Hexaphyrin(1.0.1.0.0.0): An Expanded Porphyrin Ligand for the Actinide Cations Uranyl (UO_2^{2+}) and Neptunyl (NpO_2^{+})**

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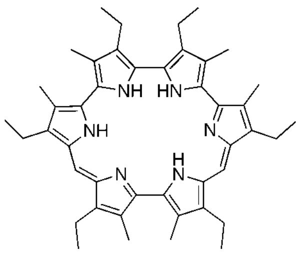
Dedicated to Professor Ernst-G. Jäger
on the occasion of his 65th birthday

Advancements made possible through applications of the unique properties of the actinides have revolutionized our modern era; however, actinide production, whether for defense purposes or the production of electricity, has generated a legacy of environmental problems with serious waste management concerns that must be addressed.[1] Since actinide production in reactors is accompanied by fission, the ability to isolate the transuranic actinides from a matrix that includes both fission products and uranium remains a problem central to actinide purification. Accordingly, efficient separation processes continue to be sought.[2]

One proposed solution to this problem involves the coordination of transuranic cations with macrocycles. Incorporation of these macrocycles into cation-selective polymers or placing the metal complex onto silica gel for use in chromatographic separation could lead to the selective isolation of the actinide cations.[3] To this end, there have been many forays into the realm of the coordination chemistry of transuranic elements with macrocycles.[4] The more widely studied macrocyclic systems include calixarenes[5–9] and crown ethers[10–14] which have been shown to complex UO_2^{2+} ions through both inner-sphere and outer-sphere coordination.[5–14] In ongoing studies calixarenes have shown some promise as selective actinide extractants,[8, 9] while the crown ethers have also been found to coordinate NpO_2^{+} ions.[15]

Porphyrins are also macrocycles that are recognized as excellent cation complexation agents, particularly for cations of the late transition series.[16] While structurally characterized U^{IV} and Th^{IV} porphyrin complexes have been reported,[17] the expanded porphyrins appear more attractive as ligands[18] for the specific purpose of actinyl cation coordination, and a select few, such as alaskaphyrin (**2**), oxasapphyrin (**3**), and pentaphyrin (**4**), have been shown to complex uranyl cations effectively.[19–21] A uranyl complex of so-called "super phthalocyanine" was also reported early on.[22]



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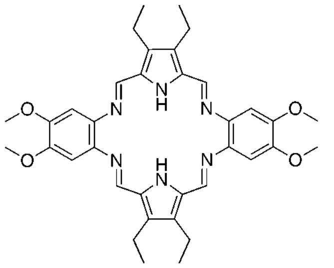

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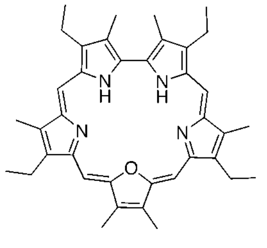

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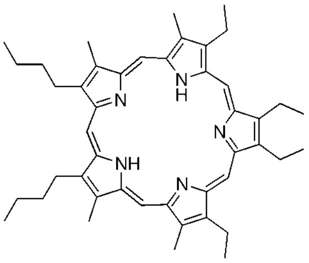

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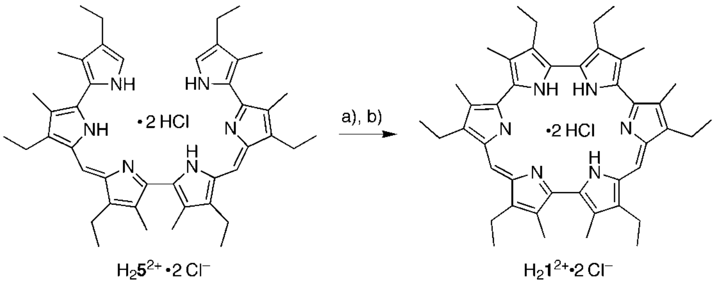
Of particular interest is the binding of pentavalent actinyl ions AnO_2^{+} (An = Np, Pu), as these ions tend to be stable under environmental conditions and are notorious for low binding constants with seemingly all available counterions, which leads to higher solubilities and thus high mobilities.[23] Herein the synthesis and characterization of the hitherto unknown expanded porphyrin, [24]hexaphyrin(1.0.1.0.0.0) (**1**) is reported, as well as the uranyl and neptunyl complexes of its oxidized, aromatic form [22]hexaphyrin(1.0.1.0.0.0).

The precursor for the synthesis of **1**, the linear hexapyrrolic precursor **5**, was obtained from the acid-catalyzed condensation of 4,4′-diethyl-5,5′-diformyl-3,3′-dimethyl-2,2′-bipyrrole with two equivalents of 4,4′-diethyl-3,3′-dimethyl-2,2′-bipyrrole, and isolated as the bis-HCl salt.[24, 25] Treatment of $H_2\mathbf{5}^{2+}\cdot 2Cl^-$ with aqueous $Na_2Cr_2O_7$ in trifluoroacetic acid (TFA)[26, 27] followed by purification by column chromatography and protonation with HCl gives rise to [24]hexaphyrin(1.0.1.0.0.0) in the form of its diprotonated salt $H_2\mathbf{1}^{2+}\cdot 2Cl^-$ in 77% yield (Scheme 1). Subsequent addition of $UO_2\cdot(OAc)_2\cdot 2H_2O$ in the presence of base was found to yield the uranyl complex **6** in 74% yield (Scheme 2). Under the latter reaction conditions, the macrocycle undergoes oxidation to produce what is formally an aromatic [22]hexaphyrin(1.0.1.0.0.0) dianionic ligand.



$H_2\mathbf{5}^{2+}\cdot 2Cl^-$

$H_2\mathbf{1}^{2+}\cdot 2Cl^-$

Scheme 1. a) $Na_2Cr_2O_7$, TFA; b) HCl.

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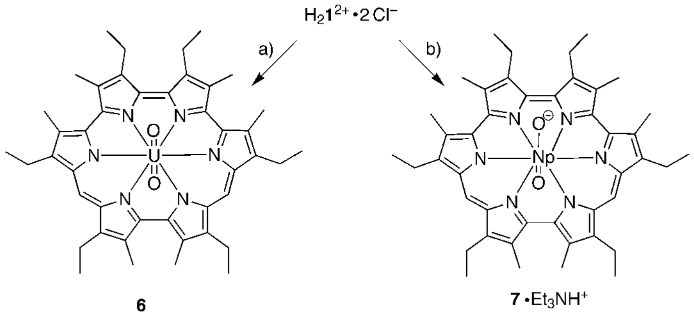

Scheme 2. a) $UO_2(OAc)_2\cdot 2\,H_2O$, Et_3N, MeOH, CH_2Cl_2; b) NpO_2Cl in 1 M HCl, Et_3N, MeOH.

Compound $H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$ possesses 24 π electrons and is antiaromatic as judged by the strong downfield shifts of its inner NH protons ($\delta = 23.7$, 23.9 and 24.2, respectively) and the upfield position of the *meso*-CH signal ($\delta = 3.4$) observed in its ^1H NMR spectrum (CD_2Cl_2). The macrocycle experiences a strong ring current effect, with the observed $\Delta\delta$ value of 20.8 being considered indicative of the antiaromaticity. Formation of the uranyl complex **6**, with its proposed 22 π-electron aromatic periphery, is accompanied by a dramatic change in the ^1H NMR spectrum (CD_2Cl_2). For example, the signal ascribed to the *meso*-C*H* protons is shifted downfield to $\delta = 10.1$. The signals of the methyl groups at the outer periphery of the macrocycle are shifted downfield from $\delta =$ 0.77, 0.82, and 1.03, in the case of $H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$ to $\delta = 3.63$, 3.71, 3.79 in the case of **6**. These findings are consistent with the ring current effects becoming "reversed" as oxidation occurs and aromaticity is induced.

Further support for the proposed aromaticity came from UV/Vis spectroscopic studies. The UV/Vis spectrum of $H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$, recorded in CH_2Cl_2 displays three Soret-like bands at 384 ($\varepsilon = 24\,000$), 497 ($\varepsilon = 59\,000$), and 597 nm ($\varepsilon = 25\,000$), with no Q-like transitions. The uranyl complex **6**, on the other hand, displays a sharp, Soret-like transition at 530 nm ($\varepsilon = 330\,000$) accompanied by two Q-like bands at 791 ($\varepsilon = 56\,000$) and 832 nm ($\varepsilon = 81\,000$). The extinction coefficient of the main transition is also increased by a factor of 5.6.

A neptunyl complex **7**, analogous to **6**, was obtained by treating **1** with a solution of neptunyl(v) chloride in the presence of base (Scheme 2). The UV/Vis spectrum exhibited by this complex also features a sharp, Soret-like band which is seen at 531 nm, but it is accompanied by a single broad Q-like transition at 830 nm, rather than bands at 791 and 832 nm as in the case of **6**.[28] Perhaps as a consequence of these small differences, solutions of **7** in CH_2Cl_2 solution are a rose color, whereas those of **6** are an intense, bright pink.

The structures assigned for **6** and **7** were confirmed by X-ray crystallographic analyses.[29] In **6** (Figure 1), the uranium center is bound to two *trans* oxo ligands and six pyrrolic nitrogen atoms from the macrocycle, with the latter donor set completely encapsulating the cation around an equatorial plane. The uranyl center is shifted towards the quaterpyrrolic subunit; as such, the coordination environment of the uranium ion is best described in terms of a distorted hexagonal bipyramid. The U–O bond length of 1.760(2) Å is typical for a UO_2^{2+} unit,[19–21] which indicates that no reduction of the metal center occurred. The average U–N bond length of 2.63(1) Å is comparable to that found in the hexacoordinate uranyl complex of alaskaphyrin (2.63(3) Å).[20] On the other hand, these bond lengths are longer than those found in pentacoordinate uranyl complexes stabilized by pentaphyrin[19] and oxosapphyrin,[21] for which average U–N bond lengths of 2.52(1) and 2.54(1) Å, respectively, were observed. The N-U-N bond angles in complex **6** range from 57.9(1) to 65.2(1)° with an average value of 61.0(2)°. The sum of the N-U-N bond angles at 366° reflects the fact that the pyrrolic nitrogen atoms deviate from planarity, presumably as a result of a need to accommodate a metal center that is slightly too small.

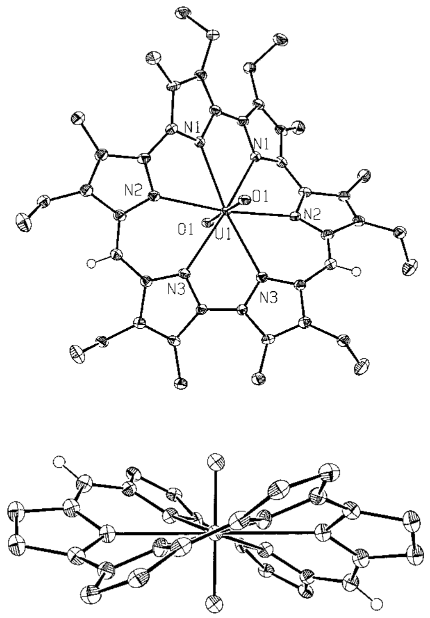

Figure 1. ORTEP diagrams showing the molecular structure of **6**. Upper structure: top view; bottom structure, side view. Most hydrogen atoms are omitted for clarity. Thermal ellipsoids are scaled to 50%.

The structure of the Np^V–hexaphyrin complex **7** (Figure 2) also reveals distortion in the ligand, albeit to a lesser extent than in the corresponding uranium system. These differences are readily apparent upon comparing the side-on views shown in Figures 1 and 2. Presumably, the reduced distortion in the case of **7** is the result of a better intrinsic fit between the hexaaza ligand core and the larger NpO_2^+ ion. Nonetheless, as in the uranium complex, the neptunium center is contained within a roughly hexagonal bipyramidal structure. The metal center is once again displaced toward the quaterpyrrolic subunit. In this structure the nitrogen atoms are close to planar (N-Np-N = 362°); however, the outer ring of the ligand is forced to twist slightly. The oxo ligands give rise to two unique Np–O bond lengths: Np–O1 is 1.762(1) Å and Np–O2 is 1.826(1) Å. These distances are short for the NpO_2^+ ion, for which bond lengths of approximately 1.85 Å are typically seen in simple metal salts.[30, 31] On the other hand, it is nearly identical to that seen in the Np^V–crown ether complex, $[NpO_2([18]crown\text{-}6)]^+$, for which a Np–O bond length of 1.800(5) Å was observed.[15]

The charge balance of the lattice system, which contains a triethylammonium cation, supports the proposal that the

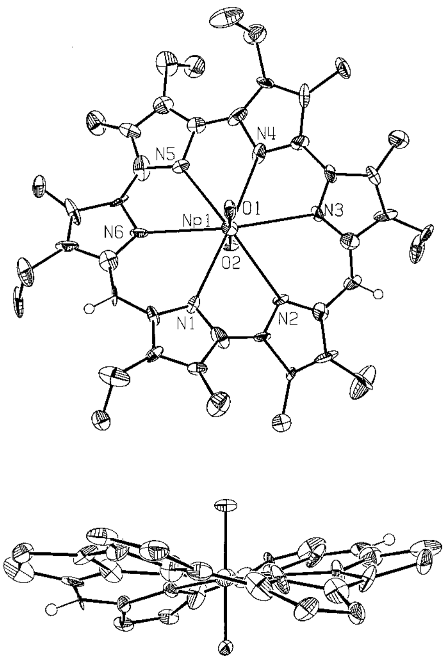

Figure 2. ORTEP diagrams showing the molecular structure of **7**. Upper structure: top view; bottom structure, side view. Most hydrogen atoms are omitted for clarity. Thermal ellipsoids are scaled to 50%.

neptunium center remains pentavalent in **7**. Further, the presence of this cation could explain the distinct difference between the two Np–O bond lengths observed in **7**. Specifically, a short N ⋯ O contact (2.70(2) Å), typical of hydrogen bonding,[32] is seen between the nitrogen atom of the triethylammonium cation and O2. The Np–N bond lengths range from 2.649(1) to 2.880(1) Å, with an average value of 2.77(2) Å. This value is approximately 0.14 Å longer than that of its uranyl analogue **6**. The presence of these longer bonds, as well as the four shorter Np–N bonds with an average length of 2.70(2) Å, is reasonable given the larger size of the neptunyl cation. It is also consistent with what is seen in one of the few structurally characterized macrocyclic neptunyl complexes, namely that of $[NpO_2([18]crown\text{-}6)]^+$ (see above). In this case, the average neptunium(V)–crown ether Np–O bond length (2.59(1) Å),[15] was found to be longer than the comparable U–O (2.55 Å) bond found in the corresponding uranyl–crown ether complex.[33]

In conclusion, a facile synthesis of a new hexapyrrolic expanded porphyrin, namely [24]hexaphyrin(1.0.1.0.0.0) (**1**) has been presented. This system, an isomer of amethyrin,[34] is the smallest macrocycle known that contains a quaterpyrrole fragment. In its oxidized, aromatic form it is capable of complexing actinide ions, specifically uranyl (UO_2^{2+}) and neptunyl (NpO_2^+), and it represents the first crystallographically characterized neptunium complex stabilized by a macrocycle with an all-aza donor set. The relatively high stability seen for both **6** and **7**, with little evidence of decomposition being seen in CH_2Cl_2 over the course of several weeks, as judged by UV/Vis spectroscopy, leads to the suggestion that these kinds of systems could see application in direct, coordination-based remediation applications. Tests of this possibility are currently in progress.

Experimental Section

$H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$: The linear hexapyrrole $H_2\mathbf{5}^{2+}\cdot 2\,Cl^-$ (59.5 mg, 0.08 mmol) was dissolved in trifluoroacetic acid (20 mL). Immediately, a solution of $Na_2Cr_2O_7\cdot 2\,H_2O$ (24.7 mg, 0.083 mmol) in water (1 mL) was added and the resulting mixture was stirred overnight. The solution was added to a mixture of $CHCl_3$ (50 mL) and water (100 mL). After phase separation, the aqueous phase was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic phases were then washed twice with a saturated aqueous solution of sodium bicarbonate. After evaporation of the solvent, the remaining residue was subjected to column chromatography, using 230–400 mesh ASTM silica gel as the stationary phase and a mixture of dichloromethane/methanol/triethylamine (99/0.5/0.5; v/v/v) as the eluent. The dark yellow band was collected and the solvent removed in vacuo. The remaining residue was dissolved in $CHCl_3$ (50 mL) and the resulting solution washed with 1 M HCl (3 × 20 mL). After evaporation to dryness and recrystallization from dichloromethane/hexanes, $H_2\mathbf{2}^{2+}\cdot 2\,Cl^-$ (45.7 mg, 77%) was obtained in the form of a dark microcrystalline solid. ^1H NMR (500 MHz, CD_2Cl_2): $\delta = 0.48$ (t, $J_{H,H} = 7.5$ Hz, 6H, CH_2CH_3), 0.56–0.61 (m, 12H, CH_2CH_3), 0.77 (s, 6H, CH_3), 0.82 (s, 6H, CH_3), 1.03 (s, 6H, CH_3), 1.30 (q, $J_{H,H} = 7.5$ Hz, 4H, CH_2CH_3), 1.35–1.41 (m, 8H, CH_2CH_3), 3.39 (s, 2H, *meso*-H), 23.66 (s, 2H, NH), 23.86 (s, 2H, NH), 24.19 (s, 2H, NH); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 9.48$, 9.57, 10.58, 13.09, 13.82, 14.13, 16.47, 17.11, 17.19, 119.59, 123.94, 126.22, 128.98, 132.04, 132.26, 133.24, 134.91, 137.50, 140.49, 148.90, 152.32, 157.75; HR-MS (CI): *m/z*: found 667.4495 $[M^+ - H^+, -2\,Cl^-]$, calcd for $C_{44}H_{55}N_6$ 667.4488, found 704.4323 $[M^+ - Cl^-]$, calcd for $C_{44}H_{57}N_6Cl$ 704.4333; UV/Vis (CH_2Cl_2): λ_{max} [nm] (ε [$dm^3 mol^{-1} cm^{-1}$]) 384 (24000), 497 (59000), 597 (25000).

6: $H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$ (35.6 mg, 0.048 mmol) was dissolved in CH_2Cl_2 and methanol (15 mL each). Triethylamine (1 mL) was then added, an addition that caused the color to change from purple to dark yellow. $UO_2(OAc)_2\cdot 2\,H_2O$ (53 mg, 0.15 mmol) was then added and the resulting mixture was stirred overnight, open to air. The resulting deep red solution was evaporated to dryness on the rotary evaporator. The residue was then subjected to column chromatographic purification, using neutral alumina as the stationary phase and a mixture of dichloromethane/hexanes (2/3, v/v) as the eluent. The red band was collected and the solvent removed in vacuo. After recrystallization from CH_2Cl_2/MeOH, **6** (33 mg, 74% yield) was obtained as a dark microcrystalline solid with a metallic luster. ^1H NMR (500 MHz, CD_2Cl_2): $\delta = 1.92$ (t, $J_{H,H} = 7.5$ Hz, 6H, CH_2CH_3), 1.98 (t, $J_{H,H} = 7.5$ Hz, 6H, CH_2CH_3), 2.00 (t, $J_{H,H} = 7.5$ Hz, 6H, CH_2CH_3), 3.63 (s, 6H, CH_3), 3.71 (s, 6H, CH_3), 3.79 (s, 6H, CH_3), 3.91 (q, $J_{H,H} = 7.5$ Hz, 4H, CH_2CH_3), 4.15 (q, $J_{H,H} = 7.5$ Hz, 4H, CH_2CH_3), 4.23 (q, $J_{H,H} = 7.5$ Hz, 4H, CH_2CH_3), 10.10 (s, 2H, *meso*-H); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 15.52$, 16.17, 16.87, 17.34, 17.64, 18.29, 20.46, 20.47, 21.73, 106.96, 134.92, 135.68, 138.96, 144.82, 145.57, 146.80, 147.87, 148.27, 151.20, 151.76, 152.11, 152.68; HR-MS (CI): *m/z*: found 933.4585 (M^+), calcd for $C_{44}H_{51}N_6O_2{}^{238}U$ 933.4581; UV/Vis (CH_2Cl_2): λ_{max} [nm] (ε [$dm^3 mol^{-1} cm^{-1}$]) 530 (330000), 791 (56000), 832 (81000).

7: $H_2\mathbf{1}^{2+}\cdot 2\,Cl^-$ (5.0 mg, 0.007 mmol) was dissolved in MeOH (5 mL) and a 0.3 M solution of neptunyl(V) chloride in 1 M HCl was added (160 mL, 0.036 mmol). Triethylamine (4 drops, approx. 80 μL) was then added. The excess solvent was evaporated to dryness and the remaining reddish solid was recrystallized from dichloromethane/hexane. The resulting dichromic (red/green) crystals were analyzed by single-crystal X-ray diffraction methods. After isolation of the complex by column chromatography using dichloromethane/MeOH as the eluent and activated alumina as the solid support, the resulting product (0.9 mg, 0.001 mmol) was dissolved in CH_2Cl_2 (8 mL). Diluting this solution 3:7 in CH_2Cl_2, generated the solution used for the UV/Vis spectroscopic studies. UV/Vis (CH_2Cl_2): λ_{max} [nm] 531, 830.[28]

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[28] While experimental difficulties limit the accuracy of these measurements, extinction coefficients [$dm^3 mol^{-1} cm^{-1}$] of $\varepsilon = 120000$ for the main transition at 531 nm and $\varepsilon = 40000$ for the Q-like transition at 830 nm were recorded.

[29] a) Crystallographic parameters for **6** (dark prisms grown from vapor diffusion of CH_2Cl_2 and hexanes): orthorhombic, space group *Pbcn*, $a = 9.0295(2)$, $b = 17.1213(4)$, $c = 24.7737(6)$ Å, $Z = 4$, $R1 = 0.0365$, $wR2 = 0.0612$, $V = 3829.9$ Å^3. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at -150 °C using a Oxford Cryostream low temperature device. The structure was refined by full-matrix least-squares on F^2 to 0.0612, with $R(F)$ equal to 0.0242 and a GOF = 1.009. The complex lies on a crystallographic twofold rotation axis at 0,*y*,¼. The twofold axis passes through the uranium atom and bisects the bipyrrole and the tetrapyrrole moieties. b) The crystallographic parameters for [Et_3NH][**7**] (red-green dichromic rods, of dimension $0.08 \times 0.08 \times 0.12$ mm^3, were grown from vapor diffusion of CH_2Cl_2 and hexanes): monoclinic, space group $P2_1/c$, $a = 15.099(2)$, $b = 22.742(3)$, $c = 14.353(1)$ Å, $\beta = 110.857(4)°$, $V = 4606(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.501$ mg m^{-3}. The data were collected at 203 K on a Bruker P4/CCD diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). A total of 18883 (5694 independent and $2\theta_{max} = 45°$) reflections were collected using a combination of ϕ and ϑ scans. The structure was solved using direct methods, and refined against F^2 to convergence, with $R(I > 2\sigma) = 0.0925$ and $wR(I > 2\sigma) = 0.1371$ for 5694 reflections and 550 L.S. parameters. The final residual electron density was 0.89 e Å^{-3}. Hydrogen atom positions were idealized and refined using a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149932 (**6**) and -150148 ([Et_3NH][**7**]). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Narrow Molecular Weight Distribution Precursors for Polymer – Drug Conjugates[**]

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Polymer – drug conjugates derived from copolymers of *N*-(2-hydroxypropyl)-methacrylamide (HPMA) can be prepared from a copolymer precursor such as **3** (Scheme 1).[1] This methodology has been used for the development of conjugate **4** which is currently undergoing Phase II trials in the UK for the treatment of cancer.[2]

To exploit more widely the biological advantages of large molecule therapeutics[1, 3a] and to examine more thoroughly how structure, molecular weight,[4] and solution properties correlate with biological profile[3] it is essential to develop preclinical conjugates that have 1) narrow molecular weight

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