Application, structure, salts and complexes of lidocaine: a review. Part III. Structure of bis(lidocaine) tetrachloridozincate(II)

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Abstract.
The review focuses on lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide): in the first part, its use in various branches of medicine was considered, and the structure of lidocaine, its salts and molecular complexes was discussed; the second part is devoted to the use of lidocaine in the composition of deep-eutectic solvents (DES) and in DES-microemulsions (ME); consideration of lidocaine as part of coordination compounds has begun: the results of studying the structure of complexes of lidocaine with zinc, copper, cobalt, platinum and iron chlorides, as well as with copper bromide, have been discussed. The third part examines the structure of bis(lidocaine) tetrachloridozincate(II), which crystallizes in the monoclinic space group P2₁/c with a = 8.8921(2), b = 19.2650(3), c = 19.3211(3) Å, β = 95.026(2)°, and consists of the ZnCl₄²⁻ slightly distorted tetrahedral anion and two protonated cations of lidocaine LidH⁺ in an outer coordination sphere; H-bonds combine neighbouring complexes in pairs 2{|LidH}ZnCl₄], while four adjacent pairs form endless layers parallel to the ac crystallographic plane and lying at a distance of 9.6325(3) Å from each other.

Keywords:
lidocaine
X-ray analysis
crystal structure
hydrogen bond
Structure of bis(lidocaine) tetrachloridozincate(II)

As noted in the second part of review, the structure of lidocaine complex with zinc chloride was first established started by Polish scientist Główka and Gałdecki [1], who noted that the structure was refined to an R value of 0.114 with rather low accuracy of interatomic distances and angles. Later, a group of scientists from the University of Mysore, India, published [2] the results of a study of the crystal structure of “lignocaine hydrochloride – zinc chloride complex”, but in this work the strange brutto-formula ZnCl₄C₂₈N₂O₂H₄₄ was given and the protonation of the amino nitrogen atom was not taken into account. / and led to conflicting conclusions, so that the study of the structure of bis(lidocaine) tetrachloridozincate(II) became one of our studies [16] and sections of this review. Given all these circumstances, we considered it necessary to include the results of our studies in this review [3].

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 (C₁₄H₂₂ON₂·HCl·H₂O). 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 C₂₈H₄₆Cl₄N₂O₂Zn: C 47.78; H 6.26; N 13.93; found: C 47.71; H 6.19; N 13.90.

The single crystal X-ray diffraction measurements were carried out with an Oxford Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated MoKα radiation (μ = 1.100 mm⁻¹, F₀₀₀ = 1422, λ = 0.71073 Å, T = 100(2)K). The data collection, cell refinement and data reduction were carried out with the CrysAlisPRO package of Rigaku Oxford Diffraction (version 1.171.38.46, 2015); theta range for data collection was up to 2θmax = 65.2°, 39836 reflections collected, 11211 unique (Rint = 0.0337). The structure was solved by direct methods and refined against F².
with full-matrix least-squares using the software complex SHELXL-2014; final $GOF = 1.001$, $R_1 = 0.0336$, $wR_2 = 0.0783$, $R$ indices based on 9057 reflections with $I > 2\sigma(I)$ (refinement on $F^2$), $|\Delta p|_{\text{max}} = 0.49(7)$ e Å$^{-3}$, 376 parameters, 0 restraints. CCDC file 1859311 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.

According to the XRD crystallography, bis(lidocaine) tetrachloridozincate(II) crystallizes in the monoclinic space group $P2_1/c$ (No. 14), as indicated by Polish [1] and Indian [2] authors; the unit cell parameters calculated by us differ slightly (discrepancy up to 2.6%) from those published previously (see Table 1), $Z = 4$.

**Table 1**

<table>
<thead>
<tr>
<th>Source</th>
<th>$a$ (Å)</th>
<th>$b$ (Å)</th>
<th>$c$ (Å)</th>
<th>$\beta$ (°)</th>
<th>$V$ (Å$^3$)</th>
<th>$\rho_c$ (Mg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2]</td>
<td>9.128(2)</td>
<td>19.196(5)</td>
<td>19.696(5)</td>
<td>95.81(1)</td>
<td>3433.43(1)</td>
<td>1.308</td>
</tr>
<tr>
<td>[3]</td>
<td>8.8921(2)</td>
<td>19.2650(3)</td>
<td>19.3211(3)</td>
<td>95.026(2)</td>
<td>3297.10(10)</td>
<td>1.366</td>
</tr>
</tbody>
</table>

**Molecular structure.** According to the XRD crystallography, bis(lidocaine) tetrachloridozincate(II) ([LidH]$_2$[ZnCl$_4$]) is a 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 LidH$^+$ cations 1 and 2 remain in an outer coordination sphere (Figure 1).

Chlorine atoms in the ZnCl$_4$ 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-Cl$_2$, Zn-Cl$_4$, and Zn-Cl$_3$ bonds, respectively, the largest is 2.954(4) Å for the Zn-Cl$_1$ bond), the angles between the Cl-Zn-Cl bonds deviate from tetrahedral with a minimum of 105.948(14)° for angle Cl$_1$-Zn-Cl$_3$ and a maximum value of
113.851(15)° for angle Cl3-Zn-Cl4. These results are completely consistent with the data of Polish scientists [1] (Zn-Cl distances 2.24-2.29 Å, angles 106-113°) and slightly differ from the parameters (2.5-3.0 Å, 101-115°) reported by Indian authors [2].

Distortions of the tetrahedral coordination are caused by the Coulomb interaction between the anion \([\text{ZnCl}_4]^{2-}\) and asymmetrically arranged cations LidH\(^+\), as well as by the hydrogen bonds in which the chlorine atoms participate (see Table 2, where D-H is the distance between the donor atom and the hydrogen atom, H-A is the distance between the hydrogen atom and the acceptor atom, D-A is the distance between the donor atom and the acceptor atom, D-H-A is the angle between the donor, hydrogen and acceptor atoms, and Figures 2a - 2c).

According to the results generated by the SHELXL software, chlorine atom Cl1 participates in the formation of a weak (distance between donor and acceptor D-A is more than 3.2 Å) hydrogen bond with the amide nitrogen atom N211 of cation 2, as well as in the formation of an even weaker (distance D-A > 3.6 Å) “non-classic” hydrogen bond C-H-Cl with the participation of strongly de-shielded carbon atom C113 of cation 1.
Table 2

<table>
<thead>
<tr>
<th>D–H (Å)</th>
<th>H–A (Å)</th>
<th>D–A (Å)</th>
<th>D–H–A (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N211–H211–Cl1</td>
<td>0.83(19)</td>
<td>2.41(18)</td>
<td>3.2349(12)</td>
</tr>
<tr>
<td>C113–H113–Cl1</td>
<td>0.99</td>
<td>2.67</td>
<td>3.6518(15)</td>
</tr>
<tr>
<td>C116–H116–Cl2</td>
<td>0.99</td>
<td>2.87</td>
<td>3.7903(18)</td>
</tr>
<tr>
<td>C213–H213–Cl2</td>
<td>0.99</td>
<td>2.93</td>
<td>3.6263(15)</td>
</tr>
<tr>
<td>N211–H211–Cl1</td>
<td>0.83(2)</td>
<td>2.50(2)</td>
<td>3.3124(13)</td>
</tr>
<tr>
<td>C213–H213–Cl1</td>
<td>0.99</td>
<td>2.96</td>
<td>3.8242(17)</td>
</tr>
<tr>
<td>N111–H111–Cl3</td>
<td>0.83(2)</td>
<td>2.50(2)</td>
<td>3.3124(13)</td>
</tr>
<tr>
<td>N114–H114–O212</td>
<td>0.88(2)</td>
<td>2.507(20)</td>
<td>3.1836(22)</td>
</tr>
<tr>
<td>N114–H114–O112</td>
<td>0.88(2)</td>
<td>2.071(18)</td>
<td>3.6424(16)</td>
</tr>
<tr>
<td>N214–H214–O212</td>
<td>0.84(17)</td>
<td>1.998(18)</td>
<td>2.7511(15)</td>
</tr>
<tr>
<td>N214–H214–O212</td>
<td>0.84(2)</td>
<td>2.496(3)</td>
<td>2.827(3)</td>
</tr>
<tr>
<td>N214–H214–O212</td>
<td>0.84(2)</td>
<td>2.00(2)</td>
<td>2.7507(27)</td>
</tr>
<tr>
<td>C215–H215–O112</td>
<td>0.99</td>
<td>2.41</td>
<td>3.1764(17)</td>
</tr>
<tr>
<td>C215–H215–O112</td>
<td>0.99</td>
<td>2.4086(32)</td>
<td>3.1757(35)</td>
</tr>
</tbody>
</table>

Symmetry codes: (i) -x+1, y-1/2, -z+1/2; (ii) -x+1, -y+1, -z+1; (iii) -x, -y+1, -z+1; (iv) -x+1, y+1/2, -z+1/2; (v) x-1, y, z.

Figure 2a

Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intra- and intermolecular (blue dotted lines) hydrogen bonds with participation of chlorine atoms viewed on the [110] plane.
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Figure 2b
Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intra- and intermolecular (blue dotted lines) hydrogen bonds with participation of chlorine atoms viewed on the [101] plane.

Figure 2c
Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intra- and intermolecular (blue dotted lines) hydrogen bonds with participation of chlorine atoms viewed on the [011] plane.
The chlorine atom Cl2 can participate in the formation of a very weak (distance D-A ~ 3.8 Å) “non-classic” hydrogen bond with the participation of the C116 carbon atom, which is not bonded to any electronegative atom; therefore, the probability of the formation of a hydrogen bond C116-H11I-Cl2 is very small. However, the SHELXL program indicates the possibility of the formation of slightly stronger hydrogen bonds between the carbon atoms C213 and C215 bounded to the amine nitrogen atom N214 and the chlorine atom Cl2ii of the neighboring complex determined by the symmetry operation ii. Calculations show that symmetric hydrogen bonds C213ii-H21Aii-Cl2 and C215ii-H21Dii-Cl2 have the same geometry, so that the chlorine atom Cl2 can also participate in the formation of intermolecular hydrogen bonds.

For the chlorine atom Cl3, the SHELXL software indicates only the possibility of participation in the formation of a weak (D-A > 3.6 Å) hydrogen bond with the C213 carbon atom. In the same time, the symmetric chlorine atom Cl4i enters into a “classical” hydrogen bond with the nitrogen atom N114, and the calculations show the same geometry for the N114iv-H114iiv-Cl4 bond, so that the chlorine atom Cl4 can participate in the formation of an intermolecular bond (see Fig. 2).

The N-H-Cl hydrogen bonds with participation of two amido nitrogen and two chlorine atoms (designated as CL2 and CL3 of molecule A) were also revealed by Indian scientists [2], reporting hydrogen atoms localized at larger distances from nitrogen atoms (0.93 – 0.96 Å) and at smaller distances from chlorine atoms (2.39 – 2.35 Å), as well as angles N-H-Cl of ~170°. Calculations show that the distances between the donor and acceptor are 3.30±0.28 and 3.31±0.28 Å for the CL2 and CL3 atoms, respectively, which is close to our results for
the chlorine atoms Cl1 and Cl3.

The third hydrogen bond N–H–Cl with participation of amido nitrogen and chlorine atoms (designated as N7 and Cl5 of molecule B), identified by Indian scientists, has the following parameters: N–H distance 0.81(13) Å, H–Cl distance 2.82(14) Å, and angle N–H–Cl ~119°, corresponding to the distance between the donor and acceptor 3.29±0.23 Å.

Probably, an intermolecular hydrogen bond of the N–H–Cl type was revealed, but to clarify this issue, one should consider the possibility of the formation of hydrogen bonds with the participation of nitrogen atoms of lidocaine molecules. These possibilities are determined by the spatial structure of lidocaine molecules, in particular, by the conformation of the chain connecting the aromatic ring with the diethylamino group.

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 [4], but the angles differ significantly from standard ones [5]. According to the values of the corresponding torsion angles (see Table 3), in the cation 1 interacting with chlorine atom Cl3 the amide group is twisted out from the plane of the aromatic ring by ~75°, in the cation 2 interacting with Cl1 – by ~106°. In a study by Indian scientists [2], torsion angles are not given.

Table 3

| Torsion angles in flexible chain between aromatic ring and diethylamino group of LidH⁺ cations |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Main-chain atoms (º) | Main-chain atoms (º) |
| C16-C11-N111-C12 | 75.38(19) | C26-C21-N211-C212 | 106.32(15) |
| C11-N111-C112-O112 | 2.6(2) | C21-N211-C212-O212 | -0.3(2) |
| C11-N111-C112-C113 | 178.45(13) | C21-N211-C212-C213 | 178.08(12) |
| N111-C112-C113-N114 | 168.10(13) | N211-C212-C213-N214 | 134.19(12) |
| O112-C112-C113-N114 | -12.89(19) | O212-C212-C213-N214 | -47.38(17) |
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 [6] and its molecular complex, when the nitrogen atoms adopt a C conformation [7].

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. These hydrogen bonds were not considered by Indian scientists, who did not take into account the protonation of lidocaine molecules.

Conformation C is realized in cation 1, the distance between the donor and the acceptor in the N114–H114–O112 bond 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 O212 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 O212. The parameters of the intramolecular hydrogen bond were calculated according to the coordinates of the atoms: the distances N214–H214, H214–O212, and N214–O212 amounted to 0.84(2), 2.496(3), and 2.827(3) Å, respectively, the angle N214–H214–O212 was 104(2) degrees.

Symmetrically, an intermolecular hydrogen bond N214–H214–O112 and an intramolecular hydrogen bond N214–H214–O212 are formed, as shown in Figures 3a – 3c.

The SHELXL software also indicates the possibility of the formation of a “nonclassic” intermolecular hydrogen bond C215–H21C–O112, and the calculations reveal the same geometry for the C215–H21C–O112 hydrogen bond (see Table 2 and Figures 3a – 3c). Thus, the central anion ZnCl₄²⁻ is bound
with cations by “classical”, but weak hydrogen bonds with the participation of chlorine atoms Cl1 and Cl3; the formation of even weaker “non-classic” hydrogen bonds with the participation of chlorine atoms Cl2 and Cl4 is also possible.

**Figure 3a**
Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intermolecular (blue dotted line) hydrogen bonds with participation of nitrogen and oxygen atoms viewed on the [110] plane.

**Figure 3b**
Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intermolecular (blue dotted line) hydrogen bonds with participation of nitrogen and oxygen atoms viewed on the [101] plane.
Intramolecular (black dotted lines), intermolecular (red dotted lines) and “non-classic” intermolecular (blue dotted line) hydrogen bonds with participation of nitrogen and oxygen atoms viewed on the [011] plane.

The strongest intermolecular interactions are hydrogen bonds between the nitrogen atoms of the amino group and oxygen atoms (N214–H214-O212$_{iii}$ and N214$_{iii}$–H214$_{iii}$-O212), while the hydrogen atoms H214 and H214$_{iii}$ through which these bonds are formed are also involved in the formation of intramolecular hydrogen bonds N214–H214-O212 and N214$_{iii}$–H214$_{iii}$-O212$_{iii}$ (see Figures 3a - 3c). The weaker interactions are “non-classic” hydrogen bonds involving oxygen atoms (C215–H21C$^i$-O112$_iv$ and C215$^i$–H21C$^i$-O112) and bonds between nitrogen and chlorine atoms (N114–H114-C14$^i$ and N114$_iv$–H114$_iv$-C14), the weakest are the hydrogen bonds between carbon and chlorine atoms (C215$^i$–H21D$^i$-C12 and C215–H21D-C12$^i$, C213–H21A-C12$^i$ and C213$^i$–H21A$^i$-C12, C218–H21J-C13$_v^{iv}$). The complete picture of intermolecular hydrogen bonds is shown in Figure 4.
Supramolecular and crystal structure.

The center of inversion $[(\text{LidH})_2\text{ZnCl}_4]^{-} \leftrightarrow [(\text{LidH})_2\text{ZnCl}_4]^{iii}$ has fractional coordinates $(0, \tfrac{1}{2}, \tfrac{1}{2})$, that is, it lies in the center of the $bc$ crystallographic plane. Thus, the $\text{N-H-O}$ bifurcated hydrogen bonds combine the molecules of the complex located in adjacent unit cells into $2[(\text{LidH})_2\text{ZnCl}_4]$ pairs, while the intermolecular bonds $\text{N-H-Cl}$ provide the connection of each pair with four neighboring pairs. Two pairs belong to the same “central” unit cell and the connection is carried out through $\text{N114-H114-Cl4}^{i}$ and $\text{N114}^{iv}-\text{H114}^{iv}-\text{Cl4}$ hydrogen bonds, the other two pairs belong to the adjacent cell through the $bc$ plane, as shown in Figures 5a – 5c, depicting a unit cell of bis(lidocaine) tetrachlorozincate(II) containing totally 340 atoms of four $\text{ZnCl}_4^{2-}$ anions and eight $\text{LidH}^+$ cations.
The planes of the aromatic rings of cations 1 and 2 are approximately perpendicular, as was noted by Indian scientists [2], but one more peculiarity of the arrangement of the aromatic rings is observed – as can be seen in Figures 5, the planes of aromatic rings are parallel to the planes of the corresponding cation rings in the neighboring unit cells. According to obtained data, the N–H–O bifurcated hydrogen...
bonds combine the molecules of the complex C(Zn) located in adjacent unit cells into C(Zn)↔C(Zn\textsuperscript{iii}) pairs. The molecule of the C(Zn) complex is also connected by the N–H–Cl hydrogen bonds to the molecules of the C(Zn\textsuperscript{i}) and C(Zn\textsuperscript{iv}) complexes, so that each C(Zn)↔C(Zn\textsuperscript{iii}) pair is linked to four pairs, partially located in the same unit cell.

Figure 6 shows part of the (LidH)\textsubscript{2}ZnCl\textsubscript{4} crystal packing and it can be seen that the hydrogen bonded pairs form endless sheets or layers lying in the plane ac, rather than herringbone packing parallel to c axis, as described in [2].

The layered structure of the packing of the (LidH)\textsubscript{2}[ZnCl\textsubscript{4}] complex is especially clearly visible in Figure 7, showing the packing of only the inorganic part (ZnCl\textsubscript{4}). The distance between the layers is \(\frac{1}{2}b = 9.6325(3)\) Å.

Thus, the anion [ZnCl\textsubscript{4}]\textsuperscript{2–} and cations Lid\textsuperscript{+} 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)\textsubscript{2}ZnCl\textsubscript{4}]. Two amido nitrogen atoms and two chlorine atoms of each pair participate in the intermolecular N–H–Cl hydrogen bonds with four adjacent pairs, arranging them into
endless layers parallel to the ac crystallographic plane and lying at a distance of 9.6325(3) Å from each other.

![Figure 6](image)

**Figure 6**
Packing of the inorganic part of the (LidH)$_2$[ZnCl$_4$] complex viewed on the ab crystallographic plane

The following parts of the review will be devoted to the structure of lidocaine complexes with copper and iron chlorides.

**References:**


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