Chemistry

Molecular and Crystal Structure of Bis(Lidocaine) Tetrachlorozincate(II)

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The present paper reports on the synthesis, molecular and crystal structure of bis(2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) tetrachlorozincate(II). The complex with the formula $(C_{14}H_{23}ON_2)_2ZnCl_4$ (or (LidH)₂ZnCl₄), crystallizes in the monoclinic space group $P2_1/c$ with a = 8.8921(2), b = 19.2650(3), c = 19.3211(3) Å, $\beta = 95.026(2)^\circ$, V = 3297.10(10) Å³, Z = 4, and $D_c = 1.366$ Mg/m³. In molecular structure the coordination of the Zn²⁺ ion with chlorine atoms generates slightly distorted tetrahedral anion ZnCl⁴²⁻, while two protonated cations LidH⁺ remain in an outer coordination sphere. The anion and cations are associated by hydrogen bonds formed by two chlorine atoms with amido nitrogen atoms, the conformation of the flexible chain of lidocaine molecules provides for the formation of an intramolecular hydrogen bond between the protonated amino nitrogen atoms also form intermolecular hydrogen bonds with the oxygen atoms of neighboring molecules of the charge-transfer complex, combining them in pairs 2[(LidH)₂ZnCl₄]. Each pair forms intermolecular N–H···Cl hydrogen bonds with four adjacent pairs, arranging them into endless sheets lying in the bc plane. © 2020 Bull. Georg. Natl. Acad. Sci.

Lidocaine complex, X-ray analysis, crystal structure, hydrogen bond

Lidocaine or lignocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide, Lid) is the most common and important local anaesthetic and antiarrhythmic drug [1]. The lidocaine base $C_{14}H_{22}ON_2$ is easily soluble in diethyl ether, but poorly soluble in water, and thus is used in form of water soluble lidocaine hydrochloride monohydrate $C_{14}H_{22}ON_2$ ·HCl·H₂O. Despite the fact that the molecular mechanism of action of lidocaine and other local anaesthetics upon the nervous system and contribution of the cell membrane to the process are still controversial [2], the ability to hydrogen bond donation is essential to the action of local anaesthetics [3].

Charge transfer complexes of lidocaine are of interest because of their role in medical and other applications. The first lidocaine complex, $(LidH)_2$ ZnCl₄, was obtained and studied back in 1981 [4]. The structure was refined to an *R* value of 0.114, and it was noted that the interatomic distances and angles are

not highly accurate. Despite this, certain conclusions were drawn: the lidocaine molecules are protonated at the dimethylamino group, the structures of both molecules are similar except the conformation relative to the chain between the amino and amido nitrogen atoms, and the $ZnCl_4^{2-}$ anion is slightly distorted. Study [4] did not concern hydrogen bonding and crystal packing; these issues were considered in work [5] reporting the crystal structure of lignocaine hydrochloride – zinc chloride complex with strange brutto-formula $ZnCl_4C_{28}N_4O_2H_{44}$. The structure was refined to an *R* value of 0.071, but the protonation of the amino nitrogen atom was not taken into account and led to conflicting conclusions.

The aim of our work was to carry out X-ray measurements and structure refinement at a modern level and to clarify all the details of the molecular and crystal structure of bis(lidocaine) tetrachlorozincate(II).

Materials and Methods

Zinc(II) complex of lidocaine was prepared in water-methanol solution with 1:2 molar ratio of the zinc chloride (ZnCl₂) and lidocaine hydrochloride monohydrate ($C_{14}H_{22}ON_2 \cdot HCl \cdot H_2O$). To avoid the hydrolysis of Zn(II) salt, 2-3 drops of concentrated hydrochloric acid were added to the solution during synthesis. Colorless prismatic crystals suitable for the X-ray measurements started to form after 4 days. The resulting crystals were washed with ether and dried in air. Isolated yield 68%. Elemental analyses were performed using a Labertherm CHN elemental analyser and a Perkin-Elmer atomic adsorption spectrometer. Elemental analyses data (wt.%): calculated for $C_{28}H_{46}Cl_4N_4O_2Zn$: C 47.78; H 6.26; N 13.93; found: C 47.71; H 6.19; N 13.90.

The crystal and molecular structure of the complex was determined by single crystal X-ray diffraction (XRD) method using crystal with sizes $0.47 \times 0.36 \times 0.35 \text{ mm}^3$. XRD measurements were carried out with an Oxford Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated MoK α radiation ($\mu = 1.100 \text{ mm}^{-1}$. $F_{000} = 1422$, $\lambda = 0.71073 \text{ Å}$, T = 100(2)K). The data collection, cell refinement and data reduction were carried out with the CrysAlis^{PRO} package of Rigaku Oxford Diffraction (version 1.171.38.46, 2015); theta range for data collection was up to $2\theta_{\text{max}} = 65.2^{\circ}$, 39836 reflections collected, 11211 unique ($R_{\text{int}} = 0.0337$). The structure was solved by direct methods and refined against F^2 with full-matrix least-squares using the software complex SHELXL-2014 [6]; final *GOF* = 1.001, $R_I = 0.0336$, $wR_2 = 0.0783$, R indices based on 9057 reflections with $I > 2\sigma(I)$ (refinement on F^2), $|\Delta\rho|_{\text{max}} = 0.49(7)$ e Å⁻³, 376 parameters, 0 restraints. CCDC 1859311 contains the supplementary crystallographic data for this contribution, and can be obtained free of charge *via* <u>https://www.ccdc.cam.ac.uk/conts/retrieving.html</u> (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

According to the XRD crystallography, the prepared compound crystallizes in the monoclinic space group $P2_1/c$ (No. 14) with unit cell parameters slightly different from those published previously (see Table 1) and Z = 4.

Sample	a (Å)	b (Å)	c (Å)	β (°)	$V(Å^3)$	$D_c (Mg/m^3)$
Prepared (LidH)2 [·] ZnCl ₄	8.8921(2)	19.2650(3)	19.3211(3)	95.026(2)	3297.10(10)	1.366
(LidH)2 [·] ZnCl ₄ [4]	9.137	19.213	19.707	95.82		1.311
ZnCl4C28N4O2H44 [5]	9.128(2)	19.196(5)	19.696(5)	95.81(1)	3433.43(1)	1.308

Table 1. Unit cell parameters

Molecular structure. The prepared compound has a molecular crystal structure of bis(lidocaine) tetrachlorozincate(II), the charge transfer complex, in which coordination of the Zn^{2+} ion with four chlorine anions generates slightly distorted tetrahedral anion $ZnCl_4^{2-}$, while two protonated cations LidH⁺ remain in an outer coordination sphere (Fig. 1).



Fig. 1. Molecular structure of the (LidH)₂ZnCl₄ showing the atom numbering scheme. Displacement ellipsoids are drawn at 50% of the probability level.

Chlorine atoms in the ZnCl₄ tetrahedron are located at approximately equal distances from the central zinc atom (the lowest values are 2.2616(4), 2.2624(4), and 2.2684(4) Å for the Zn–Cl2, Zn–Cl4, and Zn–Cl3 bonds, respectively, the largest is 2.954(4) Å for the Zn–Cl1 bond), the angles between the Cl–Zn–Cl bonds deviate from tetrahedral with a minimum of 105.948(14)° for angle Cl1–Zn–Cl3 and a maximum value of 113.851(15)° for angle Cl3–Zn–Cl4. These results are completely consistent with the data of work [4] (Zn–Cl distances 2.24-2.29 Å, angles 106-113°) and slightly differ from the parameters (2.5-3.0 Å, 101-115°) given in [5].

Distortions of the tetrahedral coordination are caused by the Coulomb interaction between the anion $ZnCl_{4}^{2-}$ and asymmetrically arranged cations LidH⁺, as well as by the hydrogen bonds in which the chlorine atoms participate (see Table 2).

D–H···A	D-H (Å)	H···A (Å)	$D \cdots A(Å)$	D–H···A (°)
N211-H211····Cl1	0.836(19)	2.415(18)	3.2349(12)	166.8(17)
N111–H111…Cl3	0.83(2)	2.50(2)	3.3124(13)	169.1(18)
N114–H114····Cl4 ⁱ	0.885(18)	2.508(19)	3.1842(13)	133.7(15)
N114-H114…O112	0.885(18)	2.071(18)	2.6424(16)	121.4(15)
N214–H214…O212 ⁱⁱ	0.844(17)	1.998(18)	2.7511(15)	148.1(16)

Table	2.	Hydrogen-ł	bond geometry
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Symmetry codes: (i) -x+1, y-1/2, -z+1/2; (ii) -x, -y+1, -z+1.

diethylamino group, and not the amido nitrogen atom, as indicated in work [5].

So, chlorine atoms Cl1 and Cl3 enter into a hydrogen bond with the amido nitrogen atoms N211 and N111, respectively. In work [5], hydrogen atoms were localized at larger distances from nitrogen atoms (0.93 - 0.96 Å) and at smaller distances from chlorine atoms (2.39 - 2.35 Å), but in general, the picture of these two hydrogen bonds corresponds to our results. The two considered hydrogen bonds connect the anion with cations; they can be considered as intramolecular. A third hydrogen bond is intermolecular, it is formed between the chlorine atom Cl4ⁱ of the neighboring anion and the protonated nitrogen atom N114 of the

Along with hydrogen bonds N–H···Cl, the SHELXL software reveals hydrogen bonds N–H···O that were not taken into account in [5]. Hydrogen bond N114–H114···O112 is intramolecular and is formed when the lidocaine molecule has a certain conformation.

Generally, the aromatic rings in the LidH⁺ cations are asymmetric, but the deviations of the C–C bond lengths and angles from the standard ones are insignificant, the torsion angles are small, and the aromatic rings can conditionally be considered flat.

The C–N, C–C and C=O interatomic distances in flexible fragments of lidocaine molecules are typical of crystalline carboxamides [7], but the angles differ significantly from standard ones. According to the values of the corresponding torsion angles (see Table 3), in the cation 1 interacting with chlorine atom Cl3 (on the left in Fig.1) the amide group is twisted out from the plane of the aromatic ring by ~75°, in the cation 2 interacting with Cl1 – by ~106°. For both cations the aromatic ring and the oxygen atom adopt a *synperiplanar* (C) conformation with respect to the carboxamide N–C bond, the amido and amino nitrogen atoms adopt the *antiperiplanar* (T) conformation. Such staggered conformation excludes the formation of an intramolecular hydrogen bond N–H…N noted in the lidocaine free base [8] and its molecular complex, when the nitrogen atoms adopt a C conformation [9].

Main-chain atoms	(°)	Main-chain atoms	(°)
θ(C16, C11, N111, C112)	75.38(19)	θ(C26, C21, N211, C212)	106.32(15)
θ(C11, N111, C112, O112)	2.6(2)	θ(C21, N211, C212, O212)	-0.3(2)
θ(C11, N111, C112, C113)	178.45(13)	θ(C21, N211, C212, C213)	178.08(12)
θ(N111, C112, C113, N114)	168.10(13)	θ(N211, C212, C213, N214)	134.19(12)
θ(O112, C112, C113, N114)	-12.89(19)	θ(O212, C212, C213, N214)	-47.38(17)

Table 3. Torsion angles in flexible chain between aromatic ring and diethylamino group of LidH⁺ cations

On the contrary, if the carbonyl oxygen atom and the nitrogen atom of the amino group adopt the C conformation, it leads to the formation of a relatively strong intramolecular hydrogen bond N–H···O in the LidH⁺ cations [10]. Conformation C is realized in cation 1, the distance between the donor and the acceptor is ~2.64 Å (see Table 2). In cation 2, the torsion angle θ (O212, C212, C213, N214) exceeds the limit determining the conformation C (±30°), and the SHELXL software does not fix the intramolecular hydrogen bond, but indicates the existence of an intermolecular hydrogen bond between the nitrogen atom N214 and the oxygen atom O212ⁱⁱ of the neighboring cation. The distance between the donor and the acceptor for the intermolecular bond is ~2.75 Å and is comparable to the same distance for the intramolecular bond, so it can be assumed that the hydrogen atom H214 forms a bifurcated hydrogen bond with both carbonyl oxygen atoms, O212 and O212ⁱⁱ. The parameters of the intramolecular hydrogen bond N414–O212, and N214–O212 amounted to 0.84(2), 2.50(8), and 2.83(9) Å, respectively, the angle N214–H214–O212 was 145(2) degrees.

Symmetrically, an intermolecular hydrogen bond N214ⁱⁱ–H214ⁱⁱ...O212 and an intramolecular hydrogen bond N214ⁱⁱ–H214ⁱⁱ...O212ⁱⁱ are formed, as shown in Fig. 2.



Fig. 2. Bifurcated hydrogen bonds viewed along [001] (left) and along [100] (right); the two-pointed arrows show the lines connecting atoms Zn and Znⁱⁱ.



Fig. 3. Unit cell of (LidH)₂ZnCl₄ viewed along [100]; only the hydrogen atoms participating in the intramolecular (thin lines) and intermolecular (bold lines) hydrogen bonds are shown; the numbers 1 and 2 on the aromatic rings indicate different cations in the molecule of the complex.

Supramolecular and crystal structure. The intermolecular bonds N–H···O located near the middle of the line connecting the atoms Zn and Znⁱⁱ combine the molecules of the complex into pairs $2[(\text{LidH})_2\text{ZnCl}_4]$, and the intermolecular bonds N–H···Cl provide the connection of each pair with four neighboring pairs, as shown in Fig, 3, which depicts a unit cell of bis(lidocaine) tetrachlorozincate(II) containing central pair and parts of four neighboring pairs, totally atoms of four ZnCl₄^{2–} anions and eight LidH⁺ cations. The planes of the aromatic rings of cations 1 and 2 are approximately perpendicular, as was noted in work [5], but one more peculiarity of the arrangement of the aromatic rings is observed – as can be seen in Fig. 3, the planes of aromatic rings are parallel to the planes of the corresponding cation rings in the neighboring unit cell.

Each pair of complex molecules located in the center of the unit cell is connected by hydrogen bonds to four pairs lying at the nodes of the unit cell, and each nodal pair is connected to four central pairs. The hydrogen bonded pairs form endless sheets lying in the plane **bc** (see Fig. 4 showing part of the crystal packing of (LidH)₂ZnCl₄), rather than herringbone packing parallel to **c** axis, as described in [5].



Fig. 4. Partial crystal packing of (LidH)₂ZnCl₄ viewed along [100].

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Conclusion

In this work, new data on the molecular and crystalline structure of the zinc complex of lidocaine obtained in water-methanol solution (pH=5-6) with 1:2 molar ratio of the zinc chloride and lidocaine are considered. The single-crystal X-ray diffraction characterization shows that the complex crystallizes in the monoclinic space group $P2_1/c$ with a = 8.8921(2), b = 19.2650(3), c = 19.3211(3) Å, $\beta = 95.026(2)$, V = 3297.10(10)Å³, Z = 4, $D_c = 1.366$ Mg/m³, and consists of the ZnCl₄²⁻ slightly distorted tetrahedral anion and two protonated cations of lidocaine LidH⁺ in an outer coordination field. In addition to the Coulomb attraction forces, the anion and cations are associated by two N–H···Cl hydrogen bonds with participation of the amido nitrogen atoms, while the amino nitrogen atoms are involved in bifurcated hydrogen bonds providing N–H···O stacks with neighbouring molecules and combining them in pairs 2[(LidH)₂ZnCl₄]. Two amido nitrogen atoms and two chlorine atoms of each pair participate in the N–H···Cl hydrogen bonds with four adjacent pairs, arranging them into endless sheets lying in the **bc** crystallographic plane.

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ქიმია

ბის(ლიდოკაინ) ტეტრაქლოროცინკატ(II)-ის მოლეკულური და კრისტალური სტრუქტურა

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ნაშრომში წარმოდგენილია ახალი მონაცემები ბის(2-(დიეთილამინო)-N-(2,6-დიმეთილფენილ) აცეტამიდ) ტეტრაქლოროცინკატ(II)-ის მოლეკულური და კრისტალური სტრუქტურის შესახებ. დადგენილია, რომ კომპლექსი ფორმულით (C14H23ON2)2ZnCl4 (ან (LidH)2ZnCl4), კრისტალიზდება მონოკლინურ სინგონიაში, P21/c სივრცით ჯგუფში შემდეგი პარამეტრებით: a = 8,8921(2), b = 19,2650(3), c = 19,3211(3) Å, $\beta = 95,026(2)^\circ$, V = 3297,10(10) Å³, Z = 4, და $D_c = 1.366$ მგ/მ³. მოლეკულურ სტრუქტურაში Zn²⁺ იონი კოორდინირდება ლიგანდებთან ტეტრაედრული ანიონის ZnCl4²⁻ სახით, ხოლო ორი პროტონირებული კატიონი LidH⁺ რჩება გარე საკოორდინაციო ველში. ანიონი და კატიონი ასევე დაკავშირებულია ერთმანეთთან ქლორის ორი ატომისა და ამიდო ჯგუფის აზოტის ატომების მონაწილეობით წარმოქმნილი წყალბადური ბმებით, ლიდოკაინის მოლეკულის მოქნილი ჯაჭვის კონფორმაცია უზრუნველყოფს შიდამოლეკულური წყალბადური ბმის წარმოქმნას ამინო ჯგუფის პროტონირებული აზოტის ატომსა და კარბოქსილის ჟანგბადის ატომს შორის. ამინო ჯგუფის პროტონირებული აზოტის ატომები აგრეთვე მონაწილეობენ მეზობელი მოლეკულების ჟანგბადის ატომებთან მოლეკულათაშორისი წყალბადური ბმების წარმოქმნაში, რაც მუხტის გადამტანი კომპლექსის მოლეკულებს აერთიანებს წყვილებში 2[(LidH)2ZnCl4]. თითოეული წყვილი წარმოქმნის N-H…Cl მოლეკულათაშორის წყალბადურ ბმებს ოთხ მეზობელ წყვილთან, რომლებიც აწყობილია ხი კრისტალოგრაფიულ სიბრტყეზე განლაგებული უსასრულო ფურცლების სახით.

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