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Original scientific paper

Synthesis and crystal structure of 1,2,3,4-tetrahydro-9-aminoacridine tetrachlorozincate(II) monohydrate

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Abstract: In the reaction of ZnCl₂ with tacrine hydrochloride in water novel tetracoordinated (C₁₃H₁₅N₂)₂[ZnCl₄]·H₂O complex was obtained and characterized by elemental analysis, molar conductivity and X-ray analysis. The complex crystallizes in the space group *P*-1 of the triclinic crystal system. The structure contains two crystallographically different molecules of protonated tacrine present as counter cations, the [ZnCl₄]²⁻ complex anion and one water solvent molecule. The counter cations slightly differ in the puckering of the cyclohexene ring. The molecules of protonated tacrine are involved in different intermolecular hydrogen bonds. In the crystal, the hydrogen bonding generates a 3D assembly. In the crystal, $\pi \cdots \pi$ stacking interactions between the rings of protonated tacrine were evidenced. The [ZnCl₄]²⁻ complex anion has a distorted tetrahedral geometry. Three out of the four Cl atoms are involved in intermolecular hydrogen bonding. The intermolecular H-bond interactions involving the Cl atoms affect the Zn–Cl bond lengths.

Keywords: Zinc; tacrine; X-ray analysis.

INTRODUCTION

Alzheimer's disease (AD) is a late-onset and the most common form of dementia affecting one in ten people over the age of 65 and one out of every two people over the age of 80. Symptoms include memory loss, anxiety, aggression, delusion, disorientation and loss of intellectual facilities, including cognition and eventually loss of physiological functions due to the advancing dementia.¹ Both genetic and environmental factors are implicated in its development.²

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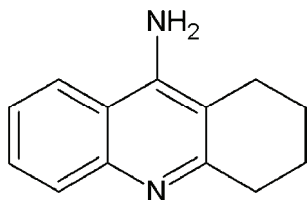
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The major hypothesis as to the cause of AD relates to the deposition in the brain of a peptide termed β -amyloid ($A\beta$).¹ β -Amyloid fragments can polymerize to form what are referred to as “plaques”.³

It is well known that the brain contains large amounts of metals (Cu(II), Zn(II) and Fe(III)).⁴ High levels of zinc, copper and iron are constitutively found in the neocortical regions which are most prone to AD pathology.² Although Zn(II), Cu(II) and Fe(III) play important roles in cortical physiology, only Cu(II) and Zn(II) are released during neurotransmission.^{4,5} These metal ions interact with the amyloid precursor protein (APP) and $A\beta$.^{6–8} Recently, research of copper/zinc chelators as inhibitors of $A\beta$ accumulation was initiated.^{9,10}

It is well known that many neurotransmitter systems are implicated in the etiology of AD; a cholinergic deficit having been clearly established. In addition, there is a decrease of choline acetyltransferase activity.² In the last two decades, various cholinergic drugs, primarily inhibitors of the enzyme acetylcholinesterase, such as tacrine, donepezil, rivastigmin and galantamin, are used in the medical treatment of AD patients.^{11,12} Tacrine is a drug that is used to treat the symptoms of mild to moderate Alzheimer’s disease. The drug retards the breakdown of acetylcholine; hence, it can build up and have a greater effect. It can improve thinking ability in some patients with AD. Bearing in mind that tacrine (Scheme 1) is widely used in the treatment of AD and that zinc is related to AD, it was considered interesting to investigate the possibilities of coordination of tacrine with Zn(II).



Scheme 1. Structure of tacrine.

EXPERIMENTAL

Synthesis of $(C_{13}H_{15}N_2)_2[ZnCl_4] \cdot H_2O$ (1)

A solution of 0.068 g (0.50 mmol) $ZnCl_2$ in 5 cm³ of water was added to a suspension of 0.234 g (1.0 mmol) tacrine hydrochloride ($C_{13}H_{14}N_2 \cdot HCl$) in 15 cm³ acetonitrile–water (9:1). The mixture was refluxed for 2.5 h (60 °C). The resulting solution was cooled to room temperature and after 16 h, a white microcrystalline product was obtained.

Synthesis of $C_{13}H_{14}N_2 \cdot 2H_2O$ (2)

An analogous reaction was performed using $Na_2[Zn(OH)_4]$ and tacrine hydrochloride whereby tacrine dihydrate was obtained. Yield: 40%.

Physical measurements

Elemental analyses were performed using an Elemental Vario EL III microanalyser. The molar conductivity of an aqueous solution of the complex (1.0×10^{-3} mol dm⁻³) was measured at room temperature on a Jenway-4009 digital conductivity meter.

X-Ray analysis

The single crystal X-ray data for compound **1** were collected on an Enraf-Nonius CAD-4 diffractometer¹³ using Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) and $\omega/2\theta$ scans in the 1.74 to 26.00° θ range. The cell constants and an orientation matrix for data collection, obtained from 24 centered reflections in the θ range 12.01 to 15.81° corresponded to a triclinic cell. The data were corrected for Lorentz and polarization effects.¹⁴ The crystal structure was solved by direct methods¹⁵ and difference Fourier methods, and refined on F^2 by the full-matrix least-square method.¹⁶ All six hydrogen atoms bonded to nitrogen atoms (N1a, N1b, N2a and N2b) as well as the two H atoms from the water molecule were taken from the ΔF map and refined isotropically. This treatment of H atoms resulted in unrealistically short X–H distances for some of the X–H (X = O,N) bonds. Due to this, all H atoms were included in the refinement at their geometrically calculated positions and treated with a riding model. Anisotropic displacement parameters were refined for all non-hydrogen atoms. PLATON,^{17,18} WinGX,¹⁹ PARST,²⁰ ORTEPIII²¹ and Mercury²² software were used for the preparation of the crystallographic materials for publication.

RESULTS AND DISCUSSION

Compound **1** was obtained in the reaction of aqueous solutions of ZnCl₂ and tacrine hydrochloride in the molar ratio 1:2 (yield: 142 mg (45 %)).

Elemental analysis of compound 1. C, 49.77, H, 5.50, N, 8.98 % corresponds to C₂₆H₃₂Cl₄N₄OZn ($FW = 623.77$); Calcd.: C, 50.04; H, 5.18; N 8.98 %. The result of the molar conductivity of compound **1** ($\lambda_M = 252$ Ω⁻¹ cm² mol⁻¹ (H₂O, 1.0×10^{-3} mol dm⁻³) is in agreement with a 2:1 electrolyte type.

Compound **2** was obtained by the same procedure as employed for **1** but starting from Na₂[Zn(OH)₄]. Elemental analysis of **2** showed it to be tacrine which had crystallized as the dihydrate. Anal. Calcd. for C₁₃H₁₈N₂O₂: ($FW = 234.3$): C, 66.64; H, 6.02; N 11.96 %. Found: C, 66.28, H, 5.50, N, 12.05 %.

Crystal data of 1. C₂₆H₃₂Cl₄N₄OZn; crystal system, triclinic; space group, P-1; unit cell dimensions: $a = 9.972(3)$ Å, $b = 11.843(3)$ Å, $c = 12.626(3)$ Å, $\alpha = 76.61(2)^\circ$, $\beta = 72.32(3)^\circ$, $\gamma = 87.10(3)^\circ$, $V = 1381.7(6)$ Å³; $Z = 2$; $\rho_c = 1.499$ mg m⁻³; $\mu = 1.303$ mm⁻¹; reflections collected, 5750; independent reflections, 5421 ($R_{\text{int}} = 0.0218$); final R indices ($I > 2\sigma(I)$), $R1 = 0.0647$, $wR2 = 0.1629$ (for 325 refined parameters); goodness-of-fit, 0.978.

The results of the single crystal X-ray analysis of **1** revealed that in the reaction of ZnCl₂ with tacrine, the more stable tetrachlorozincate(II) complex was obtained in which protonated tacrine (C₁₃H₁₅N₂⁺) serves as a counter cation (Fig. 1). This is the first structure of a typical complex compound with protonated tacrine as a counter ion. Only two crystal structures: (C₁₃H₁₅N₂Cl·H₂O, CSD refcode GICMEK01, and C₁₃H₁₅N₂[B(Ph)₄]·CH₃CN, CSD refcode

GOLFIW), containing protonated tacrine ($C_{13}H_{15}N_2^+$) were found in the Cambridge Structural Database (CSD).²³ Both of them are structures of salts of protonated tacrine. In the crystal structures of $C_{13}H_{15}N_2Cl \cdot H_2O$ (GICMEK01)²⁴ and $C_{13}H_{15}N_2[B(Ph)_4] \cdot CH_3CN$ (GOLFIW),²⁵ two and four C-atoms in the cyclohexenyl ring, respectively, are disordered. In the crystal structure of compound **1**, positional disorder was not observed. The crystal structure of **1** contains two different molecules of protonated tacrine ($C_{13}H_{15}N_2^+$), present as counter cations, and $[ZnCl_4]^{2-}$, as a complex anion, *i.e.*, two crystallographically independent molecules of protonated tacrine ($C_{13}H_{15}N_2^+$) and a $[ZnCl_4]^{2-}$ complex anion are in an asymmetric unit. There is also one molecule of crystal water in the asymmetric unit.

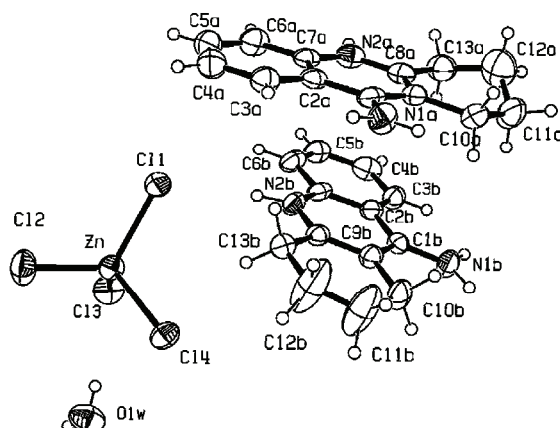


Fig. 1. The molecular geometry and atom labeling scheme of $(C_{13}H_{15}N_2)_2[ZnCl_4]H_2O$ (**1**). Selected bond distances (Å): Zn–Cl(1) = 2.282(2), Zn–Cl(2) = 2.232(2), Zn–Cl(3) = 2.293(2), Zn–Cl(4) = 2.273(2) and angles (°): Cl(2)–Zn–Cl(4) = 109.13(7), Cl(2)–Zn–Cl(1) = 114.97(7), Cl(4)–Zn–Cl(1) = 109.57(7), Cl(2)–Zn–Cl(3) = 111.49(7), Cl(4)–Zn–Cl(3) = 105.54(7), Cl(1)–Zn–Cl(3) = 105.70(7).

The cation molecules (labeled as A and B) are comparable in terms of conformational and geometrical parameters (bond lengths and angles) except in the position of the C(12) atom (from the C(12)H₂ group) that is out of plane in the case of the protonated tacrine A. The displacement from the mean plane of the C(8)–C(9)–C(10)–C(11)–C(13) fragment in the case of C(12a) is 0.58(1) Å (in the case of the protonated tacrine B, such a displacement is not significant, 0.02(1) Å for the C(12b) atom). Two molecules of protonated tacrine (A and B) form different H-bonds (Table I, Fig. 2). The most obvious difference is in the case of the pyridinium nitrogen [N(2)], which in molecule A forms a hydrogen bond with a water oxygen atom, while in molecule B it forms a weak H-bond with a chloride from $[ZnCl_4]^{2-}$. In addition, the amino group of cation A acts as a

single hydrogen bond donor, while that of cation B acts as a double hydrogen bond donor (*vide infra*). The solvent water molecule [O(1w)] serves as a double donor (to Cl(3) and Cl(3) at $-x+2, -y+2, -z$) and a single acceptor which is common for a water molecule. The chloride atoms (Cl(3) and Cl(3) at $-x+2, -y+2, -z$) help in completing the water rings around the centre of inversion at 0 0 0. The system of H-bond interactions spreads in three-dimensions. In the crystal packing, π -stacking interactions between the rings of protonated tacrine molecules occur. For example, the mean planes of the pyridinium rings are approximately parallel and they are at a distance of about 3.5 Å from each other. The cation molecules are stacked in the $\cdots A-A-B-B-A-A\cdots$ order (Fig. 2).

TABLE I. The geometry of hydrogen bonding and selected intermolecular interactions (Å and °, respectively) for compound **1**. Symmetry codes: *i*) x, y, z ; *ii*) $x-1, y, z$; *iii*) $-x+1, -y+1, -z$; *iv*) $-x+2, -y+2, -z$; *v*) $-x+1, -y+1, -z+1$; *vi*) $x, y-1, z$

D-H...A	D-H	D...A	H...A	D-H-A
N(2b)-H(2n2)...Cl(1) ⁱ	0.86	3.318(5)	2.49	162
N(1b)-H(1b)...Cl(1) ⁱⁱ	0.86	3.483(5)	2.70	153
N(1b)-H(2b)...Cl(3) ⁱⁱⁱ	0.86	3.433(6)	2.66	149
O(1w)-H(1w)...Cl(3) ⁱ	0.85	3.279(5)	2.45	163
O(1w)-H(2w)...Cl(3) ^{iv}	0.85	3.379(5)	2.59	155
N(1a)-H(2a)...Cl(4) ^v	0.86	3.260(6)	2.44	161
N(2a)-H(1n2)...O(1w) ^{vi}	0.86	2.772(6)	1.91	175

For the sake of comparison, the contacts surrounding the cations A and B in the present compound,

$C_{13}H_{15}N_2Cl \cdot H_2O$ (GICMEK01)²⁴ and
 $C_{13}H_{15}N_2[B(Ph)_4] \cdot CH_3CN$ (GOLFIW)²⁵
 are depicted in Figs. 3–6, respectively.

In two of the analyzed structures of protonated tacrine (cation B and GICMEK01), both hydrogen atoms from the amino group are involved in hydrogen bonding with chloride atoms. In the case of cation A, only one amine hydrogen is involved in NH...Cl hydrogen bonding. In the former cases, the intermolecular N-H...Cl bonds are more bent and weaker than in the latter one. In the crystal structure of $C_{13}H_{15}N_2[B(Ph)_4] \cdot CH_3CN$ (GOLFIW), one amine hydrogen is directional towards the phenyl group at the symmetry position $1-x, 1-y, 1-z$. This hydrogen is engaged in weak N-H... π (Ph) hydrogen bonding. The shortest N-H...C distance is 2.75 Å. In all the analyzed structures, the amino group is nearly coplanar with the aromatic ring system. The dihedral angle between the plane defined by the amino group and the plane defined by the aromatic ring system range from 1.6(6) to 8.6(3)°. The pyridinium nitrogen serves as a single hydrogen bond donor in the observed structures. The D-H...X angles of the two-centre hydrogen bonds involving pyridinium nitrogen are in the range 162–175°.

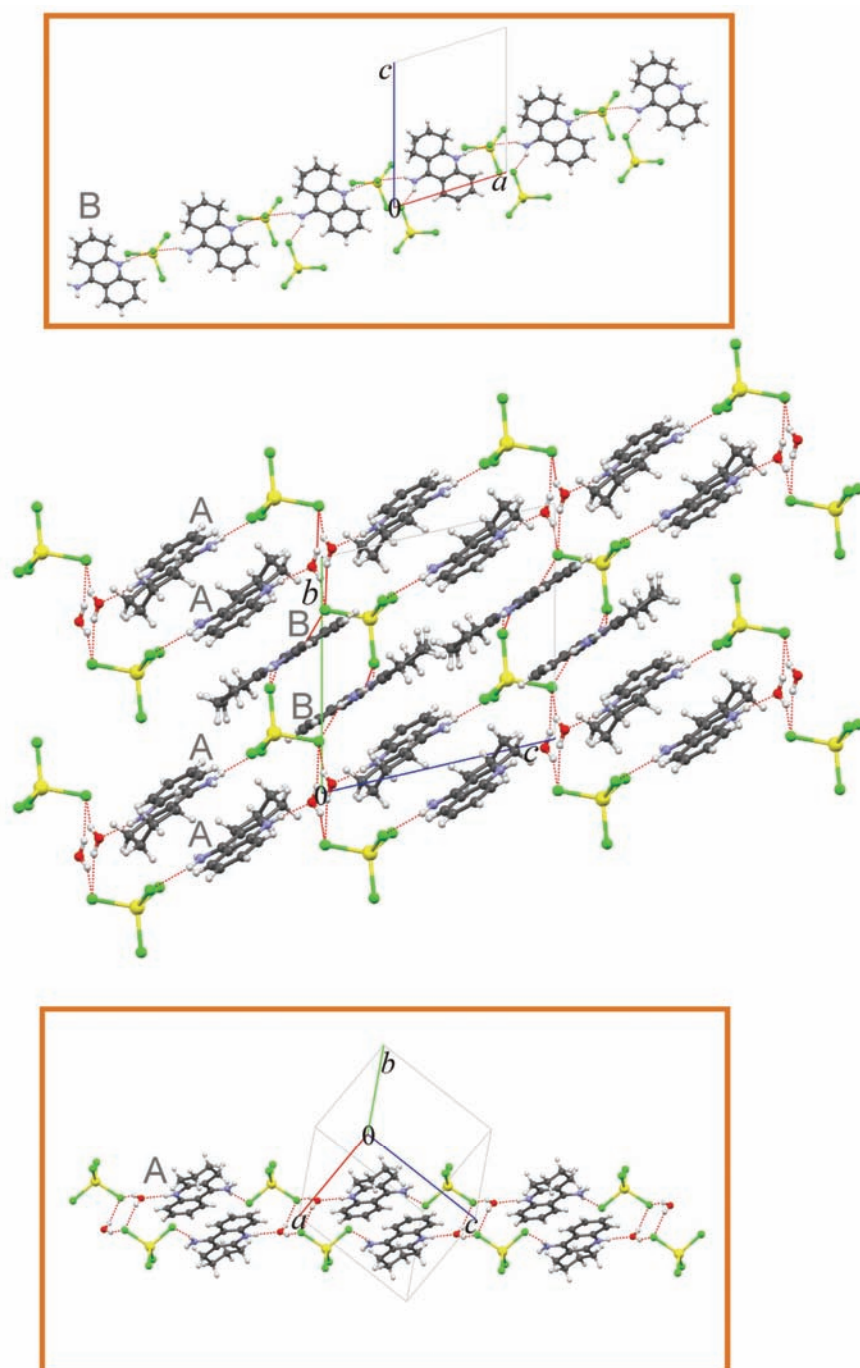


Fig. 2. The packing diagrams show intermolecular hydrogen bonding and π -stacking interactions in the crystal of (1).

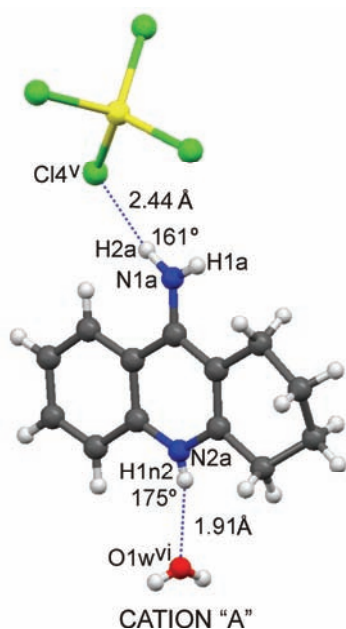


Fig. 3. The intermolecular contacts involving the functional groups of cation A. Symmetry codes: *v*) $-x+1, -y+1, -z+1$; *vi*) $x, y-1, z$.

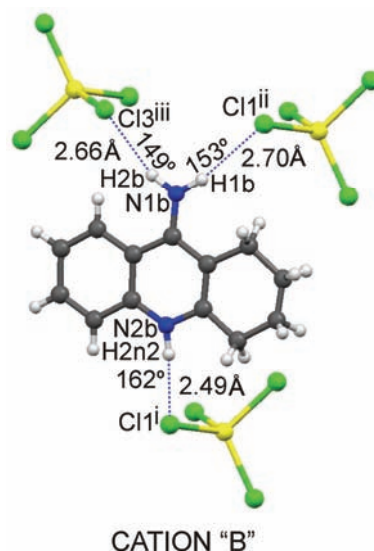


Fig. 4. The intermolecular contacts involving the functional groups of cation B. Symmetry codes: *i*) x, y, z ; *ii*) $x-1, y, z$; *iii*) $-x+1, -y+1, -z$.

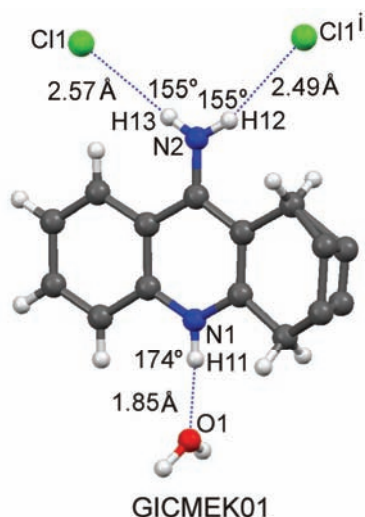


Fig. 5. The intermolecular contacts involving the functional groups of the cation in GICMEK01. Symmetry code: $3/2 - x; 1/2 + y; 1/2 - z$.

The interesting characteristics of the structure are the differences in Zn–Cl bond lengths in the $[\text{ZnCl}_4]^{2-}$ anion: Zn–Cl(2), 2.232(2); Zn–Cl(4), 2.273(2); Zn–Cl(1) 2.282(2) and Zn–Cl(3) 2.293(2) Å. The difference between the longest [Zn–Cl(3)] and the shortest bond [Zn–Cl(2)] is 0.06 Å. The differences in bond

lengths are the result of various H-bonds in which the Cl atoms participate. The Cl(3), Cl(1) and Cl(4) atoms serve as triple, double and single hydrogen bond acceptor, respectively, while the Cl(2) atom does not form any H-bond. The Zn–Cl bond length increases with increasing the number of hydrogen bonds in which the Cl atom is involved. The tetrahedral coordination geometry around the Zn atom is distorted with Cl–Zn–Cl coordination angles in the range from 105.54(7) to 114.97(7)°. These structural differences could also be explained by intermolecular interactions with involvement of the Cl atoms.

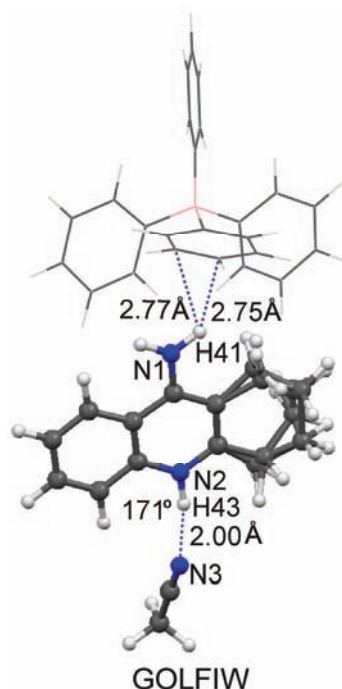


Fig. 6. The intermolecular contacts involving the functional groups of the cation in GOLFIW.

CONCLUSIONS

The $(C_{13}H_{15}N_2)_2[ZnCl_4] \cdot H_2O$ complex of distorted tetrahedral geometry was obtained in the reaction of $ZnCl_2$ with tacrine hydrochloride. The contacts surrounding the cations in the present structure and in the structures of $C_{13}H_{15}N_2Cl \cdot H_2O$ ²⁴ and $C_{13}H_{15}N_2[B(Ph)_4] \cdot CH_3CN$ ²⁵ reported elsewhere have been analyzed in detail. The prominent structural feature of $[ZnCl_4]^{2-}$ is the variation in the Zn–Cl bond lengths. The Zn–Cl bond length increases with increasing the number of intermolecular hydrogen bonds that involve the ligand atom.

Supplementary data. Cambridge Crystallographic Data Center, CCDC No. 695064, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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ИЗВОД

СИНТЕЗА И КРИСТАЛНА СТРУКТУРА 1,2,3,4-ТЕТРАХИДРО-9-АМИНОАКРИДИН-ТЕТРАХЛОРОЦИНКАТА(II) МОНОХИДРАТА

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У реакцији $ZnCl_2$ са такрин-хидрохлоридом у води, добијен је нови тетракоординовани $(C_{13}H_{15}N_2)_2[ZnCl_4] \cdot H_2O$ комплекс који је окарактерисан помоћу елементарне анализе, моларне проводљивости и рендгенске структурне анализе. Комплекс кристалише у просторној групи $P-1$ триклиничног кристалног система. Структура садржи два кристалографски различита молекула протонваног такрина који су присутни као контра-катјони, $[ZnCl_4]^{2-}$ комплексни анијон и молекул кристалне воде. Молекули катјона се незнатно разликују у степену набирања циклохексеновог прстена. Молекули протонваног такрина су укључени у различите интермолекулске водоничне везе. Интермолекулско водонично везивање у кристалу генерише 3Д молекулски скуп; $\pi \cdots \pi$ интеракције између прстенова протонваног такрина су примећене у кристалу. $[ZnCl_4]^{2-}$ има дисторговану тетраедарску геометрију. Три од четири Cl атома су укључена у интермолекулске водоничне везе. Интермолекулске водоничне интеракције које укључују Cl атоме утичу на дужину Zn–Cl веза.

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