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10 Equilibrium Study of Complex Formation Among Trivalent Metals, Glycine Peptides and Phenolates in Aqueous Solution

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16 **2014 / Accepted: 30 June 2015 / Published online: 20 October 2015 ?**
Springer Science+Business Media New York 2015 Abstract The stability of

binary and mixed-ligand complexes among trivalent transition metal ions (chromium and iron), glycine peptides (glycylglycine and glycylglycylglycine) and phenolates (ferulic acid and gallic acid) were studied by using pH-potentiometric titration in aqueous solution at 298.15 K and ionic strength of 0.15 mol⁻³dm⁻³ NaNO₃. The complexation model for each system was obtained by processing the potentiometric titration data using the HYPERQUAD2008 program. The stability constant trend of complexes in both systems

5 **and the** contributions **of deprotonated or** protonated **amide** peptides to **the stability**

of the complexes is discussed.

6 **The stability of the mixed-ligand complexes** relative to **their corresponding binary complexes was** also investigated **by calculating the Dlog₁₀ K parameter**

of each system. In addition, the Gibbs energies of reaction (DrG) obtained from the Gaussian modeling program with B3LYP/6-31G(d) basis set were used to verify

1the contributing binding sites of the ligands and to predict the structures of

the M–L complexes. Keywords Solution equilibria ? Peptides ? Phenolates ? Potentiometry ? Gaussian
Abbreviations Gp Glycine peptides G Glycine GG Diglycine GGG Triglycine Ph Phenolates FA Ferulic acid
GA Gallic acid &

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National Taiwan University of Science and Technology, Taipei 106-07, Taiwan
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Surabaya 60114, Indonesia **1** Introduction In living cells tissues, chromium (Cr³⁺) and iron (Fe³⁺) are essential micronutrients. In particular, iron is needed for transporting oxygen to tissues and for developing new cells in the human body while chromium is essential for lipid, protein, and fat metabolisms in animals and humans and is used to potentiate insulin activity in peripheral tissue. However, excessive uptake of these metals may affect human chromosomes, trigger carcinogenesis and cause clastogenesis for human leukocytes [1–4]. In more severe conditions, iron also may cause fatal cell death and tissue injury due to its ability to catalyze the generation of free radicals [5– 7]. Chelation therapy is a well-known and efficacious treatment for patients with metal poisoning [8–10]. This treatment uses metal–ligand coordination principle, in which the chelating agent acts as a ligand that will bind metal ions and form a metal ligand complex so that these excess toxic metals can be excreted from the human body in their complexed form. Study of the chelating ability of glycine peptides (Gp), in particular diglycine (GG) and triglycine (GGG), with some divalent metal ions (Co²⁺, Ni²⁺ and Cu²⁺) has shown that glycine peptides are potential metal chelators via their amine and carboxyl functional groups [11]. For GG and GGG, the occurrence of an amide bond in its backbone may also effect the stability of the formed complex. It has been shown that acid deprotonation constant of an amide nitrogen in the absence of metal ions is very high (pK_a * 15), but administration of divalent copper or nickel is able to reduce the proton ionization constant to a pK_a of 4–8, which is experimentally and biologically accessible for further use as an additional chelating binding site [12]. Phenolates (Ph)

12can act as reducing agents, as hydrogen atom-donating antioxidants, and

metal chelators [13],

12thereby reducing the metal's capacity to generate free radicals

[14, 15]. Ferulic acid (FA) and gallic acid (GA) are two common phenolates that naturally exist in plants. Both FA and GA are remarkable antioxidants and more efficient in preventing free radical oxidation than vitamin C [14–22]. The antioxidant potential of FA is caused by the occurrence of the

21 phenolic nucleus and unsaturated side chain that can readily form a resonance stabilized phenoxy radical.

FA is a potential metal chelator through its carboxyl and phenol groups [14, 23] while GA is coordinated to the metal ion through its three hydroxyl groups and one carboxyl group. A study of the activity of GA against hepatitis induced cancer suggested that the cytotoxicity of three adjacent hydroxyl groups and carboxyl group of GA makes it selective for killing cancer cells without harmful effects to normal cells [24]. Both peptides (GG and GGG) and phenolates (FA and GA) were used in this work to study their complexing ability with two trivalent metals (Cr^{3+} and Fe^{3+}). The formation constants of these complexes in

6 binary and mixed-ligand systems were determined by using the pH-

potentiometric method at 298.15 K and

5 an ionic strength of 0.15 mol⁻³ NaNO₃, which is the ionic strength of

most body fluids. Moreover, DFT calculations by the Gaussian 09W program were used to confirm the contributing binding site of the ligand, predict the structure and calculate the Gibbs energy of reaction ($\Delta_r G$) [25].

2 Experimental Section 2.1 Chemicals Used Ferric nitrate nonahydrate ($\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, 98 % purity) and chromium chloride hex-ahydrate ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 98 % purity) were purchased from Across Organics (Morris Plains, NJ). Fig. 1 Structural formulae of a glycine, b glycyglycine, c glycyglycyglycine, d gallic acid and e ferulic acid (NJ). Both of the metal salts were standardized against ethylenediaminetetraacetic acid (EDTA, 99.95 % purity), which was purchased from Sigma–Aldrich (Steinheim, Germany). The ligands used in this study

19 were purchased from Sigma–Aldrich (Steinheim, Germany) (G, 99.7 % purity;

GG, 99 % purity; GGG, 99 % purity; GA, 99 % purity and FA, 99 % purity); their structures are shown in Fig. 1. Nitric acid (Panreac, Barcelona, Spain; purity 65 %) solution, for acidifying the solutions for determination of stability constants, was prepared and standardized prior to use. Before using it as a titrant, carbonate-free sodium hydroxide (NaOH) from Across Organics (Morris Plains, NJ) was

15 standardized against potassium hydrogen phthalate (KHP, 99.95 % purity) from Sigma–Aldrich

(Steinheim, Germany). To maintain ionic strength in the solutions, sodium nitrate (NaNO_3 , 99 % purity) from Across Organics (Morris Plains, NJ) was used.

17All chemicals used in this study were of analytical grade and were used without further purification. Solutions were prepared daily in distilled deionized water

(resistance 18.3 M Ω cm). 2.2 Potentiometric Titration Prior to the measurements, the

2following solutions were prepared (total volume 50 cm³) and were titrated potentiometrically against standard carbonate-free NaOH (0.10 mol dm⁻³): (a) 5 mL of 0.03 mol \cdot dm⁻³

HNO₃ ? 10 mL of 0.75 mol \cdot dm⁻³ NaNO₃ (b) solution (a) ? 5–6 mL of 0.01 mol \cdot dm⁻³ ligand ? 2–5 mL of

20.01 mol \cdot dm⁻³ metal ion (c) solution (a) ? 5 mL of 0.01 mol \cdot dm⁻³ metal ion ? 5 mL of 0.01 mol \cdot dm⁻³ ligand Gp ? 5 mL of 0.01 mol \cdot dm⁻³

ligand Ph Solution (b) was prepared at four

9different metal-to-ligand concentration ratios (1:1, 1:2, 1:2.5 and 1:3). All of the

titrations were carried out in a 100 cm³ double-walled equilibrium cell that

1was connected to a refrigerated circulating bath to maintain the temperature of the reagents at

298.15 \pm 0.1 K.

9Each titration was repeated at least three times in the pH range

2.5–11

3with a reproducibility of ± 0.02 in pH unit. The

3potentiometric titrations were performed using a Metrohm 702 SM titrino, equipped with a 649 magnetic stirrer and a Dosino burette (model 683)

and coupled with an Ecotrode plus pH glass electrode.

3 Electrode response can be read to the third decimal place in pH units with a readability of ± 0.001 . Since the

determination of metal–ligand stability constants were carried out in high ionic strength of 0.15 mol^{dm}-3 NaNO₃ (pK_w = 13.77 at the given ionic strength and temperature), it is necessary carry out

18 a strong acid–strong base titration for the

glass electrode calibration. For this purpose, the titration curves of solution (a) were processed by using the Glass Electrode Evaluation program (GLEE) to calibrate the glass electrode in terms of hydrogen ion concentration [26]. While the titration curve of solution (a) was used in the electrode calibration, titration curves of solutions (b) and (c) were employed in determining complex formation constants in binary and mixed-ligand systems, respectively. 2.3 Data Analysis The calculations were performed using the computer program HYPERQUAD2008 by inputting the titration data. These data were obtained as volume of the base added versus the pH value, and were used for calculations without the need to convert into hydrogen ion concentrations. The

4 stoichiometry and stability constants of the complexes formed were determined by testing various possible composition models. The model selected gave the best statistical fit and was chemically consistent with the titration data without giving any systematic drifts in the various residuals. The stability constants

are presented as the overall formation constant (b_{pqrs}) with stoichiometric coefficient p, q, r, s that represent metal ions, glycine peptides, phenolates and hydrogen atoms, respectively. The formation constant is a function of the complex species concentration $[M_p G_p q Ph_r H_s]$ and free reactant concentrations $[M]$, $[G_p]$, $[Ph]$ and $[H]$, and is expressed by the equation below: $b_{pqrs} = \frac{[M_p G_p q Ph_r H_s]}{[M]^p [G_p]^q [Ph]^r [H]^s}$ A larger value of the stability constant ($\log_{10} b$) indicates that the complex is more stable. The larger is the $\log_{10} b$ value, the greater is the driving force to push the reaction to the right side [27]. In addition, the speciation diagrams of the metal–ligand complexes, based on their concentration at certain pH, are calculated by using the HySS2009 program. 2.4 Gaussian Structure Prediction In this work, the Gaussian 09 program was used to predict the binding site of the ligands that contribute to complex formation and the structure of the complexes [25]. The model structures of these complexes were

14 optimized using density functional theory (DFT) with Becke's three-parameter hybrid method combined with Lee–Yang–Parr correlation function (B3LYP) [28, 29]. For the basis set, 6-

31G with diffuse and polarization functions (6-31G(d)) was used [30–32]. Along with geometry optimization, frequency analysis was done to obtain the thermochemical properties of the complexes. The B3LYP/6-31G(d) basis set was chosen since it has been shown to be a suitable basis set for analysis of the molecular orbitals of metal complexes [30–34]. Some simplifications adopted from previous work were employed in this modeling study [35]. The validity of the structure optimization was checked by using normal-mode frequency analysis, in which the real minimum structure must exhibit positive value for all frequencies. 3 Result and Discussion Protonation constants (pKa) for glycine (G), glycine peptides (GG and GGG) and phenolates (FA and GA) at 298.15 K and ionic strength 0.15 mol/dm³ NaNO₃ have been reported in some previous work [35–37]. The pKas of the carboxyl group of G, GG and GGG are 2.32, 3.21 and 3.30 while for the amine group are 9.62, 8.31 and 7.90, respectively [35]. The pKas of the phenolate FA are 4.46 for the carboxyl group and 8.82 for its hydroxyl group [37]. For GA, the pKa of the carboxyl group is 4.25, followed by the protonation of the hydroxyl group at the para position with pKa = 8.61 and the two hydroxyl groups at the meta position with pKas of 11.03 and 12.71 [36]. These protonation constants were entered

1 into the **HYPERQUAD2008** program for determination of the metal complexes' stability constants. By considering the hydrolysis reaction of

the metal ions, the metal hydrolysis constants for [M(OH)]²⁺, [M(OH)₂]⁺ and [M(OH)₃] were also included in the determination of stability constants, which for Cr³⁺ are -4.00, -5.70 and -8.30, while for Fe³⁺ are -2.19, -3.48 and -6.33, respectively [38]. 3.1

5 Complex Formation Between Trivalent Metal Ions and Glycine Peptides

For determination of metal complex formation constant (log₁₀b), the prepared solution (c) that consists of metal and ligand in various molar ratios (1:1, 1:2, 1:2.5 and 1:3) was titrated against carbonate-free sodium hydroxide solution. Stability constants of the metal ion (Cr³⁺ and Fe³⁺) complexes with Gp (GG and GGG) are expressed as the logarithm of the overall formation constant (log₁₀b). As presented in Table 1, the stability of the complexes containing Fe³⁺ are larger than those containing Cr³⁺ and this phenomenon was observed regardless of the peptide used (log₁₀bFeGG = 8.62 [log₁₀bCrGG 7.18; log₁₀bFeGGG = 8.38 [log₁₀bCrGGG = 7.15). This might be due to the increasing charge density in going from Cr to Fe (for a given ligand and trivalent metal ion). Fe³⁺ has a higher charge density since it has a smaller ionic radius than Cr³⁺, thus allowing ligand to bind the central metal atom easier and form more stable metal complexes [39]. The Gibbs energy (G) values of free Cr³⁺ and Fe³⁺ ions also support this order, where Fe³⁺ has a more negative value (-1262.752 hartree/particle) than that of Cr³⁺ (-1043.655 hartree/particle), which indicates that Fe has a higher ionization energy than Cr; thus the complexes of Fe³⁺ will have higher stability. Glycine (log₁₀bFeG = 10.69) was found to form a more stable metal complex compared to diglycine (log₁₀bFeGG = 8.62) and triglycine (log₁₀bFeGGG = 8.38). This can be explained by the structure of the ligands. The smallest and simplest ligand glycine can form five-membered ring complexes with metal ions via the amine and carboxyl groups. On the other hand, for GG and GGG, since the N-terminus and C-terminus are at greater distance (longer chain length) than that of ligand G, thus the formed metal complexes will have a larger ring structure resulting in less stable metal complexes [12]. Table 1 Overall formation constants of trivalent metal ion (M)–glycine peptide (Gp) complexes

7 at 298.15 K and 0.15 mol⁻³ NaNO₃

Species $\log_{10} b \pm \text{S.D.}$ Gp = G Gp = GG Gp = GGG M = Fe³⁺ r*b [MGp]²? [MGpH-1]? [MGpH-2] [MGp²? [MGp²H-2]- [MGp³] M = Cr³⁺ r*b [MGp]²? [MGpH-1]? [MGpH-2] [MGp²? [MGp²H-1] [MGp²H-2]- [MGp³] 1.155 10.69 \pm 0.09 (10.83)a 7.28 \pm 0.08 3.56 \pm 0.07 20.42 \pm 0.05 (20.48)a 30.08 \pm 0.07 1.338 8.77 \pm 0.04 2.42 \pm 0.06 -3.60 \pm 0.04 15.74 \pm 0.03 21.73 \pm 0.09 1.156 8.62 \pm 0.06 5.77 \pm 0.06 5.63 \pm 0.06 1.052 7.18 \pm 0.02 1.34 \pm 0.06 6.88 \pm 0.03 -0.35 \pm 0.03 1.093 8.38 \pm 0.06 5.57 \pm 0.03 1.97 \pm 0.03 5.07 \pm 0.06 1.047 7.15 \pm 0.02 0.88 \pm 0.09 -4.20 \pm 0.03 12.19 \pm 0.05 5.92 \pm 0.04 -1.34 \pm 0.04 a Ref. [49], T = 298.15 K, I = 0.1 mol⁻³ NaNO₃ b Sigma* (r*) is the goodness of fit for a system with $\pm 95\%$ probability A peptide offers one or more amide groups and a carbonyl group as the binding sites in addition to the amine (N-terminus) and carboxyl (C-terminus) groups. The amide group is a very weak acid and tends to remain neutral throughout most of the pH range; this causes difficulty for H atom deprotonation

8 from the trigonal nitrogen to yield a negatively charged

ligand.

8 Because of the neutrality of the amide group, the amine and carboxyl groups are more effective as binding sites. The presence of metal ions enables the amide group

to deprotonate easier and also enables the amide group to participate in complex coordination. These factors were also mentioned in some studies where the amide groups were also capable of coordinating with metal ions in solution [12, 40–42] and coordination of the amide group occurred after deprotonation. Thus, in this study, the influences of protonated and deprotonated amide nitrogens in peptide bonds on the stability of complex species were compared and investigated by the following expressions: $M \text{ p Gp ? MGp } \frac{1}{2} \text{MGp? } \frac{1}{4} \text{ bMGp} \frac{1}{2} \text{M? } \frac{1}{2} \text{Gp? } M \text{ p Gp ? M} \delta \text{Gp; H?1P p H M p Gp ? M} \delta \text{Gp; H?2P p 2H MGp ? M} \delta \text{Gp; H?1P p H } \frac{1}{2} \text{M} \delta \text{Gp; H?1P? } \frac{1}{4} \text{ bM} \delta \text{Gp; H?1P } \frac{1}{2} \text{M? } \frac{1}{2} \text{Gp?} = \frac{1}{2} \text{H? } \frac{1}{2} \text{M} \delta \text{Gp; H?2P? } \frac{1}{4} \text{ bM} \delta \text{Gp; H?2P } \frac{1}{2} \text{M? } \frac{1}{2} \text{Gp?} = \frac{1}{2} \text{H?2 } \frac{1}{2} \text{M} \delta \text{Gp; H?1P? } \frac{1}{4} \text{ KM} \delta \text{Gp; H?1P } \frac{1}{2} \text{MGp?} = \frac{1}{2} \text{H? bM} \delta \text{Gp; H?1P } \frac{1}{4} \text{ KM} \delta \text{Gp; H?1P bMGp MGp ? M} \delta \text{Gp; H?2P p 2H } \frac{1}{2} \text{M} \delta \text{Gp; H?2P? } \frac{1}{4} \text{ bM} \delta \text{Gp; H?2P } \frac{1}{2} \text{MGp?} = \frac{1}{2} \text{H? bM} \delta \text{Gp; H?2P } \frac{1}{4} \text{ KM} \delta \text{Gp; H?2P bMGp}$ where a negative value of H refers to deprotonation of the amide group in metal complexes. For example, [M(Gp,H-1)] in the system containing diglycine refers to the formation of a complex between metal ion with this ligand in its deprotonated amide form [GGH-1]. As illustrated in Scheme 1, subtraction of $\log_{10} b \text{MG}$ from $\log_{10} b \text{MGG}$ and $\log_{10} b \text{MGGG}$, as well as subtraction of $\log_{10} b \text{MGG}$ from $\log_{10} b \text{MGGG}$, were carried out to evaluate the effect of the un-deprotonated amide nitrogen peptide bond on complex stability. Similarly, subtractions of $\log_{10} \text{KM(Gp,H-1)}$ and $\log_{10} \text{KM(Gp,H-2)}$ of G from those for of GG and GGG, respectively, were done to evaluate the impact of amide nitrogen deprotonation on the stability of metal complexes. The subtracted values of $\log_{10} b \text{MGp}$ are listed in Table 2. Negative values indicate the absence of participation of an protonated amide nitrogen. The negative value of $\text{Dlog}_{10} b \text{MGp}$ is also possibly due to participation of the amide nitrogen with a lower electron density than amine nitrogen. It is interesting to note that the $\text{Dlog}_{10} b \text{MGp}$ values of metal complexes involving GG and GGG are very small (-0.24 for the Fe³⁺ system and -0.03 for the Cr³⁺ system) while the subtracted values of $\log_{10} b \text{MP}$ of GG-G and GGG-G vary from

-1.59 to -2.31. The small $\Delta\log_{10}K_{M(Gp,H-1)}$ values of GGG-GG are due to the backbone length of GGG which causing a steric effect [43, 44]. But, since GG and GGG form chelates in the same manner, the stability constants of the complexes formed are also similar. In Table 2, subtraction of $\log_{10}K_{M(Gp,H-1)}$ of GG from $\log_{10}K_{M(Gp,H-1)}$ of G and subtraction of $\log_{10}K_{M(Gp,H-2)}$ of GGG from $\log_{10}K_{M(Gp,H-2)}$ of G both yield positive values. These results indicate that the deprotonated amide nitrogen participated in the complex formation reaction of the metal ions. Moreover, it also shows that $\Delta\log_{10}K_{M(Gp,H-2)}$ is more positive than $\Delta\log_{10}K_{M(Gp,H-1)}$ due to the contribution of two deprotonated amides in GGG in Scheme 1 Influence of a protonated and b deprotonated amide nitrogen of peptide bond on complex stability Table 2 Influence of amide nitrogen in the peptide bond on stability of metal-glycine peptide complexes Metal ions $\Delta\log_{10}K_{M(Gp,H-1)}$ $\Delta\log_{10}K_{M(Gp,H-2)}$ GG-G GGG-G Fe³⁺ -2.07 -0.24 -2.31 0.56 0.72 Cr³⁺ -1.59 -0.03 -1.62 0.51 1.02 which metal ions and GGG

13 complexes form three five-membered chelate rings, while in the

metal ions and GG systems the

13 complexes form two five-membered chelate rings via nitrogen in the

N-terminus, deprotonated amide nitrogen of the peptide and carboxyl in the C-terminus. Contribution from the amide nitrogen to complex stability is further supported by the optimization and frequency analysis using Gaussian 09. From the geometry optimization, structures of the complexes that formed can be predicted (Fig. 2) and thermodynamic properties such as Gibbs energy (G) can be obtained from the frequency analysis. In this program, the complex equilibrium is presented as the Gibbs energy of reaction ($\Delta_r G$) that is calculated from the following relations: $M^{2+} + L \rightleftharpoons \frac{1}{2} ML_2$ $\Delta_r G = \frac{1}{4} R G_{product} - R G_{reactant}$ where $\Delta_r G$ is proportional to the metal complex formation constant ($\log_{10}K$). Thus, according to this correlation, the more negative the $\Delta_r G$ value is, the larger the formation constant value will be and the complex formed will be more stable. For each metal Hartree/particle ligand combination, Gaussian modeling was done by considering the possible binding sites that may contribute to complex formation. Values of $\Delta_r G$ for metal-ligand formation were calculated for the possible binding site of ligands and the one which shows the most negative value of $\Delta_r G$ (reported in Table 3) was chosen as the contributing binding site, and the structure of this complex will be used as the predicted structure of the formed complex. For example, in the case of the Fe³⁺-glycine complex, glycine may form a complex with the metal ion through its amine group and/or carboxyl group. During Gaussian geometry optimization and frequency calculations, Fe³⁺ was assumed to bind to glycine through its amine group only, through its carboxyl group only, and by chelate binding through both amine and carboxyl groups with the resulting $\Delta_r G$ of -0.320, -0.395 and -0.413 Hartree/particle, respectively. Hence glycine forms a complex and binds Fe³⁺ through its amine and carboxyl groups (as shown in Fig. 2a) and acts as a chelating ligand. Similarly, GG and GGG form chelates by their nitrogen and carbonyl oxygen, while

10 gallic acid forms the most stable complex through its catechol

site and ferulic acid forms the most stable complex through its carboxylate group. From the calculated values of $\Delta_r G$ shown in Table 3, the negative $\Delta_r G$ and complex stability constant values decrease in the

following order: [M(GGG,H-2)] [[MGA]- [[M(GG,H-1)]? [[M(GGG,H-1)]? [[MFA]? [[MG]2? [[MGG]2? [[MGGG]2?. The optimized geometry of [M(GG,H-1)]? and [M(GGG,H-2)] (shown in Fig. 2c, f, respectively) and the calculated values of DrG, support the hypothesis that the deprotonated amide in GGG peptide forms three

13 five-membered chelate rings with the metal ions,

while in metal ion–GG system the complex forms two five-membered chelate rings via nitrogen in the N-terminus, deprotonated amide nitrogen of the peptide and carboxyl in the C-terminus. Fig. 2 Optimized structures of some complexes between trivalent metal ion (M) and glycine contained peptides: a [MG]2?, b [MGG]2?, c [M (GG, H-1)]?, d [MGGG]2?, e [M (GGG, H-1)]?, f [M (GGG, H-2)], g [MFA]?, and h [MGA]-; generated from Gaussian09 calculations According to the Gaussian modeling result, it seems that GA has a more negative DrG value than that of FA. This result is in agreement with the result obtained from potentiometric studies where the log₁₀bFeL values are 22.97 and 11.48 when L is GA [36] and FA [37], respectively. This phenomenon may be due to

18 formation of five-membered ring metal complexes in the case of

GA while FA forms not-so-stable four-membered ring metal complexes with the bulkier side chain. On the other hand, FA has been shown to form a more stable complex with metal ion than G, GG and GGG. This phenomenon can be elucidated by the influence of charge and chelate effects on complex formation. For both Fe³⁺ and Cr³⁺, the charge effect dominates over the chelate effect; thus the positively Table 3 Gibbs energy (DrG) of complex formation obtained from optimization and frequency calculation by using the Gaussian 09 program Complex species DrG (Hartree/particle) M = Fe M = Cr Binary system [MG]2? [MGG]2? [MGGH-1]? [MGGG]2? [MGGGH-1]? [MGGGH-2] [MFA]? [MGA]- Mixed ligand system [MFAG] [MFAGG] [MFAGGG] [MGAG]2- [MGAGG]2- [MGAGGG]2- -0.413 -0.406 -0.515 -0.403 -0.502 -0.613 -0.425 -0.605 -0.584 -0.547 -0.543 -0.668 -0.625 -0.616 -0.315 -0.302 -0.393 -0.302 -0.376 -0.517 -0.326 -0.511 -0.493 -0.456 -0.453 -0.560 -0.545 -0.545 a The calculation was done using the density functional theory (DFT)-B3LYP method combined with 6-31?G(d) as a basis set; 1 Hartree/particle = 2.626 9 103 kJ?mol⁻¹ charged Fe and Cr ions can attract the more negative charged ferulic acid and form metal– ligand complexes.

3.2 Formation of Mixed Ligand Complexes Overall formation constants of FA and GA were acquired from previous research [36, 37]. These values, together with the overall formation constants of metal ions with G, GG and GGG, were introduced to the HYPERQUAD2008 program as constants and used for determination of mixed-ligand complex stability constants involving metal ions (M), glycine peptides (Gp) and phenolic acids (Ph). Representative potentiometric titration curves of Fe³⁺ with FA and G are shown in Fig. 3. The inflection in the ternary Fe–FA–G curve at moles NaOH added = 0.25 indicates complexation of Fe³⁺ with the deprotonated G since the inflection at this point is similar to the inflection of the G system (no metal) at moles NaOH added = 0.15, followed by the inflections at 0.30 and 0.35 which indicate attachment of the FA ligand to the Fe–G complex. With regard to the metal ions, an identical trend as for the binary system is observed in all systems, where Fe³⁺ forms a more stable complex than Cr³⁺ (Table 5). Moreover, in mixed-ligand systems containing GA, the complex is more stable than that containing FA and the stability of complexes (log₁₀b) decreases in the following order of ligands GA–G [GA–GG [GA– GGG [FA–G [FA–GG [FA–GGG. As shown in Table 3, this trend is also supported by the DrG

20 values of the mixed-ligand complexes which

were obtained from Gaussian 09 modeling. A more negative DrG value indicates a more stable complex. Fig. 3 Potentiometric titration curve, represented by FA for Fe³⁺ and G for the ligand To investigate the

20 stability of the mixed-ligand complexes relative to their corresponding binary

complexes, Dlog₁₀K values were calculated using the following equation [45]: $D \log_{10} K = \frac{1}{4} \log_{10} \frac{bMGpPh}{\log_{10} bMGp \cdot \log_{10} bMPh}$. The calculated values of Dlog₁₀K are given in Tables 4 and 5. The trend of Dlog₁₀K values for both metal ions is opposite to the stability constant trend described above for the binary systems. For example, Fe³⁺ has higher stability constant values than that of Cr³⁺ in binary systems, but it yields more negative Dlog₁₀K values than those of Cr³⁺. This phenomenon can be explained based on the metal–ligand interaction behavior in binary and mixed ligand systems. If the interaction between a metal ion and a particular ligand to form a binary complex is strong, then it becomes difficult for another ligand to bind to the ligand–metal complex and form a mixed ligand complex, thus resulting in a negative Dlog₁₀K value. These negative values also may be the result of reduction in the coordination sites of the metal ion, steric hindrance and the electrostatic effect [46–48]. From the obtained equilibrium constants, species distribution diagrams of the complex species formed can be illustrated as a function of pH by the HYSS2009 program. In Fig. 4, are presented typical species distribution diagrams of Fe³⁺ with mixed ligands FA and the glycine peptides. In all of the FA–G, FA–GG and FA–GGG diagrams, it can be seen that that mixed ligand complex species such as [FeFAGH], [FeFAG], [FeFAGG], [FeFA(GG,H-1)], [FeFAGGG] and [FeFA(GGG,H-2)] predominate. A closer look at these diagrams reveals that there is competition between FA and glycine since these two ligands have similar complexing ability towards trivalent metal ions. As shown in Fig. 4a, initially at pH 2, more than 60 % of Fe³⁺ exists as [Fe(FA, G, H)], 15 % as [FeG] and 12 % as [FeFA]. Only less than 10 % of Fe³⁺ is left as free ion. As the pH is increased, [FeFAG], [FeG₂] and [FeFA₂] start to form and, at approximately pH 6, nearly the same amounts of [FeFA₂] (18 %) and [FeG₂] (19 %) are formed. Similarly, for the Fe-FA-GG system, initially at pH 2, 59 % of the Fe³⁺ exists as [FeFA] and 15 % as [FeGG].

19 At pH 7, more than 50 % of the complex species

is [FeFAGG] and the amount of this species decreases Table 4 Overall formation constants of metal on (M)–glycine peptide (Gp)–ferulic acid (FA) complexes

7 at 298.15 K and 0.15 mol·dm⁻³ NaNO₃

Species M = Fe³⁺ log₁₀b ± S.D. Dlog₁₀K M = Cr³⁺ log₁₀b ± S.D. Dlog₁₀K Gp = G r*^a 1.103 1.017
 [MGpFA] 20.07 ± 0.04 -2.10 15.87 ± 0.03 [MGpFAH]? 24.49 ± 0.07 Gp = GG r*^a 1.157 1.099 [MGpFA] 19.25
 ± 0.04 -0.85 15.15 ± 0.08 [MGpFAH]? 21.02 ± 0.04 [MGpFAH-1]- 12.52 ± 0.04 9.64 ± 0.04 Gp = GGG r*^a
 1.242 1.009 [MGpFA] 18.06 ± 0.02 -1.80 14.91 ± 0.03 [MGpFAH]? 21.36 ± 0.03 [MGpFAH-1]- 10.55 ± 0.04
 9.8 ± 0.03 [MGpFAH-2] 2- 3.17 ± 0.03 2.23 ± 0.03 -1.09 -0.22 -0.43 a Sigma* (r*) is the goodness of fit for a

system with $\pm 95\%$ probability Table 5 Overall formation constants of metal ion (M)–glycine peptide (Gp)–gallic acid (GA) complexes

7 at 298.15 K and 0.15 mol/dm³ NaNO₃

Species M = Fe³⁺ log₁₀b ± S.D. Dlog₁₀K M = Cr³⁺ log₁₀b ± S.D. Dlog₁₀K Gp = G r^a 1.091 1.106 [MGpGA]₂⁻ 29.08 ± 0.06 -4.58 24.85 ± 0.02 [MGpGAH]⁻ 37.36 ± 0.06 [MGpGAH₂] 43.38 ± 0.06 Gp = GG r^a 1.057 1.013 [MGpGA]₂⁻ 26.69 ± 0.03 -4.90 23.10 ± 0.03 [MGpGAH]⁻ 33.72 ± 0.08 30.94 ± 0.03 [MGpGAH-1]₃⁻ 18.12 ± 0.02 14.33 ± 0.04 Gp = GGG r^a 1.075 1.089 [MGpGA]₂⁻ 25.95 ± 0.03 -5.40 23.31 ± 0.02 [MGpGAH]⁻ 30.18 ± 0.02 [MGpGAH₂] 36.12 ± 0.03 [MGpGAH-1]₃⁻ 17.54 ± 0.01 13.42 ± 0.02 [MGpGAH-2]₄⁻ 6.00 ± 0.05 1.79 ± 0.06 -4.42 -4.58 -5.34 a Sigma* (r^{*}) is the goodness of fit for a system with $\pm 95\%$ probability Fig. 4 The species distribution curves of a Fe³⁺–G–FA, b Fe³⁺–GG–FA, c Fe³⁺–GGG

15–FA at T = 298.15 K, I = 0.15 mol/dm³

NaNO₃ and [M:Gp:Ph] 1:1:1. Charges are omitted for simplicity with increasing pH. At pH above 8, the major species in this system is [FeFA(GG,H-1)] (53 %) with the other two species [FeFA₂] and [Fe(GG₂,H-2)] being found in equal amounts (23.5 %). 4 Conclusion In this work, interactions between trivalent ions (Fe³⁺ and Cr³⁺), glycine peptides (G, GG and GGG) and phenolates (FA and GA) were studied at 298.15 K and ionic strength 0.15 mol/dm³ NaNO₃ by using the pH-potentiometry technique. The complex stability constants, as overall formation constants (log₁₀b_{pqrs}), were obtained by the HYPER-QUAD2008 program. In terms of the ligands, the stability constant of the complexes in binary systems decreases in the following order GA [FA [G [GG [GGG. Among the glycine peptides, the longer the linear carbon side chain is, the greater is the steric effect and thus the complex formed is less stable. From investigation of

5 the contribution of deprotonated or undeptotonated amide peptides to stability

constants, it was found that the deprotonated amide nitrogen in the peptide backbone participated in complex formation thus it enhanced the complex's stability.

3 The stability constants of complexes in both binary and mixed-ligand

systems show the same trend, where Fe³⁺ forms a more stable complex with ligands than Cr³⁺. Based on its log₁₀b values, the

6 mixed-ligand complexes formed are more stable than the corresponding binary complexes. Moreover, the **mixed-ligand**

complex containing GA is more stable than that containing FA. In mixed- ligand systems, the stability of complexes decreases in the following order of ligands: GA– G [GA–GG [GA–GGG [FA–G [FA–GG [FA–GGG. Acknowledgments

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