Research Article

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The interaction of morin and morin-5'-sulfonic acid with lead(II): Study of the 1:1 complex formation process in aqueous solution

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Abstract: This article focuses on the aqueous complexation between two flavonoids (morin and morinsulfonate) and Pb^{2+} at constant ionic strength $I=0.5$ M ($NaClO_4$). The determination of stability constants of ML complexes were performed at wide pH range. Two obtained constants are 14.8 ± 0.1 and 15.2 ± 0.1 logarithmic units for morin and morin-5'-sulfonic acid, respectively. For estimating the thermodynamic stability of the complexes studied, the Def2-SV(P)/DFT/PBEO/SMD method has been used. Different computational models were tested to describe the data obtained. The theoretical values of $\log K$ reproduce the experimental parameters within reasonable errors.

Keywords: morin; morin-5'-sulfonic acid; O-donor ligand; DFT

1 Introduction

Morin and other flavonoids are a group of natural polyphenolic chemicals, widely distributed in the world of plants. These compounds have a variety of biological

properties (Panche et al., 2016). Antioxidant (Pietta et al., 2000), anticancer (Batra and Sharma, 2013) and antibacterial (Cushnie and Lamb, 2005) activities are among the most essential characteristics of natural flavonoids. The presence of all these features results in wide applications of flavonoids and their derivatives in medicine and pharmacology.

Due to the availability of several -OH groups, all flavonoids including morin exhibit effective chelating capacity in solution. The various metal complexes of flavonoids described in the literature (Kasprzak et al., 2015; Samsonowicz and Regulska, 2017) were synthesized in aqueous media. Many of them are bioactive (de Souza and De Giovani, 2013; Stalin et al., 2014). Nevertheless, today not much is known about the chemistry of metal-morin complexes in solution. The biggest challenge to research is a low solubility of flavonoids in H_2O . The poor water-solubility makes electronic absorption spectroscopy the only method that could truly reflect a condition of morin in solution. Also, the study of bonding abilities of morin and its derivative (morin-5'-sulfonic acid or morin sulfonate) with heavy metals can help to find the new application areas for these flavonoids.

The goal of this work was to investigate the interaction of morin and morin-5'-sulfonic acid (MSA) with Pb^{2+} in aqueous solution and interpreting these data using quantum-chemical simulation.

2 Results and discussion

2.1 UV-Vis study

The appearance of a new absorption peak at 370–460 nm in morin/MSA spectra (Figure 1) indicate about bonding with Pb^{2+} . All measurements were carried out under an excess of lead(II) ions. The concentration of the ligands was constant in each series. All spectroscopic data are given in the supporting information (Tables S1 and S2).

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Figure 1: The UV-Vis spectra and absorbance at single wavelength (404 nm) for Pb²⁺-Morin system; C(Morin) = 6.87·10⁻⁵ M; pH=2.80, I=0.5 M.

$\Delta A^{\max}$ is located near 405 nm for both systems (Figures S1 and S2). All equilibrium parameters were calculated at 404 and 406 nm for morin and MSA, respectively. As can be seen, the value of ΔA depends only on the metal concentration and the position of $\Delta A^{\max}$ remains invariant for all series. In an earlier work (Bujonek et al., 1996), the domination of mono complex form of Pb²⁺-MSA has been shown. These facts attest to the formation only one complex as it is shown in Eq. 1.

The glycine-HCl buffer was used in the 2.20-3.40 pH interval. At pH below 2.2, the interaction morin/MSA-Pb²⁺ was too weak to be studied. Under these conditions, lead(II) cation can form complexes with glycine and OH⁻. Along with this, the dissociation of a ligand must be taken into account. The following equations were used for the calculation of the “true”(K) stability constant (Petrov et al., 2015):

$$K = \alpha_M \alpha_L K' \quad (2)$$

$$\alpha_M = 1 + \sum \beta_n [\text{L}]^n \quad (3)$$

$$\alpha_L = 1 + \sum K_H [\text{H}^+] \quad (4)$$

where K' – conditional constant, K_H is 1/K_a of ligands (Kopacz, 2003), is the stability constant of Pb²⁺-glycine (Casale et al., 1995) and Pb(OH)⁺ (Cruywagen and van de Water, 1993) complexes. Table 1 contains all the equilibrium parameters obtained. From these data the linear correlation between the conditional stability constants and pH is quite apparent. Figure 2 demonstrates this relationship. For both lines the inclination is approximately ≈ 1. This indicates bond breaking with one proton in course of the complexation process and formation PbL⁺ species (n=1 in Eq. 1).

Table 1: The conditional (K'), true (K) stability constants, and extinctions (ε) for morin-Pb²⁺ and MSA-Pb²⁺ systems.

Ligand	pH ± 0.01*	K'	logK' ± 0.02	logε ± 0.03**	logK ± 0.1
Morin	3.40	1423 ± 96	3.15	4.15	14.7
	3.20	1044 ± 48	3.02	4.15	14.8
	3.00	745 ± 34	2.87	4.14	14.8
	2.80	496 ± 23	2.70	4.13	14.9
	2.60	275 ± 12	2.44	4.12	14.8
MSA	2.40	182.5 ± 8.4	2.26	4.10	14.8
	3.20	2870 ± 133	3.46	3.80	15.2
	3.00	1673 ± 76	3.22	3.73	
	2.80	1125 ± 51	3.05	3.72	
	2.60	640 ± 30	2.81	3.77	
	2.40	449 ± 20	2.65	3.75	
	2.20	248 ± 11	2.39	3.72	

*The “±” values represent confidence limits (P = 0.95) throughout the article.

**The values are given for 404 (morin) and 406 (MSA) nm.

Under the same conditions, logK' is higher for MSA but the “true” stability constant is almost equal for both flavonoids. A comparison of metal complexes of morin (Malesev and Kuntic, 2007) with Cu²⁺ (logK=4.94), Zn²⁺ (logK=6.74), Ba²⁺ (logK=4.55) and Pb²⁺ shows that the latter is one of the most stable coordination compound for this ligand. In addition, from all 1:1 metal-flavonoid complexes existing in aqueous media, Pb²⁺-morin is the most stable. In fact, only Fe³⁺-rutin (logK=44.1; Kasprzak et al., 2015) complex has a higher stability than the lead complex.

2.2 The DFT calculations

All possible tautomers of the complexes studied are collected in Scheme 1. Three chelates and two linear

Figure 2: The pH-logK' relationship for Pb²⁺-MSA (1) and Pb²⁺-morin (2) systems.

Scheme 1: The keto-enol equilibria for Pb²⁺-morin (R=H) and Pb²⁺-MSA (R=HSO₃⁻).

structures were chosen for computational procedures. The DFT calculations at level Def2-SV(P)/PBE0/SMD were carried out to assess the thermodynamic stability of each tautomer.

The absolute and relative calculated energies are presented in Table 2. The typical coordination number for lead(II) with O-donor ligands is 4 (Parr, 1997). Morin and MSA, being bidentate ligands, replace two molecules of water in the lead aqua complex upon complexation. In

this regard, the assessment of dominated forms has been compiled for $[\text{Pb}(\text{H}_2\text{O})_2\text{L}]^+$ (L= morin or MSA) species.

The calculations show the greater stability of N3 (coordination *via* 3-hydroxyl and 4-carbonyl groups) isomer for both systems. The optimized geometries for these tautomers are illustrated in Figure 3. A similar chelating site was proposed for the solid state 1:2 Pb-MSA complex in previous work (Kuzniar et al., 2008).

Aiming to verification of the results obtained and in search for an optimal computational protocol for describing of Morin/MSA- Pb^{2+} systems, the theoretical values of $\log K$ were calculated. Scheme 2 shows the thermodynamic cycle used for this goal. According to (Wander and Clark, 2008) the various forms $\text{Pb}(\text{H}_2\text{O})_m^{2+}$ ($m=1-9$) can be applicable for DFT simulations in water. In this work models with $m=1, 2, 4$, and 6 were tested. The results of the calculations are summarized in Table 3.

As we can see, the optimal number of water molecules in the lead(II) aqua complex are 1 and 2 for MSA and morin, respectively. On closer scrutiny, one will also find that the sum of $\Delta G^{\text{solv.}} + \Delta G^{\text{gas}}$ is the main contributor in $\Delta \Delta G^{\text{solv.}}$ of the reaction. This could indicate the domination

Figure 3: The optimization geometry for morin-Pb (B) and MSA-Pb (A).

Scheme 2: Thermodynamic cycle for the calculation of $\log K^{\text{calc.}}$

Table 3: The results of quantum-chemical estimation.

Ligand	m	$\Delta G^{\text{soln.}} + \Delta G^{\text{gas}},$ $\text{kJ} \cdot \text{mol}^{-1}$	$\Delta E^{\text{ZPE}},$ $\text{kJ} \cdot \text{mol}^{-1}$	$\log K^{\text{calc}}$	$\log K^{\text{exp}}$
Morin	1	-144.14	-24.08	29.89	14.8
	2	-39.49	-35.57	13.51	
	4	124.63	-49.92	-12.37	
	6	219.07	-79.83	-22.95	
MSA	1	-72.90	-7.38	14.42	15.2
	2	32.11	-20.87	-1.97	
	4	196.23	-33.22	-27.84	
	6	290.67	-63.14	-38.42	

of solvent effect against covalent interaction in Pb^{2+} -flavonoid complexes.

3 Conclusions

The complexation processes of morin and MSA with Pb^{2+} have been studied spectrophotometrically in aqueous solution. Twelve conditional and two “true” equilibrium stability constants were obtained in diapason pH 2.2-3.4 at $I=0.5$ M (NaClO_4). The received $\log K$ (14.8 for morin and 15.2 for MSA) demonstrates the great stability of flavonoids- Pb^{2+} complexes. For the study of keto-enol equilibria, the DFT computations have been implemented. The tautomer with coordination *via* 3-hydroxyl and 4-carbonyl groups was chosen as the most stable isomer for both complexes. Several computational protocols were tested for verification of the results obtained. It was established that using a small number of explicit water (1-2 molecules) makes it possible to achieve discrepancies of stability constants within ± 1.0 logarithmic units.

Experimental

Materials and instrumentation

All chemicals were of analytical grade and used as supplied: HClO_4 , H_2SO_4 , glycine, $\text{Pb}(\text{NO}_3)_2$, Morin (Sigma-Aldrich, $\geq 98\%$), NaClO_4 . The region of nitrate ion absorption (295-310 nm) does not overlap with the region (390-430 nm) studied. All stock solutions were obtained by dissolution of dry salts and ligand weights. The metal salts and ligands were dissolved in distilled water. The morin was diluted in selected sample from water-ethanol solution (50:50 vol.). The concentration of ethanol did not exceed 2% in the final solution. Morin-5-sulfonic acid was

synthesized as reported in the literature (Kopacz, 2003). Its purity was tested by paper chromatography. The initial morin is not found in the final sample. Buffer solutions within the pH range from 2.20 to 3.60 were prepared with glycine- HClO_4 buffer. The concentration of glycine in all solutions was constant and equal 0.05 M. The accurate desired pH values were obtained by adjusting the molarities of the buffer components in suitable amounts (Eliseeva and Bünzli, 2011). The ionic strength was maintained with NaClO_4 .

UV-Vis measurements

Conditional stability constants (K') for monocomplex species were calculated from the Eq. 5-6 (Grebenyuk et al., 2002):

$$A_{\text{calc}}^{\lambda} = \varepsilon_L^{\lambda} (C_L - [\text{ML}]) + \varepsilon_M^{\lambda} (C_M - [\text{ML}]) + \varepsilon_{\text{ML}}^{\lambda} [\text{ML}] \quad (5)$$

$$[\text{ML}] = \frac{1}{2} \left[\left(\frac{1}{K'} + C_L + C_M \right) - \sqrt{\left(\frac{1}{K'} + C_L + C_M \right)^2 - 4C_L C_M} \right] \quad (6)$$

where $A_{\text{calc}}^{\lambda}$ is an absorbance at a given wavelength and C_M and C_L were analytical concentrations of Pb^{2+} and ligand, respectively. The ε^{λ} is a value of molar extinction coefficient at single wavelength. The optimal values for K' and ε^{λ} were found from the least squares analysis (Leggett, 1985):

$$f(C_M, C_L, K', \varepsilon_i) = \sum_{i=1}^n (A_i^{\lambda} - A_i^{\text{calc}})^2 \xrightarrow{K', \varepsilon_i} \min \quad (7)$$

Calculations of all equilibrium constants and molar extinction coefficients were performed using *Wolfram Mathematica* software package (<https://www.wolfram.com/mathematica/>).

DFT calculations

Ab initio calculations were carried out using the GAMESS US program package (Schmidt et al., 1993) on the cluster MVS-1000 M of the Institute of computational modeling SB RAS. The Def2-SV(P) (Weigend and Ahlrichs, 2005) basis set (including ECP pseudopotential for Pb) with the hybrid functional PBE0 (Adamo and Barone, 1999) under Grimme's empirical correction (Grimme et al., 2010) was used for assessment. The solvent effects were evaluated using the SMD solvation model (Marenich et al., 2009). Geometry optimization was performed by density functional theory (DFT). The stability constants

have been calculated using the Eq. 8-10 (Bryantsev et al., 2008):

$$\log K = -\Delta\Delta G^{\text{soln}} / (2.303RT) \quad (8)$$

$$\Delta\Delta G^{\text{soln}} = \Delta G^{\text{gas}} + \Delta G^{\text{soln}} + \Delta E^{\text{zpe}} + E^{\text{corr}} \quad (9)$$

where,

$$E^{\text{corr}} = -RT\ln([H_2O]) \quad (10)$$

Here, $RT\ln([H_2O])$ is a free energy change associated with moving a solvent from a standard-state solution phase concentration of 1 M to a standard state of the pure liquid, 55.34 M (Vukovic et al., 2015). E^{zpe} is the value of zero point energy calculated from the frequency analysis. Values of $G^{\text{gas}}(H^+)$ and $\Delta G^{\text{soln}}(H^+)$ (-26.28 and -1108.27 kJ·mol⁻¹, respectively) have been taken from the previous research (Lutoshkin and Kazachenko, 2017).

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