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Porphyrinyl-uridines as the First Water Soluble Porphyrinyl-nucleosides

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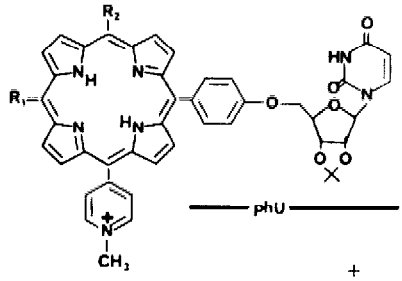
Abstract: *Meso-derivatives of porphine containing N-methyl-4-pyridinium and 5'-0-p-phenylene-2',3'-0-protected-uridine substituents were obtained as the first representatives of water soluble porphyrinyl-nucleosides.*

We have previously announced the first representatives of porphyrinyl-nucleosides.[1] These compounds were, however, water-insoluble which might impair their biochemical importance and the potential for therapeutical applications both as the free bases and the metalloporphyrinyl derivatives.

Now we describe the synthesis of a series of water soluble porphyrinyl-nucleosides, **1**, **2** and **3**, in which one, two or three porphine meso-positions are occupied by the p-phenylene-5'-0-uridine units (2',3'-0-isopropylidene protected) while the remaining positions contain the N-methyl-4-pyridinium substituents. In addition, the respective compounds metallated with Co(II) at the porphine center were obtained as the representatives of a variety of possible water soluble metalloporphyrinyl-nucleosides.



$(pyr)_{4-n}POR(C_6H_4\text{-}OCH_3)_n$ ⟶ $(pyr)_{4-n}POR(C_6H_4OH)_n$ ⟶
1a, 2a, 3a **1b, 2b, 3b**

$(pyr)_{4-n}POR(phU)_n$ ⟶ **1, 2, 3**; n = 1,2,3
1c, 2c, 3c

+ +

1 $R_1 = R_2 = H_3C\text{-}NC_5H_4$-; **2** $R_1 = H_3C\text{-}NC_5H_4$-, R_2 = phU; **3** $R_1 = R_2$ = phU

Condensation of p-anisaldehyde, 4-pyridinecarboxaldehyde and pyrrole in propionic acid[2,3] gave besides other porphyrins and polymers the meso-(4-pyridyl)$_{4-n}$-(p-methoxyphenyl)$_n$porphyrins, n = 1,2,3, **1a**, **2a**, and **3a**, separated by column chromatography on silica gel using MeOH/$CHCl_3$ 1:50 as an eluent. Demethylation with pyridine hydrochloride at 220°C for 2.5 hrs gave the respective p-hydroxyphenyl derivatives **1b**, **2b** and **3b**. The condensation of the latter with the 5'-0-tosylate of 2',3'-0-isopropylidene uridine was carried in the DMF solution containing cesium carbonate and sodium hydride at 65°C for 24 to 36 hrs. The ratio of porphyrin to the tosyluridine was 1:2 per each OH group in the porphyrin. The ratios of porphyrins **1b**, **2b** and **3b** to Cs_2CO_3 and NaH were 1:1 and 1:6; 1:2 and 1:12; and 1:4 and 1:18, respectively. Chromatography on silica gel column with $CHCl_3$/MeOH 30:1 gave as the first fraction the respective meso-(4-pyridyl)$_{4-n}$(5'-0-p-phenylene-2',3'-0-isopropylidene-uridine)$_n$-porphyrin, n = 1,2,3, **1c**, **2c** or **3c**,[4] with the yield 15-17%. N-methylation by refluxing at 70°C for 12 hrs with the mixture of CH_3I and CH_3NO_2 4:3 v/v gave the meso-tri(N-methyl-4-pyridinium) (5'-0-p-phenylene-2',3'-0-isopropylidene-uridine)porphyrin, **1**, and the respective di- and tri-uridine derivatives **2** and **3** with ca. 90% yield.[5] The Co(II) derivatives were obtained by refluxing the water

solution of free base porphyrin with twofold excess of $CoCl_2.2H_20$ for 12 hrs, followed by precipitation with a saturated solution of sodium perchlorate, yield of metallation 90%.

The solubility in water and in 10 mM tris-HCl, pH 7.2 buffer,[6] the values for the letter given in brackets, was as follows: **1**, $4.0x10^{-4}$ ($5.0x10^{-3}$); **2**, $3.3x10^{-4}$ ($4.0x10^{-3}$); **3**, $1.0x10^{-4}$; **1-Co(II)**, $3.0x10^{-4}$ ($3.3x10^{-3}$); **2-Co(II)**, $2.5x10^{-4}$ ($4.2x10^{-3}$) mg/mL.[7]

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4. **1c**: FAB-MS $(M+1)^+$ 901; 1H-NMR ($CDCl_3$) 9.04(s,4Hpy), 8.83(s,8Hβ), 8.14(m,8Hpy), 8.06(m,2Har), 7.60(d,8.1Hz,1H,H-6), 7.27(m,2Har), 5.93(s,1H,H-1'), 5.79(m,1H,H-5), 5.14(m,2H,H-2',3'), 4.75(m,1H,H-4'), 4.50(m,2H,H-5'), 1.68(s,3Hip), 1.45(s,3Hip), -2.91(s,2Hpor); UV-vis($CHCl_3$) 255, 307, 418(S), 514, 548, 589, 645, (DMSO) 262, 300sh, 360sh, 426(S), 519, 557, 649. **2c**: FAB-MS$(M+1)^+$ 1182; 1H-NMR($CDCl_3$) 9.01 (d,6Hz,4Hpy), 8.80(m,8Hβ), 8.14(m,4Hpy), 8.05(m,4Har), 7.62(d,8Hz,2H,H-6), 7.34-7.19(m,4Har), 5.89 (d,1.5Hz,2H,H-1'), 5.79(m,2H,H-5), 5.55(m,2H,H-2'), 5.12-5.04(m,2H,H-3'), 4.70(b.s,2H,H-4'), 4.43(m,4H,H-5'), 1.66(s,6Hip), 1.43(s,6Hip), -2.87(s,2Hpor); UV-vis ($CHCl_3$) 257, 306, 420(S), 516, 552, 590, 646. **3c**: FAB-MS$(M+1)^+$ 1463; H-NMR(DMSO) 9.01(d,4Hz,2Hpy), 8.87(m,8Hβ), 8.15(m,2Hpy), 8.05(m,4Har), 7.59(d,8Hz,3H,H-6), 7.53-7.19(m,8Har), 5.77(d,8.1Hz,3H,H-1'), 5.51(d,2.8Hz,3H, H-5), 5.11-4.88(c,6H,H-2',3'), 4.30(m,3H,H-4'), 3.85(m,6H,H-5'), 1.67(s,9Hip), 1.44(s,9Hip), -2.82(s,2Hpor); UV-vis ($CHCl_3$) 257, 306sh, 420(S), 516, 552, 591, 648. FAB-MS of **1c**, **2c** and **3c** show step-by-step detachment of all CH_2(5')-uridine units.
5. **1**: 1H-NMR(DMSO) 9.48(d,6.4Hz,6Hpy), 9.16(s,5Hpy), 9.05(s,1Hpy), 8.99(m,8Hβ), 8.14 and 7.44(dd,8Hz,4Har), 7.88(d,8Hz,1H,H-6), 5.96(s,1H,H-1'), 5.70(d,8Hz,1H,H-5), 5.21(d,7.8Hz,1H, H-3'), 5.09(m,1H,H-2'), 4.72(s,9H,N-Me), 4.50-4.40(m) and 3.87(m) (3H,H-4',H-5'), 1.61(s,3Hip), 1.41(s,3Hip), -3.02(s,2Hpor); UV-vis (H_2O) 221, 259, 425(S), 522, 559, 585, 643, (DMSO) 259, 427(S), 520, 554, 590, 646. **2**: 1H-NMR(DMSO) 9.47(d,6.5Hz, 4Hpy), 9.02(m,12Hz,4Hpy,8Hβ), 8.16 and 7.44(dd,8.5Hz,6Har), 8.03 and 7.26(dd,8.5Hz,2Har), 7.91(d,8.1Hz,2H, H-6), 5.99(d, 1.9Hz,2H,H-1'), 5.73(d,7.9Hz,2H,H-5), 5.25(m,2H,H-3'), 5.11(m,2H,H-2'), 4.72(s,6H,N-Me), 4.60-4.43(m) and 3.87(m) (6H,H-4,H-5'), 1.61(s,6Hip), 1.41(s,6Hip), -2.90(s,2Hpor); UV-vis (H_2O) 193, 224, 258, 432(S), 524, 563, 590, 650, (DMSO) 259, 428(S), 520, 558, 592, 648. **3**: 1H-NMR (DMSO) 9.43(d,6.6Hz,2Hpy), 9.06-8.85(m,8Hβ), 8.12 and 7.40(dd,8Hz,2Hpy,4Har), 8.02(d,8.3Hz, 2Har), 7.95-7.73(c,4Har), 7.85(d,8.1Hz,3H,H-6), 5.98(m,3H,H-1'), 5.85-5.70(c,3H,H-5), 5.25-5.08(m,6H,H-3',H-2'), 4.92-4.70(m) and 4.08(m) (9H,H-4',H-5'), 1.61(s,9Hip), 1.40(s,9Hip), -2.81(s,2Hpor); UV-vis(H_2O) 219, 258, 425(S), too small solubility for other bands to be visible, (DMSO) 259, 427(S), 520, 560, 593, 651. **1-Co(II)**: UV-vis (H_2O) 225, 261, 348, 431(S), 503. **2-Co(II)**: UV-vis (H_2O) 224, 435(S), 505.
6. Tris-(hydroxymethyl)aminomethane applied as a representative of biochemically important buffers.
7. Meso-tri(N-methylpyridinium)-p-phenylene-5'-O-thymidineporphyrin corresponding to **1** which is under investigation in this laboratory shows the solubility $5.0x10^{-4}$ ($2.0x10^{-2}$) mg/mL; the Cu(II), Ni(II) and Zn(II) derivatives of **1** and **2** show solubility in the range 10^{-3}-10^{-4} (10^{-3}-10^{-4}) mg/mL.

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