric control over an anion's approach to the equatorial binding site. Table 1 shows that the *tert*-butyl groups flanking the uranyl center did indeed decrease the affinity towards $H_2PO_4^-$ by 50-fold, but were not bulky enough to hinder the complexation of the flat AcO^- anion.[7] Consequently, on the basis of molecular models, we envisaged cyclophane **3**, whose small cavity seemed to host selectively the tiny fluoride ion, with the exclusion of the bulkier anions. At first, we actually considered the analogous macrocycle structure based on the salophen moiety. However, any attempt at reacting precursor **5** (Scheme 1) with 1,2-diaminobenzene in the presence of $UO_2(AcO)_2$ failed to yield the desired macrocycle. From this evidence, we reasoned that the more flexible salen moiety could be more easily incorporated into a strained macrocyclic structure than the rigid salophen one. The synthesis of target receptor **3** was accomplished by a two-step procedure, starting from readily available materials (Scheme 1). The X-ray crystal structure of its methanol solvate is shown in Fig. 4.‡ The cavity where the UO_2^{2+}-bound methanol is hosted has a 5.3×4.5 Å rectangular shape, which can obviously accommodate a fluoride anion, but it does not appear to be spatially suitable for linear coordination in the equatorial plane of even an anion as small as CN^-.

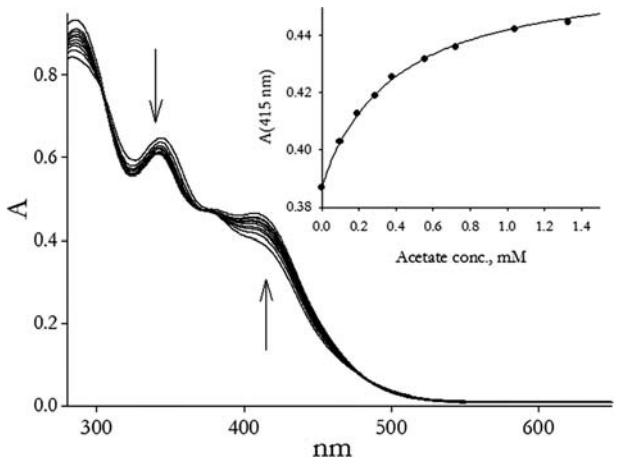


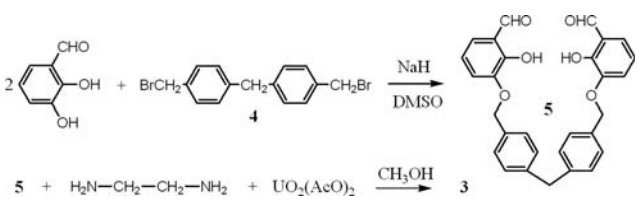
Fig. 3 UV-vis spectral changes of 3.9×10^{-5} M **1** (DMSO, 25 °C) upon addition of TMAAcO. The inset shows the fit of the experimental data to a 1 : 1 binding isotherm (415 nm).

Table 1 Log K values (K/M^{-1}) for the association of receptors **1–3** with various anions in DMSO at 25 °C

Anion[a]	1	2	3
AcO^-	3.41 ± 0.03	3.62 ± 0.04	<1
$H_2PO_4^-$	4.00 ± 0.05	2.32 ± 0.08	<1
CN^-	2.36 ± 0.05	2.32 ± 0.08	<1
F^-	6.4 ± 0.1[b]	6.5 ± 0.2[b,c]	>6[d]

[a] TBA salts (except for acetate, which is its TMA salt). [b] From competitive titrations in the presence of excess TMAAcO (see ESI). [c] Titration of dilute solutions of **2** displayed a sigmoid behavior analogous to that seen in Fig. 1. [d] See text.

The receptor properties of **3** were in line with our expectations. No spectral variations were induced by the addition of up to several hundred equivalents of the TBA salts of $H_2PO_4^-$, CN^- or TMAAcO to solutions of **3** in DMSO ($K < 10\ M^{-1}$). Titration with TBAF instead caused spectral variations that were very similar to those experienced by **1** and **2** (compare Fig. S5† with Fig. 1), showing that the affinity of **3** towards fluoride anions is comparable to those of the salophen



Scheme 1

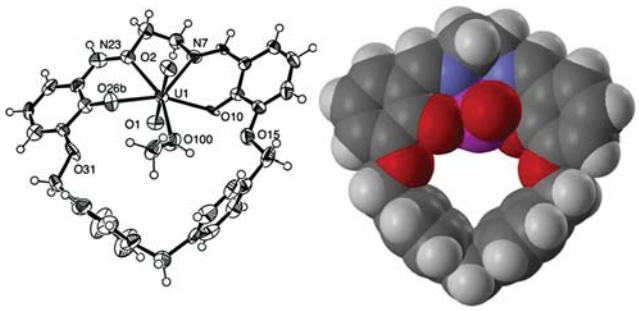


Fig. 4 X-Ray crystal structure of **3**·CH_3OH. Left: ORTEP plot (50% probability level). Right: CPK model. The UO_2^{2+}-bound methanol is omitted for clarity, and only one of the uranyl-salen–methanol complexes in the asymmetric unit is shown.

receptors.[8] It appears therefore that the selectivity of **3** towards fluoride anions relative to a large variety of anion competitors is no less than 10^5 higher, which is, to the best of our knowledge, among the highest ever recorded.

To sum up, we have shown that a remarkable specificity for fluoride anions in DMSO solution can be achieved by the rational design of a uranyl-salen receptor, in which the space surrounding the metal centre is delimited by a short bridge featuring a diphenylmethane unit.

The support and sponsorship provided by COST Action D31/0016 is acknowledged. The Academy of Finland is gratefully acknowledged by M. N. and K. R. (proj. no. 122350) for financial support.

Experimental

NMR spectra were recorded on either an AC 200 or AC 300 Bruker spectrometer. UV-vis spectra were recorded in the thermostated cell compartment of a Cary 300 spectrophotometer. Association constants were determined according to standard UV-vis titration procedures.[9] Receptor **1** was available from previous work.[5d] Bis(4-bromomethylphenyl)-methane (**4**) was prepared according to a literature procedure.[10]

Receptor 2

ortho-Phenylenediamine (0.115 g, 1.06 mmol) was added to a refluxing solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.5 g, 2.13 mmol) in methanol (50 mL) with stirring. $UO_2(AcO)_2{\cdot}2H_2O$ (0.45 g, 1.06 mmol) was added after 1 h, whereupon the solution was cooled to room temperature and stirred overnight. The red precipitate of **2** that formed was filtered-off and crystallized from hexane to give red needles (0.53 g, yield 62%). Elemental analysis: calc. for $C_{36}H_{46}N_2O_4U$: C, 53.46; H, 5.73; N, 3.46; found: C, 53.66; H, 5.53; N, 3.53%. Mass spectrum (ESI): m/z 831.45 $[M + Na]^+$ (calc. for $C_{36}H_{46}N_2O_4UNa$ 831.78). ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 2H), 7.71 (m, 2H), 7.66 (s, 4H), 7.48 (m, 2H), 1.88 (s, 9H) and 1.47 (s, 9H). ^{13}C NMR (DMSO-d_6): δ 146.8, 138.9, 137.4, 129.9, 128.1, 123.9, 119.9, 35.0, 33.4, 31.3 and 30.0.

Compound 5

To a suspension of n-pentane-washed NaH (1.1 g, 60% in oil) in DMSO (10 mL) was added a solution of 2,3-dihydroxybenzaldehyde (1.5 g, 11.3 mmol) in DMSO (10 mL) at 20–25 °C. After stirring for 1 h, a solution of **4** (2 g, 5.63 mmol) in DMSO (10 mL) was added at 20–25 °C. Stirring was continued for 24 h, whereupon the mixture was poured into water (50 mL) and extracted with $CHCl_3$ (2 × 100 mL). The aqueous layer was acidified with 6 M HCl to adjust the pH to 3, and it was again extracted with $CHCl_3$ (4 × 80 mL). The combined $CHCl_3$ layers were washed with 1 M HCl (2 × 50 mL) and then dried over $MgSO_4$. The solvent was evaporated and the residue then purified by column chromatography (silica gel, $CHCl_3$) to give pure dialdehyde **5** as a yellow solid (yield 60%). Elemental analysis: calc. for $C_{29}H_{24}O_6$: C, 74.35; H, 5.16; found: C, 74.20; H, 4.98%. Mass spectrum (ESI): m/z 469.35 $[M + H]^+$ (calc. for $C_{29}H_{24}O_6$ 469.16). ^{1}H NMR ($CDCl_3$): δ 11.04 (s, 2H), 9.91 (s, 2H), 7.36 (d, J = 8 Hz, 4H), 7.15 (m, 8H), 6.89 (t, J = 8 Hz, 2H), 5.15 (s, 4H) and 3.98 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 196.6, 152.6, 147.6, 138.1, 133.7, 129.5, 127.7, 125.4, 121.2, 120.5 119.3, 71.6 and 41.2.

Receptor 3

To a refluxing solution of **5** (0.4 g, 0.85 mmol) in methanol (40 mL) was added ethylenediamine (0.51 g, 0.60 mL, 0.85 mmol) dropwise. After 1.5 h, $UO_2(AcO)_2{\cdot}2H_2O$ (0.36 g, 0.85 mmol) was added and reflux continued for a further 30 min, whereupon the mixture was allowed to cool to room temperature overnight. The red solid formed was filtered and crystallized from methanol/DMSO (99 : 1) to afford **3** (yield 19%). Elemental analysis: calc. for $C_{31}H_{26}N_2O_6{\cdot}CH_3OH$: C, 48.49; H, 3.81; N, 3.53; found: C, 49.10; H, 3.78; N, 3.34%. Mass spectrum (ESI): m/z 783.46 (calc. for $C_{31}H_{26}N_2O_6UNa$ $[M + Na]^+$ 783.57) and 815.25 (calc. for $C_{32}H_{30}N_2O_7UNa$ $[M + CH_3OH + Na]^+$ 815.61). ^{1}H NMR (DMSO-d_6): δ 9.40 (s, 2H), 7.39 (m, 6H), 7.20 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 6.6 Hz, 4H), 6.60 (t, J = 7.9 Hz, 2H), 5.19 (s, 4H), 4.44 (s, 4H) and 3.87 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 168.5, 160.7, 151.9, 140.9, 136.2, 133.8, 128.8, 128.4, 126.4, 124.2, 121.4, 119.7, 115.2, 72.8 and 63.1.

X-Ray crystal structure determination

X-Ray data for **3** crystallized from methanol were collected from an orange needle-like crystal of size 0.05 × 0.3 × 0.5 mm on a Nonius Kappa CCD diffractometer using graphite-monochromatized Mo-K_α radiation and a temperature of 173.0 K.

Crystal data for 3

$4C_{31}H_{26}N_2O_6U{\cdot}5.5CH_3OH$, M = 3218.50 g mol^{-1}, triclinic, $P\bar{1}$ (no. 1), a = 11.3081 (2), b = 13.0762 (3), c = 21.1935 (4) Å, α = 78.420 (1), β = 84.284 (1), γ = 88.925(1)°, V = 3054.8(1) Å^3, Z = 1, μ = 5.365 mm^{-1}, 20 665 reflections collected of which 15 597 were unique (R_{int} = 0.057), final R_1 = 0.044 and w$R2$ = 0.112 for $I > 2\sigma(I)$. Flack parameter 0.011(7).‡

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6. We speculate that the "disturbance" occurring in the low concentration domain is caused by an impurity in the DMSO solvent, which sequesters a significant fraction of the added fluoride. The observed phenomena are qualitatively explained if the above species is spectroscopically silent, is present at a concentration in the order of 10^{-5} M and has an affinity toward fluoride anions comparable to that of **1**. Such a "phantom" sequestering agent might well be an acidic impurity causing the formation of $(HF_2)^-$, but not adventitious water (see ref. 2*a*) because the influence of water on the stability of $\mathbf{1}\cdot F^-$ becomes significant only at very high water concentrations (Fig. S1†).
7. We believe that the slight stability increase of the AcO^- complex on going from **1** to **2** is a real phenomenon. It might be a consequence of the operation of weak attractive van der Waals interactions between the methyl group of the bound acetate and the flanking *tert*-butyl groups.
8. Titration plots of dilute solutions ($4–5 \times 10^{-5}$ M) of receptors **1**, **2** and **3** show that saturation is reached when the concentration of added fluoride anion is *ca.* 1×10^{-4} M in all cases. As for receptors **1** and **2**, the conclusion that similar titration profiles imply similar affinities toward fluoride anions is fully corroborated by their virtually identical log *K* values in Table 1. Thus, if the affinity of **2** is very similar to that of **1**, then, by inference, so is that of **3**.
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