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A Non-Ionic Water-Soluble Pentaphyrin Derivative. Synthesis and Cytotoxicity

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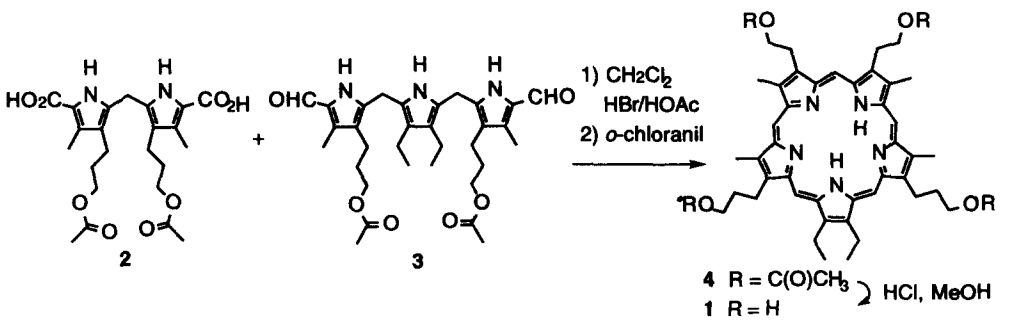
Abstract—The synthesis of the water soluble tetrahydroxypentaphyrin derivative, **1**, is described. This species, which forms complexes with both small neutral molecules and uranyl cation, has been studied as a possible cytotoxic agent. Cytotoxic studies performed with the human T lymphoma cell line (JURKAT) revealed that pentaphyrin **1** exhibits toxicity at μM concentrations comparable with other water soluble, porphyrin-type systems such as the pyridinium metalloporphyrins.

Introduction

Large polypyrrole macrocycles, or 'expanded porphyrins',[1] are of interest in the broad fields of lanthanide and actinide complexation,[1-6] anion binding,[1,7] and optics.[1,8-11] This, in turn, has made this class of molecules attractive in terms of various biomedical applications that range from magnetic resonance imaging[3] and antisense-targeted RNA hydrolysis[12] on the one hand to X-ray radiation sensitization[13] and visible light-based photodynamic therapy[14] on the other. Unfortunately, however, the very nature of these bio-targeted application opportunities requires the availability of water solubilized expanded porphyrin systems that are either across-the-board non-toxic or, better yet, suitably selective in terms of their inherent cell-based cytotoxicity. As a result, only a few expanded porphyrins have actually been studied *in vivo*.[3,10,11,15,16] We are thus currently interested in preparing new water solubilized analogues of a range of hitherto reported expanded porphyrins. As part of this effort, we wish to report here the synthesis, characterization, and cytotoxic properties of the water soluble pentaphyrin analogue **1** (Scheme 1).

Results and Discussion

Pentaphyrin, a 22 π-electron aromatic macrocycle, was first reported by Gossauer and Rexhausen.[17] It was subsequently reprepared by us.[5] In both cases, however, the syntheses did not lead to water soluble systems. Recently, however, we have found that the introduction of multiple hydroxyl groups about the periphery of an expanded porphyrin will render it water soluble.[3,18] Thus, our strategy for making pentaphyrin water soluble (Scheme 1) involved the design of a synthesis that would allow for the "attachment" of four hydroxyl groups onto the basic pentaphyrin skeleton. Specifically, it centered around the condensation of the bis-acid dipyrromethane **2**[3b] with the diformyl tripyrrane **3**.[19] This gave the tetraacetate pentaphyrin **4** that, subsequent to the hydrolytic removal of the acetate blocking groups, gave the desired tetrahydroxy pentaphyrin **1**[20] in 56% overall yield (based on **2** and **3**). Although variations were made in the choice of solvents and acid catalyst used to facilitate the pentaphyrin-forming macrocyclization reaction, the modest nature of this yield could not be improved. Further, attempts at effecting the macrocyclization using



Scheme 1. Synthetic route to tetrahydroxypentaphyrin **1**.

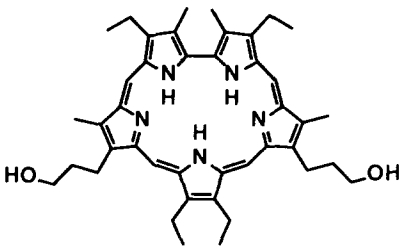
starting materials bearing unprotected hydroxy groups on the dipyrromethane and/or tripyrrane fragments (a direct preparation of **1**) led not to an augmentation, but to a reduction, in overall yield. Thus, the synthesis of **1** has to be considered as being near optimized at present.

New compounds **1** and **4** were characterized by a combination of elemental analysis, FAB mass spectrometry, and NMR, infrared and UV-visible spectroscopy. Taken together, these analyses served to confirm the proposed structures. Interestingly, the mass spectrometric studies also revealed that both the tetraacetate- and tetrahydroxypentaphyrins **1** and **4** form complexes with small neutral molecules: depending on sample preparation, peaks in the mass spectrograms corresponding to both the water and methanol adducts could be seen. These results, which were confirmed by preparation of the corresponding deuterated chelates,[21] are not surprising in view of results obtained with other expanded porphyrins.[22]

The decaalkylpentaphyrin reported previously is known to form a structurally characterized complex with uranyl cation.[5] The formation of such a well-defined complex is, however, quite unusual in the annals of the expanded porphyrin literature.[23] Thus, in an attempt to characterize our new pentaphyrins more completely, an effort was made to make such a uranyl complex using the water soluble species **1**. Fortunately, this effort proved successful. Indeed, as illustrated in Scheme 2, metallation of the water soluble pentaphyrin under standard conditions gives the corresponding *charge neutral* uranyl adduct **5** in 38% yield. Interestingly, this *organic soluble* complex dissolves but poorly in water. It thus differs dramatically from the starting material **1**. Still, its very formation provides an important proof that compound **1** is in fact a *bona fide* pentaphyrin.

The cytotoxicity (Figures 1–3) of the new water-soluble pentaphyrin **1** was evaluated using a cultured tumor cell line (human T lymphoma cells JURKAT E6-1). In these studies, the number of surviving cells in the culture fluid, measured as a function of time (at a given concentration of **1**) or as a function of the concentration ratios of **1** (at a given time), was evaluated. In general, it was found that the greater the concentration of pentaphyrin **1** in the culture fluid, the greater was the observed toxic effect. Importantly, however, compound **1** was still found to be cytotoxic even at low concentrations.

Table 1 provides a further quantitative summary of the cytotoxicity of **1**. It gives the value of ID_{50} (μM), the dose at which a 50% reduction in cancerous cells after 48 h was achieved. This table also provides an ID_{50} comparison between pentaphyrin **1**, 8,17-bis(hydroxypropyl)-3,12,13,22-tetraethyl-2,7,18,23-tetramethylsapphyrin (**6**)[18] and two kinds of commonly studied water soluble porphyrin species, namely pyridinium-substituted metalloporphyrin complexes and hematoporphyrin derivatives. Pentaphyrin **1** compares favorably in terms of cytotoxicity with other compounds of the same general macrocyclic class. However, unlike these other materials, pentaphyrin **1** is expected to display a relatively short half-life *in vivo*. In fact, as shown in Table 2, approximately 50% of compound **1** is degraded after only 2–3 days under physiological conditions.



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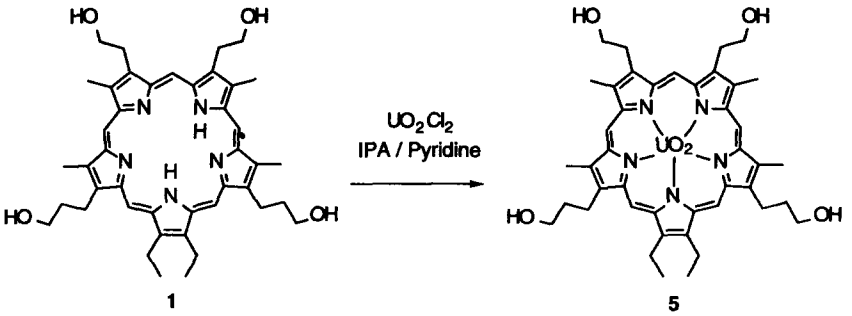
Conclusion

The combination of favorable cytotoxicity and relatively rapid decomposition makes compound **1** and its congeners attractive targets for further study: they should be free from many of the problems associated with compounds which are very stable or slowly metabolized, such as hematoporphyrin derivatives. These latter have, for instance, seen their clinical use restricted because of their long in-body retention times and the unacceptably high skin-based photosensitivity that necessarily results.[14a] The pentaphyrins, on the other hand, because they are rapidly degraded (and because they absorb in the optimal ≥ 700 nm spectral region), could find important application as photosensitizers for photodynamic therapy.[14] This rapid degradation, coupled with the high inherent cytotoxicity might also make them attractive targets for use in more classic chemotherapy-based tumor treatment protocols. Current work is directed towards an exploration of these exciting possibilities.



1 **5**

Scheme 2. Metallation of tetrahydroxypentaphyrin **1** with the uranyl cation.

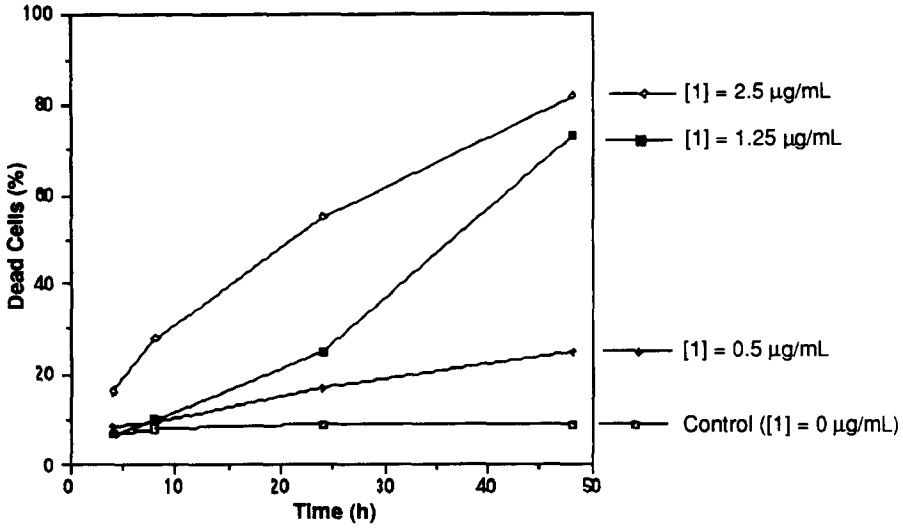


Figure 1. Cytotoxicity effect of tetrahydroxypentaphyrin 1 (1 mg/1 mL stock solution) as determined using human JURKAT E6-1 cells.

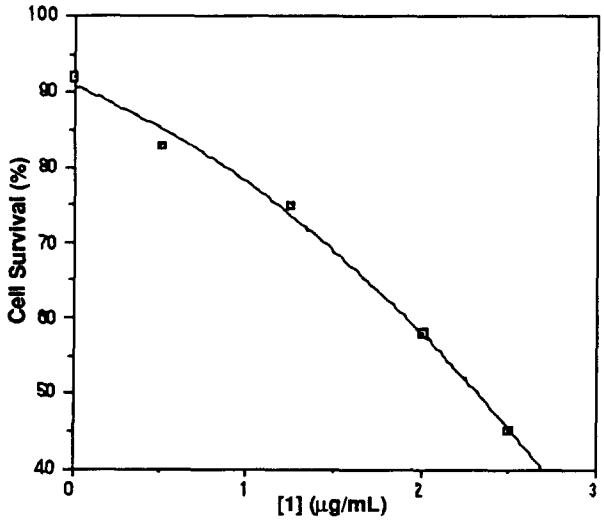


Figure 2. Concentration dependence of the cytotoxic effect of tetrahydroxypentaphyrin 1 as determined using JURKAT E6-1 cells 24 h after administration.

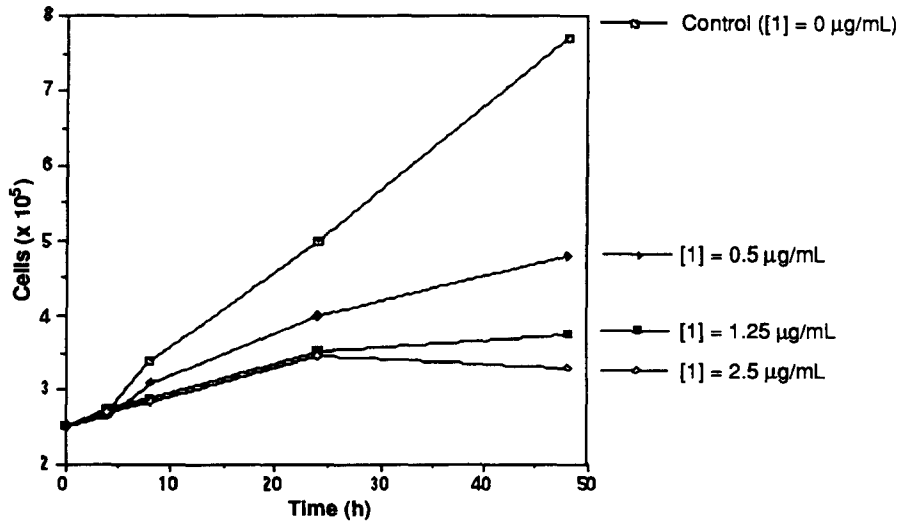


Figure 3. Growth inhibition curves for human JURKAT E6-1 cells exposed to pentaphyrin 1 at concentrations of 0 to 2.5 μg mL^{-1}.

Table 1. Comparison of tetrahydroxypentaphyrin **1** cytotoxicity with that of other aromatic macrocycles

Compound	ID_{50}(μM)	Reference	
1	1.37	this work	a
6	0.45	this work	a
Hematoporphyrin derivative	25	26	b,c
Pyridinium metalloporphyrins	0.6–2.4	27	c

[a]Tested on JURKAT E6-1 cells *in vitro*.
[b]Estimated value in $\mu g\,mL^{-1}$.
[c]Tested on leukemia L1210 cells *in vitro*.

Table 2. Absorption values of tetrahydroxypentaphyrin **1** in aqueous buffer solution (both exposed to, and shielded from, light) recorded at the Soret band maximum as a function of time

	Phosphate[a] (pH 4.0)		Bistris[b] (pH 7.0)		Trizma[b] (pH 7.4)	
Time (days)	light	dark	light	dark	light	dark
0	1.99	2.00	2.04	2.04	1.96	2.01
1	1.53	1.97	1.27	1.44	1.77	1.99
2	1.38	1.91	1.08	1.14	1.51	1.81
6	0.87	1.75	0.63	0.69	1.01	1.45
11	0.42	1.56	0.38	0.48	0.39	1.21

[a]Absorbance measured at 455 nm.
[b]Absorbance measured at 420 nm.

Experimental

12,13-Diethyl-2,8,17,23-tetraacetoxypropyl-3,7,18,22-tetramethylpentaphyrin (4)

Dipyrromethane diacid **2**[3b] (46.2 mg, 0.10 mmol) was added to dry dichloromethane (300 mL), previously degassed with argon for 30 min and then stirred under argon for an additional 30 min. Next, tripyrrane dialdehyde **3**[19] (56.6 mg, 0.10 mmol) was added with the reaction being protected from light. Then, HBr/HOAc (0.5 mL) was added as a catalyst and the reaction stirred under argon for an additional 2.5 h. Following this, *o*-chloranil (200 mg) was added and the reaction stirred under argon for a further 36 h. The solvent was then removed *in vacuo* and the residue subject to chromatographic purification on first neutral alumina (using 10:1 dichloromethane: methanol as eluent) and then silica gel (again using 10:1 dichloromethane:methanol as the eluent). This provided 65 mg (61% yield) of product **4** in the form of its dihydrobromide salt. ^{1}H NMR (300 MHz, $CDCl_3$–10% TFA): δ –5.51 (*br s*, 5H, NH), 2.18 (*s*, 12H, acetyl), 2.30 (*t*, 6H, ethyl), 3.07 (*m*, 8H, propyl), 4.51 (*s*, 12H, methyl), 4.74 (*m*, 4H, ethyl), 4.78 (*t*, 8H, propyl), 5.04 (*t*, 8H, propyl), 12.58 (*s*, 1H, *meso*), 12.63 (*s*, 2H, *meso*), 12.71 (*s*, 2H, *meso*); ^{13}C NMR (75 MHz, $CDCl_3$–10% TFA): δ 11.1, 11.4, 11.8, 17.9, 19.3, 21.00, 22.7, 30.5, 55.7, 63.6, 63.8, 90.2, 99.9, 101.2, 110.8, 112.3, 122.4, 127.2, 130.0, 139.6, 141.5, 142.4, 142.7, 142.8, 143.0, 143.5, 170.9, 171.0; UV-vis (CH_2Cl_2–1% TFA): λ_{max} (ε) 378.0 (16 680), 461.0 (251 450), 646.0 (18 930), 704.0 (10 430) nm; MS (FAB): m/z 900; HRMS (FAB): m/z calcd for $C_{53}H_{66}N_5O_8$: 900.49114, found 900.49332; anal. calcd for $C_{53}H_{65}N_5O_8$•2HBr•H_2O: C, 58.94; H, 6.44; N, 6.48; Br, 14.80; found: C, 58.62; H, 6.28; N, 6.32; Br, 14.52.

12,13-Diethyl-2,8,17,23-tetrahydroxypropyl-3,7,18,22-tetramethylpentaphyrin (1)

12,13-Diethyl-2,8,17,23-tetraacetoxypropyl-3,7,18,22-tetramethylpentaphyrin **4** (30 mg) was dissolved in methanol (30 mL) containing concentrated hydrochloric acid (0.3 mL) before being stirred for 30 h at room temperature. Subsequent to this time, the solvent was removed *in vacuo* and the residue purified chromatographically. This was done using first neutral alumina and then silica gel as the solid supports and increasing gradients of methanol in dichloromethane (5 to 10% and 5 to 25%, respectively) as the eluents. This afforded product **1** as its tris-hydrochloride salt (21 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$–30% CD_3OD): δ –5.06 (*br s*, 5H, NH), 2.30 (*t*, 6H, ethyl), 2.88 (*m*, 8H, propyl), 4.07 (*s*, 3H, methyl), 4.18 (*s*, 3H, methyl), 4.42 (*t*, 8H, propyl), 4.99 (*q*, 4H, ethyl), 5.06 (*t*, 8H, propyl), 12.61 (*s*, 2H, *meso*), 12.83 (*s*, 2H, *meso*), 13.00 (*s*, 1H, *meso*); ^{13}C NMR (75 MHz, $CDCl_3$–30% CD_3OD): δ 11.1, 11.3, 18.0, 19.6, 19.8, 20.7, 21.0, 22.5, 22.8, 22.9, 34.9, 34.9, 35.5, 37.3, 37.4, 61.5, 61.9, 90.1, 124.7, 133.7, 139.7, 139.9, 140.0, 140.1, 140.2, 140.6, 142.6, 144.2, 144.9, 145.0, 145.3, 147.9, 148.2, 149.9; UV-vis (CH_2Cl_2–1% TFA): λ_{max} (ε) 461.0 (212 200), 646.0 (11 230), 704.0 (5 800), 803.0 (2 190) nm; UV-vis (MeOH): λ_{max} (ε) 369.0 (17 850), 472.5 (53 460), 625.5 (4 890), 677.5 (5 030), 794.0 (4 710) nm; UV-vis (MeOH–1% TFA): λ_{max} (ε) 370.0 (21 100), 476.5 (92 690), 781.0 (11 410) nm; UV-vis (H_2O, pH 7): λ_{max} (ε) 370.0 (23 800), 416.0 (38 780), 636.0 (4 060), 682.0 (4 280) nm; UV-vis (H_2O–HCl, pH 1): λ_{max} 429.5, 448.0, 643.5, 703.5 nm; MS (FAB): m/z 732; HRMS (FAB): m/z calcd for $C_{45}H_{57}N_5O_4$: 731.441056, found 731.44097; anal. calcd for $C_{45}H_{57}N_5O_4$•3HCl•H_2O: C, 62.89; H, 7.27; N, 8.15; Cl, 12.38; found: C, 62.61; H, 7.17; N, 8.09; Cl, 12.58.

Uranyl 12,13-diethyl-2,8,17,23-tetrahydroxypropyl-3,7,18,22-tetramethylpentaphyrin (5)

Tetrahydroxypentaphyrin trihydrochloride **1** (5.8 mg, 4.1 μmol) and uranyl dichloride trihydrate (4.1 mg, 10.3 μmol) were dissolved into a 1:1 mixture of 2-propanol (6 mL) and pyridine (6 mL). The solution was then brought to reflux and held there for 2 h under nitrogen. After allowing the mixture to cool to room temperature, the solvents were removed *in vacuo* and the reddish residue subjected to chromatographic purification on silica gel (chloroform:methanol 9:1, eluent). This provided product **5** (2.6 mg, 37.7% yield) as a green solid that is orange–red in organic solution. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.79 (*t*, 6H, ethyl), 2.35 (*t*, 12H, propyl), 3.42 (*s*, 6H, methyl), 3.48 (*s*, 6H, methyl), 3.73 (*q*, 4H, ethyl), 3.80 (*m*, 8H, propyl), 3.97 (*t*, 8H, propyl), 9.57 (*s*, 4H, *meso*), 9.64 (*s*, 1H, *meso*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.1, 12.3, 18.0, 20.2, 23.0, 23.0, 35.1, 35.4, 62.1, 98.3, 142.1, 142.3, 143.4, 143.9, 144.3, 144.5, 144.9, 146 (2), 146.3, 148.2; IR (neat) 3332.5, 2928.2, 2862.4, 2354.7, 2326.5, 1237.2, 1058.5, 917.5 cm^{-1}; UV-vis ($CHCl_3$): λ_{max} (ε) 382.0 (23 600), 507.5 (91 500), 687.0 (7 300), 747.0 (5 300) nm; MS (FAB): m/z 1000; HRMS (FAB): m/z calcd for $C_{45}H_{56}N_5O_6U$: 1000.473846, found 1000.474472.

Cytotoxicity Assays

The human acute T cell leukemia line (E6-1) was maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum and penicillin–streptomycin at 37 °C in a humidified CO_2 incubator. For normalization of all numbers, the exponentially growing cells were divided into equal fractions (2.5 and 5 × 10^5 cells mL^{-1}) prior to experimental manipulation. Cells were exposed to various concentrations of **1** at 37 °C for 4, 8, 24 and 48 h. At designated time points, the survival of untreated and treated cells was determined by counting viable cells by the Trypan (0.2%) blue dye exclusion method. During extended exposure to **1** (48 h), approximately 25% of the cells that were still alive were distinctly smaller and showed visible signs of chromatin condensation, a characteristic that has previously been described as a phenotypic marker for apoptosis.[24]

The effect of the added macrocycle(s) was expressed as percentage survival compared to control cells and the ID_{50} determined graphically as described previously in the literature.[25] Experiments were performed three times. The data summarized in Graphs 1 to 3 thus represent average values with a variability of less than ten per cent.

Acknowledgments

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20. The systematic name for pentaphyrin **1** is: 12,13-diethyl-2,8,17,23-tetrahydroxypropyl-3,7,18,22-tetramethyl-26,27,28,-29,30-pentaazahexacyclo[21.2.1.1^{6,9}.1^{11,14}.1^{16,19}.1^{21,24}]triaconta-1(26), 2,4,6(27),7,9,11,13,15,17,19(29),20,22,24-tetradecaene.

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