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Improved deposition and deprotection of silane tethered 3,4 hydroxypyridinone (HOPO) ligands on functionalized nanoporous silica

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Abstract

An improved synthesis of a 3,4 hydroxypyridinone (HOPO) functionalized mesoporous silica is described. Higher 3,4-HOPO monolayer ligand loadings have been achieved, resulting in better performance. Performance improvements were demonstrated with the capture of U(VI) from human blood, plasma and filtered river water.

Keywords

Nanoporous sorbent; Uranium removal; HOPO; HOPO; Blood

Selective actinide separation is a critical core capability for many nuclear science and technology sectors including; nuclear fuel production, treaty verification, environmental remediation, nuclear waste disposal, nuclear medicine, and the monitoring and measurement of these processes [1–8]. The unique properties of lanthanides make them valuable to researchers and of increasing importance commercially for applications such high field strength magnets, sensing, electrooptical devices, catalysis, and unique nanomaterials [9–26]. Recent supply issues with the rare earths and the extensive challenges involved in separation and purification make methods and materials that improve lanthanide collection, recovery and recycling of increasingly significant economic and environmental relevance.

High affinity sorbents are desirable for the capture of trace level analytes from solutions for processing or analytical applications. Since actinides and lanthanides are typically present in very low levels sorbents with high affinities are of particular relevance to their separation. Self-assembled monolayers on mesoporous supports (SAMMS[®], a registered trademark of Battelle Memorial Institute) have proven to be a powerful class of organic–inorganic hybrid materials with superior sorbent properties [27–30]. These materials combine the high surface area and open porosity of a mesoporous silica support, with a high density coating of a self-assembled monolayer terminated with selected ligands, to create a nanoporous sorbent with excellent selectivity, affinity, capacity and sorption kinetics [30]. For equivalent ligand chemistries, the SAMMS materials commonly display capacity, affinity and kinetics

properties that are significantly better than polymer resin materials [29]. This is due to the rigid backbone and open pore structure leaving all the ligands available for binding at all times. Also a factor is the close proximity of the ligands to one another, making multiple metal-ligand interactions possible. The hydroxypyridinone (HOPO) ligands were developed specifically to be superior complexants for actinide cations [31–37] (Fig. 1). Previously, we reported that SAMMS built around the HOPO ligands were effective actinide sorbents [38]. In the original report, HOPO SAMMS were made by installing the HOPO ligands in protected (benzylated) form, at a ligand loading density of $\sim 0.5\text{--}0.75$ ligands/nm², and were then deprotected after monolayer formation by treating them with 10% HBr in glacial acetic acid over-night [38]. The various HOPO SAMMS were very effective for binding actinides from near neutral pH aqueous media, with distribution coefficients (K_d) typically in the range of 10^4 to 10^5 (even 10^6 in a couple of isolated cases) [38].

We were generally interested in improving the performance of HOPO SAMMS, and particularly interested in applying these nanoporous sorbent materials to removal of actinides from human blood as an alternative to chelation therapy (uranium in particular, since it is the most commonly encountered actinide) and in urine (for bioassay). Screening studies showed that the HOPO binding affinities for U(VI) were markedly reduced in human urine, blood and plasma. In these screening studies, the 3,4-HOPO ligand consistently displayed the highest U(VI) affinity, although these K_d values were only ~ 7000 , a small fraction of the values achieved in aquatic matrices such as ground water. Obviously, human blood is a much more complex matrix than simple low organic, low ionic strength aqueous solutions, and many types of competition or speciation changes could be responsible for this attenuated binding affinity. The question was also raised as to whether or not the HOPO SAMMS were fully deprotected, so we undertook a study of the deprotection chemistry in order to gain a better understanding of this process. This manuscript summarizes what we learned in these studies and reports improved deprotection conditions for surface-bound HOPO ligands, and an expeditious synthesis procedure that bypasses the need for protecting group chemistry in these depositions and enables a higher ligand density to be achieved on the surface.

Sorbent testing

Performance of these sorbents was evaluated with distribution co-efficients (K_d) is a direct measure of the affinity for the sorbent with the ion of interest. The distribution coefficient (expressed in units of mL/g), is simply a mass-weighted partition coefficient between the solid phase and the liquid supernatant phase as follows:

$$K_d = \frac{(C_o - C_f)}{C_f} \times \frac{V}{M} \quad (1)$$

where C_o and C_f are the initial and final concentrations in the solution of the target species determined by assay of solution composition. The K_d value is a mass-weighted partition coefficient, and the higher the K_d value is the higher the affinity that the sorbent has for the target analyte. For trace level concentrations K_d values provide a more meaningful measure of the sorbents performance than the more common capacity values that are typically determined at concentrations much higher than encountered in trace level processes. The K_d values were determined for the SAMMS materials, from tracer spiked nitric acidified solutions, and filtered Columbia river water, or human blood or blood plasma. A L/S ratio of 1000 was used throughout. Concentrations in solution were determined with an ICP-MS.

Sorbent synthesis

Silicas

Two different types of silica were used for these experiments, a surfactant templated mesoporous silica (MCM-41 [39,40]), and an amorphous chromatographic silica (Davisil 634 and 635, Aldrich). This batch of MCM-41 has a specific surface area of 800 m²/g, an average pore size of 35 Å (very uniform pore size distribution), and a pore volume of 1.29 cm³/g. The smaller pores of MCM-41 are more easily crowded during monolayer deposition, but the very high surface area of this support suggests that it might be possible to get a higher functional loading in the SAMMS made using this support. Also, the highly uniform pore size distribution makes it possible to monitor dimensional changes in pore size with each reaction.

The amorphous Davisil silicas used had specific surface areas of 480 m²/g, and an average pore size of ~60 Å (broad pore size distribution, up to ~200 Å), and a pore volume of 1.67 cm³/g. The difference between Davisil 634 and 635 is their granulation — Davisil 634 has 75–150 µm particles (100 to 200 mesh), while Davisil 635 has 150–250 µm particles (60–100 mesh). The larger pores of the Davisil silicas make this support more amenable to making monolayers with large bulky ligands, like the benzyl-protected HOPO ligands.

HOPO ligands

Experiments were carried out using both the 2-Me and 2-Et 3,4-HOPO ligands. For the sake of simplicity, only the 2-Me system will be described (results obtained with the 2-Et system were similar). 2-Methyl-1-carboxymethyl-3-(benzyloxy)-(1H)-pyridin-4-one (**1a**) was prepared using a procedure analogous to that of 1-(2'-carboxyethyl)-2-methyl-3-(benzyloxy)-4(1H)-pyridinone [41], substituting glycine for β-alanine. 1-carboxymethyl-3-hydroxy-2-methylpyrid-4-one (**1c**) was prepared by the literature method [42]. The structures of the HOPO moieties were confirmed by ¹H and ¹³C NMR spectroscopy.

Coupling of the protected 2-Me-3,4-HOPO ligand to a silane anchor and deposition on mesoporous silica

A variation of the literature procedure was employed [38] (see Scheme 1. A slurry of porous silica (3.0 g Davisil Grade 634, Aldrich) in 125 mL toluene was treated with water (0.27 mL, 15 mmol) and stirred for 6 h to completely hydrate the silica surface. Concurrently, a solution of **1a** (1.64 g, 6.0 mmol) in 50 mL N,N-dimethylformamide was prepared, to which 1,1-carbonyldiimidazole (1.04 g, 6.4 mmol) was added under N₂ (CO₂ evolution!). After stirring this solution at ambient temperature for approximately 30 min, 3-aminopropyltriethoxysilane (1.4 g, 6.3 mmol) was added and the mixture was then stirred for an additional 3 h. The 3,4-HOPO-silane solution was then added to the hydrated silica slurry and the mixture was heated to reflux for 6 h. After the reflux period, the reflux condenser was removed and replaced with a still-head and the ethanol by-product and residual water were removed by azeotropic distillation. After cooling to room temperature, the material was collected by vacuum filtration, washed with copious amounts of methanol, and air dried to give a near quantitative yield of a free-flowing white powder.

Optimization of deprotection of the benzylated 3,4-HOPO ligand

A series of control experiments were carried out in which reaction time and temperature was varied in order to determine optimum deprotection conditions. Deprotection efficiency was evaluated by measuring the distribution coefficient (*K_d*) for U(VI) in filtered Columbia river water. The benzylated 3,4-HOPO (which is in effect the t=0 sample for the kinetics run) produced a *K_d* for U(VI) of ~5800 (see Table 1 for a summary of the measured *K_d* values).

After 18 h at ambient temperature (the conditions originally employed), the observed K_d was $\sim 10^7$, and after 4 days the K_d was $\sim 10^8$. From these results, it is clear that the debenzylization reaction had proceeded to significant conversion after 18 h at ambient temperature, but was not yet complete. Reactions carried out at 35 °C, 50 °C and 60 °C for 18 h also produced K_d values for U(VI) of $\sim 10^8$. However, it was found that if this deprotection was carried out for long time-periods, or at even higher reaction temperatures, there was a problem with the generation of “fines” (breakdown of the silica support), which could be problematic for certain applications (e.g. packed column based separations). Therefore, we adopted 18 h at 60 °C using 10% conc. HBr in glacial acetic acid as our standard deprotection scheme to insure timely and complete debenzylization of the HOPO ligand, with minimal generation of fines.

Thermogravimetric analysis (TGA) of the 3,4-HOPO SAMMS product revealed a mass loss of 19.2% from 40 °C to 850 °C (10°/min), suggesting a coverage of approximately 1.7 silanes/nm², (corresponding to a loading of 1.1 mmol 3,4-HOPO ligand per gram of sorbent). BET surface area analysis revealed a specific surface area of 310 m²/g, a pore volume of 0.51 cm³/g, consistent with the addition of mass inside the pore volume, while maintaining an open pore structure for facile diffusion of the actinide species into the pores to bind with the HOPO ligands. Given that this amorphous silica (Davisil 634) has a fairly broad pore size distribution (<30 Å to >100 Å), it was not possible to discern any significant change in the pore diameter of the coated material.

As discussed earlier, our preliminary screening tests for binding U(VI) in human blood plasma revealed K_d values of ~ 7000 for the materials deprotected at ambient temperature (i.e. the original procedure). When we used the optimized deprotection procedure (10% conc. HBr in glacial acetic acid at 60 °C for 18 h), we obtained K_d values of $\sim 55,000$, a significant improvement in K_d . Clearly, the optimized deprotection resulted in a sorbent material that offered higher binding affinity relative to the original procedure. The earlier studies were carried out using MCM-41 [38] and these studies were performed with Davisil 634. The early MCM-41 sorbents had a surface coverage of only about 0.75 silanes/nm², so it is possible the uranyl complex may have had some interaction with the underlying silica surface (such an interaction would be anticipated to be a stabilizing interaction). The higher degree of coverage observed with the Davisil 634 sorbent (~ 1.7 silanes/nm²) should block any interaction of the uranyl ion with the silica surface, so in this system the only interaction should be between the uranyl ion and the 3,4-HOPO ligands. The higher K_d values are consistent with a stronger average metal/-ligand interaction (and inconsistent with the silica playing a role in the binding process). Since these K_d determinations were carried out well below saturation levels, the stoichiometry of the ligands relative to the U(VI) ions is not felt to have played a significant role in the K_d increase. Thus the specific surface area of the silica (which is directly related to the ligand population) is not likely to be the cause of this enhanced binding affinity. Therefore, in summation, the observed differences in K_d values are thought to arise from greater ligand availability (i.e. fewer residual benzyl groups restricting access to the active 3,4-HOPO ligands) resulting from the improved ester cleavage procedure.

Deposition of protected 3,4-HOPO on MCM-41

We also chose to perform this deposition on MCM-41 [39,40], as the tightly defined pore size of MCM-41 might allow us to monitor the change in pore diameter as each of these reactions proceeded, and the higher specific surface area of the support could potentially create a sorbent with higher overall functional loading. The MCM-41 that we used for these experiments had a specific surface area of 800 m²/g, a pore volume of 1.29 cm³/g, and an average pore diameter of 34 Å (with a very uniform pore size distribution). The benzyl

protected 3,4-HOPO ligand was coupled to the siloxane anchor as described above. The MCM-41 was hydrated as previously described [30] and then treated with the benzyl protected 3,4-HOPO silane in refluxing toluene as described above. The benzyl protected 3,4-HOPO SAMMS was found to have a specific surface area of 483 m²/g, a pore volume of 0.30 cm³/g, and an average pore diameter of 19.5 Å. Just as before, these observations are consistent with the deposition of the benzyl-protected HOPO-silane inside the nanoporous MCM-41 support. Analysis using TGA revealed an organic loading of 23.9%, corresponding to a silane population of 0.76 silanes/nm², or for this particular silane, 0.76 mmole HOPO silane per gram of sorbent. Note that this population density is approximately half that observed for the larger pore Davisil sorbents described above (in terms of silanes/nm²), but in terms of overall functional density (in terms of mmole HOPO ligand per gram sorbent) this is only 15% less than the Davisil sorbents (0.76 vs. 0.89 mmole/g). Clearly the smaller pore size of the MCM-41 support did have an impact on the ability to load the moderately bulky benzylated 3,4-HOPO ligand, but not to a severe degree.

Exposure of this material to the standardized cleavage conditions (10% conc. HBr in glacial acetic acid at 60 °C for 18 h) gave a product that had a surface area of 585 m²/g, a pore volume of 0.34 cm³/g, and an average pore diameter of 24.6 Å, all consistent with removal of mass (i.e. the benzyl protecting groups) from the 3,4-HOPO monolayer lining the pores of the sorbent. K_d values for U were 32,000 in plasma and 6100 for blood, revealing similar performance to the 3,4-HOPO SAMMS deprotected using the original procedure.

Synthesis of unprotected 3,4-HOPO silane

We also chose to explore the possibility of depositing the HOPO-silane directly, in unprotected form, as this would simplify the process, eliminate the need for deprotection chemistry, and significantly reduce the ligand's "footprint" within the monolayer and thereby potentially allow for a higher ligand loading in the final product. Higher monolayer densities could improve material affinity and capacity, particularly for chelating ligands. This approach also removes any risk of damaging the monolayer, or the support, during the deprotection process.

Coupling of the unprotected 3,4-HOPO ligand to silane anchor and deposition in Davisil 635

An analogous procedure was carried out using the unprotected 3,4-HOPO derivative **1c** and Davisil 635. TGA of the SAMMS product revealed a mass loss of 23% from 40 °C to 850 °C (10°/min), suggesting a coverage of approximately 2.2 silanes/nm² (corresponding to 1.3 mmol 3,4-HOPO ligand per gram of sorbent). BET surface area analysis revealed a specific surface area of 217 m²/g and a pore volume of 0.36 cm³/g, once again consistent with the addition of significant mass inside the pore volume. Given the lower specific surface area and pore volume of this product, this material appears to have an even higher ligand loading due to the smaller ligand footprint than the product derived from the benzylated 3,4-HOPO (above). As before, there was no discernible change in pore size as a result of the broad pore size distribution of the silica support. Based on these data, it appears that the free HOPO head group does not interfere with the hydrolysis/condensation chemistry of the siloxane self-assembly chemistry, and that it is not necessary to protect the HOPO ligand for these depositions.

K_d for U(VI) in filtered river water was >10⁷ and K_d for U(VI) in plasma was 10,000 revealing very good affinity for U(VI), similar to those results obtained with the original deprotection strategy.

Coupling of the unprotected 3,4-HOPO ligand to silane anchor and deposition in MCM-41

An analogous procedure was carried out using the unprotected 3,4-HOPO derivative **1c** and MCM-41. This material was found to have a specific surface area of 488 m²/g, and the average pore size was <20 Å. Analysis by TGA revealed an organic content of 29.5%, which corresponds to a silane population density of 1.7 silanes/nm², or a functional density of 1.6 mmole 3,4-HOPO ligand per gram of sorbent. Clearly the lack of a benzyl protecting group facilitates the deposition, particularly in the narrow pores of MCM-41. Also, these results demonstrate that the unprotected 3,4-HOPO headgroup does not interfere with the hydrolysis/condensation chemistry of the siloxane anchor. K_d values for U were similar to those on Davisil and found to be 12,000 for plasma and 8900 for blood, which suggests that even with the added ligand density there is no additional affinity for UO₂ dication.

Impact of ligand population density

The posture and conformation of the ligands in the monolayer interface can have a significant impact on the performance of these sorbents [30]. The benzyl protecting group increases the size of the molecule “footprint” of the HOPO silane during the monolayer deposition, and deprotection introduces a certain amount of conformational flexibility as a result of the void left behind when the benzyl group is removed. This flexibility appears to be important in this case since the Davisil-based sorbents derived from the benzyl protected HOPO ligands had a slightly lower ligand loading (1.7 silanes/nm²) than did the sorbents derived from the never-protected HOPO ligands (2.2 silanes/nm²; a similar trend was observed in MCM-41), but uptake of U(VI) from human blood plasma was found to be higher for the 3,4-HOPO SAMMS that had been benzyl protected (K_d of 55,000) than for the 3,4-HOPO SAMMS that had never been protected (K_d of 10,000). This could be due the need for the 3,4-HOPO ligand to chelate the uranyl cation (UO₂²⁺) in the equatorial plane (see Fig. 2), which would be facilitated by the additional conformational flexibility provided by the space formerly occupied by the benzyl protecting groups. Certain other actinide species, like the neptunyl cation (NpO₂⁺), should display similar “preference” for the greater conformational flexibility derived from the protected (or lower density unprotected) HOPO ligand due to the requirement for similar equatorial chelation, while other actinide species (e.g. Pu⁴⁺) are more flexible in terms of their chelation geometries and therefore are able to bond with the tethered HOPO ligands in multiple geometries. As a result, the binding of these other actinide cations may very well benefit from the higher ligand density and loading provided by the unprotected 3,4-HOPO deposition.

Solid-state NMR studies

Solid-state CP-MAS ¹³C NMR spectra were collected from samples made on MCM-41. This series consisted of the benzyl protected 3,4-HOPO SAMMS (derived from **1a**), the deprotected 3,4-HOPO SAMMS, and the “never protected” 3,4-HOPO materials. The silane tethered 3,4-HOPO ligand (never protected) has 11 carbon atoms associated with it, and the ¹³C NMR spectrum shows 9 partially resolved signals (170.2, 146.6, 140.6, 134.2, 112.2, 57.5, 43.1, 23.7 and 11.8 ppm). The signal at 170 ppm appears to contain the resonances for both of the carbonyl carbons. The benzyl protected material showed these same basic peaks, however it is interesting to note that the benzyl protected 3,4-HOPO ligand has the two carbonyl carbons partially resolved at 174.6 and 166.9 ppm. The benzyl protecting group displays a strong signal at 128.5 ppm for the 5 protonated phenyl carbons (the signal for C-1 of the benzene ring is buried under-neath the signals for the HOPO ligand), and a smaller peak at 73.7 ppm for the benzylic methylene. These two peaks disappeared in the deprotected materials, confirming the loss of the benzyl moiety, and the carbonyl peak coalesced back into one broad peak.

Conclusions

The original conditions employed to remove the benzyl protecting group in the HOPO SAMMS were effective but resulted in incomplete deprotection. Longer reaction times (e.g. 4 days) were found to take the reaction to completion, but also had deleterious impacts on the silica support structure and generated fines. Performing the deprotection chemistry at a moderately elevated temperature and shorter reaction times (e.g. 60 °C, 18 h) resulted in clean, efficient debenzylation of the protected 3,4-HOPO ligand. Deposition of the 3,4-HOPO silane in protected benzyl form, and subsequently deprotecting the HOPO ligand has the added benefit of generating a certain amount of conformational flexibility which allows the 3,4-HOPO ligand to accommodate the uranyl cation's need for chelation in the equatorial plane. However, even higher functional loading is possible when using the unprotected 3,4-HOPO ligand in the silane due to the lack of the steric bulk of the benzyl protecting group, and this eliminates the need for subsequent deprotection. This “never protected” strategy was particularly beneficial when working inside the smaller, more easily congested pores of MCM-41. This higher population density produced sorbents that were slightly less effective at binding the uranyl cation (relative to the 3,4-HOPO SAMMS that were made using the benzyl protected ligand), presumably due to lesser conformational flexibility due to the higher packing density of the molecules in the monolayer. 3,4-HOPO SAMMS were found to be effective at capturing U(VI) from human blood, plasma and natural waters, although the binding affinity was notably lower in biological fluids than in river water.

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References

1. Hu QH, Weng JQ, Wang JS. *J. Environ. Radioact.* 2010; 101:426–437. [PubMed: 18819734]
2. Ewing RC, von Hippel FN. *Hippel Sci.* 2009; 325(5937):151–152.
3. Arazi L, Cooks T, Schmidt M, Keisari Y, Kelson I. *Phys. Med. Biol.* 2010; 55(4):1203–1218. [PubMed: 20124656]
4. Allen BJ. *Rev. Recent Clin. Trials.* 2008; 3(3):185–191. [PubMed: 18782076]
5. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennernas B, Petersson U, Johannessen DC, Sokal M, Pigott K, Yachnin J, Garkavij M, Strang P, Harmenberg J, Bolstad B, Bruland OS. *Lancet Oncol.* 2007; 8(7):587–594. [PubMed: 17544845]
6. Wogman NA, Wigmosta MS, Swindle DW, Krey PW. *J Radioanal. Nucl. Chem.* 2001; 248(3):611–615.
7. Egorov OB, Addleman RS, O'Hara MJ, Marks T, Grate JW. *Nucl. Instrum. Methods Phys. Res., Sect. A.* 2005; 537(3):600–609.
8. Egorov OB, O'Hara MJ, Addleman RS, Grate JW. *Radioanal. Methods Interdiscip. Res.* 2004; 868:246–270.
9. The entire issue of *Chem. Rev.* 2002; 102(6):1805–2476. was dedicated to lanthanide complexes, their chemistry, and applications.
10. Kalinowski J, Mezyk J, Meinardi F, Tubino R, Cocchi M, Virgili D. *Chem. Phys. Lett.* 2008; 453(1–3):82–86.
11. Yu JB, Zhou L, Zhang HJ, Zheng YX, Li HR, Deng RP, Peng ZP, Li ZF. *Inorg. Chem.* 2005; 44(5):1611–1618. [PubMed: 15733004]

12. Zheng XL, Liu Y, Pan M, Lu XQ, Zhang JY, Zhao CY, Tong YX, Su CY. *Angew. Chem. Int. Ed.* 2007; 46(39):7399–7403.
13. Roesky PW, Bhunia A, Lan YH, Powell AK, Kureti S. *Chem. Commun.* 2011; 47(7):2035–2037.
14. Rocha J, Carlos LD, Paz FAA, Ananias D. *Chem. Soc. Rev.* 2011; 40(2):926–940. [PubMed: 21180775]
15. Maggini L, Traboulsi H, Yoosaf K, Mohanraj J, Wouters J, Pietraszkiewicz O, Pietraszkiewicz M, Armaroli N, Bonifazi D. *Chem Commun.* 2011; 47(5):1626–1628.
16. Pamies O, Andersson PG, Dieguez M. *Chem. Eur. J.* 2010; 16(48):14232–14240. [PubMed: 21140401]
17. Chatterjee DK, Gnanasammandhan MK, Zhang Y. *Small.* 2010; 6(24):2781–2795. [PubMed: 21064086]
18. Lisowski CE, Hutchison JE. *Anal. Chem.* 2009; 81(24):10246–10253. [PubMed: 19904966]
19. Lin HY, Fang YC, Chu SY. *J Am. Ceram. Soc.* 2010; 93(11):3850–3856.
20. Carlos LD, Ferreira RAS, Bermudez VD, Julian-Lopez B, Escibano P. *Chem. Soc. Rev.* 2011; 40(2):536–549. [PubMed: 21180708]
21. Kuriki K, Koike Y, Okamoto Y. *Chem. Rev.* 2002; 102(6):2347–2356. [PubMed: 12059270]
22. Birowosuto MD, Dorenbos P, van Eijk CW, Kramer KW, Gudel HU. *IEEE Trans. Nucl. Sci.* 2005; 52:1114–1118.
23. Nash KL, Jensen MP. *Sep. Sci. Technol.* 2001; 36(5):1257–1282.
24. Yantasee W, Fryxell GE, Addleman RS, Wiacek RJ, Koonsiripaiboon V, Pattamakomsan K, Sukwarotwat V, Xu J, Raymond KN. *J Hazard. Mater.* 2009; 168(2–3):1233–1238. [PubMed: 19345006]
25. Huang CC, Lo YW, Kuo WS, Hwu JR, Su WC, Shieh DB, Yeh CS. *Langmuir.* 2008; 24:8309–8313. [PubMed: 18570444]
26. Zheng XL, Liu Y, Pan M, Lü X-Q, Zhang J-Y, Zhao C-Y, Tong Y-X, Su C-Y. *Angew. Chem. Int. Ed.* 2007; 46(39):7399–7403.
27. Feng X, Fryxell GE, Wang LQ, Kim AY, Liu J, Kemner K. *Science.* 1997; 276:923–926.
28. Liu J, Feng X, Fryxell GE, Wang LQ, Kim AY, Gong M. *Adv. Mater.* 1998; 10:161–165.
29. Fryxell, GE.; Shane Addleman, R.; Mattigod, SV.; Lin, Y.; Zemanian, TS.; Wu, H.; Birnbaum, Jerome C.; Liu, J.; Feng, X., editors. *Encyclopedia of Nanoscience and Nanotechnology.* Marcel-Dekker; 2004. Environmental and sensing applications of molecular self-assembly; p. 1135–1145.
30. Fryxell GE, Mattigod SV, Lin Y, Wu H, Fiskum S, Parker K, Zheng F, Yantasee W, Zemanian TS, Addleman RS, Liu J, Kemner K, Kelly S, Feng X. *J Mater. Chem.* 2007; 17:2863–2874.
31. Gorden AEV, Xu J, Raymond KN, Durbin PW. *Chem. Rev.* 2003; 103:4207–4282. [PubMed: 14611263]
32. Xu J, Durbin PW, Kullgren B, Ebbe SN, Uhler LC, Raymond KN. *J Med. Chem.* 2002; 45:3963–3971. [PubMed: 12190318]
33. Xu J, Kullgren B, Durbin PW, Raymond KN. *J Med. Chem.* 1995; 38:2606–2614. [PubMed: 7629800]
34. Xu J, Whisenhunt DW Jr, Veeck AC, Uhler LC, Raymond KN. *Inorg. Chem.* 2003; 42:2665–2674. [PubMed: 12691574]
35. Xu J, Radkov E, Ziegler M, Raymond KN. *Inorg. Chem.* 2000; 39:4156–4164. [PubMed: 11198875]
36. Durbin PW, Kullgren B, Xu J, Raymond KN, Hengè-Napoli MH, Bailly T, Burgada R. *Radiat. Prot. Dosim.* 2003; 105:503–508.
37. White DL, Durbin PW, Jeung N, Raymond KN. *J Med. Chem.* 1988; 31:11–18. [PubMed: 2826783]
38. Lin Y, Fiskum SK, Yantasee W, Wu H, Mattigod SV, Vorpagel E, Fryxell GE, Raymond KN, Xu J. *Environ. Sci. Technol.* 2005; 39:1332–1337. [PubMed: 15787374]
39. Beck JS, Vartuli JC, Roth WJ, Leonowicz ME, Kresge CT, Schmitt KD, Chu CT-W, Olson DH, Sheppard EW, McCullen SB, Higgins JB, Schlenker JL. *J Am. Chem. Soc.* 1992; 114:10,834–10,843.

40. Kresge CT, Leonowicz ME, Roth WJ, Vartuli JC, Beck JS. *Nature*. 1992; 359(6397):710–712.
41. Dobbin PS, Hider RC, Hall AD, Taylor PD, Sarpong P, Porter JB, Xiao G, van der Helm D. *J Med. Chem.* 1993; 36:2448–2458. [PubMed: 8355246]
42. Kruck TPA, Burrow TE. *J Inorg. Biochem.* 2002; 88:19–24. [PubMed: 11750021]

1a $R = \text{CH}_2\text{Ph}$, $R' = \text{Me}$

1b $R = \text{CH}_2\text{Ph}$, $R' = \text{Et}$

1c $R = \text{H}$, $R' = \text{Me}$

Fig. 1.
The basic structure of the 1-carboxymethyl-3,4-HOPO moiety and the numbering scheme for this ligand.

Fig. 2.
Proposed 2-to-1 complex formed between the tethered 3,4-HOPO ligand and the $[UO_2]^{2+}$ cation.

Scheme 1.

Optimized synthesis of 2-Alkyl-3,4-HOPO-SAMMS: a) NaOH, Water/MeOH, PhCH₂Cl; b) NaOH, MeOH, glycine, reflux; c) 1,1'-carbonyldiimidazole, 3-aminopropyl(triethoxysilane), DMF; d) silica, water, DMF/toluene, reflux; e) 10% conc. HBr in glacial acetic acid, 60 °C, 18 h.

Table 1Effect of cleavage method and matrix on the U(VI) distribution coefficient (K_d) for 3,4-HOPO SAMMS.

Silica	Cleavage method	Matrix	K_d
MCM-41	Old ^a	Buffer	>100,000 ^b
MCM-41	Old	Blood	7000
D-634	None (Bz ether)	River water	5800
D-634	Old	River water	10,000,000
D-634	Old ^c	River water	100,000,000
D-634	New ^d	River water	100,000,000
D-634	New	Blood	55,000
MCM-41	New	Plasma	32,000
MCM-41	New	Blood	6100
D-635	Unprotected	River water	>10,000,000
D-635	Unprotected	Plasma	10,000
MCM-41	Unprotected	Plasma	12,000
MCM-41	Unprotected	Blood	8900

^aOld=18 h at 25 °C.^bRef. [38].^c4 days at 25 °C.^dNew=50–60 °C for 18 h.