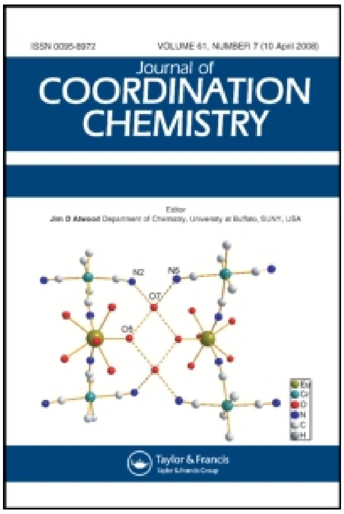

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First Sphere Coordination Chemistry of Modified Cyclodextrins: The *Bis*-$CoCl_2$ and *Bis*-$CuBr_2$ Complexes of $6^A,6^B,6^D,6^E$-Tetra-*O*-Nicotinoyl-α-Cyclodextrin

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FIRST SPHERE COORDINATION CHEMISTRY OF MODIFIED CYCLODEXTRINS: THE *BIS*-$CoCl_2$ AND *BIS*-$CuBr_2$ COMPLEXES OF $6^A,6^B,6^D,6^E$-TETRA-*O*-NICOTINOYL-α-CYCLODEXTRIN

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Substitution of the primary hydroxyl groups of α-cyclodextrin by nicotinate groups in an ABDE conformation yields a molecule having two pairs of pyridyl ligands. The compound complexes $CoCl_2$ and $CuBr_2$ in methanol or acetone to yield 1:2 complexes which are soluble in chloroform. The electronic spectrum of the blue $CoCl_2$ complex is almost identical to that of $Co(Py)_2Cl_2$, implying a molecular complex with a tetrahedral geometry. The molecular graphics study of this complex shows the two $CoCl_2$ groups positioned over and outside of the rim of unoccupied α-cyclodextrin.

Keywords: Cobalt, copper, nicotinate, cyclodextrins, synthesis, modelling

INTRODUCTION

Numerous second sphere coordination complexes of the cyclodextrins (CDs) have been obtained,[1] and in addition to direct complexation of copper or manganese by CDs,[2–4] recently specific porphyrin[5] and cyclam[6], salen[7] coordinating systems have been grafted onto the cyclodextrins. However, apart from the ethylenediamine β-CD,[8,9] the design of first sphere coordinating cyclodextrins having multiple ligating sites stereospecifically arranged over the molecular cavity and thus available for catalysis or multiple metal-active molecule transport have received little attention. Our recent work on the multiple selective functionalisation of α-CD opens up numerous possibilities for preparing such ligands,[10] and we describe here initial results on the first sphere complexation of $CuBr_2$ and $CoCl_2$, yielding bimetallic species in which the α-CD cavity remains available for inclusion.

EXPERIMENTAL

Preparation of ligands

Tetradeca-O-methyl-$6^A,6^B,6^D,6^E$-tetrahydroxyl-α-cyclodextrin (2)

To a solution of the tritylated precursor (1)[10] (3.38 g) in acetonitrile (100 cm^3), was added at room temperature a solution of tetrafluoroboric acid (3.32 cm^3, 34% in water). This mixture was stirred for one hour. Triethylamine (3.7 cm^3) was added to quench the reaction. The solvent was evaporated under reduced pressure and the

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residue was subjected to flash-column chromatography (chloroform-methanol step gradient, 95:5 → 90:10) to give 2 (1.70 g, 91%). ^{1}H-nmr data ($CDCl_3$): anomeric protons: 5.02 (2H, d), 5.10 (4H, m) *Anal.*: Calc. for $C_{50}H_{88}O_{30}$: C, 51.36; H, 7.53%. Found: C, 51.45, H, 7.45.

Tetradeca-O-methyl-6^A,6^B,6^D,6^E-tetra-O-nicotinoyl-α-cyclodextrin (3)

A mixture of 2 (300 mg), nicotinoyl chloride hydrochloride (380 mg) and *N*,*N*-dimethylaminopyridine (100 mg) in pyridine (7 cm^3) was stirred for 15 h at room temperature. The pyridine was evaporated under reduced pressure, saturated aqueous $NaHCO_3$ solution (20 cm^3) was added and this solution was extracted with ethyl acetate (3 × 50 cm^3). The combined organic extract was washed with brine (30 cm^3) and dried over anhydrous Na_2SO_4, and the solvent evaporated. Flash-column chromatography of the residue obtained (MeOH-CH_2Cl_2, 6:94) gave pure 3 (385 mg, 94%). ^{1}H-nmr data (DMSO-d_6): anomeric protons: 5.17 (2H, d), 5.05 (2H, d), 4.95 (2H, d); nicotinate protons: 9.10 (2H, s, $H\text{-}2'_{A,D\,or\,B,E}$), 8.92 (2H, s, $H\text{-}2'_{B,E\,or\,A,D}$), 8.75 (4H, m, H-4′), 8.20 (4H, m, H-6′), 7.48 (4H, m, H-5′). *Anal.*: Calc. for $C_{74}H_{100}O_{34}N_4$: C, 55.91; H, 6.34; N, 3.52%. Found: C, 55.80; H, 6.38; N, 3.49%.

Preparations of complexes

Tetradeca-O-methyl-6^A,6^B,6^D,6^E-tetra-O-nicotinoyl-α-cyclodextrin.2CuBr$_2$ (4)

To a solution of ligand 3 (70 mg) in acetone (3 cm^3), was added $CuBr_2$ (22 mg); a yellow-green product precipitated immediately. The mixture was maintained at 50°C for 1 h. The precipitate was filtered, washed with methanol and dried *in vacuo* (52 mg, 58%). *Anal.*: Calc. for $C_{74}H_{100}O_{34}N_4.2CuBr_2$: C, 43.65; H, 4.95; N, 2.75%. Found: C, 44.08; H, 5.23; N, 2.81%.

Tetradeca-O-methyl-6^A,6^B,6^D,6^E-tetra-O-nicotinoyl-α-cyclodextrin.2CoCl$_2$ (5)

To a solution of ligand 3 (70 mg) in acetone (3 cm^3), was added $CoCl_2$ (14 mg). A blue product precipitated immediately and the mixture was maintained at 50°C for 1 h. The precipitate was filtered, washed with methanol and dried *in vacuo* (65 mg, 80%). *Anal.*: Calc. For $C_{74}H_{100}O_{34}N_4.2CoCl_2$: C, 48.06; H, 5.45; N, 3.03%. Found: C, 48.58; H, 5.88; N, 3.17%.

Molecular Graphics

The ligand molecule was modelled using the SYBYL program,[11] using the coordinates of α-cyclodextrin from the Cambridge Crystallographic Data Centre. Methyl groups were first added and the energy of the resulting molecule minimized. Subsequently, the nicotinate ligands were added *via* the Building sub-program and manual rotation about the free bonds (C5–C6, C6–NH, CO–Ph) placed the ligands in a suitable conformation. The fit with $CoCl_2$ was verified by a manual docking operation using a dummy tetrahedral metal (M) with a M–N distance of 2.18 Å, this value is taken from the X-ray results on the $CoCl_2.(Py)_2$ complex.[12,13] The dummy metal was then removed and the ligand molecule energy and conformation optimized with the internal Maximum force field.

RESULTS AND DISCUSSION

The scheme of synthesis of the ligand is shown in Figure 1. Tetradeca-*O*-methyl-$6^A,6^B,6^D,6^E$-tetra-*O*-trityl-α-cyclodextrin 1 was detritylated with tetrafluoroboric acid to give the corresponding tetrahydroxyl derivative 2 in 91% yield; 2 was coupled with nicotinoyl chloride to give the ligand 3 in 94% yield.

The ^{1}H-nmr spectrum of the ligand 3 in DMSO-d_6 shows in the H-1 region of α-CD a clear 1:1:1 pattern typical of ABDE substituted α-cyclodextrin derivatives. As is common for multiply substituted α-CD derivatives the peak pattern in the ^{1}H-nmr is solvent sensitive; in $CDCl_3$ an overlapping pattern is observed. In the aromatic region all four protons of the nicotinate group are observed. The ligand thus presents two bidentate coordination sites. Due to the paramagnetism of the

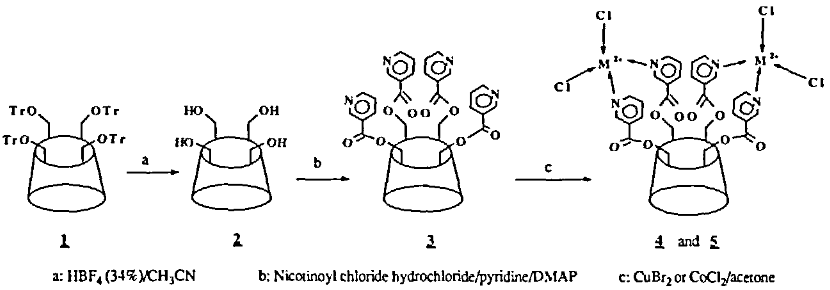

FIGURE 1 Synthetic route to $CoCl_2$ and $CuBr_2$ complexes of the ABDE tetra-nicotinate α-CD ligand.

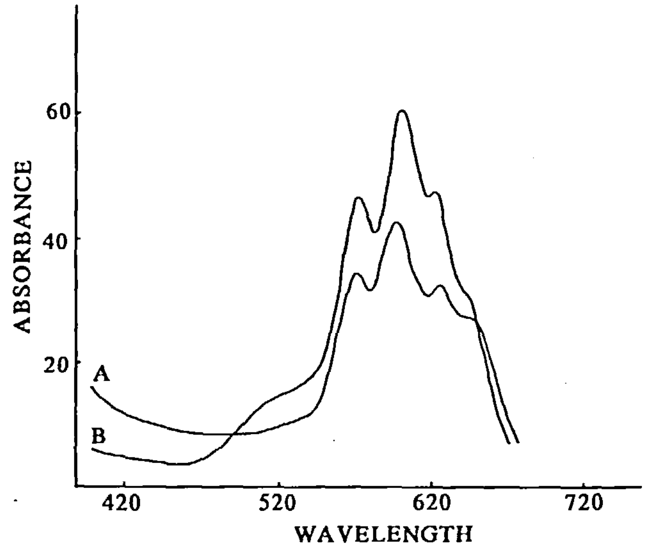

FIGURE 2 Electronic spectra of A (5), and B ($CoCl_2(Py)_2$) in $CHCl_3$.

TABLE I
Observed peaks in the electronic spectra of 5 and CoCl(Py)$_2$ in CHCl$_3$ (nm).

A [5]	576	607	638	664
B [CoCl$_2$(Py)$_2$]	574	600	629	651

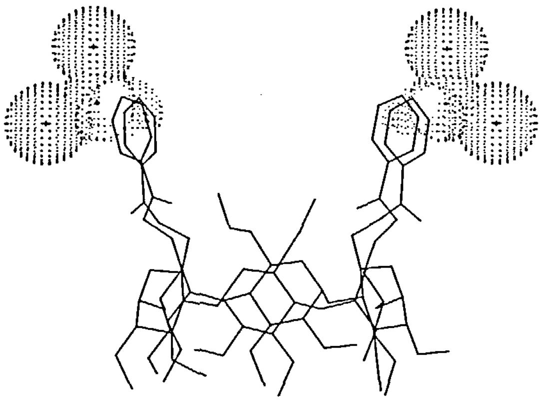

FIGURE 3 Molecular graphics generated model of 5.

metal complexes the nmr spectra of 4 and 5 show extremely broadened signals. In both complexes the microanalytical results imply a 2:1 stoichiometry, expected for coordination by the two pairs of pyridyl ligands. The electronic spectrum of 5 is shown below (Figure 2 spectrum A); four overlapping absorption bands are observed in CHCl$_3$ (Table I). The spectrum closely resembles that of known tetrahedral complex Co(Py)$_2$Cl$_2$ in CHCl$_3$[12,13] (Figure 2 spectrum B and Table I). From this result we conclude that the geometry and nature of coordination in 5 is tetrahedral.

The molecular graphics study (Figure 3) suggest that the metal halide fragments are placed over, and external to, the cyclodextrin cavity. The coordination occurs via the A+B and D+E bidentate ligands. Energy minimization of the ligand shows an absence of unfavourable van der Waals interactions (−29.2 kcal/mol).* The coordination site is capable of accepting a tetrahedrally coordinated metal atom at an $N_{nicotinate}$-M distance of 2.18 Å. The metal atoms are placed 6.5 Å above the plane of the cavity rim; the four nicotinate groups along with metal halide moieties create an open sided elongation of the α-CD cavity available for inclusion of molecules too long for complete inclusion with the unsubstituted CD.

In conclusion, we have shown that a first sphere coordination ligand based on cyclodextrins in which the metals are complexed outside the extended cavity can be synthesized and that this new ligand has been applied to the coordination of transition metals (complex fragments CoCl$_2$ and CuCl$_2$).

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* 1 cal ≡ 4.184 J.

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