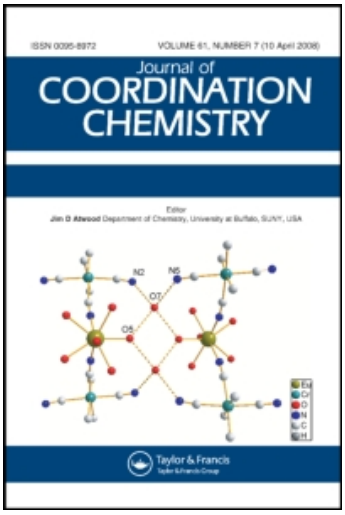

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THE SYNTHESIS AND COMPLEXATION PROPERTIES OF MULTIDENTATE *PER*-[6-DEOXY-6-THIO-(4-PYRIDYL)]-CYCLODEXTRINS

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The synthesis of chemically modified multidentate cyclodextrins capable of carrying pyridyl ligands is reported. *Per*-(6-bromo-6-deoxy)-α-, -β-, and -γ-cyclodextrins (**1**, **2**, and **3**, respectively) were treated with an excess of 4-mercaptopyridine affording *per*-[6-deoxy-thio-6-(4-pyridyl)]-α-, -β-, and -γ-cyclodextrin derivatives in very high yields (90–95% for isolated products). The solubilities of such systems in non-aqueous solvents were efficiently increased by acetylation of the secondary hydroxyl groups. The complexation properties of the derivatives with regard to copper(II) were investigated by solvent extraction, ESR and spectroscopic titration experiments.

Keywords: Chemically modified cyclodextrins; synthesis; copper(II); spectroscopy

INTRODUCTION

The complexation of transition metal cations by natural cyclodextrins is possible in various ways;[1] under basic conditions covalently bound alcoholate

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complexes form with a wide variety of transition metal[2] or metalloid cations;[3] under neutral conditions solid state complexes with magnesium[4] and calcium[5] cations have been reported.

In the case of chemically modified cyclodextrins, complex formation is possible if the electron-donating groups are built onto the cyclodextrin framework. In artificial enzyme modelling systems, usually one such group is linked to the cyclodextrin and the inclusion cavity is accessible to "substrates". A β-cyclodextrin derivative bearing a single pyridyl moiety has been synthesised and its Ni(II) and Cu(II) complexes were studied.[6] A few other *mono*-derivatives have also been studied as models of enzymes.[7,8] Recently, a new class of photo- and electroactive molecular receptors has been reported.[9] A β-cyclodextrin substituted with a 2,2′-bipyridine and its complexes with Ir(III), Rh(III), and Re(I) have been prepared and their properties examined.

There are reported derivatives having more coordinating groups such as *tetra-O*-nicotinoyl-α-cyclodextrin,[10] which readily formed Co(II) and Cu(II) complexes. The platinum(II) complex of this system was also studied.[11] Similar synthetic methodology was used for the synthesis of an α-cyclodextrin-derived siderophore analogue, in which three catechol groups were linked to the primary hydroxyl groups of the α-cyclodextrin molecule; the complexation and host–guest inclusion properties of this system were studied.[12] *Heptakis*[(6-(1-imidazoyl)-6-deoxy)]-β-cyclodextrin was obtained from corresponding *heptakis*-6-tosylate and was demonstrated to be an effective enzyme model for ribonuclease.[13]

Per-(6-bromo-6-deoxy)-α-, -β-, and -γ-cyclodextrins (**1**, **2**, and **3**) are very versatile starting materials for many transformations.[14–16] The bromine moiety on the cyclodextrin rim can be easily exchanged by many nucleophilic reagents, including aliphatic[17] and aromatic[18] thiols, leading to amphiphilic cyclodextrins.

Here we report a very simple, highly effective route to macrocyclic ligands in which ring diameter and the number of coordinating groups are defined by the size of the parent cyclodextrin. Solvent extraction and spectroscopic studies of the complexation properties of these new multidentate pyridyl-cyclodextrin derivatives with copper(II) show differences in the structure of the complex obtained depending on the parent cyclodextrin. In the case of the *octa*-dentate γ-cyclodextrin we describe the complex nature of the sequence of complexation equilibria possible as a function of ligand : copper(II) ratio.

EXPERIMENTAL

General

Melting points were determined using a Kofler-block apparatus and are not corrected. Optical rotations were measured with a JASCO DIP360 digital polarimeter at 25°C. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded in DMSO-d_6 with a Varian Gemini 200 spectrometer. Liquid matrix secondary ion mass spectrometry (SIMS) measurements were performed with an AMD604 Intectra spectrometer. Electronic spectra were measured on a Perkin λ12 spectrometer. ESR spectra were measured on a Bruker ESP-300 spectrometer with a rectangular resonance cavity (ER-4102); low temperature measurements used the variable temperature system ER-4111.

Compounds **1**, **2** and **3** were prepared as previously described.[18] All solvents were dried over appropriate drying reagents and freshly distilled prior to use.

General Method of Preparation of *per*-[6-thio(4-pyridyl)-6-deoxy]-α-, -β-, and -γ-cyclodextrin (4, 5, and 6)

To a stirred solution of commercial 4-mercaptopyridine in DMF, an excess of anhydrous triethylamine was added under an argon atmosphere, and to this solution, *per*-(6-bromo-6-deoxy)-cyclodextrin (**1**, **2** or **3**) in DMF, was added dropwise. The reaction mixture was stirred overnight at room temperature, then the white microcrystalline solid was filtered off and washed with methanol. The filtrate was evaporated to dryness, the residue treated several times with methanol, and the resulting solid was washed with the same solvent. Both solids were combined and dried under reduced pressure.

Hexakis[6-thio(4-pyridyl)-6-deoxy]-α-cyclodextrin (4)

Yield: 95%; mp 242–245°C (decomp.); $[\alpha]_D^{25}$ 109.66 (*c* 0.2, DMSO); ^{1}H NMR (DMSO-d_6) δ: 8.20 (d, $J = 5.17$ Hz, 2H, pyridyl), 7.02 (d, $J = 5.35$ Hz, 2H, pyridyl), 5.9–5.5 (2 × bs, 2H, 2 × OH), 4.96 (bs, 1H, C1-H), 4.3–3.2 (m, remaining H); ^{13}C NMR δ 149.60 (C_{IV}), 148.58, 120.70 (pyridyl), 102.26 (C1), 85.8 (C4), 73.07, 71.91, 69.44 (C2, C3, C5), 32.63 (C6); DEPT 135° the same signals except 147.78 (C_{IV} pyridyl) opposite phase of the signal at 32.63; LSIMS(+) NBA, $m/z = 1531.3$ $(M + H)^+$, 1553.3 $(M + Na)^+$.

Heptakis[6-thio-(4-pyridyl)-6-deoxy]-β-cyclodextrin (5)

Yield: 90%; mp 226–230°C (decomp.); $[\alpha]_D^{25}$ 143 (*c* 0.2, DMSO); NMR (DMSO-d_6) δ: ^{1}H 8.12 (d, $J = 4.29$ Hz, 2H, pyridyl), 6.92 (d, $J = 5.22$ Hz, 2H, pyridyl), 6.02, 5.92 (2d, 2H, $J = 6.79$ Hz $J = 1.12$, 2 × OH), 4.0–3.2 (m, remaining H); ^{13}C 150.47 (C_{IV}) 148.61, 120.42 (pyridyl), 101.94 (C1), 85.10 (C4), 72.41, 71.85, 69.87 (C2, C3, C5), 32.09 (C6); DEPT 135° the same signals except 150.47 (C_{IV} pyridyl), opposite phase of the signal at 32.09 (C6-H_2); LSIMS(+) NBA, $m/z = 1786.8$ $(M + H)^+$, 1808.4 $(M + Na)^+$.

Oktakis[6-thio-(4-pyridyl)-6-deoxy]-γ-cyclodextrin (6)

Yield: 95%; mp 250–255°C; $[\alpha]_D^{25}$ 132.5 (*c* 0.2, DMSO); NMR (DMSO-d_6) δ: ^{1}H 8.14 (d, $J = 4.3$ Hz, 2H, pyridyl), 6.98 (d, $J = 5.42$ Hz, 2H, pyridyl), 5.02 (d, $J_{12} = 1.18$ Hz, 1H, C1-H), 4.1–2.9 (m, remaining H); ^{13}C 149.42 (C_{IV}), 148.10, 120.37 (pyridyl), 101.79 (C1), 84.24 (C4), 72.31, 72.23, 70.06 (C2, C3, C5), 32.04 (C6); DEPT 135° the same signals except 149.42 (C_{IV} pyridyl), opposite phase of the signal at 32.04 (C6-H_2); LSIMS(+) GLY/TGLY, $m/z = 2042.3$ $(M + H)^+$, 2072.6 $(M + Na)^+$.

General Method of Acetylation of *per*[6-thio(4-pyridyl)-6-deoxy]-α-, -β-, and -γ-cyclodextrin to Derivatives 7, 8, and 9

A suspension of compound **4**, **5** or **6** in DMF was treated with an acetic anhydride–triethylamine mixture in the presence of catalytic amounts of DMAP. After approximately 20 h (the reaction was monitored by TLC) the reaction mixture was evaporated to dryness, and the desired product **7**, **8** or **9** was isolated by column chromatography on aluminium oxide, using a methylene chloride–96% ethanol (9 : 1) system, as eluent.

Hexakis[6-thio(4-pyridyl)-6-deoxy-2,3-di-O-acetyl]-α-cyclodextrin (7)

Yield: 80%; mp 152–156°C; $[\alpha]_D^{25}$ 70.25° (*c* 1.06, $CHCl_3$); NMR ($CDCl_3$) δ: ^{1}H 8.17 (d, $J = 6$ Hz, 2H, pyridyl), 6.82 (d, $J = 6.1$ Hz, 2H, pyridyl), 5.43 (t, $J_{23} \approx J_{32} = 9$ Hz, 1H, C3-H), 4.99 (d, $J_{12} = 3.54$ Hz, 1H, C1-H), 4.8 (d × d, $J_{12} = 3.42$ Hz $J_{23} = 10.09$ Hz, 1H, C2-H), 4.33 (m, 1H, C5-H), 3.81 (t, $J_{34} \approx J_{45} = 8.5$ Hz, 1H, C4-H), 3.2–3.6 (m, 2H, C6-H), 1.98, 2.01 (2 × s, 6H, 2 × CH_3); ^{13}C 170.44, 169.2 (2 × C=O), 149.45, 147.78 (C_{IV}), 120.62 (pyridyl), 97.29 (C1), 80.22 (C4), 70.92, 70.73, 70.41 (C2, C3, C5), 33.32 (C6), 20.76, 20.69 (2 × CH_3); DEPT 135° the same signals except 170.44 i 169.2 (2 × C=O) and 147.78 (C_{IV} pyridyl); LSIMS(+) NBA, $m/z = 2037.6$ $(M + H)^+$.

Heptakis[6-thio(4-pyridyl)-6-deoxy-2,3-di-O-acetyl]-β-cyclodextrin (8)

Yield: 85%; mp 175–182°C; $[\alpha]_D^{25}$ 63° (*c* 1.08, $CHCl_3$); NMR ($CDCl_3$) δ: ^1H 8.15 (d, $J = 5.9$ Hz, 2H, pyridyl), 6.82 (d, $J = 6.18$ Hz, 2H, pyridyl), 5.26 (t, $J_{23} \approx J_{32} = 8.5$ Hz, 1H, C3-H), 5.03 (d, $J_{12} = 3.74$ Hz, 1H, C1-H), 4.78 (d × d, $J_{12} = 3.84$ Hz $J_{23} = 9.52$ Hz, 1H, C2-H), 4.2 (t, $J_{34} \approx J_{45} = 8$ Hz, 1H, C4-H), 3.81 (t, $J_{45} \approx J_{56} = 8.5$ Hz, 1H, C5-H), 3.45–3.70 (m, 2H, C6-H), 2.04, 2.02 (2 × s, 6H, CH_3); ^{13}C 170.48 and 169.28 (2 × C=O), 149.32, 147.86 (C_{IV}), 120.51 (pyridyl), 97.18 (C1), 80.19 (C4), 70.59, 70.37, 69.92 (C2, C3, C5), 33.07 (C6), 20.70, 20.64 (2 × CH_3); DEPT 135° the same signals except 170.48, 169.28 (2 × C=O) and 147.86 (C_{IV} pyridyl), opposite phase of the signal at 33.07 (C6-H_2); LSIMS(+) NBA, $m/z = 2376.7$ $(M + H)^+$.

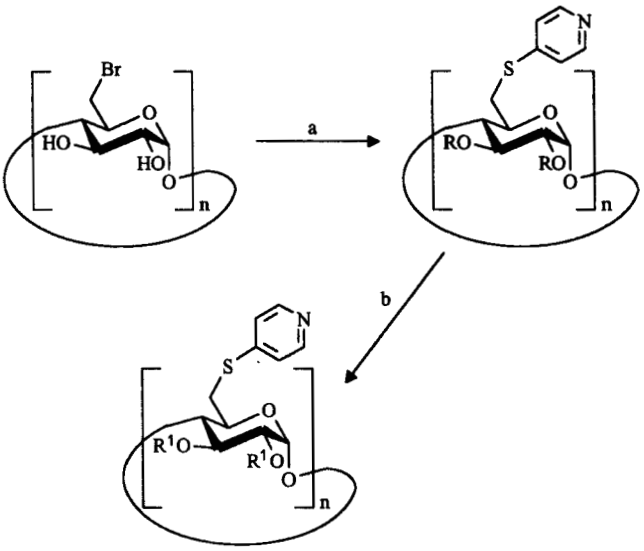
Oktakis[6-thio(4-pyridyl)-6-deoxy-2,3-di-O-acetyl]-γ-cyclodextrin (9)

Yield: 80%; mp 172–175°C; $[\alpha]_D^{25}$ 119° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ: ^1H 8.22 (d, $J = 6.08$ Hz, 2H, pyridyl), 6.89 (d, $J = 6.2$ Hz, 2H, pyridyl), 5.2–5.4 (m, 1H, C3-H), 5.05 (d, $J_{12} = 3.58$ Hz, 1H, C1-H), 4.69 (d × d, 1H, $J_{12} = 3.61$ Hz $J_{23} = 9.8$ Hz, C2-H), 4.15 (d × d, $J_{34} = 5.85$ Hz $J_{45} = 1.8$ Hz, 1H, C4-H) 3.7 (m, 2H, C6-H), 3.15–3.3 (m, 1H, C_5-H), 2.04, 2.02 (2 × s, 6H, CH_3); Homonuclear decoupling experiments were performed: selective irradiation at 5.35 ppm (C3-H) changed of the signal at 4.15 ppm to doublet 4.15 (d, $J_{45} = 6.0$ Hz, C4-H) and selective irradiation at 3.28 ppm (C5-H) changed of the signal at 4.15 ppm to doublet 4.15 (d, $J_{34} = 1.4$ Hz, C4-H), ^{13}C 170.49, 169.37 (2 × C=O), 149.37, 147.9 (C_{IV}), 120.58 (pyridyl), 96.78 (C1), 79.49 (C4), 70.43 (broad line) 68.08 (C2, C3, C5), 32.63 (C6), 20.77, 20.70 (2 × CH_3); DEPT 135° the same signals except: 170.49, 169.37 (2 × C=O) and 147.9 (C_{IV} pyridyl) and opposite phase of the signal at 32.63 (C6-H_2); LSIMS(+) NBA, $m/z = 2716.4$ $(M + H)^+$, $m/z = 2748$ $(M + Na)^+$.

RESULTS AND DISCUSSION

In the present work, *per*-(6-bromo-6-deoxy)-α-, -β-, and -γ-cyclodextrins (**1**, **2**, and **3**), dissolved in DMF, were treated with an excess of 4-mercaptopyridine in the presence of triethylamine as a base, affording products **4**, **5**, and **6**, respectively, with very high yields (90–95%),[18] (Figure 1).

Unfortunately, these derivatives are poorly soluble in most usual organic solvents (except DMSO, pyridine, and DMF). In order to transform them



n	6	7	8
R=H	**4**	**5**	**6**
R^1=Ac	**7**	**8**	**9**

a = NEt_3, DMF, HSC_6H_4N
b = Ac_2O, NEt_3, DMAP, DMF

FIGURE 1 Synthetic route to the multidentate cyclodextrin ligands.

into more soluble derivatives, the secondary hydroxyl groups were acetylated by treatment with a triethylamine–acetic anhydride mixture. The classical acetic anhydride–pyridine system was not suitable due to problems associated with isolation of acetylated products from the reaction mixture. Compounds **7**, **8**, and **9** are highly soluble in common organic solvents such as chloroform, methylene chloride, acetone, *etc.*

Two series of complexation experiments involving these new multidenate ligand systems with regard to the copper(II) cation were undertaken. First, we explored the extraction of Cu(II) from aqueous solution by **7** and **8**. In the extraction experiments CH_2Cl_2 solutions of **7** and **8** were stirred with a saturated aqueous solution of $CuSO_4$. In both cases, the organic phase immediately became coloured. The phases were then separated and

from the organic phase the Cu(II) complex was crystallised. In the case of **7**, blue-green crystals (**7Cu$_n$**) were obtained and for **8**, blue crystals (**8Cu$_n$**) were obtained; unfortunately neither set of crystals diffracted in an X-ray experiment and full structural determination has proved impossible.

ESR measurements of **7Cu$_n$** were performed in the solid state (polycrystal spectra) and in chloroform solution. Both room temperature and 77 K measurements gave the same result; a single isotropic signal was observed, ($g = 2.116$ at 77 K and $g = 2.119$ at 273 K). In the solid state measurement solid complex was placed in the ESR sample tube perpendicular to the magnetic field axis. The isotropic signal may suggest higher than axial symmetry of the unpaired electron orbital which is in accord with the high symmetry of the complex arising from the symmetrical six-fold symmetry of α-cyclodextrin and the subsequent presence of an even number, 6, of pyridyl ligands which should be expected to coordinate in a pairwise manner to copper(II).

The analogous β-cyclodextrin complex **8Cu$_n$** gave in the ESR experiment, carried out in chloroform solution, a singlet with some traces of anisotropy. The ESR spectrum of that complex recorded in the solid state displays an anisotropic signal consisting of one perpendicular component without any hyperfine structure ($g = 2.1385$) and a parallel component (less intense, $g = 2.1085$) with hyperfine structure arising from the interaction of the unpaired electron with the copper nucleus which has the nuclear spin $I = 3/2$. In this case there are an odd number, 7, of pyridyl ligands available and here pairwise coordination will lead to a non-symmetrical structure.

The ^{1}H NMR spectra of **7Cu$_n$** and **8Cu$_n$** are interesting; in the case of **8Cu$_n$** as expected the pyridine aromatic signals are strongly broadened and the CD signals remain almost unchanged. This implies that the paramagnetic centres are located at a long distance from the CD ring and that no intramolecular inclusion takes place. However in the case of **7Cu$_n$** both the pyridyl and cyclodextrin signals are strongly broadened, suggesting that the ligands are arranged so as to bring the paramagnetic copper(II) centres close to the cyclodextrin ring.

In order to further investigate the multi-bidentate nature of these ligands, a series of absorption spectroscopy titration experiments between **6** and Cu(triflate)$_2$ were undertaken; due to the low solubility of **6**, DMSO was used as the solvent. The spectra for the region 300–1100 nm are given in Figure 2.

For concentrations of copper(II) above the ratio 4 Cu(II) centres to one tetradentate ligand, **6**, uncomplexed Cu(triflate)$_2$ is observed, confirming that the cyclodextrin systems behave as multi-bidentate ligands. At **6** to copper(II) ratios above this value no free ion is observed and the band at

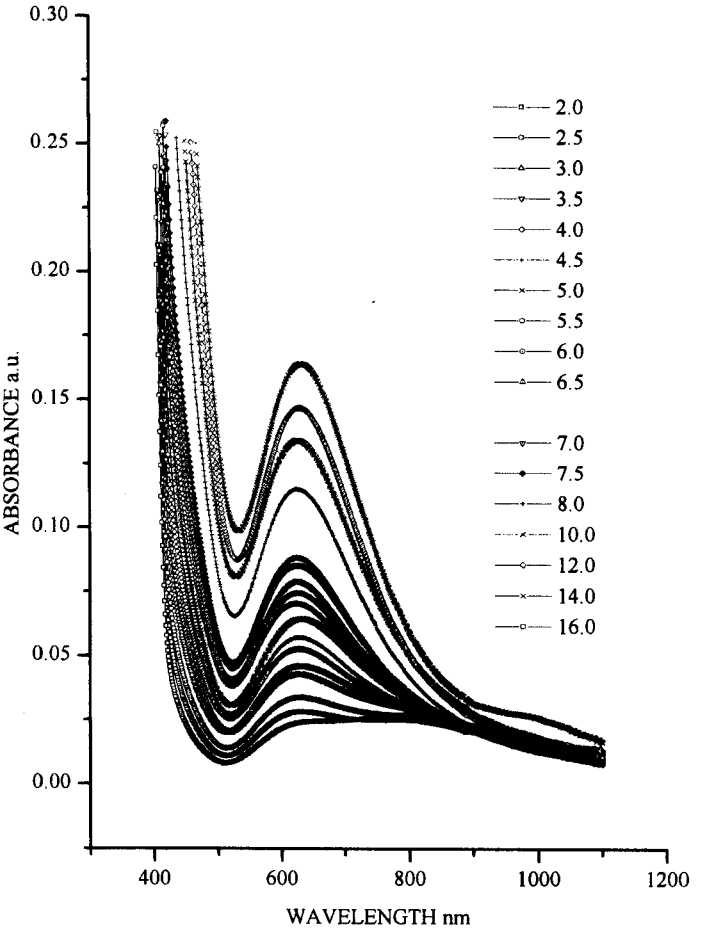


FIGURE 2 Electronic absorption spectra for complexation titration experiments between **6** and Cu(triflate)$_2$, in dimethyl sulphoxide; the numbers denote the ratio of pyridyl substituents per Cu(II) ion.

627 nm due to the complexed copper(II) is observed to increase in intensity. A number of isobestic points are observed suggesting that several species of complexed copper(II) are present. This is further confirmed by an attempted Jobs plot analysis which shows a series of maxima at 1, 2, 3 and 4 copper(II) ions per unit **6**. Thus there will exist a set of equilibria between the various complexes present in solution; apparently the differences in K_{ass} in these systems are too low to allow us to describe precisely the behaviour of the complexation processes which are schematised below in Figure 3.

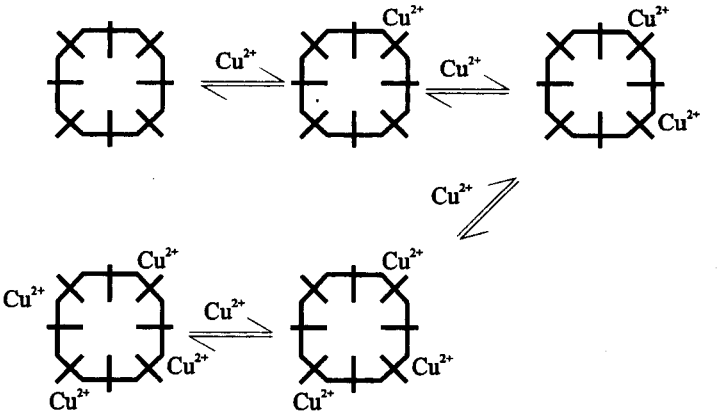


FIGURE 3 Schematic representation of the complexation equilibria present between **6** and Cu(triflate)$_2$.

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