Immobilization of a hexaphyrin(1.0.1.0.0.0) derivative onto a tentagel-amino resin and its use in uranyl cation detection†‡

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The synthesis of an isoamethyrin derivative containing two $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ moieties in the β -pyrrolic positions and its use in the colorimetric detection of the uranyl cation after immobilization onto a solid support is reported.

Nuclear waste, byproducts from weapon production and commercial power plants, is a source of potential environmental contamination and a source of strategic concern. This concern is providing an incentive to develop new methods to recognize and sense the critical components in such wastes, including *inter alia* the uranyl (UO_2^{2+}), neptunyl (NpO_2^+) and plutonyl (PuO_2^+) cations. While considerable work along these lines has been performed, particularly in the area of uranyl cation recognition, to date cation detection has typically relied on spectroscopic methods (UV-visible, fluorescence, phosphorescence or atomic absorption) or potentiometric techniques.^{1–3} Surprisingly, only a handful of simple colorimetric sensors for the high-valent actinides (*i.e.*, chemical entities that change color upon exposure to these cations) have been reported.^{4–6}

Isoamethyrin (hexaphyrin(1.0.1.0.0.0), **1**) is an expanded porphyrin that undergoes spontaneous, air-mediated oxidation and a dramatic change in both color and spectroscopic properties when exposed to the uranyl or neptunyl cations.⁶ Additionally, it was demonstrated that, with the exception of copper salts, isoamethyrin preferentially forms a coordination complex with the uranyl cation (*e.g.*, **2**) over other common metal salts.⁷ As a first step towards developing this expanded porphyrin as a potentially useful actinide sensor, we report here the synthesis of a derivative modified at two β -pyrrolic positions and its successful immobilization onto a solid support. Qualitative and quantitative evidence that the resulting system changes color upon exposure to the uranyl cation is also presented.

Immobilized sensors are attractive both for their inherent convenience and because they lend themselves to a format involving multiple sensor arrays, a modality that permits the simultaneous detection and quantitation of multiple analytes.⁸ Indeed, a range of organic ligands have been immobilized onto solid supports, such as resins, silica gel, or cotton, and studied for uranyl extraction and sensing.^{1,4,9} In the area of actinide cation detection, a notable sensor is arsenazo III, which has been used to

generate a microchip with highly selective detection limits, as well as strippable coatings.^{4a,c} Such advances notwithstanding, we felt it would be advantageous to produce immobilized systems based on isoamethyrin since previous work with this macrocycle has demonstrated greater specificity in terms of “sensing” the uranyl cation without interference from, *e.g.*, lanthanide cations. For initial work, we decided to focus on a tentagel amino-terminated polystyrene-poly(ethylene glycol) graft co-polymer resin (90 μm , 0.30 mmol g^{-1} NH) as the solid support.

This choice of an amino-terminated resin dictated the need for a carboxy-functionalized isoamethyrin derivative; symmetry considerations, coupled with a desire to mimic as closely as possible the electronic features of **1**, led us to the dicarboxylic acid **7** as our functionalized isoamethyrin target. While β -substitution of porphyrins is well known,¹⁰ reports of *expanded* porphyrins functionalized at the β -pyrrolic positions with groups other than alkyl are still surprisingly few in number.¹¹ Given this limited precedent, we considered that the use of a diformyl bis-methylester bipyrrole precursor, such as **3** (Scheme 1), would provide the simplest entry into the chemistry of β -pyrrole functionalized isoamethyrin chemistry.

Precursor **3** was prepared in eight steps from monopyrrolic precursors using standard methods as detailed in the ESI.† With it in hand, isoamethyrin **6** was obtained in two steps using a modification of previously published procedures.¹² Specifically, **3** was condensed with two equivalents of ethyl-methyl bipyrrole, **4**, to afford an open chain hexapyrrole precursor, **5**, which was immediately carried onto the next step. This involved exposing a CH_2Cl_2 solution of **5** to a solution of 1.0 M FeCl_3 in 2 M aqueous HCl for 4 h. Following chromatographic purification and an acid wash, the bis-HCl salt of isoamethyrin **6** was isolated in 40% yield.

Single crystals suitable for X-ray crystallography were grown by slow evaporation of the bis-chloride salt of **6** in a CH_2Cl_2 –cyclohexane solution.‡ The core of the macrocycle was observed to be essentially planar, in spite of the fact that the methyl ester groups are separated from one another. Further details can be found in the ESI.‡ The ^1H NMR and UV-vis spectra of $\text{H}_2\text{6}^{2+} \cdot 2\text{Cl}^-$, like those

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‡ Electronic supplementary information (ESI) available: Synthetic details for **4–8** and X-ray data for **6** and **8**. See DOI: 10.1039/b718627d

Scheme 1 Synthesis of isoamethyrins **6** and **7**.

of $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$, are consistent with the presence of an antiaromatic ring current. The UV-visible spectrum for $\text{H}_2\text{5}^{2+} \cdot 2\text{Cl}^-$ was also similar to that of $\text{H}_2\text{1}^{2+} \cdot 2\text{Cl}^-$ at 378 ($\epsilon/\text{dm}^3 \text{ mol}^{-1}$ 24 600), 494 (81 100) and 596 (32 500) nm. A minor hyperchromic effect and bathochromic shifts in the peak maxima were, however, observed.

Macrocycle **6**, like **1**, was found to interact with the uranyl cation. Specifically, adding an excess of $\text{UO}_2(\text{OAc})_2$ in CH_3OH to a solution of **6** in a 50 : 50 v/v mixture of CH_2Cl_2 – CH_3OH led to formation of the uranyl complex, **8**, in 24% isolated yield after a period of 48 h. Direct structural and spectroscopic comparisons between **8** and the previously reported isoamethyrin–uranyl complex, **2**, provided support for the proposed structure. Crystals suitable for X-ray diffraction analysis were grown from slow evaporation of a solution of **8** in CH_2Cl_2 – CH_3OH . Although three molecules of **8** were observed in the unit cell, the differences (involving the β -substituents) are minor. Thus, only one of the three molecules is shown in Fig. 1. The macrocycle must twist slightly to accommodate the relatively small size of the uranyl cation. Analysis of the ^1H NMR spectra revealed that like its analogues **1** and **2**, the ring current of **6** changes from paratropic, or antiaromatic, to diatropic, or aromatic, upon coordination of the metal cation, as is evidenced *inter alia* by an upfield shift of the *meso*-H signal (see ESI†). Again, some differences between **8** and **2** were observed in their respective UV-visible spectra. As compared to **2**, the Q-like band of **8** was found to be somewhat broader and shifted to longer wavelengths. Likewise, both the Soret and Q-like bands of **8** were significantly less intense than those of **2**.

To effect immobilization of the functionalized isoamethyrin **6** to the amino-terminated tentagel resin, the methyl ester groups were hydrolyzed to give the corresponding diacid **7** in accord with a previously established procedure.¹³ Attachment was then effected using a slight modification of the solid-phase synthetic procedures typically used to functionalize this resin.¹⁴

Given the high pigmentation of the macrocycle, successful immobilization was easily discernable by the naked eye. In fact, it was quickly determined that 100% coverage of the amino sites with isoamethyrin resulted in an opaque bead; it was so dark that

Fig. 1 Top and side views of **8** showing a partial atom labelling scheme. Ellipsoids are scaled to the 30% probability level. All hydrogens, and the alkyl substituents in the side view have been removed for clarity. U–N bond lengths lie in the range 2.5169(6)–2.7260(7) Å. The O–U–O angle is 178.2(5)° and the O–U–N bond angles range from 99.8(4) to 80.1(4)°.

it was considered likely that it would prove impossible to view any putative uranyl cation-induced color changes. Accordingly, isoamethyrin coverage levels ranging from 5–20% of the open amino groups/bead were used. This level of immobilization corresponds to 0.0015–0.006 mmol g^{-1} .

When functionalized with isoamethyrin in this way, each bead has an approximate diameter of 220 μm and was expected to act as a miniaturized cuvette ensemble for the detection of uranyl cations. The reactivity of these beads with uranyl salts was thus investigated. As has been previously established, the ‘free base’ form of the macrocycle is necessary for uranyl cation coordination. In the case of the acid salt of immobilized **7**, this ‘free base’ was formed by washing the beads with a 10% NaOH solution. Upon exposure to a 0.024 M uranyl acetate solution in methanol for 9 days,¹⁵ the bead changes from a golden yellow color to a pink–red (*cf.* inset to Fig. 2). It has been previously demonstrated that, in the case of **1** and **2**, this color change is reflected as a shift of the Soret band λ_{max} by about 40 nm.⁷

Fig. 2 Intensity values in the red (red line), green (green line) and blue (blue line) channels for a bead containing the free base of isoamethyrin (left side, 6.4% amine coverage) and a bead exposed to 0.0024 M uranyl acetate for nine days (right side).¹⁶

With the beads in hand, analysis was performed in a custom-designed flow cell, as has been described by Goodey *et al.*^{8a} The substrate-induced color changes in receptor functionalized tentagel beads were then quantified into red, green and blue channels, as is shown in Fig. 2. In this approach, the red, green and blue color intensities are extracted using a CCD video chip before and after exposure to an analyte (the uranyl cation in the present instance). Images of blank beads were used to establish the reference light intensity, while those of the derivatized beads are used to extract the absorbance values of the three effective color windows. Applying this procedure to the isoamethyrin functionalized beads, reveals a significant increase in the intensity of the red channel subsequent to treatment with the uranyl cation (*cf.* Fig. 2). By comparison, the changes in the green and blue channels are slight.

Strictly speaking, the change in the red channel reflects two events in the system, namely oxidation of the macrocycle (from antiaromatic to aromatic) and coordination of the uranyl cation to the oxidized form of the macrocycle. In our experience to date,^{6,7} these events have always been closely coupled. However, this need not be the case. Indeed, it is fully conceivable that oxidation can take place separate from and prior to metal complexation. Moreover, we believe that, unlike UV-visible spectroscopy, RGB analysis may allow us separate these two events and monitor solely metal complexation. To the extent this proves possible, it may allow us to decrease the time required for cation complexation by carrying out a preliminary ligand oxidation step. This, in turn, would lead to improved response times, as would be required for a practical sensor system. Efforts along these lines are in progress.

In conclusion, the use of a β -methyl ester bipyrrole precursor allows for the synthesis of a functionalized isoamethyrin that can be readily hydrolyzed and attached to a tentagel amino-derivatized solid support. Preliminary studies provide support for the conclusion that the resulting systems allow for the color-based detection of the uranyl cation, albeit with response kinetics that are still far short of being practical for a working sensor array. Further studies, including competition with common metal salts and kinetic studies of both the ligand oxidation and metal coordination process, are necessary and in progress.

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Notes and references

§ Crystallographic details: for **6**: $C_{48}H_{61}Cl_2N_4O_{4.50}$, $M = 864.93$, orthorhombic, space group $Pbca$, $a = 25.8233(3)$, $b = 10.4391(10)$, $c = 33.9936(16)$ Å, $U = 9163.7(10)$ Å³, $T = 153(2)$ K, $Z = 8$, $\lambda(\text{Mo-K}\alpha) = 0.71073$ Å, $\mu = 0.193$ mm⁻¹, crystal size $0.40 \times 0.07 \times 0.04$ mm, 8068 reflections collected, 8068 unique ($R_{\text{int}} = 0.0779$). The final $wR(F^2)$ was 0.1512 (all data). CCDC 661301. For **8**: $C_{123}H_{142}N_{15}O_{15}U_{2.50}$, $M = 2665.59$, monoclinic, space group $P2_1/c$, $a = 40.592(2)$, $b = 16.1043(6)$, $c = 17.9271(6)$ Å, $\beta = 94.662(2)^\circ$, $U = 11680.3(8)$ Å³, $T = 153(2)$ K, $Z = 4$, $\lambda(\text{Mo-K}\alpha) = 0.71073$ Å, $\mu = 3.528$ mm⁻¹, crystal size $0.27 \times 0.06 \times 0.04$ mm, 41835 reflections collected, 17429 unique ($R_{\text{int}} = 0.1001$). The final $wR(F^2)$ was 0.1669 (all data). CCDC 661302. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718627d

- (a) J. L. Sessler, P. J. Melfi and G. D. Pantos, *Coord. Chem. Rev.*, 2006, **250**, 816–843; (b) M. Ephritikhine, *Dalton Trans.*, 2006, 2501–2516; (c) C. J. Burns, M. P. Neu, H. Boukhalfa, K. E. Gutowski, N. J. Bridges and R. D. Rogers, in *Coordination Chemistry of the s, p, and f Metals*, ed. G. F. R. Parkin, Elsevier, Pergamon, San Diego, CA, 2004, vol. 3, pp. 189–345; (d) M. R. Maurya and R. C. Maurya, *Rev. Inorg. Chem.*, 1995, **15**, 1–108.
- S. Shinkai, H. Koreishi, K. Ueda, T. Arimura and O. Manabe, *J. Am. Chem. Soc.*, 1987, **109**, 6371–6376.
- For example: (a) M. A. Denecke, *Coord. Chem. Rev.*, 2006, **250**, 730–754; (b) R. Karminski, F. J. Purcell and E. Russavage, *Anal. Chem.*, 1981, **59**, 1093–1096; (c) D. W. Boomer and M. J. Powell, *Anal. Chem.*, 1987, **59**, 2810–2813; (d) J. Liu, A. K. Brown, X. Meng, D. M. Crokek, J. D. Istok, D. B. Watson and Y. Lu, *Proc. Natl. Acad. Sci. USA*, 2007, **104**, 2056–2061.
- (a) G. E. Collins and Q. Lu, *Anal. Chim. Acta*, 2001, **436**, 181–189; (b) A. Suresh, D. K. Patre, T. G. Srinivasan and P. R. V. Rao, *Spectrochim. Acta, Part A*, 2002, **58**, 341–347; (c) H. N. Gray, B. Jorgensen, D. L. McClaugherty and A. Kippenberger, *Ind. Eng. Chem. Res.*, 2001, **40**, 3540–3546.
- A. Suresh, D. K. Patre, T. G. Srinivasan and P. R. V. Rao, *Spectrochim. Acta, Part A*, 2002, **58**, 341–347.
- J. L. Sessler, D. Seidel, A. E. Vivian, V. Lynch, B. L. Scott and D. W. Keogh, *Angew. Chem., Int. Ed.*, 2001, **40**, 591–594.
- (a) J. L. Sessler, P. J. Melfi, D. Seidel, A. E. V. Gorden, D. K. Ford, P. D. Palmer and C. D. Tait, *Tetrahedron*, 2004, **60**, 11089–11097; (b) J. L. Sessler, P. J. Melfi, E. Tomat and V. M. Lynch, *Dalton Trans.*, 2007, 629–632.
- For example: (a) A. Goodey, J. J. Lavigne, S. M. Savoy, M. D. Rodriguez, T. Curey, A. Tsao, G. Simmons, J. Wright, S.-J. Yoo, Y. Sohn, E. V. Anslyn, J. B. Shear, D. P. Neikirk and J. T. McDevitt, *J. Am. Chem. Soc.*, 2001, **123**, 2559–2570; (b) N. A. Rakow and K. S. Suslick, *Nature*, 2000, **406**, 710–713.
- (a) P. D. Beer, M. G. B. Drew, D. Hesek, M. Kan, G. Nicholson, P. Schmitt, P. D. Sheen and G. Williams, *J. Chem. Soc., Dalton Trans.*, 1998, 2783–2785; (b) I. Tabushi, Y. Kobuke and T. Nishiyama, *Nature*, 1979, **280**, 665–666.
- M. H. Vicente, in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, CA, 2000, vol. 1, pp. 149–199.
- (a) S. Shimizu, J.-Y. Shin, H. Furuta, R. Ismael and A. Osuka, *Angew. Chem., Int. Ed.*, 2003, **42**, 78; (b) H. Rexhausen and A. Gossauer, *J. Chem. Soc., Chem. Commun.*, 1983, 275; (c) J. L. Sessler, M. J. Cyr, V. Lynch, E. McGhee and J. A. Ibers, *J. Am. Chem. Soc.*, 1990, **112**, 2810–2813; (d) V. Kral, E. A. Brucker, G. Hemmi, J. L. Sessler, J. Kralova and H. Bose, *Bioorg. Med. Chem.*, 1995, **3**, 573–578; (e) J. L. Sessler and E. A. Brucker, *Tetrahedron Lett.*, 1995, **36**, 1175–1176.
- (a) D. Seidel, V. Lynch and J. L. Sessler, *Angew. Chem., Int. Ed.*, 2002, **41**, 1422–1425; (b) J. L. Sessler, P. J. Melfi and V. M. Lynch, *J. Porphyrins Phthalocyanines*, 2007, **11**, 287–293.
- J. Davis, PhD Thesis, The University of Texas at Austin, CA, 2001.
- Solid-Phase Synthesis: A Practical Guide*, ed. S. A. Kates and F. Albericio, Marcel Dekker, Inc., New York, 2000.
- While a color change was observed after one day, this extended reaction time was employed to ensure complete coordination of the uranyl cation by the appended isoamethyrin obtained from **7**.
- Beads were arranged into a flow cell, as has been described by Goodey *et al.*,^{8a} and washed with water for 10 min before being analyzed. The camera exposure was 7.36 ms.