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Synthesis of bis(amidoxime)s and evaluation of their properties as uranyl-complexing agents

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Abstract:

Uranium pollution involves high toxicity and radioactivity and, therefore, constitutes a grave threat to human health and the environment. Chelation is an effective method for sequestering uranium. It is well known that chelators based on oxime groups are able to complex uranyl cations efficiently. To this end, various bis(amidoxime)s were synthesized by reaction of hydroxylamine with the corresponding dinitriles. In these compounds the amidoximes are separated by chains of various lengths, some including a heterocycle (pyridine or 1,3,5-triazine). The abilities of these bis(amidoxime)s to complex uranyl cation in water were evaluated by determining their affinity constants and thermodynamic parameters by means of Isothermal Titration Calorimetry (ITC). DFT calculations were also performed, to determine the optimum structures of the complexes formed between uranyl cations and the oximate groups. A tetrakis(amidoxime), also synthesized in this work, shows good affinity for uranium, and a single molecule is able chelate several uranyl cations. These results are of importance for the remediation of uranium-polluted wastewaters, and open up several perspectives for the design and synthesis of new amidoxime compounds.

Keywords: Amidoxime; Uranyl; Metal complexation; Affinity constant; Synthesis

1. Introduction

Uranium is the main fuel employed in power plants for the production of nuclear energy. Uranyl ion (UO_2^{2+}) is the form in which uranium is usually found under oxidizing conditions. The development of ligands able to complex the uranyl ion efficiently has been the subject of many studies. Such ligands may find application notably for the extraction of uranium from sea water,[1] for the recycling of spent nuclear fuel and for the remediation of uranium-contaminated soil.[2] Uranium and its salts are highly toxic and constitute a major health problem.[3] Indeed, they cause severe damage to kidney and bones, and can accumulate in the brain.[4] Therefore, the removal of uranium from contaminated aqueous solution is of great importance for the protection of the environment and of mankind.

The various types of ligand that complex the uranyl cation comprise donor atoms, which are coordinated to the uranium atom in the equatorial plane. They may contain chelating functions such as carboxylic acid, bis(phosphonate), carboxamide and catechol.[4]

Ligands containing amidoximes can also complex the uranyl cation; in particular, many studies dealing with the recovery of uranium from sea water make use of absorbents containing amidoximes.[1] Extraction of uranyl from aqueous solutions by amidoxime-functionalized ionic liquids,[6] by a mesoporous imprinted polymer containing amidoximes[7] and by amidoxime-modified mesoporous silica[8] has been reported. Interestingly, an η2 (O, N) coordination of the amidoximate moiety to the uranyl is observed in the X-ray structures of isolated complexes.[6,9] Recently, Vukovic and Hay presented the computer-aided design of bis(amidoxime)s that are structurally organized for binding the uranyl ion.[10] Such compounds can be valuable for the recovery of uranyl ions, especially if they are grafted on polymers or on nanoparticles. Uranium sequestration using a bis(amidoxime) grafted on a hydrophilic backbone was recently reported.[11]

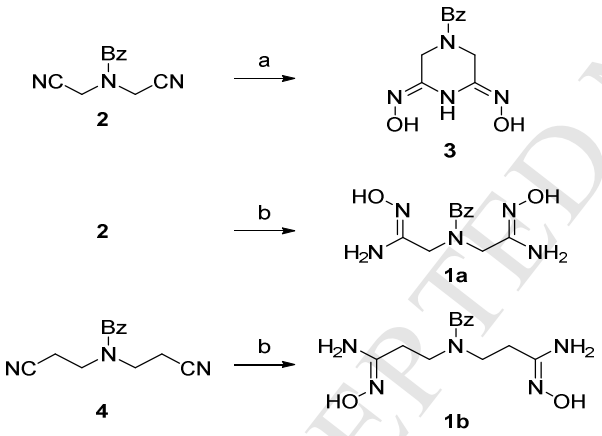
Here we report the synthesis of a series of bis(amidoxime)s **1a-f**, and a tetrakis(amidoxime) **1g**, derivatives of which could be employed for uranium sequestration. The two amidoximes in these compounds are separated by spacers of various lengths which may contain a nitrogen atom or a heterocycle. In the design of these compounds, the possibility of grafting them, or analogs of them, onto a polymer or a nanoparticle was taken into account. The uranyl-complexing abilities of these amidoximes and the corresponding thermodynamic parameters

are reported. Density Functional Theory (DFT) calculations were used in order to determine the optimum structures of the various complexes.

2. Results and discussion

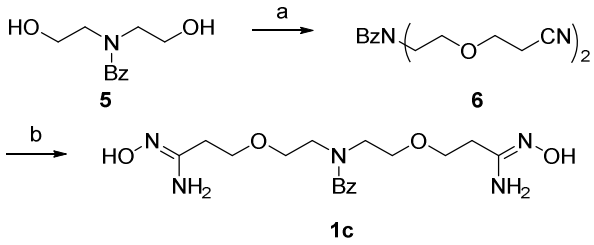
2.1. Synthesis of amidoxime derivatives

Bis(amidoxime)s **1a** and **1b** were synthesized from the corresponding dinitriles (Scheme 1). The treatment of benzamide **2**[12] with hydroxylamine hydrochloride in the presence of $NaHCO_3$[13] did not afford the expected compound **1a**, but a mixture of benzamide **2** and cyclic adduct **3**. After recrystallization, **3** was isolated in 21% yield. Compound **3**, which is analogous to glutaramide dioxime,[14] could also be a good ligand for uranyl cation. Eventually bis(amidoxime) **1a** was obtained in 84% yield by treatment of **2** with an aqueous solution of hydroxylamine in ethanol at room temperature. Likewise, treatment of benzamide **4**[15] afforded bis(amidoxime) **1b**. A similar procedure was employed for the preparation of other amidoximes.



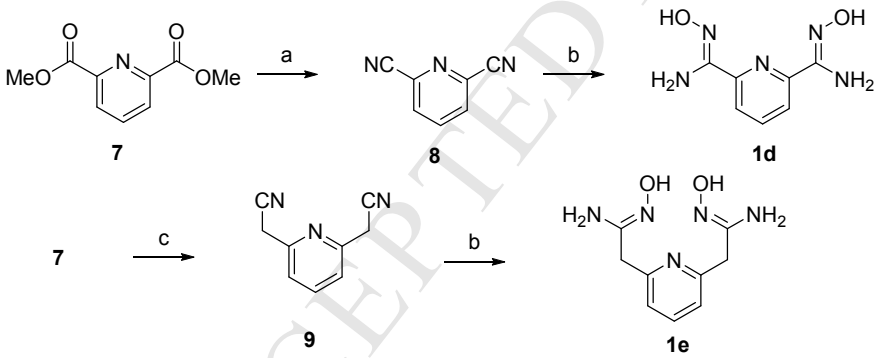
Scheme 1. Synthesis of compounds **3**, **1a** and **1b**. Reagents and conditions: a. $H_2NOH{\cdot}HCl$, $NaHCO_3$, EtOH, 80 °C, 4 h, 21% after recrystallization; b. NH_2OH (50 wt% in H_2O), EtOH, RT, 20 h (**1a**: 84%, **1b**: 98%).

As shown in Scheme 2, another benzamide-bis(amidoxime), in which the two chelating functions are separated by eleven atoms, was obtained in two steps from *N*,*N*-bis(2-hydroxyethyl)benzamide (**5**).[16] The diol was reacted with two equivalents of acrylonitrile, leading to dinitrile **6**, resulting from a double Michael addition. However, the product was obtained as a mixture with inseparable acrylonitrile oligomers. It was then converted to the corresponding bis(amidoxime) **1c**, which was purified by chromatography.



Scheme 2. Synthesis of bis(amidoxime) **1c**. Reagents and conditions: a. acrylonitrile, *t*-BuONa, *t*-BuOH, RT, 18 h, 71% (not pure); b. NH_2OH (50 wt% in H_2O), EtOH, RT, 71%.

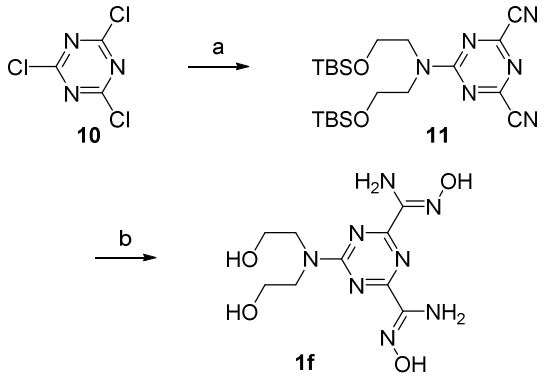
In pyridines with two amidoxime substituents in the *ortho* positions, the pyridine nitrogen atom could also participate in the complexation of the uranyl ion. Two such compounds were prepared. In the first, **1d**, both amidoxime functions are directly bonded to the pyridine ring, while in the second, **1e**, they are separated from the heterocyclic ring by methylene groups (Scheme 3). Diester **7** serves as the precursor for both bis(amidoxime)s. Treatment of **7** with aqueous ammonia in methanol, followed by dehydration, afforded dinitrile **8**,[17] which was converted to **1d**[18] in 89% yield. Dinitrile **9**[19] was obtained in three steps from diester **7** (reduction to a diol, conversion of the diol to a dibromide, and reaction of the latter with potassium cyanide). The expected bis(amidoxime) **1e** was then obtained from **9** in 81% yield.



Scheme 3. Synthesis of bis(amidoxime)s **1d** and **1e**. Reagents and conditions: a. (1) 28% aq. NH_3, MeOH, RT, 24 h, 67%; (2) $(CF_3CO)_2O$, Et_3N, THF, RT, 4 h, 90%; b. NH_2OH (50 wt% in H_2O), EtOH, RT, 48 h (**1d**: 89%, **1e**: 83%); c. (1) $NaBH_4$, EtOH, 0 °C, then RT, 15 h, 71%; (2) 48% HBr, reflux, 16 h, 23%; (3) KCN, 18-crown-6, CH_3CN, 80 °C, 15 h, 81%.

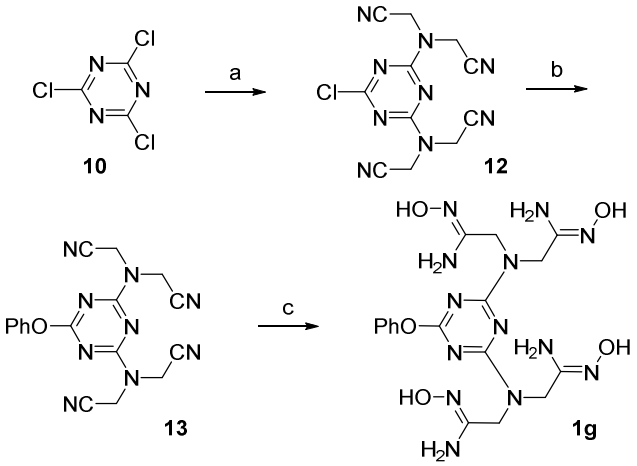
As in the case of the pyridine derivatives, the complexation of the uranyl ion by 1,3,5-triazines substituted by two amidoximes functions could involve a nitrogen atom of the heterocyclic ring. Such compounds can be synthesized from readily available cyanuric chloride (**10**), and the third hydrogen can be replaced by a substituent which could be used to

graft the triazine onto a polymer or a nanoparticle. We chose to prepare compound **1f**, which comprises a di(hydroxyethyl)amino moiety, expected to enhance the water solubility of the compound (Scheme 4). Compound **1f** was synthesized in four steps. One equivalent of the bis(*tert*-butyldimethylsilyl) ether of diethanolamine[20] was reacted with **10** in the presence of Hunig's base, leading to the corresponding dichloride, which was converted to dinitrile **11** in 51% yield by reaction with potassium cyanide at room temperature. At higher temperatures, degradation occurred. Reaction with hydroxylamine, followed by treatment with acid to remove the silyl ethers, afforded the expected bis(amidoxime) **1f**.



Scheme 4. Synthesis of bis(amidoxime) **1f**. Reagents and conditions: a. (1) $HN(CH_2CH_2OTBS)_2$, $EtNiPr_2$, THF, -78 °C to RT, 3 h, 88%; (2) KCN, CH_3CN, RT, 51%; b. (1) NH_2OH (50 wt% in H_2O), EtOH, RT, 48 h, 96%; (2) 1N HCl, EtOH, RT, 1 h, 95%.

Finally, another triazine derivative, compound **1g**, comprising four amidoximes, was also synthesized (Scheme 5). Cyanuric chloride **10** was treated with two equivalents of iminodiacetonitrile, leading to tetranitrile **12**. The remaining chlorine atom was replaced by a phenoxy group by treatment of **12** with sodium phenoxide. The four nitriles of **13** were transformed into amidoxime functions under the conditions previously employed, affording product **1g** in 77% yield.



Scheme 5. Synthesis of tetrakis(amidoxime) **1g**. Reagents and conditions: a. iminodiacetonitrile, BzCl, $EtNiPr_2$, THF, RT, 20 h, 65%; b. Phenol, NaH, THF, RT, 2.5 h, 84%; c. NH_2OH (50 wt% in H_2O), EtOH, RT, 48 h, 77%.

2.2. Complexation studies

Nano-isothermal Titration Calorimetry (ITC) was used to measure directly the heat gained or lost during the association of the synthesized molecules (L) with uranyl cation in water. This allowed us to determine, in a single experiment, the thermodynamic binding parameters: the affinity constant (K_a), the stoichiometry (n), and the enthalpy and entropy of formation ($\Delta_r H°$ and $\Delta_r S°$) of the complex formed between L and uranyl cation [equation (1)].

$$L + nUO_2^{2+} \rightleftharpoons [L\text{-}(UO_2^{2+})_n] \quad \text{(eq. 1)}$$

$$\text{with } K_a = \frac{[L - (UO_2^{2+})_n]}{[L][UO_2^{2+}]^n}$$

In Figure 1 are presented the ITC curves for the complexation of uranyl cation by compounds **1c** and **1f** at T = 298 K and at pH 6.5; this pH value was chosen to avoid any precipitation of uranyl species. In both cases, a regular heat variation with uranium concentration is observed, which establishes the interaction between L and the cation. The contribution of $T\Delta_r S°$ is lower than that of $\Delta_r H°$; complex formation is enthalpy-driven and the reaction is exothermic ($\Delta_r H° < 0$). The negative value of $\Delta_r S°$ suggests that an ordered chelator-cation complex is formed.

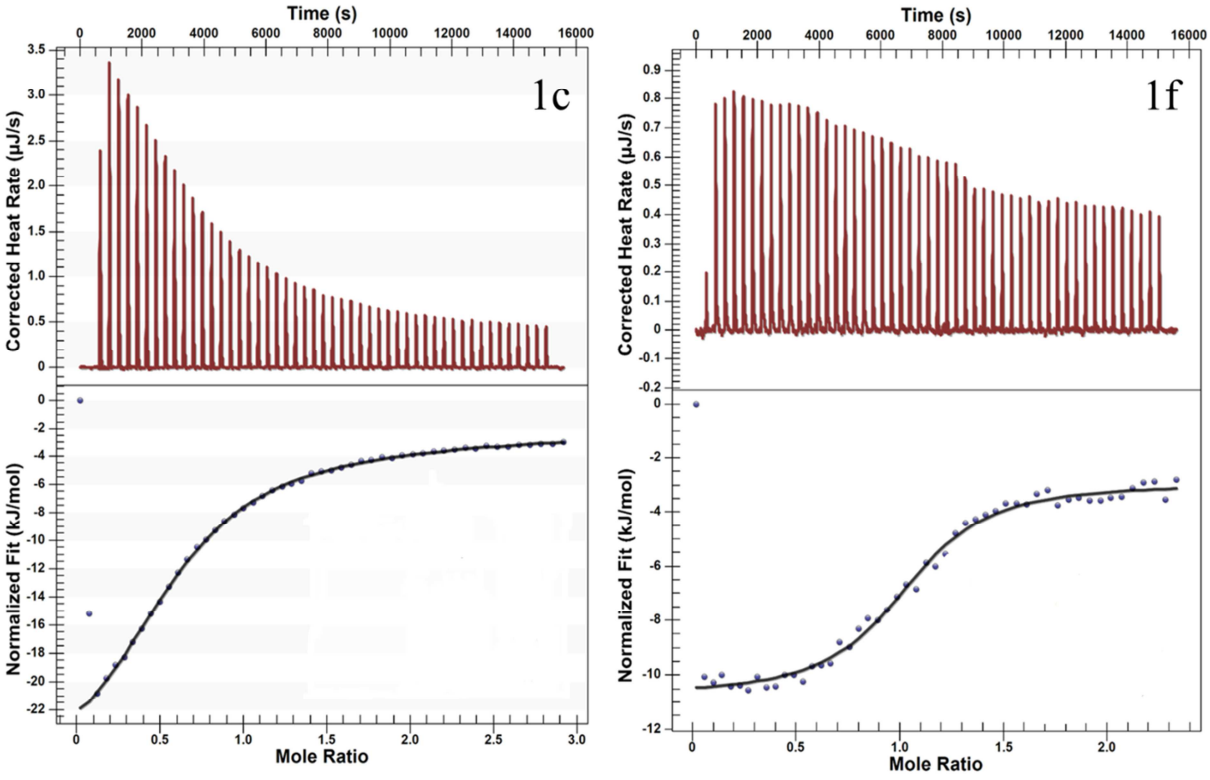


Fig. 1. Isothermal titration calorimetry (ITC) curves for the formation of complexes between amidoximes **1c** and **1f** and uranyl cation.

Table 1 summarizes the thermodynamic data obtained for all the amidoxime derivatives synthesized. For the molecules from **1a-1e**, the fitting was performed according to the "independent" model which implies one binding site. All the ligands exhibit a very good affinity for uranyl cation, with log K_a > 4. Ligands **1a**, **1b**, **1d** and **1e** complex uranyl cations with a metal/ligand stoichiometry of 0.5/1. The two amidoxime groups of one ligand molecule are unable to complex one uranyl cation, probably because of the rigidity of the molecules, and one uranyl cation is shared by two different ligands. However, in the case of molecule **1c**, where the arms are longer and therefore flexible, the metal/ligand stoichiometry is 1/1. In this molecule, one cation is complexed with one molecule of ligand. For **1f** and **1g**, multiple-site fitting was performed. Indeed, in **1f**, in addition to the two amidoxime groups, two alcohol functions are involved in the complexation of the cation, which leads to the possibility of two different binding sites. The affinity for the amidoxime sites is much higher than that for the alcohol sites. The tetrakis(amidoxime) **1g** was best fitted with the multiple-site model. The two amidoxime groups complex a single cation with a higher affinity (log K_{a1} = 5.9, n_1 = 1.2), leaving two isolated amidoxime groups which are able to complex cations by sharing with other ligand molecules, with a lower affinity (log K_{a2} = 3.8, n_2 = 0.6). These amidoxime

derivatives, and especially **1f** and **1g,** are very efficient chelators (log K_a > 5.7) for uranyl cations, since each ligand can complex more than one cation. A higher value of log K_1 (11.1) has been reported for the uranyl complex of acetamidoximate,[14,21] DFT calculations were in agreement with the observed value.[14] The discrepancies compared to the values observed in our study may be attributed to the different pH at which the complexation constants were recorded.

Table 1. Thermodynamic constants for the complexation of amidoxime derivatives **1a-g**.[a]

Amidoxime	log K_a	n	$\Delta_r H°$ *(kJ.mol^{-1})*	$T\Delta_r S°$ *(kJ.mol^{-1})*
1a[b]	5.0 ± 0.1	0.7 ± 0.1	-39.9 ±0.8	-11.3 ± 0.9
1b[b]	4.4 ± 0.1	1.2 ± 0.1	-31.2 ± 1.1	-5.9 ± 0.5
1c[b]	5.1 ± 0.1	0.6 ± 0.1	-48.7 ± 1.5	-19.6 ± 0.8
1d[b]	5.1 ± 0.2	0.6 ± 0.2	-50.9 ± 1.2	-21.8 ± 0.7
1e[b]	4.7 ± 0.1	0.5 ± 0.1	-64.2 ± 1.8	-37.2 ± 1.0
1f[c]	5.7 ± 0.3 (log K_{a1})	1.0 ± 0.1 (n_1)	-11.9 ± 0.8 ($\Delta_r H_1$)	+20.6 ± 0.9 ($T\Delta_r S_1$)
1f[c]	3.0 ± 0.1(log K_{a2})	1.0 ± 0.1 (n_2)	-63.1 ± 1.3 ($\Delta_r H_2$)	-45.9 ± 1.8 ($T\Delta_r S_2$)
1g[c]	5.9 ± 0.3 (log K_{a1})	1.2 ± 0.2 (n_1)	-12.1 ± 0.9 ($\Delta_r H_1$)	+22.1 ± 0.8 ($T\Delta_r S_1$)
1g[c]	3.8 ± 0.3 (log K_{a2})	0.6 ± 0.2 (n_2)	-96.2 ± 1.4 ($\Delta_r H_2$)	-74.6 ± 1.2 ($T\Delta_r S_2$)

[a] log of the affinity constant (log K_a), stoichiometry (n), reaction enthalpy ($\Delta_r H°$), and reaction entropy ($\Delta_r S°$) at T = 298 K and pH 6.5. [b] For compounds **1a-1e**, the values were obtained using the "independent fitting" model. [c] For compounds **1f** and **1g**, the values were obtained using the "multiple-site fitting" model.

2.3. Quantum mechanical approach

Uranyl complexes with different ligands have been widely studied in the framework of Density Functional Theory (DFT), which is a particularly powerful method for obtaining information about their geometries and energies.

The linear uranyl cation exists in solution as a complex ion with ligands equatorially bonded to the uranium. If there are no ligands in the solution, water molecules make up the first coordination shell. Although the number of water ligands can vary from 4 to 6, several

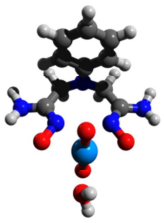
experimental and quantum mechanical studies indicate that the $UO_2(H_2O)_5^{2+}$ complex predominates in aqueous solution.[22]

The complexes of uranyl with the seven amidoximes (L), **1a-g**, were constructed by H_2O-amidoxime exchange from the $UO_2(H_2O)_5^{2+}$ complex. Upon complexation, it has been shown that amidoximes deprotonate to form neutral complexes. For this reason, DFT calculations were performed starting with the $UO_2(H_2O)_5^{2+}$ complex, and several water molecules were replaced by one or two amidoximate ligands.

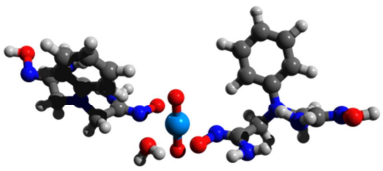
The optimized structures of the different species are shown in Figure 2. In all structures of the mono- and bis(amidoximate) complexes the uranyl unit is linear, and both the water molecules and the amidoximates are symmetrically distributed in the equatorial plane perpendicular to the O=U=O axis. The amidoximate acts as a bidentate ligand, binding the uranyl through the N-O bond in a η_2 motif. This result is in agreement with several theoretical and experimental studies[9,23] and confirms the accepted view about the coordination of the deprotonated amidoxime with UO_2^{2+}.

The distances between U and O or N in the complexes $UO_2L(OH_2)$ are all around 2.3 Å, except for **1d** (Figure 2). This indicates a strong interaction between uranyl and ligand, leading to charge transfer from the latter to the former. Interestingly, in the bi-deprotonated amidoxime complex with **1d** the U-O distance is significantly longer. This is probably because the geometry of the bis-amidoximate unit in this ligand cannot accommodate the coordination site of uranyl. In all the calculated structures, the oximate N-O and C-N distances are close to 1.350 Å and 1.300 Å, respectively, indicating a partially delocalized oximate group.[24]

1a

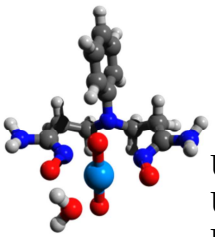


U…O_1=2.317 Å
U…O_2=2.318 Å
U…N_1=2.307 Å
U…N_2=2.308 Å

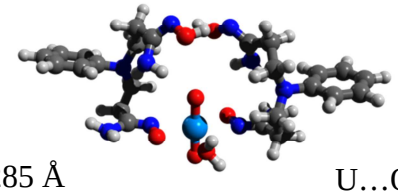


U…O_1=2.953 Å
U…O_2=2.305 Å
U…N_1=2.376 Å
U…N_2=2.400 Å

1b



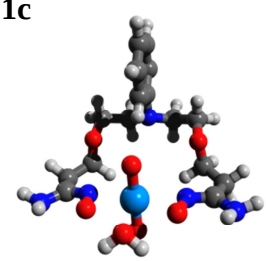
U…O_1=2.285 Å
U…O_2=2.275 Å
U…N_1=2.368 Å
U…N_2=2.394 Å



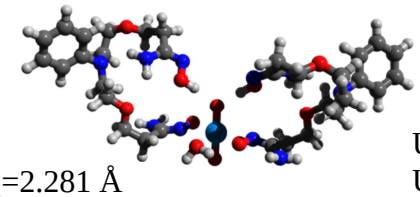
N…HO_1=1.910 Å
O_2H…N=1.906 Å

U…O_1=2.287 Å
U…O_2=2.281 Å
U…N_1=2.393 Å
U…N_2=2.408 Å

1c



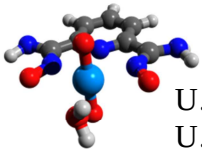
U…O_1=2.281 Å
U…O_2=2.282 Å
U…N_1=2.409 Å
U…N_2=2.409 Å



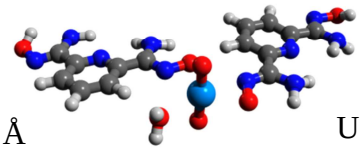
O_1H…OU=1.836 Å
O_2H…OU=1.832 Å

U…O_1=2.271 Å
U…O_2=2.275 Å
U…N_1=2.369 Å
U…N_2=2.408 Å

1d



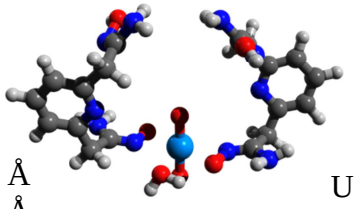
U…O_1=3.393 Å
U…O_2=3.404 Å
U…N_1=2.530 Å
U…N_2=2.536 Å



U…O_1=2.274 Å
U…O_2=2.260 Å
U…N_1=2.391 Å
U…N_2=2.420 Å

1e

U…O_1=2.271 Å
U…O_2=2.269 Å
U…N_1=2.392 Å
U…N_2=2.415 Å



U…O_1=2.296 Å
U…O_2=2.307 Å
U…N_1=2.380 Å
U…N_2=2.407 Å

1f

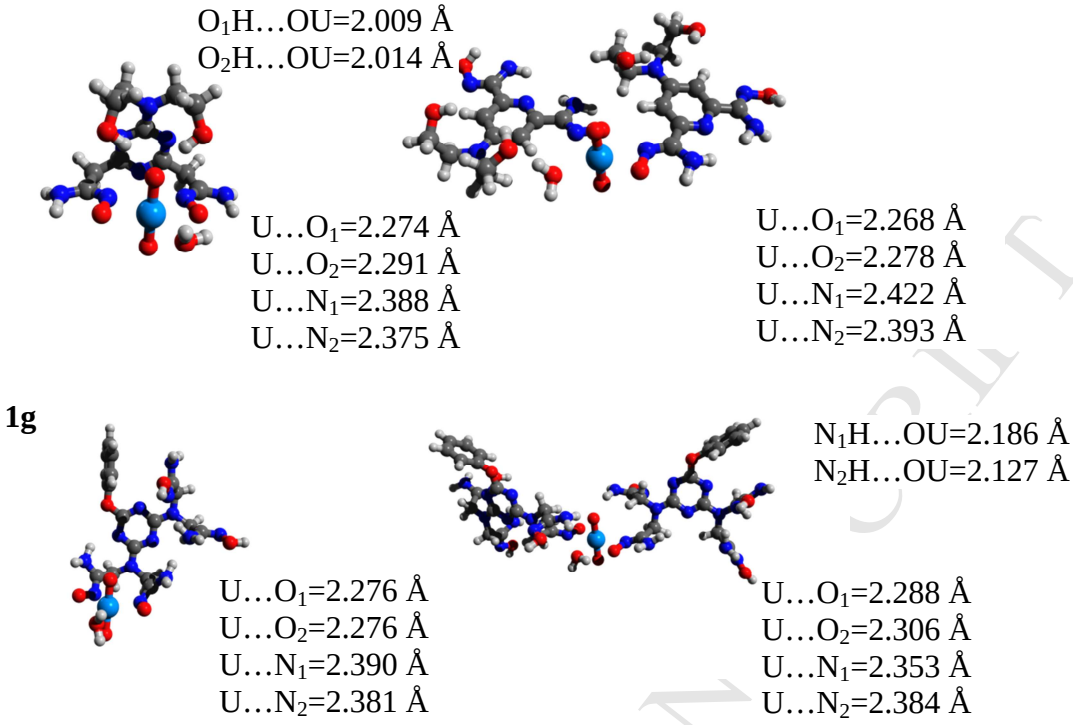


Fig. 2. Optimized structures of complexes between uranyl cation and bi-deprotonated amidoxime $UO_2L(OH_2)$ (left) and two mono-deprotonated amidoximes $UO_2L_2(OH_2)$ (right). Bond distances (Å) are listed with the structures, and the subscripts 1 and 2 indicate the left or right atom of the oximate ligand, respectively. The color code is: C gray, H white, O red, and N blue.

From an energetic point of view, the ability of a ligand to complex uranyl can be determined from DFT calculations by using the following equations (2) and (3) for mono- and bis(amidoximate) complexes, respectively.

Table 2. Enthalpies of reaction of the complexes [$UO_2L(OH_2)$] and [$UO_2L_2(OH_2)$] calculated from equations (2) and (3).

Amidoxime	Stoichiometry	Δ_rH (kcal.mol^{-1})
1a	n=1	-90.2
	n=2	-77.2
1b	n=1	-92.2
	n=2	-81.8
1c	n=1	-82.2
	n=2	-54.6
1d	n=1	-61.9
	n=2	-65.1
1e	n=1	-88.3
	n=2	-83.3

1f	n=1	-75.3
	n=2	-70.1
1g	n=1	-72.4
	n=2	-56.1

$$[(UO_2(OH_2)_5]^{+2} + L^{2-} \rightleftharpoons UO_2L(OH_2) + 4(OH_2) \quad \text{(eq. 2)}$$

$$[(UO_2(OH_2)_5]^{+2} + 2L^{-} \rightleftharpoons UO_2L_2(OH_2) + 4(OH_2) \qquad \text{(eq. 3)}$$

It should be noted that these energies cannot be directly compared with experimental values since the thermodynamics for the deprotonation of the ligand have not been calculated. As indicated in Table 2, reactions (1) and (2) are both exothermic, whatever the nature of the ligand, suggesting a high complexing character of amidoxime toward uranyl cation, as inferred from experimental data.

3. Conclusion

We have synthesized several compounds containing two amidoxime functions and one compound containing four. By an experimental approach, we have shown that all these compounds complex uranyl cation with high affinities. These amidoxime derivatives are clearly good candidates for uranium uptake. By a theoretical approach we have elucidated the optimized structures for the different complexes. We are pursuing our approach by selecting the ligands with the highest affinities (**1a**, **1f**, **1g**) for grafting onto the surface of magnetic nanoparticles in order to remove uranium from contaminated wastewaters or soils by magnetic harvesting.[25]

4. Experimental section

4.1. Synthesis

4.1.1. General. Non-aqueous reactions were performed in an inert atmosphere using a balloon filled with argon. TLC: Silica Gel $60F_{254}$ plates with detection by UV light and by an aqueous solution of $KMnO_4$. Column chromatography was carried out with Combiflash Serlabo Rf75 (silica gel columns RediSep® Rf, 35-60 μm). Melting points were recorded using a Büchi B-540 apparatus. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform." IR spectra were recorded using a Spectrum Two FT-IR spectrometer (Perkin-Elmer). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advanced 400 spectrometer at 400.133 and

100.624 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are in parts per million and are referenced to residual H in the deuterated solvent; coupling constants (J) are in Hertz.

*4.1.2. [(3Z,5Z)-3,5-Bis(hydroxyimino)piperazin-1-yl](phenyl)methanone (**3**)*

Hydroxylamine hydrochloride (556 mg, 8.0 mmol, 4 equiv.) and $NaHCO_3$ (672 mg, 8.0 mmol, 4 equiv.) were added to a solution of *N*,*N*-bis(cyanomethyl)benzamide[12] (**2**; 398 mg, 2.0 mmol, 1 equiv.) in ethanol (10 mL). The brown suspension was heated at 80 °C for 4 h. After cooling to room temperature, the solvent was removed under vacuum. THF and brine were added and, after dissolution of all the solids, the layers were separated. The aqueous phase was extracted four times with THF and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting solid was recrystallized from ethanol to yield the title compound as a white powder (103 mg, 21%); mp 218-219 °C (dec.); IR: ν_{max} 3394, 3306, 2918, 1670, 1636, 1365, 1276, 1074, 926, 641, 587 cm^{-1}; δ_H (DMSO-d_6) 10.38 (s, 2H, O*H*), 8.30 (s, 1H, N*H*), 7.53-7.42 (m, 5H, *H*-Ar), 4.33 (br s, 4H, CH_2); δ_C (DMSO-d_6) 169.8 (*C*O), 140.9 (2C, *C*(NH)NOH), 134.6 (*C*CO), 130.9 (*C*H-Ar *para*), 129.1 (2C, *C*H-Ar meta), 127.6 (2C, *C*H-Ar *ortho*); HRMS (ESI): $[M+H]^+$, found 249.0992. $C_{11}H_{13}N_4O_3$ requires 249.0988.

4.1.3. General procedure for the preparation of amidoximes from nitriles by treatment with an aqueous hydroxylamine solution.

A 50 wt% solution of hydroxylamine in water (8.0 mmol, 4 equiv., 2 equiv./nitrile function) was added to a solution of dinitrile (2.0 mmol, 1 equiv.) in ethanol (10 mL), and the solution was stirred for 20 h at room temperature. The solvent was evaporated under vacuum. The resulting compound was either chromatographed on silica gel or washed with an appropriate solvent and recrystallized.

4.1.4. N,N-*Bis[(Z)-2-amino-2-(hydroxyimino)ethyl]benzamide (**1a**)*

N,*N*-Bis(cyanomethyl)benzamide (**2**; 398 mg, 2.0 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (490 µL, 8.0 mmol, 4 equiv.) were used following the general procedure. The resulting solid was recrystallized from ethanol to yield the title compound as brown crystals (444 mg, 84%); mp 173-174 °C; IR: ν_{max} 3486, 3372, 3233, 2844, 1660, 1553, 1464, 1275, 1011, 918, 798, 721, 691 cm^{-1}; δ_H (DMSO-d_6) 9.30 (br s, 1H, O*H*), 9.18 (br s, 1H, O*H*), 7.51-7.41 (m, 5H, H-Ar), 5.45 (s, 4H, NH_2), 4.03 (br s, 2H, CH_2N), 3.80 (br s, 2H, CH_2N); δ_C

(DMSO-d_6) 171.8 (*C*O), 149.5 (*C*(NH)NOH), 148.8 (*C*(NH)NOH), 136.3 (*C*CO), 130.1 (*C*H-Ar *para*), 128.6 (2C *C*H-Ar *meta*), 127.1 (2C *C*H-Ar *ortho*), 48.5 (CH_2), 45.5 (CH_2); HRMS (ESI): MH^+, found 266.1252. $C_{11}H_{16}N_5O_3$ requires 266.1253.

4.1.5. N,N-*Bis[(Z)-3-amino-3-(hydroxyimino)propyl]benzamide (**1b**)*

N,*N*-Bis(2-cyanoethyl)benzamide[19] (**4**; 454 mg, 2.0 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (490 µL, 8.0 mmol, 4 equiv.) were used following the general procedure. The resulting solid was washed with diisopropyl ether, to yield the title compound as a white solid (576 mg, 98%); mp 60-61 °C; IR: ν_{max} 3453, 3323, 3173, 2826, 1657, 1594, 1427, 1358, 1317, 1025, 927, 703 cm^{-1}; δ_H (DMSO-d_6) 8.88-8.84 (m, 2H, O*H*), 7.42-7.40 (m, 3H, *H*-Ar), 7.33-7.31 (m, 3H, *H*-Ar), 5.44 (br s, 2H, NH_2), 5.29 (br s, 2H, NH_2), 3.59 (br s, 2H, CH_2-N), 3.36 (br s, 2H, CH_2-N), 2.32 (br s, 2H, CH_2C(NH_2)NOH), 2.16 (br s, 2H, CH_2C(NH_2)NOH); δ_C (DMSO-d_6) 171.0 (*C*O), 151.2 (*C*(NH)NOH), 150.4 (*C*(NH)NOH), 137.6 (*C*CO), 129.4 (*C*H-Ar *para*), 128.7 (2C *C*H-Ar *meta*), 126.7 (2C *C*H-Ar *ortho*), 46.8 (CH_2N), 42.4 (CH_2N), 30.7 (CH_2C(NH_2)NOH), 29.5 (CH_2C(NH_2)NOH); HRMS (ESI): MH^+, found 294.1571. $C_{13}H_{20}N_5O_3$ requires 294.1566.

4.1.6. N,N-*Bis[2-(2-cyanoethoxy)ethyl]benzamide (**6**)*

A 0.22 M solution of sodium *tert*-butoxide was prepared by adding sodium (15.3 mg) to anhydrous *tert*-butanol (3 mL). This mixture was stirred overnight at room temperature (until total dissolution of sodium). Acrylonitrile (398 µL, 6.0 mmol, 5 equiv.) and the previously prepared solution of *tert*-butoxide (540 µL, 0.12 mmol, 0.1 equiv.) were successively added to a solution of *N*,*N*-bis(2-hydroxyethyl)benzamide[16] (**5**; 250 mg, 1.20 mmol, 1 equiv.) in 0.5 mL of anhydrous *tert*-butanol. After stirring for 24 h at room temperature, the volatiles were removed under vacuum to give an orange oil. Chromatography on silica gel (1/1 to 1/9 heptane/ethyl acetate) yielded a pale yellow oil containing the desired product and an unidentified oligomer of acrylonitrile (270 mg, 71%). The product was used without further purification; IR: ν_{max} 3059, 2875, 2249, 1625, 1460, 1416, 1114, 786, 735, 707 cm^{-1}; δ_H (DMSO-d_6) 7.51-7.24 (m, 5H), 3.73-3.53 (m, 6H), 3.54-3.35 (m, 6H), 2.79-2.66 (m, 4H); δ_C (DMSO-d_6) 171.4, 137.2, 129.4, 128.6, 127.0, 119.7, 119.6, 68.2, 65.5, 53.3, 49.1, 44.4, 18.5; HRMS (ESI): $[M+H]^+$, found 316.1657. $C_{17}H_{22}N_3O_3$ requires 316.1653.

4.1.7. N,N-*Bis{2-[(Z)-3-amino-3-(hydroxyimino)propoxy]ethyl}benzamide (**1c**)*

Dinitrile **6** (500 mg, 1.59 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (389 µL, 6.34 mmol, 4 equiv.) were used following the general procedure. The product was purified on silica gel (95/5 to 9/1 CH_2Cl_2/MeOH) to afford the title compound as a colorless oil (430 mg, 71%); IR: ν_{max} 3322, 3174, 2829, 1655, 1594, 1426, 1357, 1025, 924, 702 cm^{-1}; δ_H (DMSO-d_6) 8.81 (s, 2H, *H*O-N), 7.44-7.40 (m, 3H, *H*-Ar), 7.37-7.34 (m, 2H, *H*-Ar), 5.37 (s, 2H, *H*-NH), 5.34 (s, 2H, *H*-NH), 3.60 (br s, 4H, C*H*$_2$O), 3.48-3.35 (m, 8H, C*H*$_2$O and C*H*$_2$N), 2.25-2.16 (m, 4H, C*H*$_2$C(NH$_2$)NOH); δ_C (DMSO-d_6) 171.4, 150.9, 150.8, 137.3, 129.3, 128.7, 127.1, 68.2, 68.0, 49.2, 44.6, 31.8; HRMS (ESI): $[M+H]^+$, found 382.2085. $C_{17}H_{28}N_5O_5$ requires 382.2082.

*4.1.8. (2*Z*,6*Z*)-*N'*2,*N'*6-Dihydroxypyridine-2,6-bis(carboximidamide) (**1d**)*

Dinitrile **8**[17] (844 mg, 6.54 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (1.60 mL, 26.2 mmol, 4 equiv.) were used following the general procedure. The resulting solid was washed with diethyl ether to yield the title compound[18] as a white solid (1.13 g, 89%); mp 220 °C; IR: ν_{max} 3483, 3355, 3089, 2791, 1654, 1630, 1560, 1387, 1075, 955, 827, 645 cm^{-1}; δ_H (DMSO-d_6) 9.83 (s, 2H, *H*O-N), 7.84-7.71 (m, 3H, *H*-Ar), 6.27 (br s, 4H, N*H*$_2$); δ_C (DMSO-d_6) 150.0 (2C, *C*$_{ar}$-N or *C*(NOH)NH$_2$), 149.4 (2 C, *C*$_{ar}$-N or *C*(NOH)NH$_2$), 137.0 (*C*H *para*), 119.6 (2C, *C*H *meta*); HRMS (ESI): MH^+, found 196.0827. $C_7H_{10}N_5O_2$ requires 196.0834.

*4.1.9. (1*Z*,1'*Z*)-2,2'-(Pyridine-2,6-diyl)bis(*N'*-hydroxyacetimidamide) (**1e**)*

Dinitrile **9**[19] (450 mg, 2.86 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (705 µL, 11.5 mmol, 4 equiv.) were used following the general procedure. The resulting solid was washed with diisopropyl ether to yield the title compound as a white solid (532 mg, 83%); mp 190 °C (dec.); IR: ν_{max} 3448, 3330, 3172, 2778, 1660, 1595, 1573, 1457, 1349, 982, 915, 884, 763, 621 cm^{-1}; δ_H (DMSO-d_6) 8.98 (s, 2H, *H*O), 7.65 (t, *J* = 7.7 Hz, C$_{ar}$-*H para*), 7.18 (d, *J* = 7.7 Hz, 2H, C$_{ar}$-*H meta*), 5.47 (br s, 4H, N*H*$_2$), 3.42 (s, 4H, C*H*$_2$); δ_C (DMSO-d_6) 156.8 (2C, *C*$_{ar}$-N), 151.0 (2C, *C*(NOH)NH$_2$), 137.1 (*C*$_{ar}$-H *para*), 120.8 (2C, *C*$_{ar}$-H *meta*), 39.6 (2C, *C*H$_2$); HRMS (ESI): MH^+, found 224.1140. $C_9H_{14}N_5O_2$ requires 224.1069.

4.1.10. N,N-*Bis{2-[(*tert-*butyldimethylsilyl)oxy]ethyl}-4,6-dichloro-1,3,5-triazine-2-amine*

A solution of bis{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}amine[20] (1.947 g, 5.83 mmol, 1 equiv.) in anhydrous THF (10 mL) was slowly added to a solution of cyanuric chloride (1.076 g, 5.83 mmol, 1 equiv.) and diisopropylethylamine (0.983 mL, 1 equiv.) in anhydrous THF

(50 mL) cooled at -78 °C. The reaction mixture was stirred for 15 min at -78 °C, then allowed to warm at room temperature and stirred for 3 h. After concentration under vacuum, dichloromethane (50 mL) was added. The organic phase was washed with water (3 x 15 mL), then dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (heptane/ethyl acetate: 97/3 to 95/5) to yield the title compound as white crystals (2.475 g, 88%); mp 60.3 °C; IR: ν_{max} 2955, 2930, 2854, 1570, 1460, 1089, 828, 771 cm^{-1}; δ_H ($CDCl_3$) 3.82 (s, 8H, C*H*$_2$), 0.89 (s, 18H, C*H*$_3$Si), 0.05 (s, 12H, C*H*$_3$C); δ_C ($CDCl_3$) 169.8 (*C*Cl), 164.7 (*C*(N_2)N), 60.3 (*C*H_2O), 51.4 (*C*H_2N), 25.8 (*C*H_3C), 18.1 (*C*CH_3), -5.4 (*C*H_3Si). HRMS (ESI): MH^+, found 481.1984. $C_{19}H_{39}Cl_2N_4O_2Si_2$ requires 481.1983.

*4.1.11. 6-(Bis{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}amino)-1,3,5-triazine-2,4-dicarbonitrile (**11**)*

Potassium cyanide (106.7 mg, 1.64 mmol, 4 equiv.) was added to a solution of the dichloride prepared above (200 mg, 0.41 mmol, 1 equiv.) in anhydrous acetonitrile (4 mL) under argon. The suspension was stirred at room temperature for two days and then concentrated under vacuum. Dichloromethane (25 mL) and water (15 mL) were added. After decantation, the phases were separated and the organic phase was washed with water (2 x 15 mL), then dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (heptane/ethyl acetate: 100/0 to 95/5) to yield the title compound as yellow crystals (98 mg, 51%); mp 79.8 °C; IR: ν_{max} 2954, 2929, 2854, 2252, 1595, 1553, 1472, 1483, 1104, 807, 837, 828, 772 cm^{-1}; δ_H ($CDCl_3$) 3.91-3.86 (m, 4H, *C*H_2O), 3.85-3.81 (m, 4H, *C*H_2N), 0.90 (s, 18H, C*H*$_3$Si), 0.05 (s, 12H, C*H*$_3$C); δ_C ($CDCl_3$) 163.1 (*C*CN), 152.6 (*C*(N_2)N), 113.6 (*C*N), 60.1 (*C*H_2O), 51.6 (*C*H_2N), 25.7 (*C*H_3C), 18.1 (*C*$(CH_3)_3$Si), -5.5 (*C*H_3Si); HRMS (ESI): MH^+, found 463.2670. $C_{21}H_{39}N_6O_2Si_2$ requires 463.2667.

*4.1.13. 6-(Bis{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}amino)-*N'2,N'4*-dihydroxy-1,3,5-triazine-2,4-bis(carboximidamide)*

The dinitrile prepared above (100 mg, 0.21 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (53 µL, 0.86 mmol, 4 equiv.) were used following the general procedure. The resulting solid was washed with diethyl ether, to yield the title compound as a white powder (110 mg, 96%); mp 246.3 °C; IR: ν_{max} 3494, 3340, 2952, 2928, 2855, 1658, 1556, 1509, 1094, 976, 834, 773, 718 cm^{-1}; δ_H (DMSO-d_6) 10.38 (s, 2H, O*H*), 6.01 (s, 4H, N*H*$_2$), 3.79 (s, 4H, C*H*$_2$-O), 3.33 (s, 4H, C*H*$_2$-N), 0.82 (s, 18H, C*H*$_3$Si), -0.03 (s, 12H, C*H*$_3$C); δ_C (DMSO-d_6) 165.5

(*C*(NOH)NH_2), 164.6 (*C*(N_2)CNH_2), 148.7 (*C*(N_3)), 60.7 (*C*H_2O), 50.7 (*C*H_2N), 26.1 (*C*H_3C), 18.2 (*C*$(CH_3)_3$Si), -5.1 (*C*H_3Si); HRMS (ESI): MH^+, found 529.3097. $C_{21}H_{45}N_8O_4Si_2$ requires 529.3096.

*4.1.14. (2Z,4Z)-6-[Bis(2-hydroxyethyl)amino]-N'2,N'4-dihydroxy-1,3,5-triazine-2,4-bis(carboximidamide) (**1f**)*

A solution of the bis(amidoxime) prepared above (20 mg, 37.8 µmol, 1 equiv) in ethanol (1.6 mL) and 1N HCl (0.5 mL) was stirred for 45 min, then ethanol was removed under vacuum. The aqueous phase was washed with diethyl ether (2 x 1 mL). Concentration under vacuum afforded the title compound as a slightly yellow powder (10.8 mg, 95%); mp 246.3 °C; IR: ν_{max} 2952, 2422, 2237, 1679, 1574, 1496, 1025, 894, 749 cm^{-1}; δ_H (D_2O) 3.95 (br s, 4H), 3.84 (br s, 4H); δ_C (D_2O) 164.3 (C(NOH)NH_2), 159.4 (C(N_2)CNH_2), 152.8 (C(N_3)), 58.2 (CH_2O), 49.8 (CH_2N); HRMS (ESI): MH^+, found 301.1367. $C_9H_{17}N_8O_4$ requires 301.1367.

*4.1.15. 2,2'-[(4-{[2-(λ^2-azanylidene)-2λ^3-ethyl](cyanomethyl)amino}-6-chloro-1,3,5-triazin-2-yl)azanediyl]diacetonitrile (**12**)*

To a solution of cyanuric chloride (500 mg, 2.71 mmol, 1 equiv.) and diisopropylethylamine (0.92 mL, 5.42 mmol, 2 equiv.) in 10 mL THF cooled at 0 °C, was added dropwise a solution of iminodiacetonitrile (515 mg, 5.42 mmol, 2 equiv.) in 5 mL THF. After 20 h stirring at room temperature, the organic solvent was removed under vacuum. The residue was purified by silica gel chromatography (heptane/ethyl acetate: 1/1) to yield the title compound as a white solid (536 mg, 65%); mp 217-218 °C; IR: ν_{max} 3009, 2953, 2256, 1560, 1518, 1407, 1234, 806, 739 cm^{-1}; δ_H (DMSO-d_6) 4.89 (s, 4H), 4.79 (s, 4H); δ_C (DMSO-d_6) 169.8 (C), 164.7 (2C), 116.2 (CH_2), 116.0 (CH_2), 36.7 ($2CH_2$); HRMS (ESI): MH^+, found 302.0664. $C_{11}H_9ClN_9$ requires 302.0664.

*4.1.16. 2,2',2'',2'''-[(6-Phenoxy-1,3,5-triazine-2,4-diyl)bis(azanetriyl)]tetraacetonitrile (**13**)*

Sodium hydride (60% dispersion in mineral oil, 111 mg, 2.78 mmol, 1.2 equiv.) was suspended in dry THF (3 mL) under argon at 0 °C. A solution of phenol (261 mg, 2.78 mmol, 1.2 equiv.) in dry THF (3 mL) was added slowly enough to prevent the excessive formation of foam. The resulting mixture was then stirred 10 min at 0 °C and a solution of tetranitrile **12** (700 mg, 2.32 mmol, 1 equiv.) in dry THF (3 mL) was added dropwise. After 2.5 h stirring at room temperature, a saturated aqueous solution of NH_4Cl was poured into the flask and the

aqueous phase was extracted twice with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (heptane/ethyl acetate: 7/3 to 4/6) to yield the title compound as brown crystals (702 mg, 84%); mp 146-147 °C; IR: ν_{max} 3005, 1567, 1547, 1488, 1394, 1209, 940, 814, 775, 690 cm^{-1}; δ_H ($CDCl_3$) 7.46 (t, *J* = 7.8 Hz, 2H, *H*-Ar *meta*), 7.32 (t, *J* = 7.4 Hz, 1H, *H*-Ar *para*), 7.19 (d, *J* = 7.6 Hz, 2H, *H*-Ar *ortho*), 4.60 (m, 8H, CH_2N); δ_C ($CDCl_3$) 171.1 (*C*(N_2)O), 166.0 (2C, *C*(N_2)N), 151.5 (C_{ar}-O), 129.6 (2C, *C*H *meta*), 126.3 (*C*H *para*), 121.5 (2C, *C*H *ortho*), 114.0 (2C, *C*N), 113.9 (2C, *C*N), 35.7 (2C, *C*H_2), 35.5 (2C, *C*H_2); HRMS (ESI): MH^+, found 360.1327. $C_{17}H_{14}N_9O$ requires 360.1321.

*4.1.17. (1Z,1'Z,1''Z,1'''Z)-2,2',2'',2'''-[(6-Phenoxy-1,3,5-triazine-2,4-diyl)bis(azanetriyl)]tetra-kis(N'-hydroxyacetimidamide) (**1g**)*

Tetranitrile **13** (200 mg, 0.56 mmol, 1 equiv.) and 50 wt% hydroxylamine in water (274 µL, 4.48 mmol, 8 equiv.) were used following the general procedure. The resulting solid was washed with diethyl ether, to yield the title compound as a white solid (212 mg, 77%); mp 157-158°C; IR: ν_{max} 3472, 3344, 2870, 1661, 1566, 1488, 1206, 890, 808, 603 cm^{-1}; δ_H (DMSO-d_6) 9.13 (s, 2H, O*H*), 9.08 (s, 2H, O*H*), 7.42 (t, *J* = 7.4 Hz, 2H, *H*-Ar *meta*), 7.24 (t, *J* = 7.2 Hz, 1H, *H*-Ar *para*), 7.19 (d, *J* = 7.2 Hz, 2H, *H*-Ar *ortho*), 5.41 (s, 4H, NH_2), 5.20 (s, 4H, NH_2), 4.07 (s, 4H, CH_2) 3.95 (s, 4H, CH_2); δ_C (DMSO-d_6) 170.6 (*C*(N_2)O), 166.8 (2C, *C*(N_2)N), 152.5 (C_{ar}-O), 150.0 (2C, $CH_2C(NH_2)NOH$),149.3 (2C, *C*H_2C(NH_2)NOH), 129.9 (2C, *C*H *meta*), 125.7 (*C*H *para*), 122.1 (2C, *C*H *ortho*), 46.8 (2C, *C*H_2), 46.3 (2C, *C*H_2); HRMS (ESI): MH^+, found 492.2179. $C_{17}H_{26}N_{13}O_5$ requires 492.2180.

4.2. Complexation studies

Thermodynamic assays were carried out in water by using a Nano-Isothermal Titration Calorimeter (Nano-ITC, TA Instruments, USA) with an active cell volume of 0.988 mL and a 250 µl stirring syringe. Nano-ITC uses a semiconductor thermoelectric heating and cooling system to precisely control temperature and a single removable syringe assembly for efficient and accurate distribution of the titrant reagent. The power curve (heat flow as a function of time) was integrated by means of the NanoAnalyze program to obtain the overall heat produced or absorbed during the reaction. All solutions were thoroughly degassed by stirring under vacuum. Titrations were performed at 298 K and pH 6.5 by an automated sequence of 50 injections, each of 5 µL uranyl acetate solutions (1.2 mM), into the sample cell containing

the amidoxime solution (0.1 mM). The injections were spaced by 300 s to ensure complete equilibration. Three titrations were carried out for each measurement. The reported experimental data are the best-fit values.

4.3. Density Functional Theory (DFT) calculations

DFT calculations of the geometries, vibrational frequencies, and electronic structures of the uranyl complexes with the amidoxime ligands were performed with the Gaussian 09 software package[26] using the PBE1PBE1 functional.[27] The Stuttgart/Dresden small core (SC) relativistic effective core pseudo-potential (RECP), replacing 60 core electrons,[28] was used for the U atom, and the total electron 6-311+G(d,p) basis set was used for the C, H, O and N atoms. Frequencies at the same level were calculated to verify that the optimized geometries are local minima on the potential energy surfaces and to obtain the thermodynamic quantities of the reaction (enthalpies of reaction). Solvation effects of water were taken into account by means of the polarizable continuum model using the integral equation formalism variant (IEFPCM)[29] with default convergence criteria.

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Synthesis of bis(amidoxime)s and evaluation of their properties as uranyl-complexing agents

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Graphical abstract: