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RE-REFINEMENT OF CRYSTAL STRUCTURE OF BIS(LIDOCAINE) DIAQUATETRATHIOCYANATONICKELATE(II)

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Abstract. This paper reports on the synthesis and structure re-refinement of bis(lidocaine) diaquatetrathiocyanatonickelate(II). The compound with the formula $(LidH)_2[Ni(NCS)_4(H_2O)_2]$, where Lid is (2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, crystallizes in the monoclinic space group $P2_1/c$ with a= 18.3509(5), b= 7.6532(2), c= 14.9585(4) Å, β= 109.964 (2)°, V= 1974.57 (9) $Å^3$, and Z= 2. Coordination of the Ni^{2+} ion with thiocyanate ions and water molecules generates the slightly distorted octahedral anion $[Ni(NCS)_4(H_2O)_2]^{2-}$ with *N*-bonded thiocyanate groups, while two protonated cations $LidH^+$ remain in an outer coordination field. The anion and cations are associated through hydrogen bonds formed by sulphur atoms with amido nitrogen atoms; water molecules and an amino nitrogen atom are involved in the formation of hydrogen bonds with sulphur atoms of neighbouring unit cells arranging alternating $[Ni(NCS)_4(H_2O)_2]^{2-}$ anions and $LidH^+$ cations into endless sheets lying in the *ac* plane.

Keywords: lidocaine complex, nickel(II), crystal structure, hydrogen bond.

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Introduction

Lidocaine or lignocaine (2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, Lid, see Figure 1) is a drug used as an anesthetic and for the treatment of chronic pain [1]. The lidocaine base is easily soluble in diethyl ether, but poorly soluble in water, and thus is used as its chlorohydrate salt $Lid{\cdot}HCl{\cdot}H_2O$, which is water soluble.

Analytical profiles of lidocaine and its salt are discussed in [2], and current data are given in [3,4]. Despite the fact that the molecular mechanism of action of local anesthetics upon the nervous system and contribution of the cell membrane to the process are still controversial [4], as was suggested about half a century ago [5], the ability to hydrogen bond donation is essential to the action of local anesthetics [5].

The crystal structure, hydrogen-bonding arrangement and conformation of the lidocaine molecule are significantly different for the free base, hydrochloride and other salts. Thus, the structure of lidocaine is characterized by the presence of two independent molecules in the asymmetric unit and by chains of hydrogen-bonded molecules in the crystal structure (space group: $P2_1/c$, a= 12.9590(3) Å, b= 13.8003(3) Å, c= 18.8288(5) Å, α= 90°, β= 122.340(3)°, γ= 90°). The intermolecular hydrogen bond is formed between the amido nitrogen and aceto oxygen atoms with N···O distance of 2.8746(17) Å and N–H–O angle of 140.9(18)° [6].

Lidocaine hydrochloride monohydrate crystals, $Lid{\cdot}HCl{\cdot}H_2O$, are monoclinic, $P2_1/c$, Z= 4; if not taking into account the alternative structure present at about 5% occupancy, then the predominant structure is fully hydrogen bonded, with adjacent lidocaine cations linked by water molecules into endless chains parallel to *b* axis. Adjacent chains related by the screw axes are joined in pairs by chlorine ions, which bind N^+H and H_2O groups in different chains [7,8].

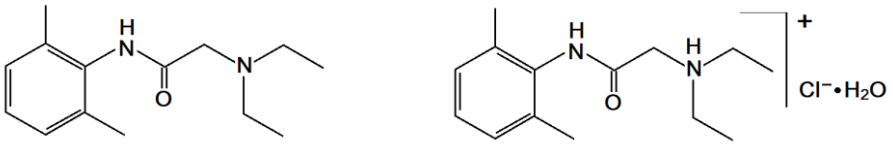

Figure 1. Lidocaine base (left) and lidocaine hydrochloride monohydrate (right).

The crystals of lidocaine hydrohexafluoroarsenate, $LidH{\cdot}AsF_6$, are monoclinic, *C*2/*c*, *Z*= 8; the lidocaine moiety was found to be in the biologically active cationic form, with the protonated amino nitrogen atom. This atom is strongly hydrogen-bonded to the oxygen atom of an adjacent cation and joins pairs of cations across the centers of symmetry, while the amido nitrogen atom is weakly hydrogen-bonded to a fluorine atom of the hexafluoroarsenate anion [9]. The lidocaine bis-*p*-nitrophenylphosphate, $[LidH]^+$ $[C_{12}H_8N_2O_4P]^-$, crystallizes in the monoclinic space group $P2_1/c$, *Z*= 4; both the amino and the amide hydrogen atoms participate in hydrogen bonds to the phosphate group, with N···O distances of 2.690 and 2.801 Å, respectively [10].

Lidocaine barbiturate, $[LidH]^+[C_4H_3N_2O_3]^-$, was synthesized and studied not for medical use, but as a nonlinear optical material. All nitrogen atoms participate in hydrogen bonding with N···O distances from 2.697(2) to 2.833(2) Å and N–H–O angles from 151 to 177°, forming tapes lying in the *bc* plane [11].

Bis(lidocaine) tetrathiocyanatocobaltate(II) hydrate crystals, $Lid_2[Co(NCS)_4](H_2O)$, are triclinic, space group no. 2, *Z*= 2; the packing shows a layered arrangement along *c* axis, lidocaine remains in the free base form and its layer is penetrated by the sulphur atom of one of the thiocyanate groups [12]. For crystals of lidocaine tetrachlorocobaltate(II) (monoclinic, space group $P2_1/c$, Z= 2), $Lid_4(CoCl_4)_2$ [13], and crystals of lidocaine tetrabromozincate(II) (orthorhombic, space group *P*bca, Z= 8), $Lid_4(ZnBr_4)_2$ [14], the asymmetric unit has four ligand molecules and two metal groups; the molecules are stacked and the metal and ligands do not form independent layers. In the cobalt(II) and nickel(II) complexes (Lid_2MX_2, where M is Co^{2+} or Ni^{2+}, X is dicyanamide $C_2N_3^-$ or thiocyanate SCN^-) lidocaine chelates metal ions through the amide and amino groups [15]. The tetrathiocyanatopalladate(II), $(LidH)_2[Pd(SCN)_4]$, crystallizes in the monoclinic space group $P2_1/n$, *Z*= 4; the palladium atom is in a square planar coordination, the coordination polyhedron is undistorted and it does not show any hydrogen bonding with protonated lidocaine, the packing of the molecules shows a strongly layered arrangement [16], same as in the crystal structures of bis(lidocaine) tetrabromocuprate(II) (monoclinic, $P2_1/c$, Z= 4), Lid_2CuBr_4 [17], and the lignocaine hydrochloride – nickel thiocyanate complex (monoclinic, $P2_1/a$, Z= 4) [18]. All of the listed lidocaine coordination compounds were obtained for medical use, but only for the cobalt(II) and nickel(II) complexes with lidocaine as a bidentate ligand, it was reported, that metal coordination enhanced the DNA binding activity, cleavage activity and cytotoxic properties of lidocaine [15].

The purpose of our work was to obtain new complexes of lidocaine and define their physico-chemical properties and structure; this contribution concerns bis(lidocaine) diaquatetrathiocyanatonickelate(II).

Experimental

Generalities

All solvents and reagents were obtained from commercial sources and were used as received without further purification.

Synthesis

Starting materials were lidocaine free base $C_{14}H_{22}N_2O$ (Lid), nickel chloride hexahydrate $NiCl_2{\cdot}6H_2O$, and anhydrous potassium thiocyanate KSCN. Nickel(II) complex of lidocaine was prepared in water-methanol solution (pH 5-6) with 1:2:4 molar ratio of the nickel chloride, lidocaine, and potassium thiocyanate. The prepared mixture was filtered, placed on a magnetic stirrer with heating for a while, and then left at room temperature for slow evaporation, details are given in [19]. Crystals suitable for X-ray measurements started to form after 2-3 days. The resulting crystals were washed with ether and dried in air. Isolated yield 67%. Elemental analyses data (wt.%) calculated for $C_{32}H_{50}N_8NiO_4S_4$: C 48.18; H 6.32; N 14.04; Ni 7.36; O 8.02; S 16.04; found: C 48.12; H 6.29; N 14.01; Ni 7.39; O 8.05; S 16.07.

Physical measurements

Fourier transform infrared spectra were recorded on a AgilentCary 630 FTIR spectrometer over the wavenumber range 4000–400 cm^{-1} using KBr pellets.

Elemental analysis was performed using a Labertherm CHN elemental analyser and a Perkin-Elmer atomic absorption spectrometer.

Melting point values have been measured on the Dynalon SMP_{10} device.

X-ray diffraction measurements were carried out with an Oxford Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated MoKα radiation. The data collection, cell refinement and data reduction were carried out with the CrysAlis^{PRO} package of Rigaku Oxford Diffraction [20]. The structure (Table 1) was solved by direct methods and refined against F^2 with full-matrix least-squares using the programs complex SHELXL-2014 [21].

Table 1

Crystal data and details of data collection for $(LidH)_2[Ni(NCS)_4(H_2O)_2]$.

Parameter	*Value*
Empirical formula	$C_{32}H_{50}N_8NiO_4S_4$
Fw	797.75
T, K	100(2)
Space group	$P2_1/c$ (No. 14)
a, Å	18.3509(5)
b, Å	7.6532(2)
c, Å	14.9585(4)
β, °	109.964(2)
V, Å^3	1974.57(9)
Z	2
ρ_{calc}, g·cm^{-3}	1.342
μ, mm^{-1}	0.748
Crystal size, mm	0.39x0.31x0.27
2Θ range, °	5.9 to 65.3
Reflections collected	41880
Independent reflections	6860 (R_{int}= 0.0338)
Data/restrains/parameters	5884/0/244
R_1 [a]	0.0314
wR_2 [b]	0.0755
GOF[ac]	1.000
$\|\Delta\rho\|_{max}$, e Å^{-3}	0.48(6)

[a] $R_1 = \Sigma||F_0| - |F_c||/\Sigma|F_0|$,
[b] $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2/\Sigma[w(F_o^2)^2]\}^{½}$,
[c] $GOF = \{\Sigma[w(F_o^2-F_c^2)^2]/(n-p)\}^{½}$, *where n is the number of reflections and p is the total number of parameters refined.*

CCDC 1859310 contains the supplementary crystallographic data for this contribution, and can be obtained free of charge *via https://www.ccdc.cam.ac.uk/conts/retrieving.html* (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Results and discussion

The reaction between nickel chloride, lidocaine, and potassium thiocyanate in methanol solution leads to the formation of a new complex; it crystallizes in a form of pale green prisms, has a melting point at 188°C, and is slightly soluble in water and readily soluble in ethanol and acetone. The results of elemental analysis [19] indicate the presence of two protonated lidocaine moieties, four thiocyanate groups, and two water molecules per nickel atom in the composition of the prepared complex, which differs from the composition of the known nickel(IV) thiocyanate complex having two unprotonated lidocaine molecules in its structure.

The IR spectrum of the lidocaine complex showed the same bands as for the lidocaine free base and its salts, including sharp absorption peaks at 3270 cm^{-1} (3250, 3172 and 3235 cm^{-1} for lidocaine free base, hydrochloride monohydrate and thiocyanide, respectively) due to amide N–H stretch, at 1690 cm^{-1} (1667, 1673 and 1660 cm^{-1}) due to amide C=O stretch, and at 1506 cm^{-1} due to aromatic C=C bending vibrations. The benzene ring in lidocaine molecule also gives the peak at about the 3030 cm^{-1} due to aromatic C–H stretch vibrations, other weak but resolved peaks are observed at 1590 cm^{-1} (1476, 1592 and 1546 cm^{-1}) and 1272 cm^{-1} (1292, 1272 and 1280 cm^{-1}) due to amide band II and III vibrations, as well as a peak in the fingerprint region at 780 cm^{-1} (765, 774 and 770 cm^{-1}) due to deformations of the 1,2,3-trisubstituted aromatic ring.

As in the long-standing work on the IR spectra of lidocaine salts [22] and other publications [2,3,14,17] no attempt was made to disentangle and assign the generally poorly resolved C–H stretching bands near 3000 cm^{-1} arising from the *N*-ethyl substituents ($\nu_{asym}(CH_2)$ near 2930±10 cm^{-1}, $\nu_{asym}(CH_3)$ near 2960±10 cm^{-1}, and $\nu_{sym}(CH_3)$ near 2870±10cm^{-1}) and the methyl substituents of the phenyl ring usually giving prominent bands near 2925 and 2865 cm^{-1} as well as variable intensity

bands near 2975 and 2945 cm^{-1}. Perhaps the band at 2800 cm^{-1} in the spectrum of lidocaine free base can be assigned to $\nu_{sym}(CH_2)$ for the methylene group at the nitrogen atom with a stretching frequency usually lowered from its value in hydrocarbons near 2850 cm^{-1}, but this effect is completely eliminated when nitrogen acquires a positive charge in amine salts.

The IR spectra of lidocaine salts and complexes show absorption peaks due to NH^+ stretching vibrations. In the IR spectrum of lidocaine hydrochloride monohydrate, all eight peaks and shoulders at 2640–2460 cm^{-1} are observed, but for complexes these peaks have higher frequencies, as is the case with salts of strong acids [22]. In addition, in complexes, NH^+ stretching peaks overlap with C–H stretching bands.

The IR spectrum of Lid·HCl·H_2O also shows two narrow peaks near 3460 and 3390 cm^{-1} due to O–H stretching vibrations in hydrogen-bonded water molecules, these peaks are also visible in the spectrum of lidocaine complex. It is believed that IR is a tool that allows identification of the formation of hydrogen bond interactions, by the shift of the bands of the functional groups involved in the formation of hydrogen bonds. However, this tool does not always lead to correct results. For example, according to the IR study of Neville, G.A. and Regnier, Z.R. [22], the lidocaine hydrohexafluoroarsenate is essentially free of hydrogen bonding, but the X-ray analysis [9] is in conflict with this conclusion.

The IR spectrum of the lidocaine thiocyanate, LidH·NCS, shows a very strong peak at 2068 cm^{-1} corresponding to the first fundamental frequency [23] of the thiocyanate C–N stretching, and weak peaks of the second (396 cm^{-1}) and third (770 cm^{-1}) fundamental frequencies. According to the data of Bertini, I. and Sabatini, A. [24], the IR spectra of substituted thiocyanate complexes showed the C–N stretching of characteristic forms and values: >2100 cm^{-1} and a sharp peak for *S*-bonded thiocyanates, and ≤2100 cm^{-1} and broad peaks for *N*-bonded ones. The second and third fundamental frequencies are also sensitive to the type of bonding: 450-490 and 760-880 cm^{-1} for *N*-bonded thiocyanates, 400-440 and ≈700 cm^{-1} for *S*-bonded thiocyanates. The IR spectrum of LidH NCS presents peaks at 2068, 496 and 790 cm^{-1} corresponding to *N*-bonding. However, for the obtained Ni(II) lidocaine thiocyanate complex, consideration of these IR bands does not allow us to unambiguously determine the type of bonding. So, in the spectrum of the complex the first fundamental frequency is observed at 2124 cm^{-1}, which indicates *S*-bonding, but the peak is rather narrow (<4 cm^{-1} at half height), as well as the second and third fundamental frequencies are registered at 480 and 810 cm^{-1}, respectively, and this indicates *N*-bonding.

According to the X-ray crystallography, the investigated compound has a molecular crystal structure of bis(lidocaine) diaquatetrathiocyanatonickelate(II), in which coordination of the Ni^{2+} ion with four thiocyanate (rhodanide) anions and two water molecules generates the slightly distorted octahedral anion $[Ni(NCS)_4(H_2O)_2]^{2-}$ with *N*-bonded thiocyanates, while two protonated cations $LidH^+$ remain in an outer coordination field (Figure 2).

The Ni(II) in the $[Ni(NCS)_4(H_2O)_2]^{2-}$ anion is in an octahedral NiN_4O_2 coordination geometry, being ligated by four nitrogen atoms from the monodentate thiocyanate groups and two trans-related aqua ligands. Oxygen atoms from water molecules are spaced from the central atom by the same distance of 2.0987(9) Å.

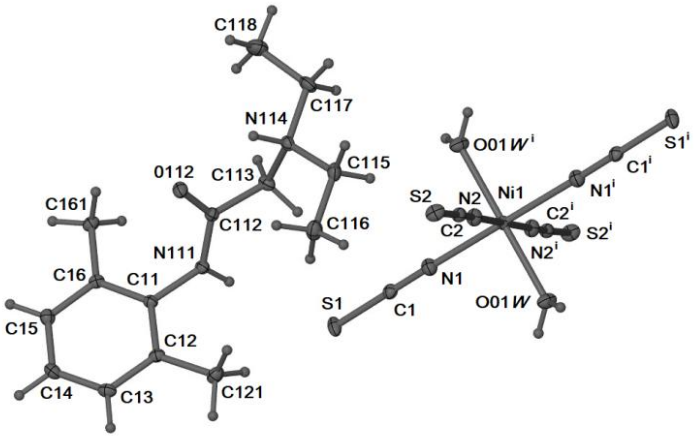

Figure 2. Cation and anion in the crystal structure of the $(LidH)_2[Ni(NCS)_4(H_2O)_2]$, showing the atom numbering scheme. Displacement ellipsoids are drawn at 50% of the probability level.

In the same anions of bis(4,4'-bipyridinium) diaquatetraisothiocyanato nickellate(II) dinitrate [25] and mixed ligand cationic–anionic nickel(II) complex containing 1,4-diazepane [26], this distance is somewhat smaller and amounts to 2.071(4) Å, but in the nickel thiocyanate complex described in a previous study this distance is larger and is 2.169(5) Å [18]. Nitrogen atoms in the NiN_4O_2 octahedron are located at different distances from the central nickel atom as shown in Figure 3, and the angles between the N–Ni–N bonds slightly deviate from 90° with a minimum of 87.89(4)° for angle $N1^{i}$–Ni–N2 and a maximum value of 92.11(4)° for angles N1–Ni–N2 and $N1^{i}$–Ni–$N2^{i}$ (Symmetry code: (i) *−x+1, −y+1, −z+1*). The Ni–N distances depend on the nature of the complex, in the cationic-anionic diazepane complex [26] they are the smallest, 1.905(4) and 1.918(3) Å, in the dipyridinium complex [25] they are comparable with our results, 2.055(3) and 2.107(4) Å, and in the thiocyanate complex [18] they are slightly larger, 2.13(2) and 2.18(3) Å.

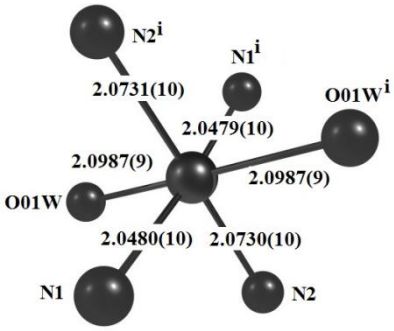

Figure 3. Length (Å) of Ni–O and Ni–N bonds in the $Ni[(NCS)_4(H_2O)_2]^{2-}$ ion.

The aromatic ring in $LidH^+$ is asymmetric, but the deviations of the C–C bond lengths (from 1.3887(16) to 1.4016(15) Å) and angles (from 117.79(10) to 122.37(10)°) from the standard ones are insignificant, the torsion angles are small (from -1.47(16) to 1.04(16)°), and the aromatic ring can conditionally be considered flat.

The C11–N111, N111–C112, C112–O112, and C112–C113 bond lengths are 1.4366(14), 1.3412(14), 1.2253(13), and 1.5281 Å, respectively, which is typical of crystalline carboxamides [27]. The amide group of Lid^+ is twisted out from the plane of the aromatic ring by 66.74(14)° (torsion angle C16–C11–N111–C112). The torsion angle C11–N111–C112–O112 is 3.93(18)°, so that the aromatic ring and the oxygen atom adopt a *synperiplanar* (*cis*) conformation with respect to the N111–C112 bond, while the aromatic ring and diethylamino chain adopt the *antiperiplanar* (*trans*) conformation (torsion angle C11–N111–C112–C113 is −174.10(10)°).

The nitrogen atoms N111 and N114 adopt an *antiperiplanar* conformation with respect to the N111–C112–C113–N114 torsion angle of −152.36(10)°. Such staggered conformation excludes the formation of an intramolecular hydrogen bond N111–H111···N114 noted in the lidocaine free base [6] and in the molecular complex of lidocaine with phloroglucinol, when the nitrogen atoms adopt a *synperiplanar* conformation [28]. On the contrary, the carbonyl oxygen atom and the nitrogen atom of the amino group adopt the *synperiplanar* conformation (torsion angle O112–C112–C113–N114 is 29.46(14)°), which leads to the formation of a strong intramolecular hydrogen bond N114–H114···O112 in $LidH^+$. In addition to the Coulomb attraction force, the anion $[Ni(NCS)_4(H_2O)_2]^{2-}$ and cations $LidH^+$ are associated by the N–H···S hydrogen bond between the amide nitrogen atoms N111 and sulphur atoms of the thiocyanate groups.

Hydrogen bonding also determines the nature of supramolecular structure through the interaction between neighbouring unit cells. In the water molecule, hydrogen atoms H01*A* and H01*B* are included in hydrogen bonding between the oxygen atom O01*W* and the sulphur atoms $S2^{ii}$ and $S2^{iii}$ of the neighbouring unit cells. The diethylamino-*N*-group is protonated, and corresponding hydrogen atom H114 forms a bifurcated hydrogen bond with the carbonyl oxygen atom O112 (intramolecular hydrogen bond described above) and the sulphur atom $S1^{iv}$ of the neighboring unit cell. Interatomic distances and valence angles for the intramolecular N–H···O and the intermolecular N–H···S, N–H···S, and O–H···S hydrogen bonds are given in Table 2.

The general picture of intermolecular hydrogen bonding in $(LidH)_2[Ni(NCS)_4(H_2O)_2]$ is shown in Figure 4, representing the unit cell and part of the crystal packing along the *b* crystallographic axis. Due to the O–H···S hydrogen bonds, anions $[Ni(NCS)_4(H_2O)_2]^{2-}$ form endless chains lying along the *c* axis, the $LidH^+$ ions are stacked with the anions by the N–H···S hydrogen bonds, the anions alternate with cations and together they form sheets lying in the *ac* plane.

Table 2

Hydrogen bonds geometry.

D–H···A	*D–H (Å)*	*H···A (Å)*	*D···A (Å)*	*D–H···A (°)*
N114–H114···O112	0.894 (16)	2.152 (16)	2.6824 (12)	117.3 (12)
N111–H111···S1	0.846 (19)	2.682 (19)	3.4942 (10)	161.4 (16)
O01*W*–H01*A*···S2^{ii}	0.85 (2)	2.45 (2)	3.2914 (10)	170.0 (18)
O01*W*–H01*B*···S2^{iii}	0.85 (2)	2.51 (2)	3.3110 (10)	158.5 (19)
N114–H114···S1^{iv}	0.894 (16)	2.499 (15)	3.2800 (10)	146.2 (13)

Symmetry codes: ^{ii} *−x+1, y+1/2, −z+1/2;* ^{iii} *x, y+1, z;* ^{iv} *x, y−*1, *z.*

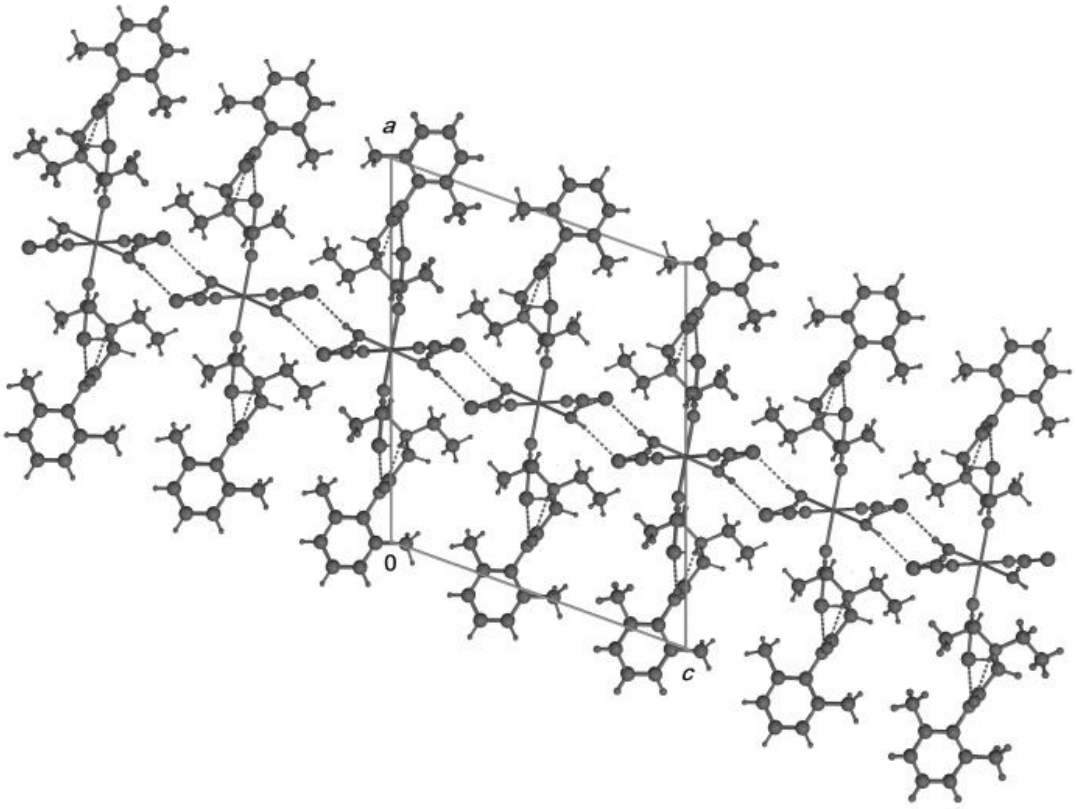

Figure 4. Unit cell of $(LidH)_2[Ni(NCS)_4(H_2O)_2]$ and partial crystal packing viewed along [010].

Conclusions

This work reports the synthesis and structure re-refinement of bis(lidocaine) diaquatetrathiocyanatonickelate(II). The synthesis of bis(lidocaine) diaquatetrathiocyanatonickelate(II) was carried out in water-methanol solution (pH=5-6) with 1:2:4 molar ratio of the nickel chloride, lidocaine, and potassium thiocyanate, resulting in pale green prismatic crystals.

The FTIR spectrum contains all the bands of corresponding functional groups, but the fundamental frequencies and the shape of the thiocyanate C–N stretching vibrations do not make it possible to unequivocally determine the nature of the bonding of thiocyanate to the nickel atom.

The single-crystal X-ray diffraction characterization shows that the complex crystallizes in the monoclinic space group $P2_1/c$ with a= 18.3509(5), b= 7.6532(2), c= 14.9585(4) Å, β= 109.964 (2)°, Z= 2, and consists of the $Ni[(NCS)_4(H_2O)_2]^{2-}$ slightly distorted octahedral anion with *N*-bonded thiocyanate groups and two protonated cations of lidocaine $LidH^+$ in an outer coordination field. Along with the Coulomb interaction, the anion and cations are associated by the N–H···S hydrogen bonds, while the N–H···S and O–H···S hydrogen bonds provide links with neighbouring unit cells, so the $[Ni(NCS)_4(H_2O)_2]^{2-}$ anions alternate with the $LidH^+$ cations and form endless sheets lying in the *ac* plane.

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