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# Hydroxypyronate, thiohydroxypyronate and hydroxypyridinonate derivatives as potential $Pb^{2+}$ sequestering agents

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ABSTRACT

Solution equilibrium study on Pb(II) complexes of 3-hydroxy-2-methyl-4-pyrone (maltol, maltH) and its two derivatives, 3-hydroxy-2-methyl-4*H*-pyran-4-thione (thiomaltol, thiomalH) and 3-hydroxy-1,2-dimethyl-4-pyridinone (dhpH) have been performed by using pH-potentiometry, $^1$H NMR, ESI MS methods. Out of the studied ligands, the (S,O)-chelating thiomalt was found to form the most stable mono- and bis-chelated type species, $[PbL]^+$ and $[PbL_2]$, but limited water solubility hindered the examination on this system above pH 7. The Pb(II)-binding capabilities of malt and especially dhp are still very good and the higher extent of electron delocalization in dhp compared to malt results not only in the increased stability of the 5-membered (O,O) dhp chelate, but also the possibility of some involvement of the $6s^2$ lone electron pair of Pb(II) in the bonding. Furthermore, dhp, compared to malt, is not just a more effective Pb(II) chelator, but also shows better selectivity toward Pb(II) against Zn(II).



## 1. Introduction

Numerous results support the various ways of Pb(II) poisoning [1–3], what, in many cases, is in direct correlation with well-defined affinity of this metal ion toward complexation with different bioligands, for instance, proteins [3]. In some part, the toxicity of Pb(II) is attributed to the displacement of physiologically relevant metal ions (like Zn(II), Ca(II) ions) in proteins [1,4]. Treatment of Pb(II) poisoning is frequently carried out by chelating agents [5], but very often, selectivity defects cause unwanted side-effects. With a better understanding the factors determining the interaction between a ligand and Pb(II), or by controlling the selectivity of a ligand for Pb(II) against Ca(II) and especially against Zn(II), one might be able to design more efficient molecules for the treatment of lead intoxication [6–9]. To search for ligands forming discrete complex(es) with improved solubility, affinity and selectivity for Pb(II) is one of the main goals in our work nowadays [10–13]. In a previous paper of ours, the high chelating ability of α-aminohydroxamates to this metal ion was found. This, however, occured only at high pH and resulted in the formation of polynuclear species [11]. In another recent work, we have done a systematic solution equilibrium study on Pb(II)-amino acid, Pb(II)-small peptide/derivative systems. The effects of the arrangement of different type of donor atoms (N, O, S) on the Pb(II)-binding ability as well as on the selectivity for Pb(II) over Zn(II) were evaluated. Significant Zn(II) preference of the investigated N-donor ligands was found, while the ability of the studied O-donor ligands for binding Zn(II) or Pb(II) was roughly the same. Out of the 25 investigated molecules, penicillamine was found to have the best Pb(II) binding ability, but compared to this ligand, a somewhat better selectivity for Pb(II) over Zn(II) was achieved with the S-containing dipeptide, alanyl-cysteine [12]. Systematic investigation on Pb(II) complexation of two hydroxamate based siderophores, desferrioxamine B and desferricoprogen, however, also showed a significant effect of the extent of the electron delocalization on the chelating function [13]. Following this line, three heterocyclic compounds have been involved into the present study.

Hydroxypyrones, thiohydroxypyrones and hydroxypyridinones have 6-membered ring scaffold and their deprotonated forms are effective metal ion chelators [14–19]. To find some answer for the question, whether or not these compounds can be candidates as potential Pb(II) sequestering agents was the main reason, why Pb(II) complexes of 3-hydroxy-2-methyl-4-pyrone (maltol, maltH) and its two derivatives, 3-hydroxy-2-methyl-4*H*-pyran-4-thione (thiomaltol, thiomalH) and 3-hydroxy-1,2-dimethyl-4-pyridinone (dhpH) (see Scheme 1 for their formulae) have been included into this study. These simple heterocyclic compounds are especially interesting because there are several ways for their entering into a human body. For example, maltH is known as a non-toxic compound, its use is allowed e.g. in the baking industry as food additive [20]. Deferiprone (dhpH) is one of the best known

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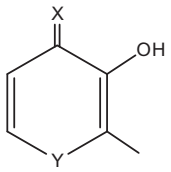


**Scheme 1.** Structure of maltH (X = O, Y = O), thiomalH (X = S, Y = O) and dhpH (X = O, Y = N-$CH_3$).

hydroxypyridinone derivatives, appears quite frequently in many bioactive compounds as pharmaceutical drug (e.g. as iron sequestering agent in the therapy of Thalassemian patients) and its scaffold is considered as "privileged" structure in the design of new chelating drugs [14]. Because S-donor ligands are especially favoured by Pb(II) ion [6,7,12], thiomalH was also included into our study.

Any previous solution equilibrium results have not been found for the Pb(II) complexes of these ligands in the literature, only a single solid state work was published for the Pb(II)-dhp dinuclear bis-complex [20]. The results obtained by us and summarized in the present paper are based, first of all, on pH-potentiometric measurements, but $^1$H NMR and ESI-MS techniques were also used.

## 2. Material and methods

### 2.1. Chemicals

MaltH was commercially available (Aldrich). ThiomalH was synthesized using maltol and phosphorus-pentasulphide in abs. dioxane according to Ref. [19] while dhpH was obtained via the reaction of maltol and methylamine as previously published in Ref. [15]. Both of these ligands were characterized via $^1$H NMR and ESI-TOF-MS. The purity of all the ligands and the concentrations of the ligand stock solutions were checked and determined by Gran's method [21]. The Pb(II) stock solution was prepared by dissolving $Pb(NO_3)_2$ (Reanal, Hungary) in diluted $HNO_3$ (0.001 mol dm$^{-3}$). The concentration of the Pb(II) was determined by complexometry using EDTA (Aldrich) as titrant.

### 2.2. Potentiometric and spectroscopic studies

Both pH-potentiometric and NMR measurements were carried out at an ionic strength of 0.20 mol dm$^{-3}$ $KNO_3$. Temperature was always 25.0 ± 0.1 °C. Carbonate-free KOH solution (0.2 mol dm$^{-3}$) was used as titrant. $HNO_3$ stock solution was prepared from conc. $HNO_3$. Their concentrations were determined by pH-potentiometric titrations using the Gran's method [21].

A Mettler Toledo T50 titrator equipped with a Metrohm double junction electrode (type 6.0255.100) was used for the pH-metric measurements. The electrode system was calibrated according to Irving et al. [22] and the pH-metric readings could, therefore, be converted into hydrogen concentration. The water ionization constant ($pK_W$) determined is 13.73 ± 0.01.

All the pH-potentiometric titrations were performed over the pH range of 2–11 or up to precipitation. The initial volume of the samples was 15.00 cm$^3$ in all cases. The ligand concentration was 0.004 or 0.002 mol dm$^{-3}$ in each system measured and the metal ion concentration was varied in the range of 0.001–0.004 mol dm$^{-3}$. The samples were completely deoxygenated by bubbling purified argon for approx. 20 min before the measurements. The equilibrium calculations were performed by using the SUPERQUAD program for the protonation constants [23] and PSEQUAD computer program for the metal complexes [24]. The constants were calculated for the equilibrium: pM + qH + rL = $[M_pH_qL_r]$. The overall constants can be defined as: $\beta_{pqr} = [M_pH_qL_r]/[M]^p[H]^q[L]^r$. Since the hydrolysis of the Pb(II) ion starts at pH ca. 6, the hydrolytic processes can compete with the complex formation and are necessary to take into account. The hydrolysis model was determined in a previous work and the following stability constants ($\log\beta$) were calculated: $[PbH_{-1}]^+$: −7.32, $[Pb_4H_{-4}]^{4+}$: −19.98, $[Pb_6H_{-8}]^{4+}$: −42.62 ($H_{-1}$ relates to the metal-induced ionization of the coordinated water) [10]. These species, with their fixed equilibrium constants, were always included in our equilibrium models when the experimental data for the Pb(II)-ligand systems were fitted.

$^1$H NMR measurements were made on a Bruker DRX 360 MHz FT-NMR apparatus by using $D_2O$ (Aldrich) as solvent, $DNO_3$ and NaOD as titrants, as well as TSP ((3-trimethylsilyl)-1-propane sulfonic acid, sodium salt) as standard under the following conditions: metal ion to ligand ratios in the samples were 1:1 and 1:2, and the analytical concentration of the ligands was 0.01 mol dm$^{-3}$. Individual samples were equilibrated at least for two hours before measurements. pH* values (direct pH-meter readings in a $D_2O$ solution of a pH-meter calibrated in $H_2O$ according to Irving et al. [22]) were converted to pD based on the equation pD = pH* + 0.44 or to pH values measureable at an ionic strength of 0.20 M using the following equation: pH = 0.930pH* + 0.40 [25].

ESI-TOF-MS analysis was made on all of the studied systems at 0.0015 mol dm$^{-3}$ ligand concentration, at 1:3 metal to ligand ratio. The pH was set with addition of the desired amount of $HNO_3$ or KOH solution and measured with a Radiometer pHM 84 instrument equipped with Metrohm combined electrode (type 6.0234.110). A Bruker micrOTOF-Q instrument equipped with a Cole Palmer 74900 Series pump (sample flow rate of 2 μl/min) was used to perform ESI-MS measurements. Temperature of drying gas ($N_2$) was 180 °C. The pressure of the nebulizating gas ($N_2$) was 0.3 bar. The flow rate was 3 μL/min. The spectra were accumulated and recorded by a digitalizer at a sampling rate of 2 GHz. DataAnalysis (version 3.4) was used for the calculations.

## 3. Results and discussion

### 3.1. Protonation studies on the ligands

MaltH and thiomalH, each has one dissociable proton, while $dhpH_2^+$ has two of them. Because of the low solubility of $PbCl_2$, KCl cannot be used during solution equilibrium studies on Pb(II)-containing systems. $KNO_3$ as electrolyte is generally used and this was also the case in the present work. Consequently, also the protonation constants have been determined in the presence of 0.20 M $KNO_3$.

For all the three ligands investigated, the protonation constants were determined by using potentiometric titrations and curve fitting analysis with the SUPERQUAD program [23]. The stepwise values can be seen in Table 1.

If the corresponding constants determined previously for maltH and dhpH in the presence of 0.20 M KCl [15,16] and presently at 0.20 M $KNO_3$ (see Table 1) are compared, the differences are not significant, they are always less than 0.1 log unit. In the case of thiomalH the value determined in presence of 0.16 M KCl is in good agreement with our data [19]. As a conclusion, we can state that replacement of 0.20 M $Cl^-$ by 0.20 M $NO_3^-$ does not cause any significant change in the acid–base properties of the investigated molecules. It is well-known from previous results that the acidity order of the hydroxyl groups in our molecules is thiomalH > maltH > dhpH. In $dhpH_2^+$ (although, existence of different bonding isomers can be assumed [15]), the first protonation constant is assumed to relate to the negatively charged oxygen on the pyridinone ring while the second one is attributed to the N-pyridinyl group [17].