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Thermodynamic investigation on acid-base equilibria of deferiprone and deferasirox at different ionic strengths and various temperatures

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ABSTRACT

The acid–base equilibria of two iron chelating drugs, deferiprone (DFP) and deferasirox (DFX), have been studied in aqueous solution using potentiometric and spectrophotometric methods at different ionic strengths (0.100–3.200 and 0.100–1.548 mol kg^{-1} NaCl for DFP and DFX, respectively) and various temperatures (293.15–310.15 K). Owing to the low solubility of DFX in aqueous medium, in this case, the experiments were performed in aqueous solution of 30% (v/v) DMSO. The results showed that by increasing of temperature, all the protonation constants of the both drugs decreased indicating exothermic reactions. The thermodynamic functions of protonation including ΔG°, ΔH° and ΔS° at the mean temperature (301.15 K) were determined at different ionic strengths using a modified van't Hoff equation. The relative contributions of enthalpy (ζ_H) and entropy (ζ_{TS}) were also calculated for the protonation steps of the drugs. The dependence of protonation constants of DFP and DFX on ionic strength was modelled by seven different approaches at 298.15 K. The log K^o values (at zero ionic strength) of the drugs were also determined. Finally, the experimental protonation constants of DFP were compared with the literature data and comparison has been made and discussed between the different models.

1. Introduction

The protonation constant is one of the most frequently used physicochemical parameters which play an important role in understanding the ionic behaviour of many biological molecules. Accordingly, an accurate knowledge of this property and its determination is of interest in a wide range of research fields as well as pharmaceutical science which helps understanding the mechanism of drug action in various processes. Most of drugs depending on their molecular structures have acidic or basic functionalities and involve one or more protonation step(s). Therefore, in a wide pH range, different species of a drug may exist in the solution, including neutral, cationic, or anionic forms, which often have different properties such as aqueous solubility, UV–vis absorption spectra, *etc.* [1–4].

There are several methods for determination of protonation constants which are illustrated in the literature [5]. Traditionally, among this wide range of methods, a combination of potentiometric and spectrophotometric approach has been the most useful technique and convenient to determine equilibrium constants, because of its good reproducibility and accuracy. In this method solubility is not a serious problem due to a small amount of chemical reagent is required. Moreover, it may be possible to determine different protonation constants of polyprotic substances using a suitable computer program [6–8].

In spite of iron benefits for humans and its requirement for many essential metabolic processes, excessive amount of iron accumulated in the body, called iron overload, may become extremely toxic to the human [9]. Blood transfusion that is a useful way to treat patients, who have β-thalassemia major, is the main factor of iron overload [10]. At the present, there are different ways to assess the degree of iron overload in the body, such as testing serum ferritin levels, liver biopsy, MRI, *etc.* [11]. In the last two decades iron chelation therapy is the most convenient way to defend patients from the toxic effects of iron overload and consequently saving their life [12].

Although, there are some difficulties in using deferoxamine (DFO) such as non-oral effectiveness, high cost, short half-life inside the organism, *etc.*, it was used as the only iron chelating drug before the year 2000 [13]. However, the research efforts of clinicians and chemists have led to the introduction of two new oral chelators known as deferiprone (DFP) and deferasirox (DFX). These two drugs are more effective and cheaper than DFO and easier to use in chelation therapy [14]. However, the associated side effects of these two drugs have limited their use [13,14]. There are also

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some literature data about designing and synthesizing new compounds as iron chelators [15–17].

In the present work, the stepwise protonation constants of DFP and DFX were determined in aqueous solution using a combination of spectrophotometric and potentiometric methods in different conditions (293.15–310.15 K and ionic strength of (0.100–3.200 and 0.100–1.548) mol kg^{-1} NaCl for DFP and DFX, respectively). Because of the low solubility of DFX in aqueous solution [18], in this case, all the experiments were performed in aqueous solution of 30% (v/v) dimethylsulphoxide. The stepwise thermodynamic functions of protonation (enthalpy, Gibbs energy, and entropy changes) were calculated using a modified van't Hoff method. Moreover, the ionic strength dependence of protonation constants at 298.15 K was modelled using seven different approaches including extended Debye–Hückel [19], Guggenheim [20–23], Scatchard [24,25], Davies [26], De Stefano [27], SIT (Specific Ion Interaction Theory) [25] and Millero [28–30]. The calculated values of protonation constants, log K^{o}, values (at zero ionic strength) of the drugs were also determined. Finally, comparison has been made and discussed between the different models.

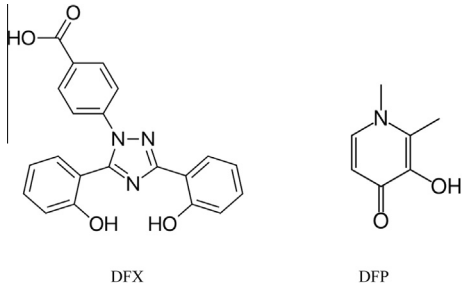
2. Materials and method

2.1. Materials

DFP and DFX, Scheme 1, were obtained as a gift from Arasto Pharmaceutical Chemicals Inc. (Iran). The purity of the drugs was checked by alkalimetric titration. Hydrochloric acid and sodium hydroxide solutions prepared from concentrated ampoules. For fixing the ionic strength in each experiment, sodium chloride solution was prepared by weighing appropriate pure salt that previously dried in an oven. Dimethylsulphoxide was obtained as reagent grade material. All dilute solutions were prepared from deionized water with a conductance equal to (2.0 ± 0.1) μS. The details on chemicals used in this work are given in Table 1.

2.2. Apparatus

The emf (electromotive force) values were measured using a Jenway pH-meter, model 3520 (resolution ± 0.1 mV), equipped with a glass-pH electrode (Jenway). The spectra of solutions were recorded on a UV–Vis Shimadzu 2100 spectrophotometer using 10 mm quartz cell equipped with a circulating water bath to keep the temperature constant within ±0.1 °C. The measurement cell was of the flow type. A peristaltic pump allowed circulation of the solution under study from the potentiometric cell to the spectrophotometric cell, so the absorbance and the emf of the solution could be measured simultaneously. To exclude carbon dioxide and oxygen from the system, a stream of purified nitrogen was passed through a sodium hydroxide solution and then bubbled slowly through the reaction solution.



DFX DFP

Scheme 1. The chemical structures of the drugs.

Table 1
Purities and sources of materials used in this work.

Materials	Purification method	Mass fraction	Sources
DFP	Used as received	0.99	Arasto Pharmaceutical Chemicals Inc. (Iran)
DFX	Used as received	0.99	Arasto Pharmaceutical Chemicals Inc. (Iran)
Hydrochloric acid		Solution	Merck
Sodium hydroxide		Solution	Merck
Sodium chloride	Dried 2 h at 383.15 K	0.99	Merck
DMSO	Used as received	0.99	Merck

2.3. Procedure and measurements

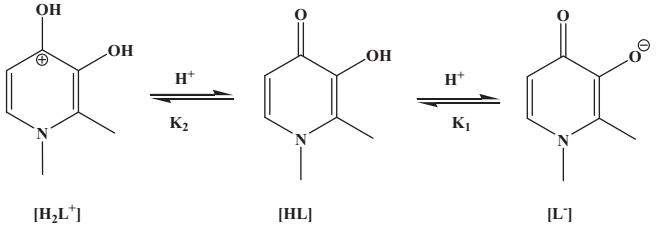
The protonation constants of the drugs were calculated based on the relation of $A = f(pC_H)$ by analysing the UV–Vis spectrophotometric titration data [31]. The measured absorbance, A, and pC_H ($-\log [H^+]$) from the potentiometric–spectrophotometric titration were conducted with the computer programs STAR (STability constants by Absorbance Reading) [32]. STAR is a non-linear regression program for the refinement of equilibrium constants of different systems [33].

The electrode system calibration was performed daily using the Gran's procedure [34]. For this purpose, a measured amount of an acidic solution (0.01 mol kg^{-1} hydrochloric acid), at the same condition of temperature and ionic strength to be used in later experiments, was titrated with a strong base (0.1 mol kg^{-1} sodium hydroxide, each addition 50 μ dm^{-3}). The emf was allowed to stabilize after each addition and the recorded values were then used to obtain the E_{cell}. Then, 0.5 m dm^{-3} of the drug solution (0.005 mol kg^{-1}) with desired ionic strength was added to the above solution. The solution was again titrated with a sodium hydroxide. The emf and the absorbance values in the range of (200–350) nm were then measured. The procedure was repeated in different ionic strengths and various temperatures. The recorded emf values were then converted to pC_H using the method described in the literature [35].

According to the Nernst equation, the potential of the potentiometric cell was calculated by Eq. (1):

$$E_{cell} = E^0_{cell} + k.\log[H^+] + k.\log\gamma_{H^+} + E_{LJ}, \quad (1)$$

where E^0_{cell} is the standard potential of the cell, E_{LJ} is the liquid junction potential, $k = 2.303RT/F$ in which R, T and F have the usual meaning, and γ^+_H is the activity coefficient of hydrogen ion. Difficulties in computing the activity coefficients of hydrogen ion in different conditions, lead to measurement of emf versus H^+ concentration in solution. Because the ionic strength of the solution is kept constant, in each run, so the activity coefficient of hydrogen ion is constant too. The non-ideality of solutions is then included in E'_a (the specific constant of the potentiometric cell), so



$[H_2L^+]$ [HL] $[L^-]$

Scheme 2. Dissociation steps of DFP.