Synthesis and Characterization of a Zinc(II) Complex of Bispicen

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The synthesis of a Zn(II) complex of bispicen, the tetradentate ligand *N*,*N*′-bis(2-pyridylmethyl)-ethylenediamine, of composition $[Zn(bispicen)Cl(H_2O)]_2[ZnCl_4]$ is reported. Its crystal and molecular structure was determined by single-crystal X-ray diffraction methods. It crystallizes in the monoclinic space group $C2/c$ with $Z = 4$ molecules per unit cell. The Zn(II) cation in the $[Zn(bispicen)Cl(H_2O)]^+$ complex is in a distorted octahedral environment, coordinated to a neutral bispicen molecule acting as a tetradentate ligand through its two amine nitrogen atoms, at *cis* positions, and its two pyridyl N atoms, at *trans* positions. The six-fold coordination is completed by a chloride ion and a water molecule. The tetrahedral $[ZnCl_4]^{2-}$ counter-ion lies on a crystallographic twofold axis. The complex was further characterized by FTIR spectroscopy, and its vibrational behavior compared with that of the dihydrated tetrahydrochloride of free bispicen.

Key words: Zn(II)-bispicen Complex, Crystal Structure, FTIR Spectra

Introduction

Alzheimer's disease (AD) is one of the main forms of dementia, characterized by the loss of cholinergic neurons and the progressive deterioration of cognitive function, memory and self-care. It has long been associated with the accumulation of insoluble amyloid "plaques" in the brain. These plaques are formed by a process called *amyloidosis*, whereby a 40 to 43-residue polypeptide called β-amyloid ($A\beta$) aggregates into insoluble fibers [1 – 4].

On the other hand, increasing evidence indicates that metal ion homeostasis is altered in AD, and a number of cations such as Cu(II), Zn(II) and Fe(III), accumulate in the neuropil of the AD brain and are further enriched within amyloid deposits. In particular, $A\beta$ binds these metal ions very avidly, and this may explain their enrichment in plaque pathology. Plaque deposits also generate oxidative damage, which may originate in the formation of H_2O_2 and free radicals in the presence of redox-active metal cations [1, 4 – 7]. This oxidative stress typifies AD neuropathology and precedes $A\beta$ deposition in this disease [3 – 5, 8] and is considered as one of the main triggers of aging in the brain, increasing with age and leading to a progressive decline in cell and tissue functions [4, 9].

As a result, if one admits that metal ions play a central role in Alzheimer's and related diseases, chelation therapy would be an interesting option for its treatment [3, 4, 10]. Obviously, a logical property of an adequate chelating agent is to target $A\beta$ oligomerization and $A\beta$-related generation of free radicals. Another important property of a potentially useful agent is its possibility to cross the blood-brain barrier. At the present time, there is no obvious solution to the design of a non-toxic ligand with high affinity for iron, zinc and copper and the ability to mobilize such metals from intracellular sites [4]. A new concept of metal-protein attenuating compound (MPAC) was introduced to describe an approach consisting of the introduction of a chelating agent to disrupt specific, abnormal metal-protein interactions [3, 4, 6]. This approach is very dif-

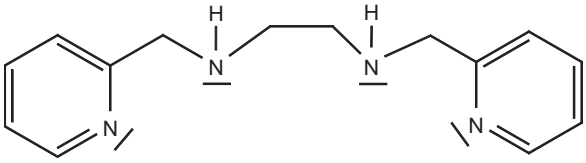

Fig. 1. Formula drawing of bispicen.

ferent from the process of chelation and excretion of bulk metal cations, which is the usual concept adopted in classical chelation therapies [4, 11].

One of the most interesting and recently explored chelators of this type is clioquinol (CQ, 5-chloro-7-iodo-8-hydroxyquinoline) [3, 4, 10]. Based on the promising properties of this ligand in the generation of very stable $M(CQ)_2$ complexes with Cu(II) and Zn(II), it was suggested that similar, structurally related, tetradentate ligands could form even more stable complexes. The first investigated ligand of this type was 2,2′-methylenedi-8-quinolinol [12] the structural and spectroscopic properties of which were also reported [13].

A number of similar chelating agents, with different linkers between the two 8-quinolinol moieties were subsequently explored [14], and most recently it was shown that another tetradentate ligand, *N*,*N*′-bis(2-pyridylmethyl)-ethylenediamine (bispicen) (Fig. 1), effectively competes with aggregated $A\beta$ polypetides for both Cu(II) and Zn(II) ions and is able to resolubilise the amyloid precipitates [15].

More recently, we have solved the crystal and molecular structure of the tetrahydrochloride of this interesting ligand and investigated its spectroscopic behavior [16]. As a contribution to the physical chemistry of bispicen complexes with metal ions, relevant in the control of neurodegenerative pathologies, we present here the preparation, solid-state molecular structure and vibrational properties of a new zinc complex of this ligand, namely $[Zn(bispicen)Cl(H_2O)]_2[ZnCl_4]$.

Results and Discussion

Synthesis of the complex

The complex was prepared using a slightly modified version of the procedure developed by Mohamadou *et al.* for the synthesis of metal complexes of the related *N*,*N*′-bis(2-pyridylmethyl)-1,3-propanediamine [17], reacting equimolecular amounts of ethanolic solutions of bispicen and $ZnCl_2$.

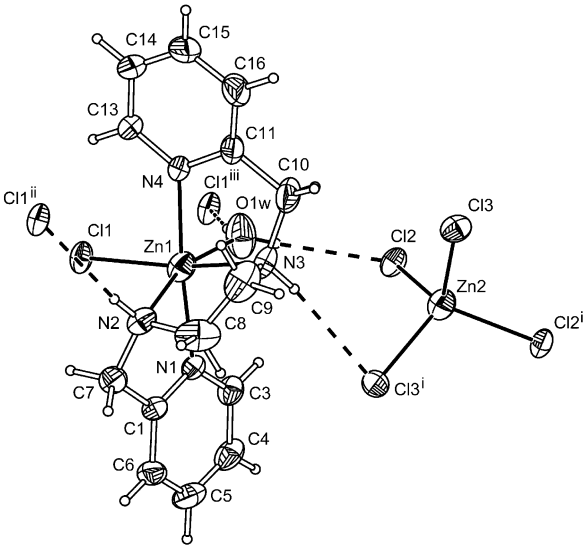

Fig. 2. View of the complex $[Zn(bispicen)Cl(H_2O)]_2[ZnCl_4]$ showing the labeling of the non-H atoms (displacement ellipsoids at the 50 % probability level). For clarity, a complete $[ZnCl_4]^{2-}$ ion has been included in the drawing. Zinc(II)-ligand bonds are indicated by full lines and hydrogen bonds by dashed lines. Crystal symmetry operations: (i) $-x$, y, $-z+1/2$; (ii) $-x+1/2$, $y+1/2$, $-z+1/2$; (iii) $-x+1/2$, $y-1/2$, $-z+1/2$.

Crystal and molecular structure of the complex

An ORTEP [18] plot of $[Zn(bispicen)Cl(H_2O)]_2[ZnCl_4]$ is shown in Fig. 2. Intramolecular bond lenghts and angles around the Zn(II) ion in the $[Zn(bispicen)Cl(H_2O)]^+$ complex are given in Table 1. The metal cation is in a distorted octahedral environment, with the typical *cis*-α-conformation of bispicen, usually found for tetradentate ligands [19]. Neutral bispicen coordinates through its two amine nitrogen atoms [Zn–N distances of 2.157(3) and 2.183(3) Å] at *cis* positions, and its two pyridyl N atoms [Zn–N distances of 2.193(2) and 2.170(3) Å], at *trans* positions. The remaining two (*cis*) positions are occupied by a chloride anion [*d*(Zn–Cl) = 2.4097(8) Å] and a water molecule [*d*(Zn–Ow) = 2.139(3) Å]. *trans* L–Zn–L angles are in the range from 162.9(1) to 173.8(1)°, and *cis* L–Zn–L angles are in the 76.1(1)–102.6(1)° interval. The compound is isostructural to the corresponding Mn(II) complex, $[Mn(bispicen)Cl(H_2O)]_2(MnCl_4)$, found as a by-product during the synthesis of $[Mn(bispicen)Cl_2]$ [19].

Table 1. Bond lengths (Å) and angles (deg) around Zn(II) in the cationic complex $[Zn(bispicen)Cl(H_2O)]^+$.

N(1)–Zn(1)	2.193(2)	N(2)–Zn(1)–N(3)	81.8(1)
N(2)–Zn(1)	2.157(3)	N(4)–Zn(1)–N(3)	76.8(1)
N(3)–Zn(1)	2.183(3)	O(1W)–Zn(1)–N(1)	90.2(1)
N(4)–Zn(1)	2.170(3)	N(2)–Zn(1)–N(1)	76.1(1)
O(1W)–Zn(1)	2.139(3)	N(4)–Zn(1)–N(1)	173.8(1)
Cl(1)–Zn(1)	2.4097(8)	N(3)–Zn(1)–N(1)	97.0(1)
		O(1W)–Zn(1)–Cl(1)	95.21(8)
O(1W)–Zn(1)–N(2)	162.9(1)	N(2)–Zn(1)–Cl(1)	95.43(9)
O(1W)–Zn(1)–N(4)	89.9(1)	N(4)–Zn(1)–Cl(1)	94.42(8)
N(2)–Zn(1)–N(4)	102.6(1)	N(3)–Zn(1)–Cl(1)	169.82(9)
O(1W)–Zn(1)–N(3)	89.9(1)	N(1)–Zn(1)–Cl(1)	91.74(7)

As mentioned above, we recently reported the crystal structure of the *N*,*N*′-bis(2-pyridylmethyl)-ethylenediamine tetrahydrochloride dihydrate salt where bispicen appears as a cationic (+4) molecule. The four positive charges are located at the amine $–NH_2^+$ and pyridyl $–NH^+$ groups hence giving rise to intra-molecular electrostatic repulsions that favors the extended conformation observed for this organic ion [16]. We can compare this with the neutral ligand by noting that deprotonation of the charged molecule at those groups creates four available binding sites in the neutral bispicen. This affords the folding of the molecule around the metal ion and its acting as the tetradentate chelator found in the isostructural *M*(II)-bispicen (*M*(II) = Zn, Mn) and other metal-bispicen complexes, including mononuclear and binuclear Fe(III) complexes [20], binuclear Mn(II), Co(II) and Cu(II) complexes [21] and trinuclear Mn(II) complexes [22].

The $[ZnCl_4]^{2-}$ counter-ion present in the investigated complex is on a crystallographic twofold axis and shows its expected tetrahedral molecular structure (Zn–Cl distances of 2.2761(8) and 2.2621(9) Å; Cl–Zn–Cl angles in the 106.24(3) – 111.31(7)° range).

The crystal is further stabilized by >N–H···Cl hydrogen bonds (N····Cl distances of 3.324 and 3.414 Å and N–H···Cl angles of 173.1 and 160.7°, respectively) and also by Ow–H···Cl hydrogen bonds (Ow···Cl distances of 3.120 and 3.204 Å and Ow–H···Cl angles of 171.6 and 176.4°). Further details of the hydrogen bonding structure are provided as Supplementary Information available online (Table S5; see note at the end of the paper for availability).

In the zinc(II) complexes derived from the related ligands *N*,*N*′-bis(2,2′-bipyridin-6-yl)methyl)-cyclohexane-1,2-diamine [23] and *N*,*N*′-bis(quinolin-2-yl-)methyl)cyclohexane-1,2-diamine [24] also relatively strong Zn(II)–N bonds are generated, with similar bond lengths as those found in the present case.

Vibrational spectra

The FTIR absorption spectrum of the new Zn(II) complex was compared with that of [bispicen·4HCl·2H$_2$O] [16]. The most informative spectral range, between 1800 and 400 cm^{-1}, is shown in Fig. 3. The proposed assignment is presented in Table 2 and briefly discussed as follows:

In the highest frequency region (not shown in Fig. 3) we have identified the characteristic CH_2 and $CH_{pyridine}$ stretching bands. The O–H stretching vibrations of the water molecule are well-split in the form of a triplet structure. The position of this OH bands suggest the presence of hydrogen bonds of medium length [25, 26].

Most of the characteristic high-frequency pyridine ν(CC) vibrations are slightly displaced to lower frequencies upon complex formation.

The characteristic $\delta(CH_2)$ deformational mode is observed as a very strong band in the complex, whereas in the free ligand it absorbs weakly.

Deformational modes of the pyridine ring are scarcely affected by complexation.

Metal-to-ligand vibrations are difficult to assign, notwithstanding we have tentatively assigned the observed 492/466 cm^{-1} doublet to one of the expected Zn–N stretching modes because they lie in a similar

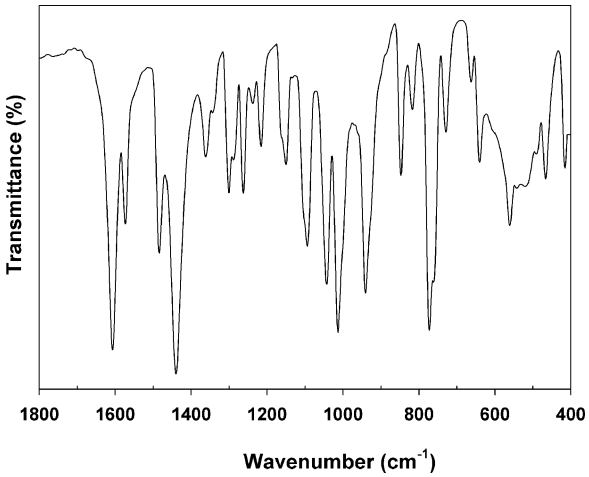

Fig. 3. FTIR spectrum of $[Zn(bispicen)Cl(H_2O)]_2[ZnCl_4]$ in the spectral range between 1800 and 400 cm^{-1}.

Table 2. Assignment of the FTIR spectrum of [Zn(bispicen)-Cl(H_2O)]$_2$[$ZnCl_4$].

Band position (cm^{-1})[a]	Proposed assignment
3397 s, 3323 m, 3229 vs	ν(OH) (H_2O)
3066 w, 3025 vw	ν(CH)py
2928 m, 2882 sh	$\nu(CH_2)$
1606 vs, 1573 m	ν(C–C)py + $\delta(H_2O)$
1483 s	ν(C–C)py
1440 vs	$\delta(CH_2)$
1361 m, 1344 sh	ν(C–C)py
1299 s, 1290 sh	$\tau(CH_2)$
1262 s, 1239 w,1216 m	ν(C–C)py + ν(CN)
1155 s, 1096 s	ν(C–C)CH_2
1044 vs	ρ(CH)py
1012 vs, 940 vs	ν(C–C)py
847 s, 817 m, 771 vs	δ(CH)py
728 m	δ(CC)py
663 w, 639 m	δ(CC)py + $\rho(H_2O)$
560 s, 540 sh, 521 w	δ(CC)py
492 sh, 466 m	ν(Zn–N)

[a] vs, very strong; s, strong; m, medium; w, weak; vw, very weak; sh, shoulder.

range as that recently found in the case of a number of Zn(II)/amino acid complexes [27]. Besides, Zn–O and Zn–Cl stretching vibrations are expected to appear below 400 cm^{-1} [28].

Vibrational modes of the tetrahedral $[ZnCl_4]^{2-}$ counter anion are also expected to absorb below 300 cm^{-1} [25, 28], out of the reach of our instrument and therefore not identified in the present study.

Experimental Section

Materials and measurements

All chemicals and reagents were obtained in analytical quality from commercial sources and used as purchased. *N*,*N*′-Bis(2-pyridylmethyl)-ethylenediamine tetrahydrochloride dihydrate (bispicen·4HCl·2H_2O) was obtained from 2-pyridylcarboxaldehyde and ethylenediamine in a three step synthesis, as described in our previous paper [16]. It was recrystallized from absolute ethanol, giving the product as a colorless powder, m. p. 209 – 211 °C, and its purity was additionally confirmed by elemental analysis, and ^{1}HNMR and FTIR spectroscopy.

The infrared absorption spectra were recorded on a FTIR Bruker EQUINOX-55 spectrophotometer in the spectral range between 4000 and 400 cm^{-1}, using the KBr pellet technique.

Synthesis of the complex

Sodium acetate trihydrate (0.54 g, 4 mmol) and bispicen·4HCl·2H_2O (0.42 g, 1 mmol) were dissolved in 30 mL of absolute ethanol and stirred for 10 min over a water bath. After cooling, the precipitated NaCl was filtered off. Then 0.14 g (1 mmol) of $ZnCl_2$, dissolved in 20 mL of absolute ethanol, was dropwise added to the filtrate, and the resulting solution was stirred for 15 min at room temperature. The solution was filtered to remove any undissolved material, and then it was left to stand in open air. The colorless crystalline precipitate obtained after a few days was collected and dried at room temperature (yield: *ca*. 50 %). The purity of the obtained complex was confirmed by elemental analysis, using a Carlo Erba model EA 1108 elemental analyzer. $C_{28}H_{40}Cl_6N_8O_2Zn_3$ (929.49): calcd. C 36.18, H 4.34, N 12.05; found C 36.10, H 4.40, N 12.00.

Single crystals adequate for X-ray diffraction structure studies were selected from the crystalline mass employing a microscope.

Crystal structure determination

The measurements were performed on an Oxford Xcalibur, Eos, Gemini CCD diffractometer with graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). X-Ray diffraction intensities were collected (ω scans with

Table 3. Crystal data and numbers pertinent to data collection and structure refinement for [Zn(bispicen)Cl(H_2O)]$_2$ [$ZnCl_4$].

Empirical formula	$C_{28}H_{40}Cl_6N_8O_2Zn_3$
Formula weight	929.49
Crystal dimension, mm^3	0.47 × 0.38 × 0.10
Crystal shape; color	prism; colorless
Temperature, K	292(2)
Crystal system	monoclinic
Space group	$C2/c$ (n° 15)
a, Å	28.281(2)
b, Å	8.4601(3)
c, Å	19.073(1)
β, deg	122.693(9)
Volume, Å^3; Z	3840.5(4); 4
Calculated density, g cm^{-3}	1.61
Absorption coefficient, mm^{-1}	2.3
F(000), e	1888
θ range for data collection, deg	3.26 – 26.00
Index ranges *hkl*	$-33 \le h \le 34$, $-10 \le k \le 5$, $-23 \le l \le 23$
Reflections collected	8314
Independent reflections/R_{int}	3752/0.0263
Observed reflections [$I > 2\,\sigma(I)$]	3083
Max./min. transmission	0.7999/0.4125
Data/restraints/ref. parameters	3752/0/229
Goodness-of-fit on F^2	1.055
Final indices $R1/wR2$ [$I > 2\,\sigma(I)$]	0.0339/0.0754
Final indices $R1/wR2$ (all data)	0.0454/0.0833
Largest peak/hole, e Å^{-3}	0.70/ − 0.47

ϑ and κ offsets), integrated and scaled with the CrysAlisPro [29] suite of programs. The unit cell parameters were obtained by least-squares refinement (based on the angular settings for all collected reflections with intensities larger than seven times the standard deviation of measurement errors) using CrysAlisPro. Data were corrected empirically for absorption employing the multi-scan method implemented in CrysAlisPro. The structure was solved by Direct Methods with SHELXS-97 [30] and the molecular model refined by full-matrix least-squares procedures on F^2 with SHELXL-97 [31]. All hydrogen atoms were located in a difference Fourier map phased on the heavier atoms. However, all bispicen H atoms but the ones attached to the amine nitrogen atoms were geometrically positioned and refined with the riding model. The amine and the water H atoms were refined at their found positions with isotropic displacement parameters. Crystal data and details of data collection and structure refinement are summarized in Table 3.

CCDC 906000 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Supporting information

Atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, hydrogen atom coordinates and isotropic displacement parameters, full bond lengths and angles, and H bond distances and angles are given as Supporting Information available online (DOI: 10.5560/ZNB.2013-3193).

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