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Dear Referees,

The present study deals with several major factors which determine the crystal structure of coordination complexes of phosphonium carboxylate betaines with biologically important metals Zn(II), Cd(II), Hg(II), Cu(II).

These are:

- The coordination geometry requirements of the metal
- The role of the solvate water or alcohol molecules in stabilizing the non-bound-to-metal carboxylate oxygen via hydrogen bonding
- Conformational flexibility of ligands
- And the presence of asymmetric carbon atom in some of the ligands which results in formation of complexes of various stereochemistry.

There were some difficulties in crystal structure refinement, as some of the crystals were studied at ambient temperature due to technical problems. Thus, we present a detailed experimental part which might be partially moved to the supplementary material. May be you could advise on this topic.

And thank you in advance for refereeing the manuscript.

Sincerely yours

Olga Kataeva

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Crystal structure of phosphonium carboxylate complexes. The role of the metal coordination geometry, ligand conformation and hydrogen bonding

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A series of new mononuclear and heteronuclear complexes of carboxylate phosphonium betaines with biologically important metals (Zn(II), Cd(II), Hg(II), Cu(II)) were obtained in aqueous media at ambient temperature. X-ray single crystal diffraction showed that carboxylate phosphonium betaines exhibit versatile complexation ability, producing monomeric, dimeric, tetrameric homonuclear and mixed metal complexes, water playing an important role in crystal formation. The binding mode was found to change in the series of Zn(II), Cd(II), Hg(II) complexes with the increase of the cation radius. In case of α- and β-substituted phosphabetaines the crystallization of various stereoisomers was observed including rare case of co-crystallization of two diastereomers in one crystal.

Introduction

A range of factors determining the crystal structure of coordination compounds is really unlimited, these are reaction conditions, the ratio of reagents, the nature of ligands and metals, the solvents used, etc. For biologically active compounds it is very important to study their interaction with transition metals in the media conditions (e.g. water) typical for biological systems, on the other hand the metal coordination geometry is even more important for the crystal structure of coordination compounds. This study is intended to understand the role of metal coordination geometry and hydrogen bonding in the crystalline phosphonium carboxylate complexes, the interplay of both factors determining the orientation of the flexible ligands, their denticity in respect to various transition metals and thus their contribution to the crystal structure of coordination compounds.

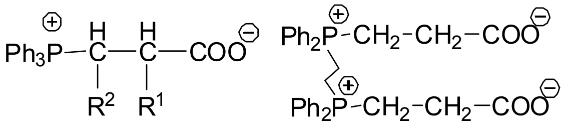
The chemistry of betaines has gained considerable attention because of their important role in biological systems [1]. Many betaines belong to the alkaloid family [2, 3], to phospholipids [4-6] and have numerous therapeutical activities like anti-cancer [7-10], antiprotozoal and antifungal [11, 12], antioxidant [13]. Some betaines are efficient antibiotics of the penicillin [14, 15] and cephalosporin [16] family or proved to be efficient drug carriers for intracellular delivery [17]. Of vital importance is the application of betaines in the field of biomaterials. Silicone compounds including zwitterionic phosphoryl choline groups [18] are used for production of ophthalmic lenses, poly(sulfobetaine methacrylate) derivatives find use as antimicrobial wound dressings [19]. Betaine compounds [20-23] are the building blocks of a great number of antifouling polymers which prevent the formation of biofims by pathogenic bacteria.

Further important biological functions of betaines are related to their coordination properties. It is known that many betaines bind to a metal in metalloenzymes [1, 24-26]. Their metal fixation ability may serve to obtain antidotes against poisoning by heavy metals [27], betaines ensure the bioavailability of metal ions [28, 29], participate in biomineralization [30], they can deliver specific metal ions intracellularly and provide sustained release of these ions [28, 29], they can deliver radiotracers selectively to the tumor cells for cancer diagnostics [31, 32].

The ability of betaines to bind metal ions is determined by the presence of functional groups, such as phosphate, sulfate, hydroxy-, carboxylate. Carboxylate derivatives are especially versatile ligands, giving metal complexes of various coordination types and architecture: mononuclear with monodentate [33] and bidentate coordination [34], binuclear dimeric complexes [35], 1D-chain and 2D-layered coordination polymers [36-38] with a great variety of metals.

Besides the anionic group, which binds the metal, the cationic head group is no less important. The nature of the head group in surfactants [39] was shown to affect DNA-surfactant interactions, critical micellar concentrations etc. The role of the cationic group appeared to be important in gene therapy. It was reported that the substitution of the most abundant in biologically active systems ammonium group by phosphonium and arsonium cations results in higher transfection activity and lower cytotoxicity of the cationic vectors [40-42]. It should be mentioned that unlike other arsenic compounds many arsonium derivatives are not toxic, e.g. arsenobetaines are found in sea food and marine animals [43-46]. In addition, phosphonium and arsonium compounds appeared to be more stable, than ammonium derivatives [43-46].

Thus, a combination of the onium (N, P, As) head group and the anionic carboxylate moiety in one molecule to obtain metal complexes is very promising in terms of biocompatible drug design. In this paper we present the data on the complexation properties of a series of phosphonium betaines (Scheme 1), in which phosphonium head group is linked with the carboxylate moiety by a short aliphatic spacer.



(**L1**) $R^1=R^2=H$ (**L2**)
(**L3**) $R^1=$ Me, $R^2=H$
(**L4**) $R^1=H$, $R^2=$ Me
(**L5**) $R^1=H$, $R^2=$Ph

Scheme 1

In contrast to analogous ammonium and arsonium betaines, which are abundant in nature, the reported phosphorus derivatives are of synthetic origin. Their synthesis and reactivity were reported in a number of papers [47-54]. Fragmentary data on the complexes of the betaine **L1** can be found in [55-59]. However, the coordination chemistry of phosphonium betaines **L3**-**L5** bearing methyl and phenyl substituents in the α- or β- position and of bis(betaine) ligand **L2** is not explored to the best of our knowledge. A series of new complexes with the bioimportant metals, such as Zn(II) and Cu(II), as well as important toxic trace metals Cd(II) and Hg(II) is reported in this paper. From the point of view of biological activity especially important is to evaluate the similarities and differences of the coordination geometry in the series of metal complexes upon going from Zn(II) to Cd(II) and Hg(II) compounds. Of major importance is also the role of water in coordination properties of phosphonium betaines, thus all reactions were carried out in aquatic media.

Experimental

Syntheses. General considerations. All reactions were carried out in room atmosphere. Solvents were freshly distilled before use as described [60, 61]. Carboxylate phosphonium betaines **L1-L5** were prepared following methods [49-54]; other reagents were obtained commercially (Aldrich Chemicals) and used as supplied. $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer using 85% H_3PO_4 as external reference. IR spectra were taken on a spectrophotometer Specord 251R in the range 400-3700 cm^{-1} from mulls in mineral oil between KBr plates.

Diastereomeric ratio of metal complexes of **L3-L5** was not analyzed, the best single crystals being taken for X-ray diffraction study.

Complex (1). To a solution of $ZnCl_2$ (68 mg, 0.5 mmol) in water (3 ml) at $80^{o}C$ was added dropwise **L1** (334 mg, 1.0 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at $80^{o}C$. After 3 weeks at room temperature colorless crystals were separated, washed with water and ethanol and dried in *vacuo*. Complex **1** was obtained in 82.8% yield (332 mg). Mp $287.8^{o}C$. 31P NMR ($CDCl_3$, 161 MHz) δ28.4.IR (cm^{-1}, KBr): 1625s. Anal. Calc. for $C_{42}H_{52}Cl_2O_{11}P_2Zn$ (%): C, 54.17; H, 5.59; P, 6.66. Found: C, 53.93; H, 5.34; P, 6.91.

Complex (2a). To a solution of $ZnCl_2$ (68 mg, 0.5 mmol) in water (3 ml) at $80^{o}C$ was added dropwise **L2** (270 mg, 0.5 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at $80^{o}C$. After 3 weeks at room temperature colorless crystals were obtained, washed with water and ethanol and dried in *vacuo*. Crystals **2a** were obtained in 91.3% yield (308.5 mg). Mp $96.8^{o}C$. 31P NMR ($CDCl_3$, 161 MHz) δ26.27. IR (cm-1, KBr): 1615s. Anal. Calc. for $C_{36}H_{44}Cl_2O_6P_2Zn$ (%): C, 57.12; H, 4.95; P, 9.14. Found: C, 57.03; H, 5.08; P, 8.87.

Complex (2b). To a solution of $HgCl_2$ (135.8 mg, 0.5 mmol) in water (3 ml) at $80^{o}C$ was added dropwise **L2** (270 mg, 0.5 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at $80^{o}C$. After 2 weeks at room temperature colorless crystals were obtained, washed with water and ethanol and dried in *vacuo*. Crystals **2b** were obtained in 74.7% yield (303 mg). Mp $135^{o}C$. 31P NMR ($CDCl_3$, 161 MHz) δ28.13. IR (cm^{-1}, KBr): 1620s. Anal. Calc. for $C_{36}H_{44}Cl_2HgO_6P_2$ (%): C, 49.71; H, 3.98; P, 7.32. Found: C, 49.73; H, 3.56; P, 7.27.

Complex (3). To a solution of $CdCl_2$ (91.7 mg, 0.5 mmol) in water (3 ml) at $80^{o}C$ was added dropwise **L2** (270 mg, 0.5 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at $80^{o}C$. After 3 weeks at room temperature colorless crystals were obtained in 85.2% yield (308.1 mg). Mp $117^{o}C$. 31P NMR ($CDCl_3$, 161 MHz) δ27.17. IR: (cm^{-1}, KBr): 1700s. Anal. Calc. for $C_{64}H_{66}CdCl_4O_8P_4$ (%): C, 46.02; H, 4.55; P, 7.43. Found: C, 45.78; H, 4.37; P, 7.23.

Complex (4). To a solution of salts $CdCl_2$ (91.7 mg, 0.5 mmol) and $CuCl_2$ (67.3 mg, 0.5 mmol) in water (10 ml) at $80^{o}C$ was added dropwise **L1** (334 mg, 1.0 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at $80^{o}C$. After 3 weeks at room temperature green crystals were obtained in 64.0% yield (315.5 mg). Mp $250.7^{o}C$.31P NMR ($CDCl_3$, 161 MHz) δ32.10.IR (cm^{-1}, KBr): 1625s. Anal. Calc. for $C_{84}H_{88}Cd_2Cl_8Cu_2O_{14}P_4$ (%): C, 50.70; H, 4.03; P, 6.15. Found: C, 51.33; H, 4.21; P, 6.01.

Complex (5). To a solution of salts CdCl+ (91.7 mg, 0.5 mmol) and $ZnCl_2$ (68 mg, 0.5 mmol) in water (10 ml) at 80^oC was added dropwise **L1** (334 mg, 1.0 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 2 weeks at room temperature colorless crystals were obtained in 83.0% yield (430. mg). Mp 282.1^oC. 31P NMR ($CDCl_3$, 161 MHz) δ27.13. IR (cm^{-1}, KBr): 1595s. Anal. Calc. for $C_{84}H_{76}Cd_2Cl_8O_8P_2Zn_2$ (%): C, 51.02; H, 3.85; P, 6.28. Found: C, 51.20; H, 3.80; P, 6.33.

Complex (6). To a solution of $ZnCl_2$ (68 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L3** (174 mg, 0.5 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 4 weeks at room temperature colorless crystals were separated, washed with water and dried in *vacuo*. Complex **6** was obtained in 82.6% yield (200 mg). Mp 127.7^oC.31P NMR ($CDCl_3$, 161 MHz) δ26.3.IR (cm^{-1}, KBr): 1565s. Anal. Calc. for $C_{22}H_{23}Cl_2O_3PZn$ (%): C, 52.55; H, 4.58; P, 6.17. Found: C, 52.24; H, 4.81; P, 6.42.

Complex (7). To a solution of $HgCl_2$ (135.8 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L3** (174 mg, 0.5 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 4 weeks at room temperature colorless crystals were separated, washed with water and dried in *vacuo*. Complex **7** was obtained in 82.3% yield (255 mg). Mp 127.0^oC.31P NMR ($CDCl_3$, 161 MHz) δ30.15. IR (cm^{-1}, KBr): 1560s. Anal. Calc. for $C_{44}H_{42}Cl_4Hg_2O_4P_2$ (%): C, 42.61; H, 3.39; P, 5.00. Found: C, 42.31; H, 3.23; P, 5.09.

Complex (8). To a solution of $CdCl_2$ (91.7 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L4** (348 mg, 1 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 3 weeks at room temperature colorless crystals were separated, washed with water and dried in *vacuo*. Complex **8** was obtained in 67.6% yield (370 mg). Mp 132.7^oC. 31P NMR ($CDCl_3$, 161 MHz) δ29.48.IR (cm^{-1}, KBr): 1565s. Anal. Calc. for $C_{44}H_{50}CdCl_2O_8P_2$ (%): C, 55.50; H, 5.26; P, 6.52. Found: C, 55.87; H, 4.83; P, 6.81.

Complexes (9, 10). To a solution of $ZnCl_2$ (68.2 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L4** (348 mg, 1 mmol) in water (10 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 4 weeks at room temperature colorless crystals were separated, washed with water and dried in *vacuo*. Complexes **9** and **10** were obtained in 84% yield (350 mg). Mp 106.2^oC. 31P NMR ($CDCl_3$, 161 MHz) δ28.1 (9), 32.1 (10). IR (cm^{-1}, KBr): 1570s and 1630s.

Complex (11). To a solution of $CdCl_2$ (91.7 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L5** (410 mg, 1 mmol) in water (15 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 4 weeks at room temperature colorless crystals were separated, washed with water and dried in *vacuo*. Complex **11** was obtained in 44.5% yield (224 mg). Mp 151.7^oC. 31P NMR ($CDCl_3$, 161 MHz) δ27.27. IR (cm^{-1}, KBr): 1630s. Anal. Calc. for $C_{54}H_{50}CdCl_2O_6P_2$ (%): C, 62.34; H, 4.43; P, 5.96. Found: C, 62.37; H, 4.87; P, 6.31.

Complex (12). To a solution of $CuCl_2$ (67.2 mg, 0.5 mmol) in water (3 ml) at 80^oC was added dropwise **L5** (410 mg, 1 mmol) in water (15 ml) at the same temperature. The stirring was continued for 15 min at 80^oC. After 2 weeks at room temperature green crystal were separated, washed with water and dried in *vacuo*. Complex **12** was obtained in 47.6% yield (227 mg). Mp 131.7^oC. 31P NMR ($CDCl_3$, 161 MHz) δ24.30. IR (cm^{-1}, KBr): 1625s, 1560s. Anal. Calc. for $C_{126}H_{124}Cl_2Cu_2O_{21}P_4$ (%): C, 67.80; H, 5.11; P, 5.82. Found: C, 67.52; H, 5.27; P, 5.98.

X-ray Structure Determination

Data sets for single crystals **1**, **2b**, **3**, **5**, **8** were collected on a Bruker AXS Kappa APEX and for single crystals **2b**, **4**, **6**, **7**, **9-12** on a Bruker AXS Smart APEX diffractometers with graphite-monochromated Mo K_α radiation (λ= 0.71073 Å). Programs used: data collection APEX2 [62], data reduction SAINT [63], absorption correction SADABS version 2.10 [64], structure solution SHELXS97 [65], structure refinement by full-matrix least-squares against F2 using SHELXL-97 [65]. Hydrogen atoms were placed into calculated positions and refined as riding atoms in unequivocal cases. The figures were generated using ORTEP-3 [66] and Mercury CSD 2.0 [67] programs. Crystal data are given in table 1 and the principal geometrical parameters of Zn(II), Cd(II), Hg(II) complexes in table 2. One should note that a series of data collections was carried out at room temperature due to technical problems, thus large thermal displacement parameters are observed, however the structure of the complexes was determined unambiguously. Further details for individual structures are given below.

COMPLEX 1 – CCDC 927945. Besides the molecule of the complex, the unit cell contains 7 water molecules in the asymmetric unit, solvate water hydrogens were located from the difference Fourier map and refined isotropically, two water molecules being refined with geometrical constraints.

COMPLEX 2A – CCDC 964968. The crystal **2a** is isostructural to **2b**. The crystal structure was solved and refined in monoclinic space group C2/c, β-angle being equal 90.2^0. The symmetry check using equivalent reflections gave the value of R(sym)=0.53 for orthorhombic system and 0.03 for monoclinic system. The molecule is in a special position on a two-fold axis, both phenyl rings are disordered over two positions with the occupation ratio 0.7:0.3 for both of them and refined with geometrical constraints. The crystal contains one solvate ethanol molecule in the asymmetric part of the unit cell, which forms a strong hydrogen bond with the carbonyl oxygen atom with the following parameters O17-H17…O2, O17-H17 0.82 Å, H17…O2 1.91 Å, O2…O17 2.69 Å, ∠O17-H17…O2 158.5^0.

COMPLEX 2B – CCDC 927938. The crystal **2b** is isostructural to **2a**. The crystal structure was solved and refined in monoclinic space group C2/c, monoclinic angle being equal 90.0^0. The symmetry check using equivalent reflections gave the value of R(sym)=0.32 for orthorhombic system and 0.04 for monoclinic system, moreover it was impossible to solve the structure in orthorhombic space groups. The molecule is in a special position on a two-fold axis, both phenyl rings are disordered over two positions with the occupation ratio 0.7:0.3 for both of them and refined with geometrical constraints. One peak of the rest electron density 1.37 e/A^3 is located in the vicinity of metal ion. The crystal contains one solvate ethanol molecule in the asymmetric part of the unit cell, which forms a strong hydrogen bond with the carbonyl oxygen atom with the following parameters O17-H17…O2, O17-H17 0.84 Å, H17…O2 1.89 Å, O2…O17 2.70 Å, ∠O17-H17…O2 161.2^0.

COMPLEX 3 – CCDC927940. The cation is in a special position on a two-fold axis and bears the charge of +1, with one carboxyl group being deprotonated, while the second is not. However only one half of the ligand is in the asymmetric unit, thus, the hydrogen atom was refined with half occupancy. It was located from a difference Fourier map and refined isotropically resulting in the position equidistant from two oxygen atoms from the neighbouring cations, which are very close to each other: O…O 2.42 Å. The ratio of the ligand cation to $CdCl_4^{2-}$ anion is 2:1.

COMPLEX 4 – CCDC927937. The molecule is in a special position, both Cu and Cd atoms occupy 4i Wyckoff positions. Besides the coordinated water molecules two solvate water molecules were located in the asymmetric part of the unit cell from the difference Fourier map and refined anisotropically, one with full occupancy, the other disordered over two positions. Hydrogens atoms were also found from the difference Fourier map and refined with geometrical constrains. No other significant rest electron density peaks were found although the program “Platon” [68] indicates a solvent accessible void of 159 Å^3, most probably filled with disordered water molecules. The disorder accounts for the low ratio of observed reflections, which gives alert B in checkCif report.

COMPLEX 5 – CCDC 927944. The crystal contains channel voids filled with disordered water molecules along the b-axis. The expected volume for solvent molecules as estimated using the program “Platon” [68] is about 460 Å^3 per unit cell volume. As it often happens with channels filled with solvents, it was impossible to find a reasonable model for solvate water in the channels, thus the ‘Squeeze’ option of “Platon” was applied to obtain solvent-free reflection file which was further used for the refinement.

COMPLEX 6 – CCDC927941. All hydrogen atoms were placed into calculated positions except coordinated water molecule, these hydrogen atoms being located from the difference Fourier map. All of them were refined using the riding model, for water molecule using AFIX 3 mode.

COMPLEX 7 – CCDC927942. The molecule is in a special position in the inversion center. The methyl group is disordered over two positions with the occupancy 0.78:0.22.

COMPLEX 8 – CCDC 927939. The crystal contains solvate water molecules: in the asymmetric part of the unit cell 3 water molecules with full occupancy and one water molecule disordered over two sites with half-occupancy. Hydrogen atoms of water molecules were revealed from the difference Fourier map and then refined as riding atoms using AFIX3 constrain, while the hydrogen atoms of two water molecules were refined using geometrical constrains on OH bond lengths and H…H distances. One of the water molecules with partial occupancy gives alert B – “no hydrogen bonding for hydrogen atom”, however no other possible hydrogen positions could be reliably refined. The crystal was weakly diffracting at higher angles due to disorder, thus the completeness of the data set is 96% up to $\theta=25^0$.

COMPLEX 9 – CCDC 927943. The crystal **9** is a thin plate with the ratio of reflections greater than I > 2σ(I) only 42% due to disorder. The asymmetric part of the unit cell contains two independent molecules of the complex and disordered water molecules, one with full occupancy and 6 sites half-populated. Thus, it appeared impossible to locate hydrogen atoms from the difference Fourier map, their positions were calculated using XHYDEX program incorporated into WinGX package [67] and refined as riding atoms using AFIX 3 constrain. All water molecules are at the ‘hydrogen-bond’ distance with the oxygen atoms of the complex, the neighboring water molecules, or chlorine atoms. Room-temperature data and disorder of solvate water molecules did not allow locating hydrogen atoms more reliably.

COMPLEX 10 – CCDC 927936. Complex 10 gave poor quality twinned crystals. The unit cell was determined using “Cell_now” program, the data was processed as a two-domain twinned crystal with a twin law (-0.997, 0.001, 0.006/ 0.000, -1.000, 0.002/1.153, -0.009, 0.997). The structure was refined using “hklf 5” data file composed of corrected reflections from both domains, obtained after scaling and absorption correction using “Twinabs” program, Rint = 0.0979 for all 52894 observations and Rint = 0.0401 for all 10138 observations with I > 3σ(I). Both programs “Cell_now” and “Twinabs” are incorporated into APEX2 package [62]. Two peaks in electron density difference map slightly larger than 1 e are located near metal atoms, two other peaks were modeled as a disordered water molecule with half occupancy, hydrogen atoms were impossible to locate. The level B alert in checkcif report is a false alert originating from the two-domain data set, the same reason accounts for large discrepancy between calculated and reported Tmin, Tmax transmission coefficients.

COMPLEX 11 – CCDC 927946. The molecule of the complex is in a special position on a 2-fold axis. The crystal contains solvate disordered water molecules. The two water molecules per complex were modeled as disordered over 4 positions, one half populated, oxygen atoms being refined anisotropically, the rest three positions with occupancy 0.25, 0.125, 0.125 were refined isotropically. Hydrogen atoms were not found, but were taken into account in the sum formula, which resulted in two alerts C indicating discrepancy between calculated and reported formula and F(000).

COMPLEX 12 – CCDC 927947. The crystal is composed of the copper containing cation with the charge 2^+, which is in a special position in the centre of symmetry, two chlorine counter anions and 9 solvate water molecules per cation. Three water molecules in the asymmetric part have the occupancy of 0.5

and three sites are fully occupied. In spite of the room temperature measurement it appeared to be possible to find hydrogen atoms attached to 4 water molecules and to refine them with geometrical constraints. For two half-populated water molecules it was impossible to locate hydrogens, which results in alerts C: "calc. and reported SumFormula strings differ", "reported F000 differs from calcd". The cinnamic acid residue coordinating copper atoms is disordered over two positions with nearly equal (0.46) occupancy.

Preliminary antimicrobial testing of the complexes

Primary in vitro activity tests of **1**, **2a**, **2b**, **6**, **7**, **11** and **12** against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Salmonella and Candida Albicans* were carried out using the agar disk-diffusion method (200μg/8 mm disc) using Műller-Hilton agar medium [69]. All tests were performed in triplicate. Activity was determined by measuring the diameter of zones showing complete inhibition (mm), gentamicin, ampicillin and clotrimazole - control drugs. The MIC for the active compounds **1**, **7** and **11** against the same microorganism, used in the primary tests, were carried out using the microdilution susceptibility method in Műller-Hilton Broth and Sabouraud Medium [70].

Calculations

The quantum chemical calculations of ligands **L1**, **L3**, **L4** were performed using Gaussian 03 software package [71]. Full geometry optimizations have been carried out with the density functional theory (DFT) framework using the hybrid exchange correlation functional, B3LYP employing the 6-31G(d) basis which proved to be reliable for various systems and can be used for preliminary estimations of the conformational properties of the "free" ligands. All possible combinations of conformers resulting from internal rotation around the PC-CC and CC-CO bonds were used as starting geometry.

Results and Discussion

The structure of ligands

The ligands **L1**-**L5** possess positively charged phosphonium head group separated by a flexible aliphatic spacer from the negatively charged carboxylate group. In the crystalline phase carboxylate phosphonium betaine **L1** was found to be stabilized by various proton donor solvate molecules via C-O-…H-X (X=O, N) hydrogen bonds [47, 48, 72]. In certain conditions **L1** is protonated and forms crystals with various anions stabilized by the –C(O)-OH…X- (X= O-, Cl-) hydrogen bonding [47, 54]. The protonated form of **L5** was observed in the crystal of its phosphonium chloride [52] also stabilized by the C-OH…Cl- hydrogen bond. The crystal structure of the bisphonium ligand **L2** pentahydrate is published [47], however hydrogen atoms were not determined. The crystal structure of methyl-substituted ligands **L3** and **L4** is not reported.

To get preliminary information about the structure and conformational behaviour of carboxylate phosphonium betaines we have performed DFT calculations of the parent ligand **L1** and its α and β-methyl substituted derivatives **L3** and **L4** at the B3LYP/6-31G(d) level of theory.

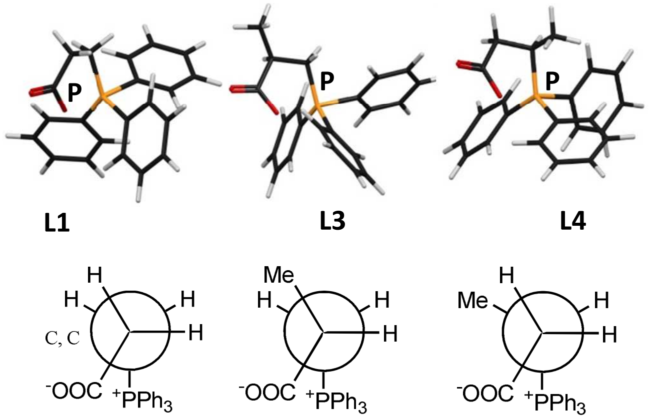


Fig. 1. The minimum energy structures of **L1** and methyl-substituted ligands as optimized by DFT method.

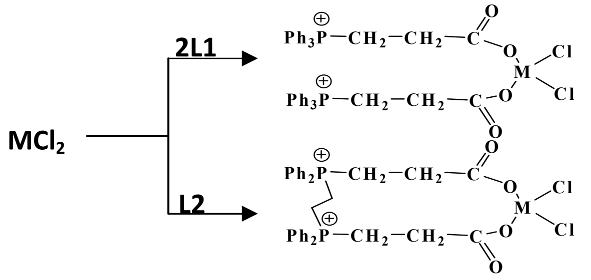
The geometry optimization was carried out for all possible staggered conformers which can result from the internal rotation around the PC-CC bond. The conformations with different orientation of the carboxylate group arising from internal rotation around the CC-CO bond were also checked. For all three ligands the most stable conformer is the one in which the charged groups are close together with the torsional angles P-C-C-C being in the range $32\text{-}39^0$ (Fig.1) and the carboxylate group close to eclipsed conformation with the C-C-C-O angles equal $18\text{-}22^0$. These electrostatic intramolecular interactions determine the structure of "free" ligands, the next conformation corresponding to the energy minimum is by 13-14 kcal/mol higher in energy and corresponds to a less folded structure with the P-C-C-C torsional angle being in the range $120\text{-}130^0$. In crystals the intermolecular hydrogen bonds stabilize the conformer in which negatively charged carboxylate group and positively charged phosphorus atom are in *trans* position, with the P-C-C-C torsional angle being in the range $155\text{-}175^0$. According to the DFT calculations this conformer is by 20-22 kcal/mol less favourable than the energy minimum form for **L1** and **L4**, while for **L3** trans-conformer does not correspond to an energy minimum at all due to steric hindrance between the phenyl and methyl groups, being higher in energy by 31 kcal/mol.

Thus, electrostatic and steric interactions determine the structure of "free" ligands, intermolecular electrostatic interactions in crystals result in significant conformational changes. It is also known that electrostatic interactions of the carboxylate group with metal ions play an important role in the formation of complexes. For example, charged carboxylate groups, e.g. aspartates or glutamates, bind metals more readily than those not charged [73]. Thus, for the evaluation of the coordination properties it was also important to estimate the charge distribution in the carboxylate group in the ligands. For this purpose the NBO charges were calculated which appeared slightly different on two oxygen atoms, the closer to phosphorus atom bearing negative charge ca -0.78 e, which is larger than the charge on the second oxygen atom by 0.15 e. The natural charges are very similar for all ligands, thus one may expect that their coordination properties are very close.

In spite of the similar coordination properties there is a substantial difference between the parent ligand **L1** and the substituted ligands **L3**-**L5**, the latter possess an asymmetric carbon atom and can form stereoisomeric metal complexes which are of special interest in terms of biological activity.

Complexes of L1 and L2

Simple mononuclear complex **1** is formed with Zn(II) (Scheme 2), the metal to ligand ratio being equal to 1:2.



(**1**) **L1**, M = Zn, (**2a**) **L2**, M = Zn, (**2b**) **L2**, M = Hg

Scheme 2

In complex **1** zinc ion has tetrahedral coordination with Zn-O bonds equal to 1.93, 1.95 Å, the other oxygen atoms are apart from the metal ion by 3.10 and 3.25 Å (Fig. 2). Thus, two ligand molecules exhibit monodentate coordination. The non-bound negatively charged oxygen atoms are stabilized by strong hydrogen bonding interactions with solvate water molecules. Positively charged phosphorus atoms in the complex are far away from each other (9.7 Å). Thus, the space between triphenylphosphonium groups is filled by 7 solvate water molecules, which form hydrogen bonded hydrophilic layers (Fig. 2).

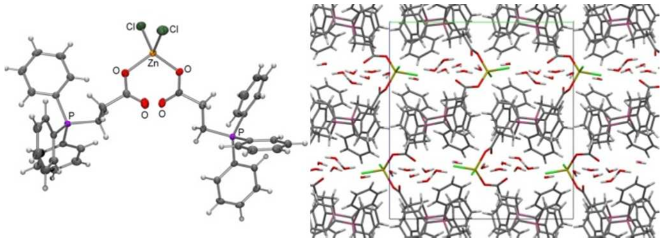


Fig. 2. Molecular structure of complex **1** and a fragment of crystal packing showing hydrophilic water layers (view along *a* axis).

The Cd complex of the same stoichiometric ratio was reported earlier [58], however the Cd ion in this complex possesses additional weak coordination to oxygen atoms (summary table 2). Thus, the ligands exhibit bidentate chelating coordination in this complex and at the same time participate in the hydrogen bonding with solvate water molecules. In spite of the different space groups the two crystals of Zn(II) and Cd(II) complexes have very similar packing arrangement.

In case of bis(phosphabetaine) ligand **L2** the respective position of the phosphonium head groups is restrained by the ethylene bridge, nevertheless similar monodentate coordination of the carboxylate fragments as in complex **1** is observed in isostructural complexes **2a** and **2b** (Scheme 2) of zinc (II) and mercury(II) (Fig. 3). Being iso-structural, these complexes nevertheless exhibit considerably different coordination geometry of Zn(II) and Hg(II), this especially refers to O-M-O and Cl-M-Cl bond angles (Table 2). The ethylene bridge determines the P…P distance to be equal 4.4 Å, 13-membered chelate ring being formed with completely different packing pattern. Instead of layered structure as in crystal **1**, there are channels filled with ethanol molecules which stabilize the "free" carboxylate oxygens in both crystals. The chelation of the metal ions is provided by the flexibility of the aliphatic spacers between the carboxylate and phosphonium groups, their *gauche* orientation being realized. The X-ray study of the "free" **L2** ligand [47] revealed completely different conformation with *trans*-orientation of the carboxylate groups, stabilized by multiple hydrogen bonds with solvate water molecules.

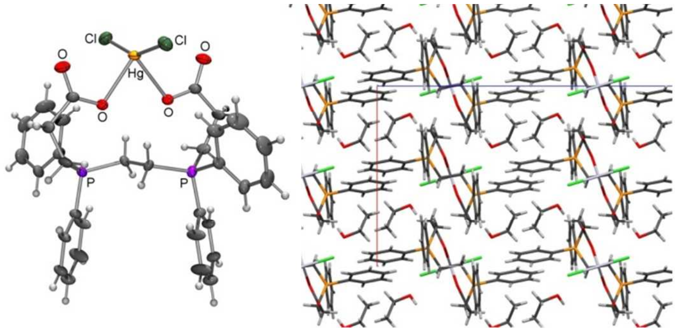
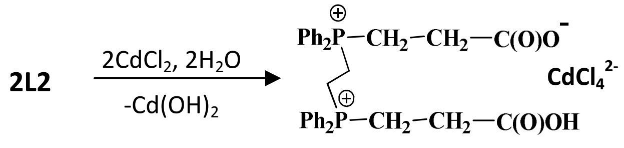


Fig. 3. Molecular structure of isostructural complexes **2(a**, **b)** and a fragment of their crystal packing (view along *b*-axis).

One should note that these two complexes have a two-fold symmetry with 11 non-hydrogen atoms being approximately in one plane and two phosphorus atoms twisted in opposite directions from this plane.

Interesting enough the corresponding reaction with Cd dichloride (Scheme 3) gave completely different salt-like crystal structure **3** composed of positively charged ligand and cadmium tetrachloride anion in the ratio of 2:1 (Fig. 4).



(3)

Scheme 3

One of the carboxyl groups of the ligand is deprotonated while the other is not. In the crystal very strong intermolecular hydrogen bonds are formed (Fig. 4), which belong to a special type of strong symmetric hydrogen bonds [74, 75]. The distance between the two oxygen atoms is extremely short O…O 2.42 Å. In such low-barrier hydrogen bonds the hydrogen atom is located between the two donor atoms in a single well potential [74, 75]. In complex **3** hydrogen position was refined to be at the equal distance of 1.23 Å from both oxygen atoms, and the infinite zigzag chain is formed along the *b*– direction.

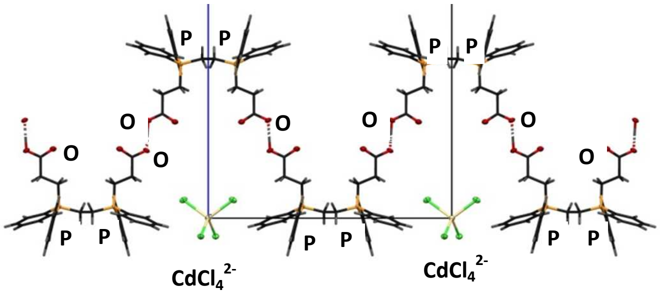
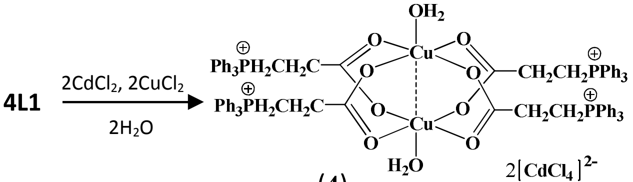


Fig. 4. A fragment of crystal packing (view along *a* axis) showing hydrogen bonding pattern of complex **3**.

The different geometry of the ligand in complexes **2a**, **b** and in complex **3,** as well as that of the "free" ligand reflects the ability of the flexible ligand to adopt conformation which provides the coordination with metal ion and the formation of the chelate ring.

The formation of the $CdCl_4^{2-}$ anion being favorable, it is also observed in the reaction of the **L1** ligand with a mixture of cadmium and copper dichlorides (Scheme 4).



(4)

Scheme 4

In crystal **4** (Fig. 5) the cation has a structure of a "chinese lantern" typical for binuclear Cu(II) complexes (1217 hits in the Cambridge Structural Database, version 5.35, Nov. 2013 [76]).

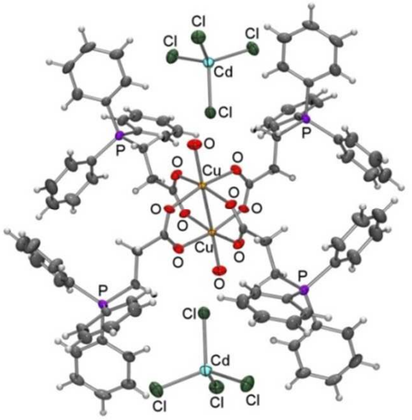
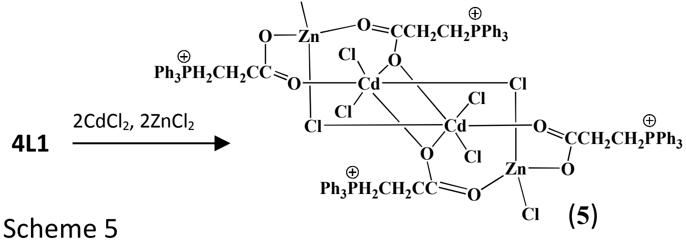


Fig. 5. Molecular structure of complex 4.

Four ligands coordinate two copper atoms, and two water molecules are in the axial positions. Cadmium is not coordinated by the ligand but is in the form of cadmium tetrachloride counter-ion with its ratio to binuclear copper cation equal 2:1.

At the same time similar reaction with a mixture of Cd and Zn dichlorides (Scheme 5) gave tetranuclear Cd and Zn containing cluster **5**.



(5)

Scheme 5

The cluster consists of two octahedrally coordinated Cd ions and two tetrahedrally coordinated Zn ions, which form two heteronuclear pairs doubly bridged by **L1** ligands, Zn and Cd ions from different pairs are additionally bridged by chlorine atoms and two Cd ions are bridged by oxygen atoms (Fig. 6).

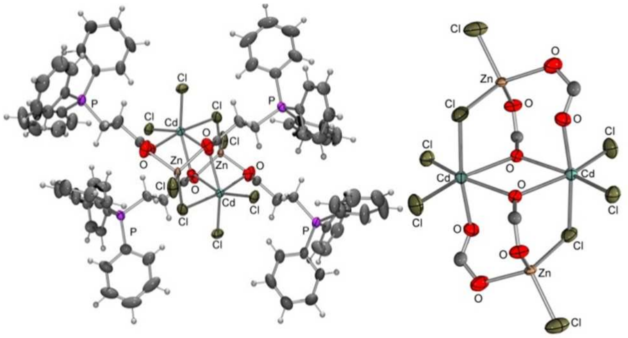


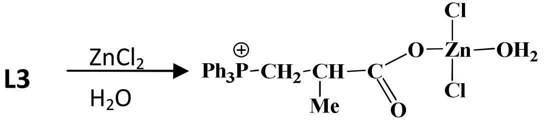
Fig. 6. Molecular structure of tetranuclear complex **5** and its heavy-atom core.

The four ligands in this complex exhibit two types of bridging coordination: μ_2 and μ_3. Spare coordination sites of metal ions are occupied by chlorine atoms. Previously a tetrameric homonuclear complex with Cd dibromide was reported in [58]. Both tetrameric complexes have similar heavy atom core, and the major difference between the mixed and homonuclear clusters refers to the coordination geometry of Zn(II) and Cd(II) ions, the latter has additional weak coordination by the carboxylate oxygen atoms with the following Cd-O distances: 2.245 and 2.707 Å, while the Zn ions in cluster **5** are bound to only one oxygen atom of each carboxylate group.

Complexes of α-substituted ligand L3

It is important to note that in case of ligands **L3-L5** a chiral center appears at α- or β-carbon atom.

The complex **6** of α-Me-substituted ligand **L3** was obtained (Scheme 6) with the ligand to metal ratio 1:1.



Scheme 6

(6)

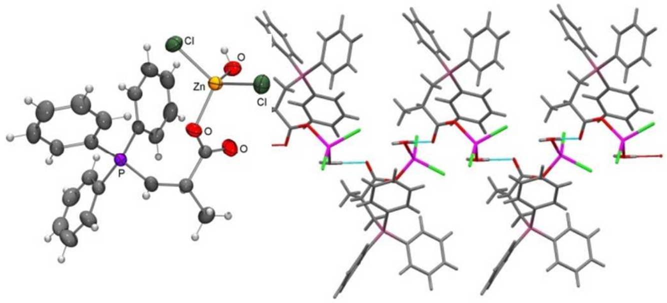
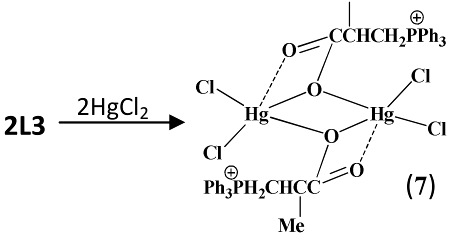


Fig. 7. Molecular structure of complex **6** and a fragment of crystal packing showing intermolecular hydrogen-bonded chain.

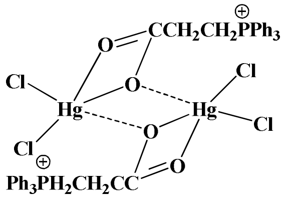
The racemic crystal was formed. Zinc ion has tetrahedral coordination and is bound to the ligand, two chlorine atoms and a water molecule (Fig. 7). The ligand exhibits monodentate coordination, the second oxygen atom being by more than 3.1 Å away from Zn ion (Table 2). No solvate water molecules are present in the crystal, a system of strong intermolecular hydrogen bonds between the coordinated water molecule and the carbonyl oxygen atom results in a supramolecular helical arrangement along the two-fold screw axis. It is important to note that unlike complexes of unsubstituted phosphonium betaine **L1**, in complex **6** *gauche*-conformation is realized with the dihedral angle P-C-C-C equal 75.2^0 (Table 2), as the *trans*-form does not correspond to an energy minimum. Such folded arrangement results in the steric shielding of the metal ion by the triphenylphosphonium group, thus the fourth coordination site of Zn(II) was occupied by water molecule but not the second ligand molecule as it is observed for unsubstituted ligand **L1**.

The reaction of ligand **L3** with mercury dichloride (Scheme 7) gave binuclear 1:1 complex **7** (Fig. 8).



Scheme 7

Earlier [77] the formation of 1:1 mononuclear complexes with Hg(II) dihalides was observed (Scheme 8) for unsubstituted ligand **L1**.



Scheme 8

Both complexes have very similar spatial arrangement, however complex **7** is a coordination dimer with two Hg ions doubly bridged by oxygen atoms and with the Hg-O bond lengths in the four-membered cycle 2.3 and 2.6 Å, while its counterpart with unsubstituted **L1** ligand is a supramolecular dimer with the distance between the monomeric units equal 2.9 Å (Scheme 8) [77].

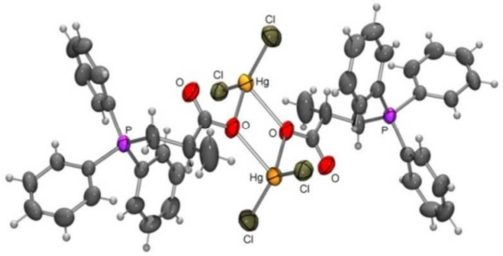


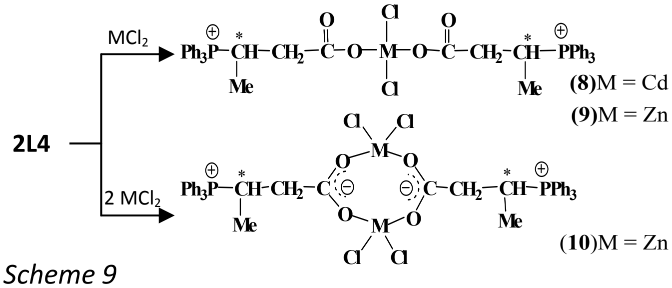
Fig. 8. Molecular structure of the binuclear complex **7.**

Thus, the introduction of the methyl group into α-position resulted in the redistribution of the coordination bonds in comparison with the complex formed by ligand **L1** in spite of very close structural arrangement. Such structural differences might be explained by the different conformational preferences of substituted and unsubstituted ligands. The *gauche* conformation of ligand **L3** (Table 2) is realized in complex **7** with one oxygen atom being attracted to positively charged phosphorus, thus only one oxygen binds mercury ions in a μ_2 bridging fashion. Such coordination results in formation of the dimeric complex **7** (Scheme 7). In case of unsubstituted phosphonium betaine ligand (Scheme 8) the carboxylate group is in *trans*-position to phosphorus atom, which makes chelating bidentate coordination possible with formation of the monomeric complex.

In complex **7** the methyl group in α-position is disordered over two sites with the occupancy ratio 0.8:0.2. This disorder is accompanied by the inversion of the carbon configuration. The complex is centrosymmetric, crystallizing in the P1bar space group.

Complexes of β-substituted ligands L4-L5

A series of interesting complexes was obtained for β-substituted ligand **L4** (Scheme 9).



Scheme 9

The formation of the 1:2 complex **8** (Fig. 9) similar to complex **1** was observed with cadmium dichloride. In this complex two β-carbon atoms have the opposite configuration, thus this racemic crystal contains R,S-diastereomer. The coordination mode of two ligands in this complex is different (Table 2): one can be considered as bidentate with Cd-O distances 2.18 and 2.62 Å while another exhibits monodentate coordination (Cd-O 2.18 and 2.93 Å). The packing motif containing a layer of water molecules (4 water molecules per complex) alternating with hydrophobic regions is very similar to crystal **1**.

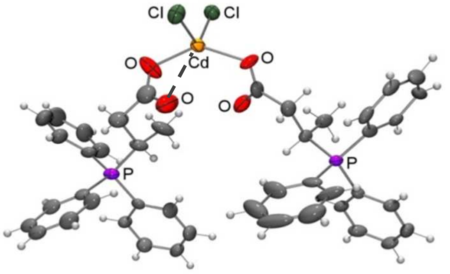


Fig. 9. Molecular structure of complex **8**.

The formation of the similar monodentate 1:2 complex **9** of **L4** was found for $ZnCl_2$ (Scheme 9), however no additional weak Zn-O coordination is observed. The crystal packing as well as the stereochemistry of obtained complexes were also different. In crystal **9** the co-crystallization of two chiral diastereomers (S,S) and (S,R) (space group $P2_1$) was observed (Fig. 10).

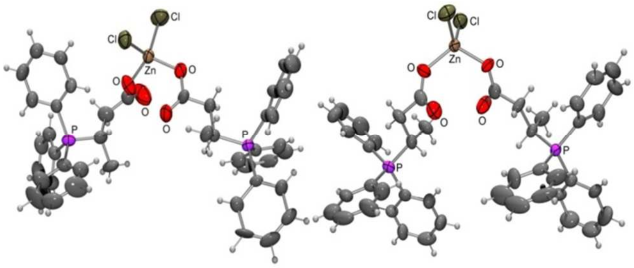


Fig. 10. Molecular structure of the (S,S) diastereomer (left) and the (S,R) diastereomer (right) co-crystallizing in crystal **9**.

Besides the relative configuration of the chiral centers in coordinating ligands, two co-crystallizing complexes differ by the conformation of the P-C-C-COO chains: in the (S,R) diastereomer both P-C-C-COO chains have *trans* configuration while in (S,S) diastereomer one of the chains is skewed with the torsional angle P-C-C-C equal 140^0. The coordination mode of both diastereomers is similar (Table 2).

From the same reaction mixture (Scheme 9) a racemic crystal **10** of a different stoichiometric composition was crystallized. This is a binuclear (1:1) complex of S,S diastereomer (Fig. 11). Both ligands in the complex exhibit *trans*-conformation and monodentate coordination (Table 2).

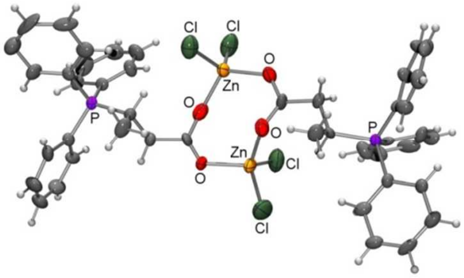
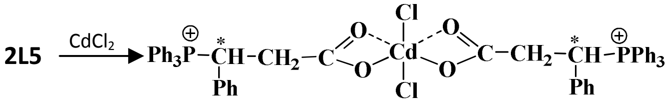


Fig. 11. Molecular structure of complex **10**

The ligand **L5,** containing phenyl group in the β-position, forms the complex **11** with Cd(II) dichloride of the stoichiometric ratio Cd:L = 1:2 (Scheme 10).



Scheme 10

(11)

Both ligands in this complex exhibit the same coordination which may be considered bidentate with Cd-O distances equal 2.27 and 2.57 Å (Fig. 12, table 2). Complex **11** crystallizes in a centrosymmetric P2/c group, the molecule being in a special position on a two-fold axis. The configuration of the chiral carbon atoms is the same in two ligands of the complex to give racemic S,S diastereomer. The packing consists of the layers of complexes separated by the layers of solvate water molecules (Fig. 12).

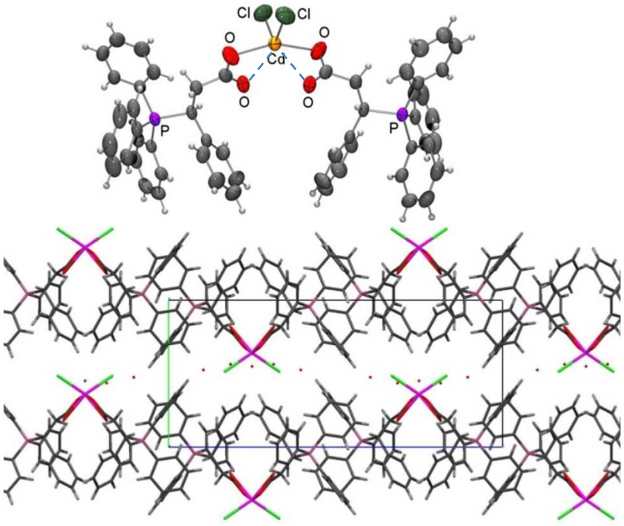
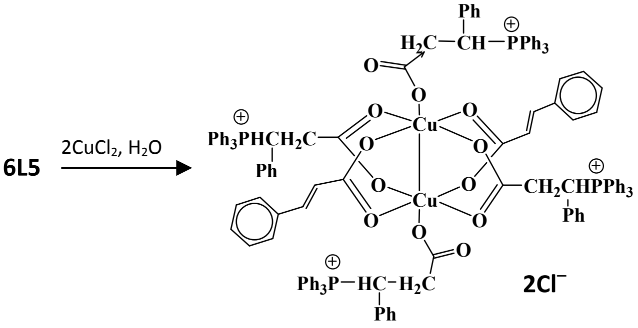


Fig. 12. Molecular structure of complex **11** and a fragment of crystal packing (view along *a*axis).

An interesting 1:2 complex **(12)** was obtained from the reaction of ligand **5** with copper dichloride (Scheme 11).



Scheme 11

(12)

Copper binuclear cation has a structure of the chinese lantern. One should note, that four ligands in this complex exhibit two types of coordination mode: two copper atoms are bridged by two ligands exhibiting bidentate coordination, and each copper atoms is also bound to one ligand, exhibiting monodentate coordination. Copper atoms are also bridged by cinnamic acid, resulting from the decomposition of the ligand into its precursors. Crystal **12** contains only one R,S,R,S – centrosymmetric diastereomer (Fig. 13): two bidentate ligands have R and S configuration related via the inversion center and two monodentate R and S ligands are also related via the center of symmetry.

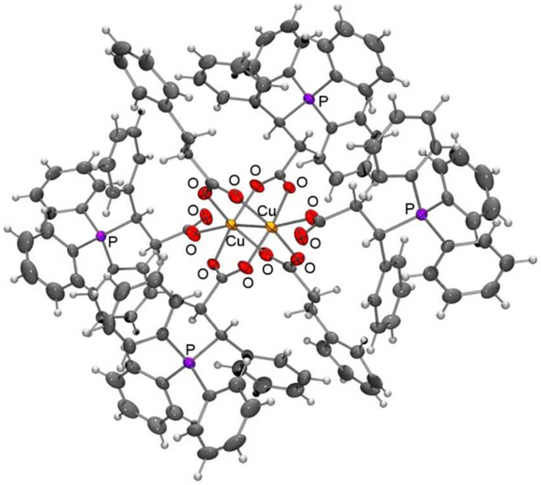


Fig. 13. Molecular structure of the cation **12**.

Preliminary tests on biological activity of the complexes

Some of the newly synthesized complexes **1**, **2a**, **2b**, **6**, **7**, **11** and **12** were tested for *in vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabi*lis, *Salmonella* and *Candida Albicans*. Compounds **1**, **7** and **11** displayed broad-spectrum antimicrobial activity, while compounds **2a**, **2b**, **4**, **6** and **12** showed good activity against *Candida Albicans*. The activity of complex **7** against various bacterial pathogens and fungi was evaluated in comparison with its inorganic precursor $HgCl_2$. It was shown that complex **7** is highly active against all pathogenic strains in contrast to mercury dichloride.

The minimal inhibitory concentration (MIC) for the active compounds **1**, **7** and **11** were in accordance with the results obtained in the primary screening.

Conclusions

Carboxylate phosphonium betaines were shown to exhibit versatile complexation ability, producing monomeric, dimeric, tetrameric homonuclear and mixed metal complexes with biologically important metals.

For Zn(II) complexes tetrahedral coordination of the metal ion is characteristic, and the ligands exhibit either monodenate coordination via one carboxylate oxygen, or bidentate μ_2 bridging mode, in the latter case dimeric complexes are formed. Chelating coordination of Zn ions was not observed. The second non-bound oxygen atom forms strong hydrogen bonds with solvate water or alcohol molecules.

The formation of similar complexes was observed upon going from Zn(II) to metal ions with larger ion radii Cd(II) and Hg(II). The substantial difference is that the binding mode of the carboxylate moiety has changed, chelating mode being possible or additional weak coordination by the second carboxylate oxygen being observed. The additional coordination to metal ion in complexes with Cd(II) and Hg(II) is more preferable than the stabilization of the carboxylate oxygen by proton donors.

All ligand molecules in crystalline complexes adopt conformation with trans orientation of the carboxylate and phosphonium groups except the α-methyl-substituted ligand **L3** for which *trans* conformation does not correspond to the energy minimum and *gauche*-form is observed in the complexes. These specific conformational behavior results in a different binding mode observed in the complexes of α-methyl-substituted ligand.

In case of α- and β-substituted phosphabetaines, bearing asymmetric carbon atom the crystallization of various stereoisomers was observed including rare case of co-crystallization of two diastereomers in one crystal.

The biological activity against pathogenic bacteria and fungi was revealed for Zn(II) and Hg(II) complexes.

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Notes and references

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† Electronic Supplementary Information (ESI) available: CCDC 927936- 927947, and 964968 contain the crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

1 J. Yon-Kahn, G. Herve, *Molecular and Cellular Enzymology, Springer-Verlag Berlin Heidelberg*, 2010, 783 p.
2 T. Aniszewski, *Alkaloids - Secrets of Life: Alkaloid Chemistry, Biological Significance, Applications and Ecological Role*, first ed., Elsevier Science, 2007.
3 G. A. Cordell, *The Alkaloids, Natural Products Inc.*, Evanston, 2010.
4 Z. Wang, E. Klipfell, B.J. Bennett, R. Koeth, B.S. Levison, B. DuGar, A.E. Feldstein, E.B. Britt, X. Fu, Y.-M. Chung, Y. Wu, P. Schauer, J.D. Smith, H. Allayee, W.H. Wilson Tang, J.A. DiDonato, A.J. Lusis & S.L. Hazen, *Nature* 2011, **472**, 57.

5 E.K. Perttu, A.G. Kohli, F.C. Szoka, *J. Am. Chem. Soc*. 2012, **134**, 4485.
6 X. Yu, J. Zheng, *J. Mol. Biol.* 2012, **421**, 561.
7 F. Mollinedo, C. Gajate, S. Martín-Santamaria, F. Gago, *Current Medicinal Chemistry,* 2004, **11**, 3163.
8 E. Oldfield et al., *Bisphosphonate compounds and methods,* US Patent EP 2001486 A2, 2006.
9 S. Azzouz, M. Maache, R.G. Garcia, A. Osuna,. *Basic & Clinical Pharmacology & Toxicology,* 2005, **96**, 60.
10 S.B. Kondapaka, S.S. Singh, G.P. Dasmahapatra, E.A. Sausville, and K.K. Roy, *Mol. Cancer Ther.* 2003, **2**, 1093.
11 T.P. Dorlo, P.P. van Thiel, A.D. Huitema, R.J. Keizer, H.J. deVries, J.H. Beijnen, P.J. deVries, *Antimicrob. Agents Chemother.* 2008, **52**, 2855.
12 F. Widmer, L. Wright, D. Obando, R. Handke, R. Ganendren, D. Ellis, T. Sorrell, *Antimicrob. Agents Chemother.* 2006, **50**, 414.
13 K. Barhwal, S.K. Hota, V. Jain, D. Prasad, S.B. Singh, G. Ilavazhagan, *Neuroscience*, 2009, **161**, 501.
14 C. Danelon, E.M. Nestorovich, M. Winterhalter, M. Ceccarelli and S.M. Bezrukov, *Biophysical Journal,* 2006, **90**, 1617.
15 E.M. Nestorovich, C. Danelon, M. Winterhalter, S.M. Bezrukov, *PNAS*, 2002, **99**, 9789.
16 H. Mikamo, K. Kawazoea, K. Izumia, S. Hachiyab, M. Satohb, K. Munakatab, T. Tamayaa, *International Journal of Antimicrobial Agents*, 1997, **8**, 7.
17 R. Mo, Q. Sun, N. Li, C. Zhang, *Biomaterials*, 2013, **34**, 2773.
18 V. Iyer et al., *Phosphorylcholine-based amphiphilic silicones for medical applications*, US Patent EP 2444448 A1, 2009.
19 R. Lalani and L. Liu, *Biomacromolecules,* 2012, **13**, 1853.
20 Z. Zhang, T. Chao, S. Chen, S. Jiang, *Langmuir,* 2006, **22**, 10072.
21 M. Binazadeh, M. Kabiri, L.D. Unsworth, *Poly(ethylene glycol) and Poly(carboxybetaine) Based Nonfouling Architectures: Review and Current Efforts. In “Proteins at Interfaces III. State of the Art”* Horbett, T., et al.; ACS Symposium Series; American Chemical Society: Washington, DC, 2012, p.621-643.
22 B. Mrabet, A. Mejbri, S. Mahouche, S. Gam-Derouich, M. Turmine, M. Mechouet, P. Lang, H. Bakala, M. Ladjimi, A. Bakhrouf, S. Tougaard, M. Chehimi, *Surf. Interface Anal*., 2011, **43**, 1436.
23 Q. Tu, J.-C. Wang, R. Liu, Y. Zhang, J. Xu, J. Liu, M.-S. Yuan, W. Liu, J. Wang, *Colloids and Surfaces B: Biointerfaces,* 2013, **102**, 331.
24 H.J. Smith, C. Simons (Eds.), *Enzymes and their Inhibition: Drug Development*, CRS Press, Boca Raton - London - New York - Singapore, 2005, 308 p.
25 Z. Ma, F.E. Jacobsen, D.P. Giedroc, *Chem. Rev.* 2009, **109**, 4644.
26 C. Castro, N.S. Millian, T. Garrow, *Arch. Biochem. Biophys*. 2008, **472**, 26.
27 T. Dudev, C. Lim, *Chem. Rev*. 2003, **103**, 773-787.
28 K. L. Haas and K. J. Franz, *Chem. Rev*. 2009, **109**, 4921.
29 N. J. Lakhkar, I.-H. Lee, H.-W. Kim, V. Salih, I. B. Wall, J. C. Knowles, *Advanced Drug Delivery Reviews*, 2013, **65**, 405.
30 P. Liu, J. Song, *Biomaterials,* 2013, **34**, 2442.
31 C.-T. Yang, Y. Li, S. Liu, *Inorg. Chem.* 2007, **46**, 8988.
32 R. Sakai, K. Suzuki, K. Shimamoto, H. Kamiya, *J. Org. Chem.* 2004, **69**, 1180.
33 B. Nath, D. Kalita, J. B. Baruah, *Solid State Sciences,* 2012, **14**, 880.
34 J.-X. Chen, W.-E. Lin, C.-Q. Zhou, L. F. Yau, J.-R. Wang, B. Wang,W.-H. Chen, Z.-H. Jiang, *Inorganica Chimica Acta*, 2011, **376**, 389.
35 C. Litos, S. Parsons, A. Karaliota, *Polyhedron*, 2007, **26**, 1397.
36 X.-M. Zhang, X.-B. Li, E.-Q. Gao, *J. Coord. Chem*. 2011, **64**, 244.
37 X.-L. Zhao, Q.-M. Wang, T. C. W. Mak, *Chem. Eur. J.* 2005, **11**, 2094.
38 X.-M. Zhang, Y.-Q. Wang, E.-Q. Gao, *Eur. J. Inorg. Chem*. 2010, **8**, 1249–1254.
39 Dasgupta, P. K. Das, R. S. Dias, M. G. Miguel, B.1rn Lindman, V. M. Jadhav, M. Gnanamani, S. Maiti, *J. Phys. Chem. B*, 2007, **111**, 8502.
40 V. V. Floch, S. Loisel, E. Guénin, A. C. Hervé, J. C. Clément, J. J. Yaouanc, H. des Abbayes, C. Férec, *J. Med. Chem.* 2000, **43**, 4617.
41 E. Guénin, A. C. Hervé, V. V. Floch, S. Loisel, J. J. Yaouanc, J. C. Clément, C. Férec, H. des Abbayes, *Angew. Chem. Int. Ed.* 2000, **39**, 629.
42 Fraix, T. Montier, T. L. Gall, C. M. Sevrain, N. Carmoy, M. F. Lindberg, P. Lehnb, P.-A. Jaffrès, *Org. Biomol. Chem*. 2012, **10**, 2051.
43 T. Sakurai, K. Fujiwara, *British Journal of Pharmacology,* 2001, **132**, 143.
44 J.S. Edmonds, K.A. Francesconi, *Appl. Organometal. Chem.* 1988, **2**, 297.
45 C. Kojima, T. Sakurai, M. Ochiai, H. Kumata, W. Qu, M.P. Waalkes, K. Fujiwara, *Appl. Organometal. Chem.* 2002, **16**, 421.
46 T. Rezanka, K. Sigler, *Phytochemistry,* 2008, **69**, 585.
47 S.-L. Li, T.C.W. Mak, *J. Mol. Struct.* 1996, **384**, 135.
48 S. W. Ng, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun*. 1999, **55**, 646.
49 V. I. Galkin, Yu. V. Bakhtiyarova, N. A. Polezhaeva, R. A. Shaikhutdinova, V. V. Klochkov, R.A. Cherkasov, *Russian J. Gen. Chem.* 1998, **68**, 1052.
50 V. I. Galkin, Yu. V. Bakhtiyarova, A. N. Zaripova, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, A. N. Pudovik, *Phosphorus, Sulfur Silicon Relat. Elem.* 2002, **177**, 2063.
51 V. I. Galkin, Yu. V. Bakhtiyarova, N. A. Polezhaeva, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russian J. Gen. Chem.* 2002, **72**, 376.
52 V. I. Galkin, Yu. V. Bakhtiyarova, N. A. Polezhaeva, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russian J. Gen. Chem.* 2002, **72**, 384.
53 V. I. Galkin, Yu. V. Bakhtiyarova, R. I. Sagdieva, I. V. Galkina, R. A. Cherkasov, *Heteroatom Chemistry*, 2006, **17**, 557.
54 Yu. V. Bakhtiyarova, R. I. Sagdieva, I. V. Galkina, V. I. Galkin, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russian J. Gen. Chem.* 2007, **43**, 207.
55 S.-L. Li, T. C. W. Mak, *J. Chem. Soc., Dalton Trans.* 1995, 1519.
56 S.-L. Li, T. C. W. Mak, *Polyhedron,* 1996, 15, 3755.
57 S.-L. Li, T. C. W. Mak, *Aust. J. Chem.* 1997, **50**, 79.
58 S.-L. Li, T. C. W. Mak, *Inorg. Chim. Acta,* 1997, **258**, 11.
59 D. J. Irvine, S. A. Preston, D. J. Cole-Hamilton, J. C. Barnes, *J. Chem. Soc., Dalton Trans.* 1991, 2413.
60 W.L.F. Armarego, C.L.L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Burlington, 2009.

61 J.A. Riddick, W.B. Bunger, T.K. Sakano, Organic Solvents. *Physical properties and methods of purification,* J. Wiley and Sons, New York, 1986.

62 Bruker. *APEX2 Software Suite for Crystallographic Programs,* Bruker AXS,Inc., Madison, WI, USA, 2009.

63 Bruker. *Area detector control and integration software.* Version 5.x. In: SMART and SAINT. Madison, Wisconsin (USA): Bruker Analytical X-ray Instruments Inc.; 1996.

64 G.M.Sheldrick, *SADABS*, University of Göttingen, Institut für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1997.

65 G.M. Sheldrick, *Acta Crystallogr*. 2008, **A64**, 112.

66 L. J. Farrugia, *J. Appl. Cryst.* 2012, **45**, 849.

67 C.F. Macrae, I.J. Bruno, J.A. Chisholm, P.R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streekand P. A. Wood, *J. Appl. Cryst.* 2008, **41**, 466.

68 A.L. Spek, *Acta Cryst.* 2009, **D65**, 148.

69 P.R. Murray, E.J. Baron, M.A. Pfaller, F.C. Tenover, R.H. Yolken, editors, *Manual of Clinical Microbiology*, Ed. American Society for Microbiology: Washington, DC, USA, 1995.

70 National Committee for Clinical Laboratory Standarts (NCCLS). Approved Standart document M7A; NCCLS: Villanova, PA, USA, 1985.

71 *Gaussian 03, Revision C.02*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

72 V. I. Galkin, Yu. V. Bakhtiyarova, R.I. Sagdieva, I. V. Galkina, R. A. Cherkasov, D. B. Krivolapov, A. T. Gubaidullin, I. A. Litvinov, *Russian J. Gen. Chem.* 2006, **76**, 430.

73 T. Dudev, C. Lim, *Annu. Rev. Biophys.* 2008, **37**, 97.

74 C.L. Perrin, *Acc. Chem. Res.* 2010, **43**, 1550.

75 T.Steiner, *Angew. Chem. Int. Ed.* 2002, **41**, 48.

76 F.R. Allen, *Acta Cryst.* 2002, **B58**, 380.

77 S.-L. Li, T. C. W. Mak, *J. Chem. Cryst.* 1997, **27**, 91.

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Table 1. Crystal data for complexes **1-12**, to be continued.

Compound reference	**(1)**	**(2a)**	**(2b)**	**(3)**	**(4)**	**(5)**	**(6)**
Chemical formula	$C_{42}H_{52}Cl_2O_{11}P_2Zn$	$C_{36}H_{44}Cl_2O_6P_2Zn$	$C_{36}H_{44}Cl_2HgO_6P_2$	$C_{64}H_{66}CdCl_4O_8P_4$	$C_{84}H_{88}Cd_2Cl_8Cu_2O_{14}P_4$	$C_{84}H_{76}Cd_2Cl_8O_8P_4Zn_2$	$C_{22}H_{23}Cl_2O_3PZn$
Formula Mass	931.05	770.92	906.14	1341.25	2080.90	1976.47	502.64
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Tetragonal	Monoclinic	Triclinic	Monoclinic
a/Å	13.1245(5)	13.451(2)	13.439(4)	19.110(2)	19.851(1)	13.1156(4)	9.565(1)
b/Å	17.9402(6)	12.557(2)	12.495(4)	19.110(2)	19.805(1)	14.2632(4)	9.761(1)
c/ Å	18.6539(7)	22.015(3)	21.984(5)	17.309(2)	12.606(1)	14.7819(4)	23.907(3)
α/°	90.00	90.00	90.00	90.00	90.00	95.833(1)	90.00
β/°	90.00	90.216(2)	90.006(5)	90.00	105.370(3)	101.823(1)	91.139(2)
γ/°	90.00	90.00	90.00	90.00	90.00	115.618(1)	90.00
Unit cell volume/Å^3	4392.2(3)	3718.4(10)	3691.6(18)	6321.1(12)	4778.8(5)	2383.17(12)	2231.6(4)
Temperature/K	150(2)	293(2)	150(2)	150(2)	296(2)	198(2)	296(2)
Space group	$P2_12_12_1$	$C2/c$	$C2/c$	I-$42d$	$C2/m$	P-1	$P2_1/n$
No. of formula units per unit cell, Z	4	4	4	4	2	1	4
Absorption coefficient, μ/mm^{-1}	0.811	0.933	4.444	0.669	1.225	1.276	1.432
No. of reflections measured	82904	17903	19787	17149	39663	71161	23627
No. of independent reflections	12257	4058	4449	4754	5628	11501	4872
R_{int}	0.0289	0.0617	0.0623	0.0814	0.1062	0.0613	0.0201
Final R_1 values (I> 2σ(I))	0.0279	0.0421	0.0413	0.0332	0.0392	0.0421	0.0268
Final $wR(F^2)$ values (I> 2σ(I))	0.0694	0.1226	0.0798	0.0616	0.0699	0.1187	0.0706
Final R_1 values (all data)	0.0322	0.0472	0.0495	0.0463	0.1684	0.0623	0.0316
Final $wR(F^2)$ values (all data)	0.0715	0.1264	0.0825	0.0648	0.0985	0.1240	0.0729

Table 1. Crystal data for complexes **1-12**, continuation.

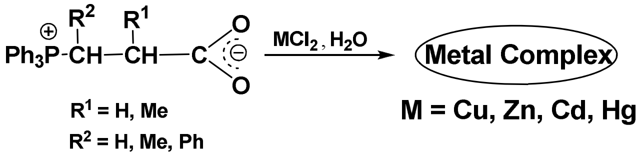
Compound reference	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**	**(12)**
Chemical formula	$C_{44}H_{42}Cl_4Hg_2O_4P_2$	$C_{44}H_{50}CdCl_2O_8P_2$	$C_{44}H_{46}Cl_2O_6P_2Zn$	$C_{44}H_{41}Cl_4O_5P_2Zn_2$	$C_{54}H_{50}CdCl_2O_6P_2$	$C_{126}H_{124}Cl_2Cu_2O_{21}P_4$
Formula Mass	1239.70	952.08	869.02	984.25	1040.18	2296.11
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic
a/Å	9.822(1)	18.380(10)	18.129(3)	13.296(1)	9.991(3)	12.296(1)
b/Å	9.894(1)	12.946(7)	12.883(2)	20.271(2)	10.612(3)	15.163(2)
c/Å	12.303(1)	18.556(10)	18.871(3)	18.723(1)	24.958(6)	16.486(2)
α/°	76.679(1)	90.00	90.00	90.00	90.00	91.587(1)
β/°	80.871(1)	97.26(1)	98.154(2)	114.535(3)	104.450(9)	95.492(1)
γ/°	76.246(1)	90.00	90.00	90.00	90.00	104.080(1)
Unit cell volume/Å^3	1123.22(19)	4380(4)	4363(1)	4590.6(6)	2562.4(12)	2963.5(6)
Temperature/K	296(2)	198(2)	296(2)	296(2)	296(2)	296(2)
Space group	P-1	$P2_1/c$	$P2_1$	$P2_1/n$	$P2/c$	P-1
No. of formula units per unit cell, Z	1	4	2	4	2	1
Absorption coefficient, μ/mm^{-1}	7.175	0.745	0.804	1.389	0.640	0.525
No. of reflections measured	14585	25711	62162	52894	41302	22499
No. of independent reflections	4643	7453	19177	16719	5026	11444
R_{int}	0.0260	0.1323	0.1104	0.0979	0.0523	0.0529
Final R_1 values ($I > 2\sigma(I)$)	0.0210	0.0702	0.0551	0.0868	0.0471	0.0554
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.0507	0.1691	0.1185	0.1801	0.1583	0.1393
Final R_1 values (all data)	0.0239	0.1267	0.1553	0.2010	0.0584	0.0906
Final $wR(F^2)$ values (all data)	0.0522	0.1924	0.1443	0.2413	0.1653	0.1525

Table 2. Principal geometrical parameters of Zn(II), Cd(II), Hg(II) complexes.

Complex	L	M-O*	M-O**	τ(PC-CC)	τ(CC-CO*)	C-O*	C-O**	Cl-M-Cl	O-M-O
1. $ZnCl_2L_2{\cdot}7H_2O$	L1	1.948(1) 1.929(1)	3.096(1) 3.246(1)	-152.5(1) 165.3(1)	82.9(1) -178.4(1)	1.261(2) 1.269(2)	1.234(2) 1.234(2)	106.34(2)	113.21(5)
$CdCl_2L_2{\cdot}7H_2O$ [58]	L1	2.307 2.287	2.567 2.576	-177.92 -172.49	-156.3 -167.4	1.279 1.268	1.246 1.225	108.80	139.49
2a. $ZnCl_2L{\cdot}2C_2H_5OH$	L2	1.994(2)	3.061(2)	-68.4(3)	9.6(4)	1.269(3)	1.224(3)	126.17(5)	91.0(1)
2b. $HgCl_2L{\cdot}2C_2H_5OH$	L2	2.364(3)	3.074(3)	-66.8(6)	8.7(8)	1.257(6)	1.244(5)	152.12(6)	77.50(15)
5. $Cd_2Zn_2Cl_8L_4$	L1	2.056(3) 2.025(3) 2.341(2) 2.355(2)	3.035(3) 2.977(3) 2.421(2)	176.67(4) 171.60(4)	-158.28(4) 148.88(4)	1.254(4) 1.273(5)	1.257(4) 1.235(5)	110.50(4) 110.49(4) 92.64(4) 96.53(3)	106.15(12) 90.82(9) 70.68(9) 82.88(9)
6. $ZnCl_2L(H_2O)$	L3	1.954(1)	3.081(3)	75.2(2)	13.6(2)	1.270(2)	1.227(2)	113.66(2)	109.97(5)
7. $Hg_2Cl_4L_2$	L3	2.319(2)	2.557(2) 2.836(2)	73.5(4)	-171.2(3)	1.266(3)	1.225(4)	138.26(4)	73.45(8)
8. $CdCl_2L_2{\cdot}4H_2O$	L4	2.185(6) 2.188(6)	2.932(6) 2.622(6)	-169.0(6) -174.8(6)	-160.5(8) 101.01(10)	1.192(9) 1.165(10)	1.305(9) 1.280(10)	118.81(7)	138.6(2)
9. $ZnCl_2L_2{\cdot}2H_2O$ S,S-diastereomer	L4	1.953(5) 1.955(6)	3.038(5) 3.413(6)	170.5(6) 139.9(7)	171.0(7) -56.2(10)	1.261(8) 1.256(9)	1.243(8) 1.179(9)	110.28(10)	115.7(2)
9. $ZnCl_2L_2{\cdot}2H_2O$ S,R-diastereomer	L4	1.961(4) 1.954(5)	3.113(5) 3.126(5)	-166.5(5) 172.3(6)	-163.8(7) 106.7(7)	1.271(8) 1.264(9)	1.214(8) 1.248(9)	115.20(9)	120.8(2)
10. $Zn_2Cl_4L_2{\cdot}H_2O$	L4	1.969(5) 1.989(6) 1.960(5) 1.997(6)		155.1(6) 157.5(5)	3.4(11) -66.3(9)	1.285(8) 1.231(8)	1.196(8) 1.185(8)	119.66(11) 117.67(14)	115.3(2) 105.1(2)
11. $CdCl_2L_2{\cdot}2H_2O$	L5	2.279(3)	2.478(1)	-164.1(3)	-176.2(4)	1.250(5)	1.210(5)	114.97(6)	157.69(18)

O*- the carboxylate oxygen atom forming the shortest coordination bond with metal ion

O**- the second carboxylate oxygen atom


$Ph_3\overset{\oplus}{P}-CH(R^2)-CH(R^1)-CO_2^{\ominus}$
MCl_2, H_2O
Metal Complex
R^1 = H, Me
R^2 = H, Me, Ph
M = Cu, Zn, Cd, Hg