J. Chem. Thermodynamics 77 (2014) 98–106

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Thermodynamics of proton binding and weak (Cl^-, Na^+ and K^+) species formation, and activity coefficients of 1, 2-dimethyl-3-hydroxypyridin-4-one (deferiprone)

Clemente Bretti, Rosalia Maria Cigala, Francesco Crea, Gabriele Lando, Silvio Sammartano *

Dipartimento di Scienze Chimiche, Università degli Studi di Messina, Viale Ferdinando Stagno d'Alcontres, 31, I-98166 Messina (Vill. S. Agata), Italy

ARTICLE INFO

Article history:
Received 20 January 2014
Accepted 6 May 2014
Available online 22 May 2014

Keywords:
Deferiprone
Medium effect
Solubility
Activity coefficients
Pitzer
Weak complexes

ABSTRACT

The acid base properties of 1,2-dimethyl-3-hydroxypyridin-4-one (also known as deferiprone, *def*, figure 1), together with the solubility and the distribution ratio have been studied potentiometrically at different temperatures and ionic strengths in NaCl, KCl and in $(CH_3)_4NCl$ aqueous solutions. The total solubility of deferiprone is fairly high (0.100 mol · dm^{-3} in pure water) and decreases with increasing salt concentration (salting out effect); this behaviour is greater in NaCl than in $(CH_3)_4NCl$ aqueous solutions. From the analysis of the solubility and the distribution measurements it was possible to determine the Setschenow and the activity coefficients of the neutral species. Deferiprone shows two protonation steps, whose protonation constants are $\log K_1^H = 10.088$ and $\log K_2^H = 3.656$ at infinite dilution and $T = 298.15$ K. The ionic strength dependence of the protonation constants was interpreted both in terms of variation of the activity coefficients, using the Debye–Hückel, the SIT (Specific ion Interaction Theory) and the Pitzer approaches, or considering the formation of weak species with the ions of the supporting electrolyte (e.g. Na^+, K^+ and Cl^-). Moreover, temperature gradients were provided for the two protonation constants. The stepwise protonation enthalpy values are negative in all cases (e.g. $\Delta H_1 = -19.2$ kJ · mol^{-1} and $\Delta H_2 = -13.8$ kJ · mol^{-1} at infinite dilution and $T = 298.15$ K) and become more negative increasing both temperature and ionic strength. It was observed that the proton binding process is mainly entropic in nature for the first protonation step and enthalpic for the second. The results are in good agreement with literature data.

1. Introduction

Deferiprone is a synthetic compound first designed in Professor R.C. Hider's laboratories at the University of Essex [1]. It is a bidentate ligand (1,2-dimethyl-3-hydroxypyridin-4-one, see figure 1), chemically it is a white to off-white crystalline powder and it belongs to the family of the alpha-ketohydroxypyridines, which is commonly present in nature. Deferiprone is used worldwide to treat many diseases, for example cancer, leukaemia and in haemodialysis [2–4]. This molecule, thanks to its metal-chelating properties, is an orally active chelator for treatment of iron overload (thalassemia) [5–8]. Moreover deferiprone may be used in the detoxification of other metals, such as aluminium, plutonium, uranium, and in the treatment of copper overloading conditions (Wilson's disease) [3,4,9]. Commercially deferiprone is known as Ferriprox ®, clinical studies have demonstrated that this drug is effective in promoting iron excretion and can lower serum ferritin [10] and iron stores in tissues of transfusion dependent thalassaemia patients (the precise mechanism is unknown). It is rapidly absorbed from the gastrointestinal tract and is eliminated via the kidneys, mainly in the form of glucuronide metabolite and iron-deferiprone complex. As reported in the safety data sheet of the Ferriprox ® drug, from clinical trials, it has been shown that deferiprone can affect the haemic and lymphatic system causing neutropenia and agranulocytosis, but can cause other effects as nausea, vomiting, abdominal pain and also severe arthritis. As already mentioned, there are many data from thermodynamic studies of deferiprone with metals such as iron, aluminium, gallium, zinc, vanadyl ion [9,11–14], but few are the data present on the behaviour of deferiprone in aqueous solution at different temperatures and at different ionic strengths or ionic media. To our knowledge, some important papers have been published and are summarized in the most common stability constant databases [15–17]. Among them, worthy of mention is the paper of Nurchi et al. [14], where the deferiprone protonation is studied at two temperatures (298.15 and 310.15) K and five ionic strengths in KCl.

* Corresponding author. Tel.: +39 090 6765747; fax: +39 090 392827.
E-mail addresses: cbretti@unime.it (C. Bretti), rmcigala@unime.it (R.M. Cigala), fcrea@unime.it (F. Crea), glando@unime.it (G. Lando), ssammartano@unime.it (S. Sammartano).

http://dx.doi.org/10.1016/j.jct.2014.05.006
0021-9614/

In this paper, the acid base and thermodynamic properties of deferiprone were studied in NaCl, KCl and $(CH_3)_4NCl$. Protonation constants, solubility and distribution data were collected to determine the activity coefficients of the charged and neutral species. The ionic strength dependence of protonation constants was interpreted both in terms of variation of activity coefficients (with the Debye–Hückel, Specific ion Interaction Theory and Pitzer approaches) and in terms of formation of weak complexes between the ions of the supporting electrolyte and the ligand.

2. Experimental section

2.1. Chemicals

1,2-dimethyl-3-hydroxypyridin-4-one solutions were prepared weighing pure compound (Sigma, p.a.) without further purification; their purity was checked by acidimetric titrations and was always >98%. Sodium chloride, potassium chloride solutions were prepared weighing the pure salt (Sigma, p.a.) previously dried in an oven at $T = 383.15$ K for two hours. Tetramethylammonium chloride ($(CH_3)_4NCl$) was purified from methanol as described by Perrin et al. [18].

Standard sodium hydroxide, tetramethylammonium hydroxide and hydrochloric acid solutions were prepared diluting concentrated ampoules and were standardized against potassium hydrogen phthalate (for bases) and sodium carbonate (for acid), respectively, previously dried in an oven at $T = 383.15$ K for two hours. Soda lime traps were used to preserve the NaOH solutions from atmospheric CO_2. All solutions were prepared in grade A glassware and with twice distilled water (conductivity < 0.1 μS).

2.2. Apparatus and procedure for potentiometric, distribution and solubility measurements

To avoid systematic errors two different potentiometric apparatus were used in our experimental approach, (a) model 809 Metrohm Titrando, equipped with a combined pH glass electrode (from Methrom 6.032.100); (b) model 713 Metrohm potentiometer connected to a Metrohm 665 automatic burette and to a model 8101 Ross type Orion electrode, coupled with a standard calomel electrode. For both systems the estimated precision was ±0.20 mV and ±0.001 cm^3 for e.m.f. and titrant volume readings, respectively. A PC was connected to the apparatus and automatic titrations were performed using the Metrohm TiAMO 1.0 software to control titrant delivery and data acquisition.

For the determination of the deferiprone protonation constants different potentiometric titrations were performed in NaCl, KCl and $(CH_3)_4NCl$ at different ionic strengths and temperatures. The solutions under analysis consisted of a 25 cm^3 aqueous solution containing different amounts of deferiprone (5 to 10) mmol · dm^{-3}, dissolved in the desired ionic medium, sodium chloride, potassium chloride or tetramethylammonium chloride at different ionic strengths. The solutions under analysis were titrated with sodium hydroxide up to pH ~ 10.5. During the titrations, the solutions were magnetically stirred and $N_{2(g)}$ was bubbled through the solution to prevent $O_{2(g)}$ and $CO_{2(g)}$ adsorption. Before each experiment, independent titrations of HCl solutions with standard sodium hydroxide (or $(CH_3)_4NOH$) were performed to determine the formal electrode potential (E°) in the same experimental conditions (temperature, ionic medium and ionic strength) of the systems under investigation. The free hydrogen ion concentration scale was used ($pH \equiv -\log[H^+]$).

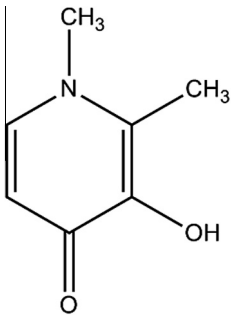

FIGURE 1. Structure of 1,2-dimethyl-3-hydroxypyridin-4-one.

Solubility measurements were performed as follows: saturated solutions were prepared in thermostatted vessels adding an excess of deferiprone to NaCl or $(CH_3)_4NCl$ aqueous solutions at fixed salt concentrations (0.1 to 3.0) mol · dm^{-3} at $T = 298.15$ and 310.15 K and then stirred for (18 to 24) h. Preliminary conductivity tests showed that longer stirring times are unnecessary, and a time of (4 to 6) h is sufficient. After the stirring, the solutions were filtered with MFMillipore (MCEmembrane) filters 0.45 μm. To minimize the systematic errors, several independent experiments were carried out for each ionic strength. The titrations on the supernatant were carried out by potentiometry using NaOH or $(CH_3)_4NOH$ standard as titrant, as previously reported.

Distribution measurements were carried dissolving known amounts of ligand (c_L = 10 to 20 mmol · dm^{-3}) in the salt aqueous solution (NaCl)/organic phase (2-methyl-1-propanol) mixtures (25 cm^3 of ligand plus 25 cm^3 of organic phase); the mixtures were shaken for at least 4 h and after successive separation of two immiscible phases, potentiometric titrations were performed to determine the distribution ratio of the ligand.

2.3. Calculations

The parameters of the acid base titrations (E^0, the junction potential coefficient j_a, log K_w, analytical concentration of components) were refined using ESAB2M [19] computer program. BSTAC and STACO [20] were also used to determine protonation constants of deferiprone and ES2WC [21] was adopted for the determination of the weak complexes between deferiprone and the ions of the supporting electrolyte. The non linear least squares computer program LIANA [20] was used for the refinement of the ionic strength and temperature dependence parameters of protonation constants, solubility and distribution data. Concentrations, protonation constants and ionic strengths are expressed in the molar and in the molal concentration scales and the conversions between these two scales were made using appropriate density values as described elsewhere [22]. Protonation constants refer to the equilibria:

$$H^+ + def^- = Hdef \qquad K_1^H \tag{1}$$

$$H^+ + Hdef = H_2def^+ \qquad K_2^H \tag{2}$$

The complex formation equilibria are given according to the following equilibrium:

$$jB^z + iH^+ + def = B_jH_idef^{(i+jz-1)} \qquad \beta_{ji}^B \tag{3}$$

where B^z can be Na^+, K^+ or Cl^-.

3. Results and discussion

3.1. Solubility and distribution measurements

The solubility and the distribution measurements were performed, in the experimental conditions of table 1, to determine the activity coefficient of the neutral species. The data analysis