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SUMMARY OF DOCTORAL THESIS

STUDIES OF ACID-BASE AND COMPLEX-FORMATION EQUILIBRIA OF COPPER(II), ZINC(II), MAGNESIUM(II) OR CALCIUM(II) METAL IONS IN AQUEOUS SOLUTIONS OF SELECTED *N,N*-SUBSTITUTED DERIVATIVES OF AMINOMETHANE-1,1-DIPHOSPHONIC ACID

Diphosphonic acids, $\text{PO}_3\text{H}_2\text{-X-PO}_3\text{H}_2$, constitute a diverse class of bifunctional ligands, in which each phosphonate group provides one, two or three oxygen atoms capable of coordinating metal ions. Extending the X fragment and adding functional groups within it leads to the formation of new compounds with different chemical and biological properties. This doctoral thesis concerns one important subgroup of compounds belonging to this class, which contain the P–C–P backbone (commonly named bisphosphonates). They are chemically stable synthetic analogs of inorganic pyrophosphoric acid (P–O–P), a naturally occurring compound, which is an important regulator of calcium metabolism in living organisms.

This class of compounds is easily taken up from the bloodstream by the bone tissue where they can prevent the resorption of bone. This makes them the primary agents in the current pharmacological arsenal against osteoclast-mediated bone loss due to osteoporosis, Paget disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy. A wide spectrum of applications has become the cause of active design of new compounds, as well as undertaking research in the field of determining their biological activity. Linking this activity with the structure and complex forming properties resulted in numerous literature reports over the years on the synthesis and properties of subsequent compounds belonging to the first, second, third and even fourth generation.

The above facts have been an inspiration to undertake the research aimed at determining the type of species formed in aqueous solutions by *N,N*-substituted derivatives of aminomethane-1,1-diphosphonic acid (compounds assigned as **N-BP_1** – **N-BP_9**, potentially

fourth-generation drugs) depending on the pH, with particular emphasis on the physiological pH. Their stability and coordination modes in complexes formed by these ligands have also been investigated. The coordination properties of these ligands have been studied in relation to biologically important divalent metal ions, such as copper(II), zinc(II), magnesium(II) and calcium(II).

In order to create a full characterization of the complex-forming equilibria occurring in aqueous solution of a series of diphosphonic acids towards the metal ions the systematic investigations have been undertaken by the use of potentiometric method completed with the data obtained from UV–Vis and EPR spectroscopy, ESI–MS spectrometry, ^1H and ^{31}P NMR methods.

In the literature part of the doctoral thesis, the spatial structure of diphosphonic acids containing two geminally bound phosphonic groups are characterized, as well as their tendency to form hydrogen bonds. In the further part of this chapter, the acid-base properties of the ligands belonging to this class of compounds are described, with particular emphasis on the protonation sites and the effect of hydrogen bonds on the dissociation of functional groups. Next, the coordination properties of diphosphonic acids in relation to selected metal ions in aqueous solutions and in the solid state are discussed. The last part of the literature overview provides a short summary of selected examples of applications of these compounds in pharmacology and industry.

In the experimental part of the dissertation, the chemical reagents, the research apparatus and methodology, as well as the research conditions are characterized. The choice of the methods applied depends on the type of metal ion contained in the studied binary systems.

In the study area of the dissertation, the acid-base equilibria of the investigated *N,N*-substituted derivatives of aminomethane-1,1-diphosphonic acid are discussed. The influence of the nature of the different substituents attached to the amino nitrogen atom (linear or branched alkyl, cycloheptyl ring, phenylalkyl or pyridine ring) on the basicity of the functional groups is analyzed. Their higher basicity, compared to mono-substituted (RNH_2^+) diphosphonic acids, may be attributed to the inductive effect of the methyl substituent.

In the further part of this chapter, the complex-formation abilities of the studied ligands towards the divalent metal ions are presented. The obtained results indicate that in all studied systems mononuclear protonated equimolar and bis complexes are formed. In acidic and neutral solutions, the formation of the protonated dinuclear species has been confirmed.

The amino nitrogen atom present in the molecules of the **N-BP_1** – **N-BP_7** compounds remains protonated in the whole pH range studied and the Zn(II), Mg(II) and Ca(II) ions are coordinated exclusively through oxygen atoms of the phosphonate groups in all detected complex species. The involvement of the nitrogen atom in coordination has been confirmed only in the deprotonated Cu(II) complexes formed in the systems with these ligands in strongly alkaline solutions. In all complexes, one or two chelate rings are formed. The dependence between the relative stabilities of the [M(HL)] complexes and the basicity of coordinating donor groups in the studied M(II) – L binary systems are presented and the R substituent effect on the stability of the complexes is discussed.

The binding of the second ligand molecule is disfavored, much more in the case of **N-BP_8** and **N-BP_9** than for the ligands **N-BP_1** – **N-BP_7**. In the ligands **N-BP_1** – **N-BP_7** a positive charge density on the protonated amino nitrogen atom partially compensates the electrostatic repulsion of highly charged phosphonate groups.

Spectroscopic studies indicate that the coordination in all complexes formed in the systems with ligands containing pyridine substituent (ligands **N-BP_8** and **N-BP_9**) is likely to occur only by oxygen atoms of phosphonate groups, without the participation of nitrogen atoms present in the ligand molecule.

The final chapter of the dissertation summarizes the conclusions of the scientific investigation. The work ends with a list of references and an annex containing the results of the ESI–MS research, which allowed to verify the stoichiometry of the complexes formed in the studied systems.