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SYNTHESIS OF A BINUCLEAR COPPER(II) WATER-SOLUBLE PORPHYRINIC COMPLEX Cu_2(tMPyP)(BiPy)

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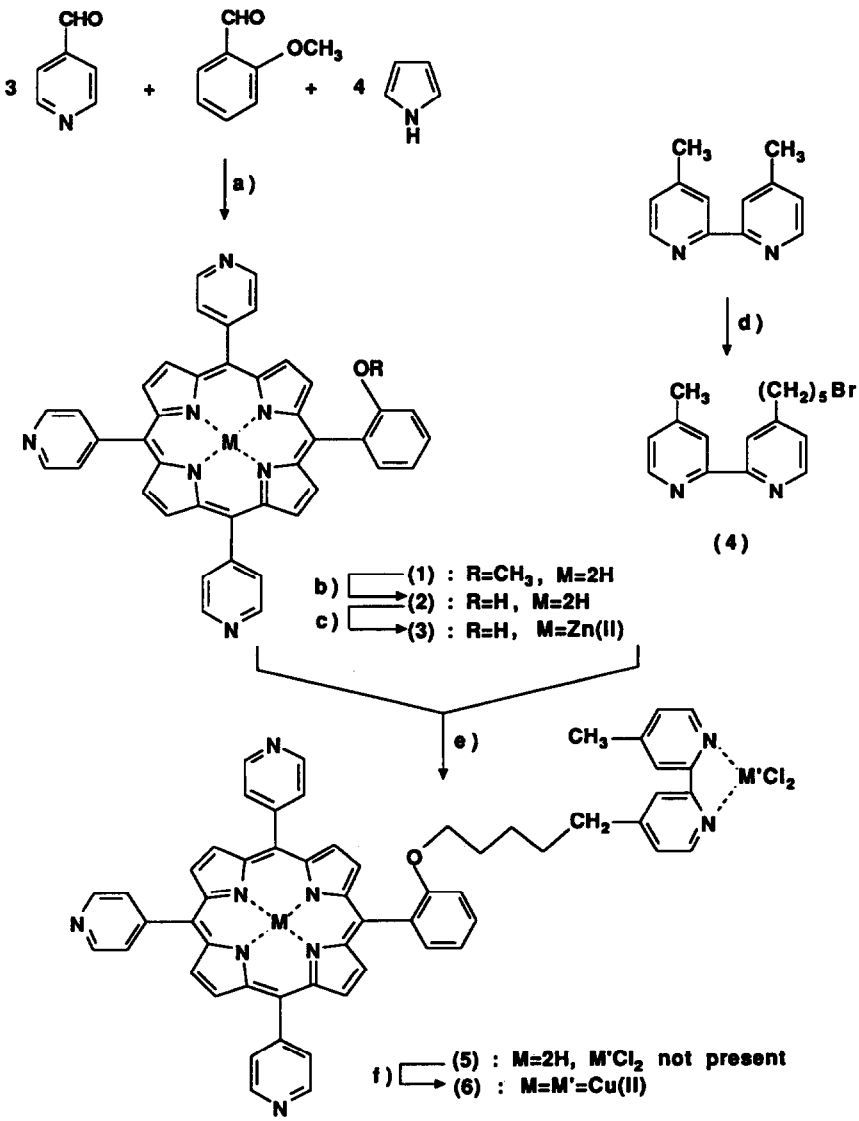
Summary: Synthesis of a binuclear copper(II) water-soluble porphyrinic complex, a potential restriction enzyme model, is described and preliminary data on its interactions with DNA are presented.

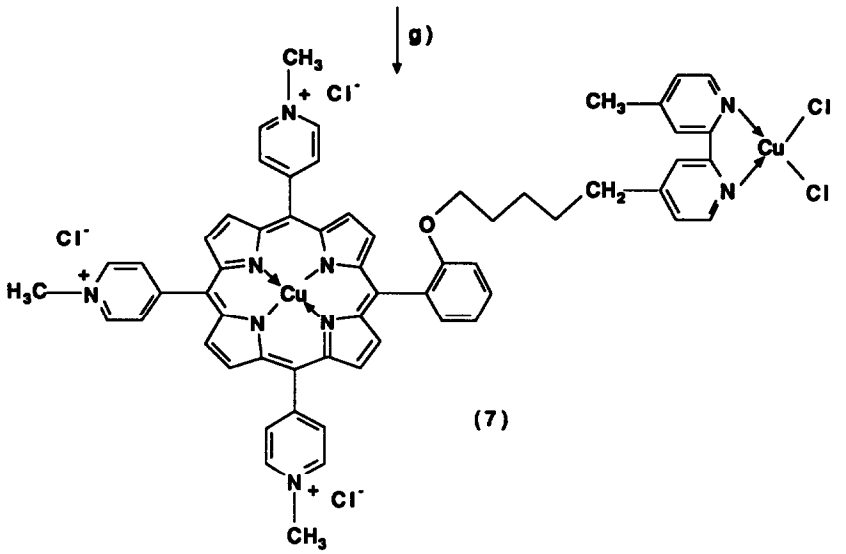
Elucidation of pathways in DNA cleavage reactions has been aided by the availability of restriction enzyme models. A number of metal complexes linked to DNA intercalators have been synthesized and these have proven particularly useful in investigations of this type [1]. The basis for the present study is, in part, the now well-established ability of meso-tetrakis(4-N-methylpyridyl)porphine (H_2TMPyP-4) and its metal derivatives containing no axial ligands (e.g. CuTMPyP-4) to intercalate between base pairs of DNA, and especially in regions rich in GC content [2]. A variety of different techniques have been used to demonstrate the various binding modes specificities of these symmetrical cationic porphyrins [3].

Reviews are available on asymmetrical porphyrins and their utility for biomimetic studies [4], but relatively few reports have appeared on the synthesis of cationic derivatives [5]. In this paper, we report the synthesis of Cu_2(tMPyP)(BiPy), a tri cationic porphyrin linked to a bipyridyl moiety, (see (7) below), as a potential restriction enzyme model and present preliminary data on its interaction with DNA. The bipyridyl ligand has been chosen because of the known ability of $Cu(bipy)^{2+}$ to catalyse the hydrolysis of phosphate esters [1b].

Condensation of o-anisaldehyde, 4-pyridinecarboxaldehyde and pyrrole in propionic acid [6] gives a mixture of six isomers and polymers. The desired isomer (1) [7] is separated by chromatography on silica gel using CH_2Cl_2/CH_3OH as an eluent. Demethylation with ethanethiol and sodium hydride in DMF [8a,b] gives the hydroxy derivative (2) [7]. We have not succeeded in getting (2) directly from condensation of o-hydroxybenzaldehyde, 4-pyridinecarboxaldehyde and pyrrole, possibly because of solubility and purification difficulties [8b,c]. Metalation of (2) with zinc chloride in DMF yields the zinc derivative (3) [7]. This compound is of some considerable interest because it can be used to covalently attach a series of ligands to the porphyrin ring via an ether linkage, thereby producing water-soluble models of metalloproteins. Such a synthetic strategy has been used previously with mono(o-

hydroxyphenyl)tritolylporphine [9]. 4-methyl 4'-(5-bromopentyl) 2,2'-bipyridine (4) [7] is synthesized by reaction of 4,4'-dimethyl 2,2'-bipyridine with lithium diisopropylamine and 1,4-dibromobutane in THF at room temperature, and purified by chromatography on basic alumina using hexane and acetone as eluent. Reaction of porphyrin (3) with (4) and K_2CO_3 in DMF gives the bipyridyl-porphyrin compound (5) [7]. A similar approach has been used to synthesize a derivative with p-tolyl groups instead of p-pyridyl





(7)

a) CH_3CH_2COOH (refluxing temp., 1.5h) (7%); b) EtSH(10eq.) / NaH(10eq.) / DMF under argon (refluxing temp., 2h) (87%); c) $ZnCl_2$(3eq.) / DMF (refluxing temp., 3.5h) (95%); d) Lithium diisopropylamine(1.1eq.) / $Br(CH_2)_4Br$(10eq.) / THF under argon (63%); e) 1- K_2CO_3(2eq.) / (4)(2eq.) / DMF under argon (60°C, 48h), 2- HCl(10%), 3- NaOH(10%) (43% in 3 steps); f) $CuCl_2.2H_2O$(4eq.) / DMF (70°C, 1h) (71%); g) 1- CH_3I(100eq.) / DMF (110°C, 45min), 2- Dowex 1X8/Cl^- (91% in 2 steps).

groups. This reaction has been attempted with the water-soluble derivative of (3) but has not consistently yielded the desired product. Treatment of (5) with $CuCl_2.2H_2O$ in DMF provides the derivative (6) [7]. Microanalysis of (6) is consistent with the structure shown ($Cu_2C_{57}H_{43}N_9OCl_2.4H_2O$: calculated: C 60.04, H 4.51, N 10.79, Cu 11.15; found: C 59.31, H 4.43, N 9.76, Cu 11.50.). Methylation of the pyridyl groups of (6) using CH_3I in DMF followed by treatment with anion exchange resin Dowex 1X8 in the chloride form yields the new binuclear water-soluble porphyrinic complex (7) [7].

Concerning the interaction of (7) with calf thymus DNA, visible absorption spectroscopy shows both a bathochromic shift and hypochromicity of the Soret band similar to what has been observed with CuTMPyP-4 [10], which has been shown to intercalate. Circular dichroism experiments of (7) with calf thymus DNA give only small features. However, because of this linked second chromophore to the porphyrin moiety, spectroscopic data are much more difficult to interpret unambiguously. Further studies on DNA binding and cleavage properties of (7) and of its isomer having the bipyridyl moiety in the meta position of the phenyl group are presently under investigation.

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7. The spectral data are in accord with the structures assigned. Only selected data are cited:
   (**1**): λ (nm)(CH_2Cl_2): 417, 512, 546, 586, 646. ^1H NMR δ (ppm)($CDCl_3$) : 9.06(6H, dd, J = 5.7, 1.9 Hz), 8.88(2H, d, 4.9 Hz), 8.85(4H,s), 8.80(2H, d, 4.9 Hz), 8.18(6H, d, 5.7 Hz), 8.00(1H, dd, 7.8, 1.9 Hz), 7.81(1H, td, 7.8, 1.9 Hz), 7.39(1H, t, 7.8 Hz), 7.37(1H, d, 7.8 Hz), 3.63(3H, s), -2.84(2H, s). (**2**): λ (nm)(CH_2Cl_2): 415, 511, 544, 587, 641. ^1H NMR δ (ppm)(DMSO-d6): 9.75(1H, s), 9.05(6H, d, 5.7 Hz), 8.89(8H, m), 8.28(6H, d, 5.7 Hz), 7.92(1H, dd, 7.9, 1.7 Hz), 7.69(1H, td, 7.9, 1.7 Hz), 7.34(1H, d, 7.9 Hz), 7.27(1H, t, 7.9 Hz), -3.00(2H, s). (**3**): λ (nm)(DMF): 424, 558, 598. ^1H NMR δ (ppm)(DMSO-d6): 9.61(1H, s), 9.02(6H, d, 5.8 Hz), 8.84(2H, d, 4.7 Hz), 8.83(4H, s), 8.78(2H, d, 4.7 Hz), 8.24(6H, d, 5.8 Hz), 7.87(1H, dd, 7.8, 1.5 Hz), 7.65(1H, td, 7.8, 1.5 Hz), 7.31(1H, d, 7.8 Hz), 7.23(1H, t, 7.8 Hz). (**4**): IR (cm^{-1}) (film): 2955, 2920, 1690, 1590, 1490, 1450, 1370. ^1H NMR δ (ppm)($CDCl_3$): 8.57(1H, d, 4.8 Hz), 8.55(1H, d, 4.8 Hz), 7.16(2H, d, 4.8 Hz), 3.42(2H, t, 6.7 Hz), 2.73(2H, t, 7.6 Hz), 2.45(3H, s), 1.91(2H, q, 7.1 Hz), 1.75(2H, q, 7.5 Hz), 1.52(2H, q, 7.5 Hz). (**5**): λ (nm)(CH_2Cl_2): 417, 512, 547, 587, 643. ^1H NMR δ (ppm)($CDCl_3$): 8.89(6H, d, 4.8 Hz), 8.76(8H, m), 8.38(1H, d, 5.1 Hz), 8.06(7H, m), 8.00(1H, dd, 7.4, 1.5 Hz), 7.90(1H, d, 5.1 Hz), 7.79(1H, t, 7.4 Hz), 7.56(1H, s), 7.38(1H, t, 7.4 Hz), 7.33(1H, d, 7.4 Hz), 7.07(1H, d, 5.1 Hz), 5.85(1H, d, 5.1 Hz), 3.90(2H, t, 6.0 Hz), 2.39(3H, s), 1.34(2H, t, 7.8 Hz), 1.00(2H, q, 7.5 Hz), 0.75(2H, q, 7.1 Hz), 0.40(2H, q, 6.9 Hz), -2.90(2H, s). (**6**): λ (nm)(DMF): 414, 539. (**7**): λ (nm)(ε ($M^{-1}.cm^{-1}$))(H_2O): 427($1.5x10^5$), 550($3.8x10^4$).
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