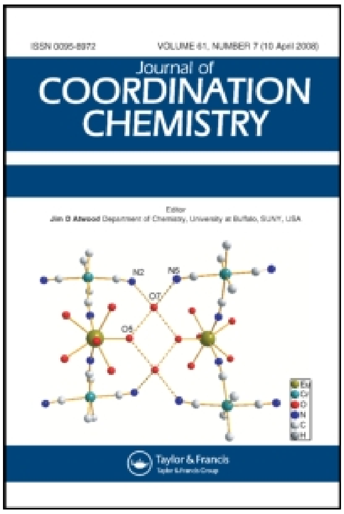

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1ST SPHERE COORDINATION CHEMISTRY OF MODIFIED CYCLODEXTRINS: PART II. THE bis(cis-PtCl$_2$) COMPLEX OF TETRADECA-*O*-METHYL-6^A,6^B,6^D,6^E-TETRA-0-NICOTINOYL-α -CYCLODEXTRIN

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NOTE

1ST SPHERE COORDINATION CHEMISTRY OF MODIFIED CYCLODEXTRINS: PART II. THE *bis*(*cis*-$PtCl_2$) COMPLEX OF TETRADECA-*O*-METHYL-$6^A,6^B,6^D,6^E$-TETRA-*O*-NICOTINOYL-α-CYCLODEXTRIN

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The modified α-cyclodextrin system having four nicotinate groups with an ABDE symmetry presents two pairs of preferentially *cis*-coordinating pyridyl ligands. The molecule in dmso-d_6 has been shown by ^{1}H NMR to complex two *cis*-$PtCl_2$ moieties. The observed non-equivalence of the pyridyl ligands may be explained by a molecular graphics study which places the metal above and outside the rim of the α-cyclodextrin with the two coordinating ligands in sites parallel and antiparallel to the molcular axis.

KEY WORDS: *cis*-platinum, cyclodextrin, complexation, NMR, modelling.

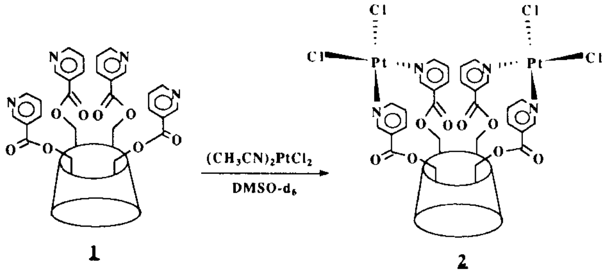
INTRODUCTION

The use of both native cyclodextrins (CDs)[1–4] or chemically modified derivatives[5–7] for the first sphere coordination of metals is known. Recently, ethylenediamine-β-cyclodextrin[5,6] and histidyl β-CD derivatives have been shown to both coordinate metals and form inclusion compounds. We are interested in the transport of multiple pharmacologically active metals or the combination of such metals and organic drugs in CD derived systems. As a first step we have recently described the multiple complextion of Co (II) and Cu (II).[7] In this paper we wish to describe first shere *bis*-coordination complexes of platinum in a *cis*-geometry, a metal system well known as an anti-cancer agent.[8]

EXPERIMENTAL

Complexation Experiments

To a solution of tetradeca-*O*-methyl-$6^A,6^B,6^D,6^E$-tetra-*O*-nicotinoyl-α-cyclodextrin (5 mg, 0.003 mmoles) (**1**) in dmso-d_6 was added *cis*-$PtCl_2(CH_3CN)_2$ in small quantities



and the formation of the complex monitored by ^1H NMR. At *cis*-$PtCl_2(CH_3CN)_2$ concentrations in excess of 9 equivalents no further shifts in the nicotinate proton chemical shifts occur and we consider that complete complexation has taken place to give *bis*[*cis*-$PtCl_2$]-tetradeca-*O*-methyl-*6^A,6^B,6^D,6^E-tetra-O-nicotinoyl-α-cyclodextrin* (**2**).

Molecular Graphics

A model structure for the ligand was produced using the SYBYL Molecular Graphics program[9] based initially on the coordinates of a structurally similar *bis*-$CoCl_2$ complex in which the metal is present in a tetrahedral geometry.[7] Manual docking combined with changing dihedral angles in the α-CD-nicotinate linkage was used to introduce two equivalent *cis*-$PtCl_2$ sites in a square planar conformation and with an N-Pt distance of 1.99 Å, a Cl-Pt distance of 2.30 Å (values from X-ray crystal data for *cis*-$PtCl_2$-pyridine complexes).[10] The dummy metal atom M was then removed and energy calculations using the built-in force field carried out to verify that no unfavourable van der Waals contacts were present (−56.43 kcal/mol; 1 cal = 4.184 J).

RESULTS AND DISCUSSION

The ^1H NMR spectrum of ligand **1** at 200 Mhz in dmso-d_6 is given in Figure **1a**. The anomeric protons (H-1) are observed as a 1:1:1 pattern at 5.19, 5.06 and 4.97 ppm, confirming that axial ABDE symmetry is retained.[11] Two proton systems for the nicotinate cycles (AD and BE) are observed. The 6-OMe signals of the CF glucopyranose units are observed at 2.93 ppm.

In Figure **1b** is shown the ^1H spectrum of **2**. The spectrum is generally broad but axial symmetry is retained as evidenced by the retention of the 1:1:1 pattern observed for the anomeric protons (5.02, 5.08, 5.16 ppm). The 6-OMe protons of CF are now shifted to 3.10 ppm and are still present as a singlet. The signals of the nicotinate ring undergo considerable modification and are observed as two independent systems for the 4 protons: 7.65, 8.50, 8.90 and 9.15 ppm and 7.75, 8.50, 9.15 and 9.40 ppm, respectively. This sequence has been confirmed by 2D-COSY experiments. From the NMR results the molecule retains an ABDE axial symmetry, in which the AD and BE nicotinate rings are now strongly differentiated, and apparently with some change in the nicotinate-OMe_{CF} interactions as evidenced by ring current effects.

The model obtained for **2** using molecular graphics methods is shown in Figure **2**.

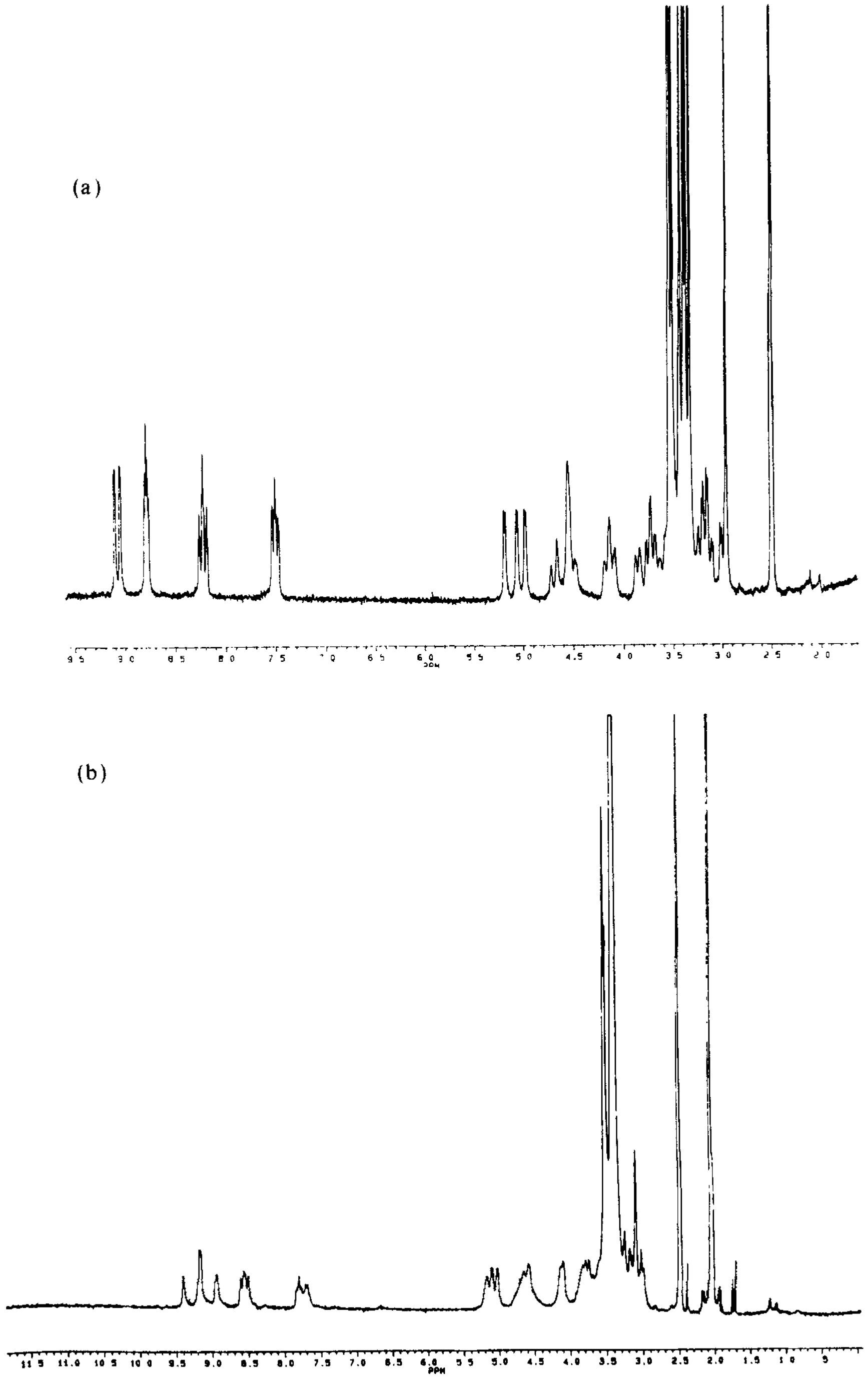


Figure 1 ^{1}H NMR spectra of **a**: free ligand **1**; **b**: ligand + *cis*-Pt(CH_3CN)$_2$$Cl_2$ (9 equivalents) in DMSO-d_6.

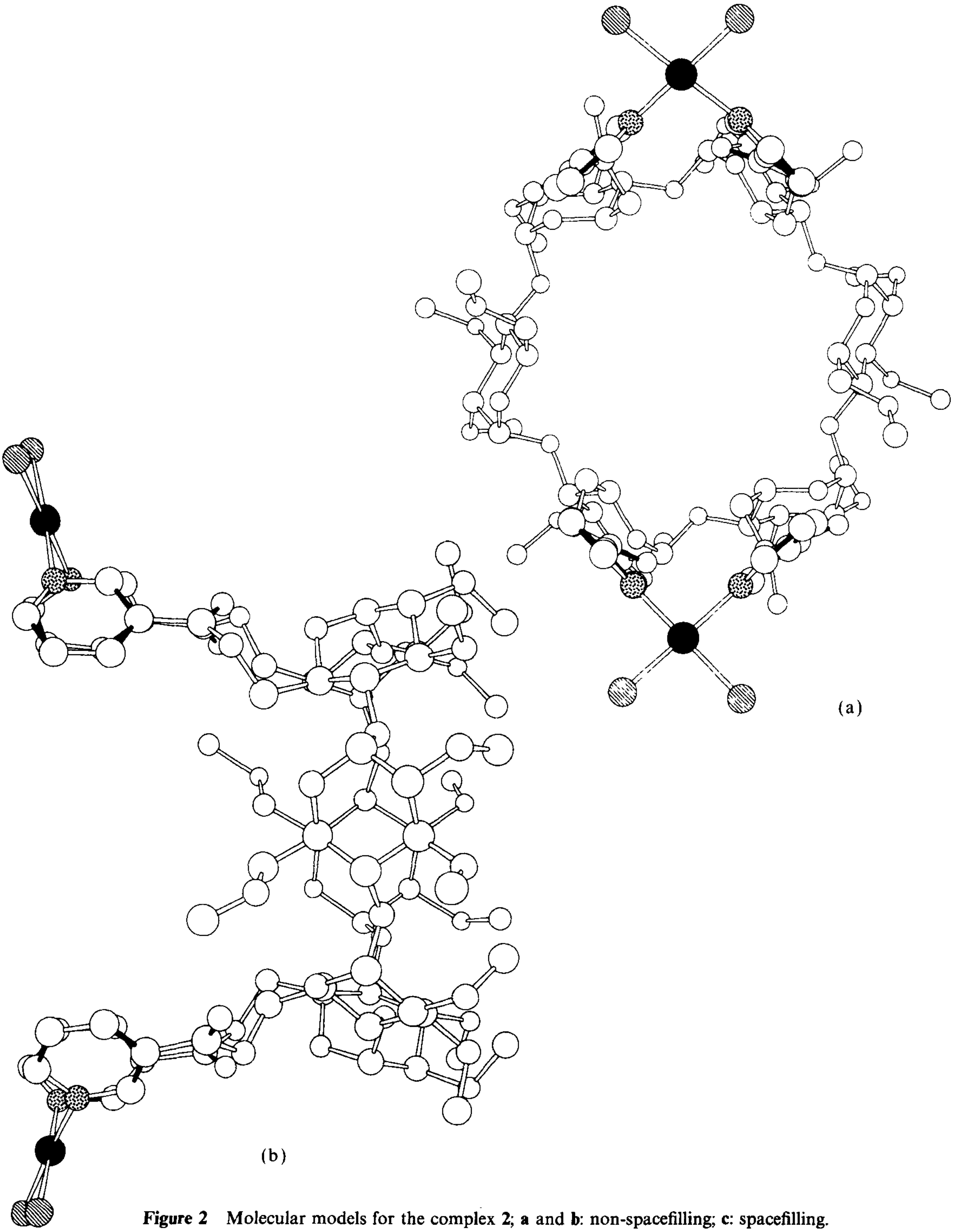
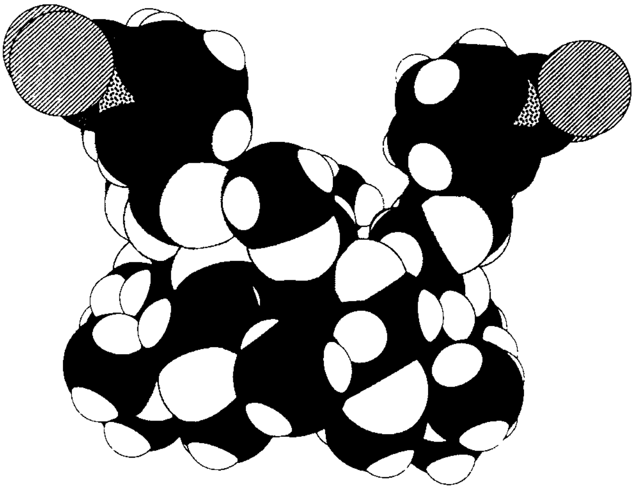


Figure 2 Molecular models for the complex **2**; **a** and **b**: non-spacefilling; **c**: spacefilling.



(c)

It is clear that the cis-platinum moieties are above (6.50 Å) and exterior to the molecular cavity, and that the nicotinate groups form an extended open sided hydrophobic cavity. The Pt-Pt distance (15.19 Å) excludeds any cooperative interactions. Non-equivalence of the nicotinate groups relative to the rotational axis is clear, with one parallel and the other antiparallel to the glucopyranose rings. The molecular orientation of these groups places the methyl groups of the CF glucopyranose units in a zone of ring current-induced deshielding: hence the shift from 2.93 to 3.10 ppm for the CH_3 signals.

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