

Uptake of iron (III)-ethylenediamine-*N,N,N',N'*-tetraacetic acid complex by phosphatidylcholine lipid film: Part I. Effect of bulk pH

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ABSTRACT

We studied a ternary solutes aqueous solution of NaOH, iron (III)-ethylenediamine-*N,N,N',N'*-tetraacetic acid complex (Fe-edta), and 1,2-diheptanoyl-*sn*-glycero-3-phosphatidylcholine (DHPC)/air interface system to clarify the interactions between iron complexes and lipids with a phosphatidylcholine head group. The solution surface tension and pH were measured as functions of the total molality of NaOH, Fe-edta and DHPC, and the mole fractions of NaOH and DHPC. Rigorous thermodynamic equations were derived, in which the overall proton dissociation equilibria of Fe-edta and DHPC were taken into consideration, and applied to experimental data to obtain phase diagram of adsorption. It was found that (1) adsorption of Fe-edta at the solution/air interface with a DHPC monolayer was about 50–130 times higher than that without a DHPC monolayer and (2) when the bulk mole fraction of NaOH was high, Fe-edta tended to be expelled from the adsorbed film. The last finding suggests that the ambient pH significantly affects passive transport of the iron complex through a phospholipid-containing membrane into the cell interior.

1. Introduction

Iron is an essential element for animals and plants. It is necessary for the synthesis of chlorophyll and cytochromes, and plays important roles in electron transmission or enzyme activation in respiration, photosynthesis and many other life-supporting mechanisms. Iron, an environmentally abundant element, exists mostly as iron (III) oxide-hydroxide, which is easily transformed into unavailable forms above pH 3, therefore special mechanisms are needed for its transport into living cells and subsequent use.

In 1976, Takagi reported that an iron-solubilizing substance is secreted from iron-deficient rice plants and oats (Takagi, 1976). Mugenic acids (MA), which is a phytosiderophore that is excreted into the rhizospheres of graminaceous plants (Sugiura and Nomoto, 1984), has two α -aminocarboxylate binding centers and a single α -hydroxycarboxylate unit; it functions as a hexadentate ligand (Mori, 1998). MA chelates with iron (III) and is then absorbed through Fe-MA transporters anchored in the cell membrane. This mechanism has been developed by many graminaceous plants. It is one of three mechanisms proposed to explain iron uptake by plants, and is referred to as Strategy II. However, not much is understood about the specific mechanistic details. Major

global food grains are graminaceous plants. Investigation of Strategy II is therefore important in terms of securing a stable food supply.

In this study, we investigated the passive transport of Fe-MA complexes, i.e., diffusion across the cell membrane. In the 1970s and 1980s, the binding of cations to phosphatidylcholine lipids was studied using ³¹P NMR spectroscopy (Hauser et al., 1976, 1977; Grasdalen et al., 1977; McLaughlin et al., 1978; Akutsu and Seelig, 1981; Chrzesczyk et al., 1981). With the recent surface-sensitive X-ray spectroscopic techniques, combined with Langmuir monolayer studies, Wang et al. reported pH sensitive interactions between lipid monolayers and trivalent ions, namely iron (III) and lanthan (III) (Wang et al., 2011a,b). According to their studies, interactions between lipid monolayers and lanthan (III) are Coulombic, while iron (III), dissolved as FeCl₃ in the aqueous subphase, has been found to form different types of complexes with OH⁻ depending on the pH, and to interact differently with fatty acid and phosphate lipid monolayers, which suggests that the nature of binding is specific rather than Coulombic. The most studied bio-related ligands and metal complexes are porphyrins, phthalocyanines, and their complexes with transition metals, which have many π bonds and generally low water solubilities. However, to the best of our knowledge, the interactions between transition metal complexes ligated by organic

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ligands with high water solubilities and lipid membranes have hardly been studied, although living cells contain variety of metal complexes that are essential for life support.

Metal complexes have an organic moiety, and can therefore be more lipophilic and amphiphilic than the bare metal ions. Additionally, siderophores are often polyprotic ligands and the valence number of a complex ion depends on the solution pH. Three dissociation constants for MA have been reported, namely 3.23, 7.94, and 9.85. Differential potentiometric titration in the presence of iron (III), has shown that the fourth proton dissociates when an iron complex is formed. In the literature, the quadrivalent MA forms a stable complex species with iron (III) with the total charge -1 in the pH range 5–7, and its pK_a is ca. 2.5 (Murakami et al., 1989). The membrane affinity of an iron complex with such siderophores is therefore expected to depend on the pH of the soil in the vicinity of the plant roots.

Previously, we studied the adsorption behavior of an iron (III) complex with ethylenediamine-*N,N,N',N'*-tetraacetate (Fe-edta) at its aqueous solution/air interface to clarify the effects of the nature of the counter ion or co-ion and the proton concentration on its surface activity (Villeneuve et al., 2014). Fe-edta has a water molecule bound to the iron opposite the nitrogen atoms; it is a polyprotic acid in aqueous solution, and can potentially dissociate up to three protons. At ambient temperature and pressure, two pK_a values for Fe-edta have been reported, i.e., 2.2 and 7.6 (Lambert et al., 1963). In addition, dehydration condensation, i.e., olation, takes place at pH higher than 9 and the dimerization constant is $10^{1.88}$ (Motekaitis et al., 1980). The reason why Fe-edta is a good substitute for Fe-MA is that they have similar proton dissociation constants, and the coordination structure of iron (III) in the Fe-MA (Kato et al., 2011) and Fe-edta are also similar.

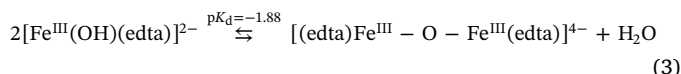
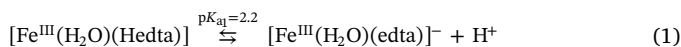
It has been found that (1) the order of the surface activities of Fe-edta complex species is nonionic complex > monoanionic complex > dianionic complex (and the tetraanionic dimer formed by olation of the dianionic species) and (2) when the counter ion of the anionic complex is a structure former, such as Na^+ , the Fe-edta complex is adsorbed negatively at the aqueous solution/air interface under most pH conditions, and when the counter ion is a structure breaker, such as K^+ , positive adsorption is more likely (Villeneuve et al., 2014). In this previous study, the aqueous solution/air interface was regarded as the simplest model of a cell membrane, with no specific chemical structure. The present study is designed to make the model closer to a real system, i.e., a cell membrane composed of a phosphatidylcholine lipid, which is one of the most common phospholipids found in plants and animals. The model system consisted of NaOH as a pH modulator, Fe-edta as a substitute for the Fe-MA complex, and 1,2-diheptanoyl-*sn*-glycero-3-phosphatidyl choline (DHPC) as the cell membrane. Common biological buffers such as 2-(*N*-morpholino)ethanesulfonic acid, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, *N,N*-bis(2-hydroxyethyl)glycine and tris(hydroxymethyl)aminomethane (Tris) were not used. Tris is known to induce a ripple gel phase in supported unilamellar phospholipid bilayers (Mou et al., 1994) and most of the above buffers modify the hydration state of the charged interface (Trewby et al., 2016). Additionally, the buffer constituents are likely to have surface activities similar to that of the iron complex under investigation. The use of such buffers would therefore cause confusion in interpretation of the experimental data. The results of this study are expected to give a straightforward picture of the effects of pH on the interactions between iron complexes and lipid monolayers, without any unexpected or unnoticed complications. There may be some differences in the physical properties between lipid monolayers and bilayers, namely the lipid density, molecular packing, fluidity, and so on (Linseisen et al., 1997; Mansour et al., 2001; Watkins et al., 2014). Nevertheless, monolayers can be regarded as a simple model of one leaflet of a lipid bilayer, and the hydrophilic side of a lipid monolayer simulates the surface of a membrane with respect to the adsorption of water-soluble substances. Therefore, the information obtained from this study would enable one to draw a reasonable inference on the

interaction between iron complexes and lipid bilayers.

Thermodynamic equations were developed for analyzing the surface tension data of a ternary solutes aqueous system involving compounds with weakly acidic groups and a base. In this study, the affinity of an iron (III) complex for a phospholipid monolayer was evaluated in terms of incorporation of the iron (III) complex into a DHPC monolayer at a constant base ratio in NaOH–Fe-edta–DHPC and at a constant bulk solution pH.

2. Thermodynamic equation applied to a ternary solutes solution/air capillary system

Fe-edta has three dissociable protons. The following proton dissociations, at pH 2.2 and 7.6, respectively (Lambert et al., 1963), and the olation reaction (Motekaitis et al., 1980) are known.



Chemical equilibria involving Fe-edta, water, and a base (MOH, where M is a metal) therefore have to be taken into consideration. Additionally, as shown in Fig. 1, protonation of the phosphate group of DHPC occurs at low pH and this also has to be considered.

$$\mu_{c0} = \mu_{c1-} + \mu_{H^+} \quad (4)$$

$$\mu_{c1-} = \mu_{c2-} + \mu_{H^+} \quad (5)$$

$$2\mu_{c2-} = \mu_{cd} + \mu_{H_2O} \quad (6)$$

$$\mu_{H_2O} = \mu_{H^+} + \mu_{OH^-} \quad (7)$$

$$\mu_{MOH} = \mu_{M^+} + \mu_{OH^-} \quad (8)$$

$$\mu_{DHPC} + \mu_{H^+} = \mu_{DHPCH^+} \quad (9)$$

μ is the chemical potential, and the subscripts $c0$, $c1-$, $c2-$, and cd represent the nonionic species $[Fe^{III}(H_2O)(Hedta)]$, the monoanionic species $[Fe^{III}(H_2O)(edta)]^-$, the dianionic species $[Fe^{III}(OH)(edta)]^{2-}$, and the tetraanionic dimer $[(edta)Fe^{III}-O-Fe^{III}(edta)]^{4-}$, respectively and the subscript $DHPCH^+$ stands for DHPC with a protonated phosphate group. The following equilibrium constants, and the dimerization constant, corresponding to Eqs. (4)–(6), respectively have been reported in the literature (Lambert et al., 1963; Motekaitis et al., 1980).

$$K_{a1} = a_{c1-} \cdot a_{H^+} / a_{c0} \quad (10)$$

$$K_{a2} = a_{c2-} \cdot a_{H^+} / a_{c1-} \quad (11)$$

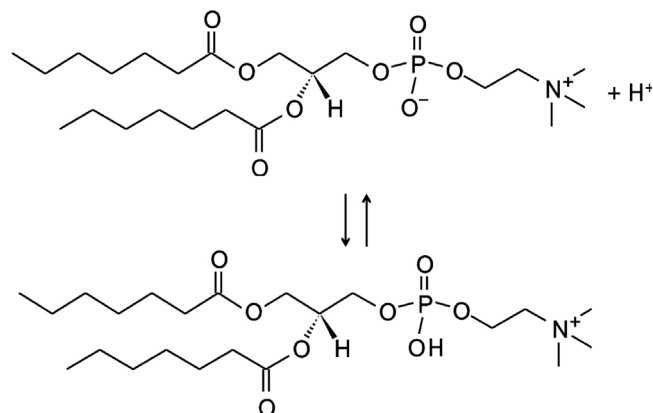


Fig. 1. Protonation of phosphate group in DHPC under strongly acidic conditions.

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