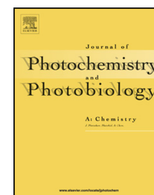
Journal of Photochemistry and Photobiology A: Chemistry 289 (2014) 14–21

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

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



Photoinduced transformation of iron chelator deferiprone: Possible implications in drug metabolism and toxicity

V.A. Timoshnikov [a,b], V.I. Klimentiev [a,b], N.E. Polyakov [a,*], G.J. Kontoghiorghes [c]

[a] Institute of Chemical Kinetics & Combustion, Novosibirsk, Russia
[b] Novosibirsk State University, Novosibirsk, Russia
[c] Postgraduate Research Institute of Science, Technology, Environment and Medicine, Limassol, Cyprus

ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 8 May 2014
Accepted 24 May 2014
Available online 2 June 2014

Keywords:
Deferiprone
Iron chelation
Photolysis
Electron transfer
Free radical
Phototoxicity

ABSTRACT

Deferiprone (L1) is an effective iron chelating drug which is widely used for the treatment of iron overload diseases. Although L1 itself does not absorb visible light, the absorption spectra of its Fe(III) complexes exhibit intensive absorption bands between 300 and 800 nm. It was found that L1–Fe(III) complex is stable under irradiation with visible light but undergoes fast decomposition under UV irradiation (with quantum yield more than 0.7). Decomposition of L1 has been observed in the presence of Fe(II) in a dark process. Free, non iron bound L1 exhibits both electron accepting and electron donating abilities. Free radicals of L1 were detected by the chemically induced dynamic nuclear polarization (CIDNP) method during irradiation of its aqueous solution in the presence of quinones, amino acids and NADH. It indicates the ability of deferiprone to produce free radicals not only by direct UV irradiation, but also in photosensitized electron transfer reactions with various biomolecules. Phototransformation of L1 was elucidated by using CIDNP, UV–vis, NMR and mass-spectroscopy techniques. The structures of the products of L1 photolysis include 1,2-dihydro-2,3,4-trihydroxy-1,2-dimethylpyridine. It appears that the metabolism of drugs with iron binding properties can be affected by sunlight, as shown by the iron complexes of L1 and such changes may cause phototoxic and pharmacological effects in patients undergoing treatment.
© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Deferiprone (L1) is an effective iron-chelating drug developed for the treatment of iron overload toxicity in thalassaemia and other iron related toxicity conditions. One can say that a new era in effective iron chelation therapy began with the discovery of L1, which is orally active and widely distributed in the body thus targeting toxic iron in many tissues and organs [1,2]. Moreover, chelators are supposed to be effective antioxidants which prevent oxidative stress and biomolecular, subcellular, cellular and tissue damage caused mostly by iron and copper induced free radicals formation in vivo [1 and refs. therein]. Free radical formation is a natural process leading to the production of highly reactive free radical species such as the superoxide, nitric oxide and hydroxyl radicals. Free radicals and other active oxygen species can also cause modification or damage of all known organic biomolecules including DNA, sugars, proteins and lipids [3–6]. Deferiprone has been shown to be effective and safe in the prevention of oxidative stress related tissue damage in iron loading and non iron loading conditions such as cardiomyopathy in thalassaemia, acute kidney disease and Friedreich ataxia [see review 1, for example]. In vitro, in vivo and clinical data suggest that L1 is the most potent antioxidant drug because of its high therapeutic index, ability to reach extracellular and intracellular compartments of many tissues and ability to inhibit both iron and copper catalyzed free radical reactions [1,2].

The physicochemical properties of L1 including ^{1}H NMR, IR, mass spectra, melting point, pK_{a1-3}, water/lipid partition coefficient etc. have been previously characterized [2,7–11]. Similarly, the iron and other metal binding properties of L1 at different pHs, stability constants, inhibition of iron catalyzed free radical toxicity, etc. have also been previously determined [1,2,7–12]. Under neutral pH conditions, L1 forms a red/orange $FeL1_3$ complex with Fe(III) (3:1 molar ratio) [2]. At acidic pH, e.g. pH = 2 an FeL1 (1:1 molar ratio) complex is formed [2,7,8]. Although it was demonstrated that $FeL1_3$ complex is redox inactive at physiological conditions, nothing is known about its photochemical activity [1,12,13]. This property may be important for the thousands of patients treated with L1. Usually the therapeutic dose of L1 ranges between 75 and

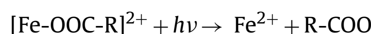
* Corresponding author at: Institute of Chemical Kinetics & Combustion, Institutskaya Str., 3, Novosibirsk 630090, Russia. Tel.: +7 383 3332947; fax: +7 383 3307350.
E-mail address: polyakov@kinetics.nsc.ru (N.E. Polyakov).

http://dx.doi.org/10.1016/j.jphotochem.2014.05.012
1010-6030/© 2014 Elsevier B.V. All rights reserved.

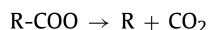
100 mg/kg/day divided into 2–3 doses per day, peak blood concentration can range between 50 and 500 μM and is cleared from blood within about 6 h [2,10,12]. In humans L1 is mostly metabolized to a glucuronide conjugate, which has no iron chelation properties. No other metabolites of L1 were detected during the pharmacological studies [2]. Overall the pharmacological properties of L1 suggest that very high concentrations of the drug can pass through blood and other human tissues also [1,2].

Although L1 itself does not absorb visible light, the absorption spectra of its Fe(III) complexes exhibit intensive absorption bands between 300 and 800 nm [7,8,11,14]. This light can penetrate through the skin and reach the capillaries. It may be possible that irradiation of the L1–Fe(III) complexes with visible light can result in the decomposition of L1 and the formation of free radicals or toxic secondary products which might cause toxicity such as photodermatitis, a toxic side effect observed with other drugs [15,16]. The study of the photochemical stability of L1 and L1–Fe(III) complexes is particularly important since iron overload diseases like thalassaemia are mainly distributed in the Mediterranean, Middle East and South East Asian countries where extremely high sun light irradiation level is present.

Electron transfer reactions are well known in photochemistry [17,18]. For example, irradiation of Fe(III) complexes with various organic acids by visible light results in electron transfer from the ligand to Fe(III) ion and subsequently the formation of redox active Fe(II) ion and a set of free radicals [18].



$$[\text{Fe-OOC-R}]^{2+} + h\nu \rightarrow \text{Fe}^{2+} + \text{R-COO}$$



$$\text{R-COO} \rightarrow \text{R} + CO_2$$

According to published data, L1 does not form stable chelate complexes with Fe(II) ions but oxidizes Fe(II) to Fe(III) and forms a red/orange L1–Fe(III) complex [2,12,19]. After one-electron reduction of this complex by hydrated electron, the decay of absorption at 450 nm in microsecond time scale was detected. However, it was not evident from this experiment, if the absorption decay is due to complex dissociation or chemical transformation of L1. The high reactivity of L1–Fe(II) and related complexes follows in particular from its ability to reduce water [19,20].

We can conclude that up to date, a significant gap exists in our knowledge on the free radical intermediates of L1, as well as their formation and chemical transformations in Fe(III) and Fe(II) complexes in physiological or photoinduced processes. In the present study we have tried to fill this gap using CIDNP (chemically induced dynamic nuclear polarization) and other physical techniques. The results of this study may also provide a new insight into possible mechanism of the phototoxicity of L1 induced by UV light due to reaction with various biomolecules. Within this context the photochemistry of L1 and its iron complexes are of chemical, biochemical, pharmacological and toxicological importance.

2. Materials and methods

Deferiprone was received from LIPOMED INC, Switzerland. Deuterated solvents for NMR, CD_3OD and D_2O (Aldrich) were used as supplied. Phosphate buffer (50 mM) with addition of KOH or HCl was used in optical and NMR experiments to adjust pH value measured by Knick Portamess 911 pH meter.

The mechanisms of phototransformation of L1 and the L1–Fe(III) complex were elucidated by using CIDNP, UV–vis, NMR and mass-spectroscopy techniques.

Optical spectra of L1 were measured in distilled water using Shimadzu UV-2401-PC spectrophotometer with 1 cm quartz cuvette. Iron complexes formation was studied at pH 5.5 using UV–vis spectroscopy at different molar ratios between the reactants (Fig. 1).

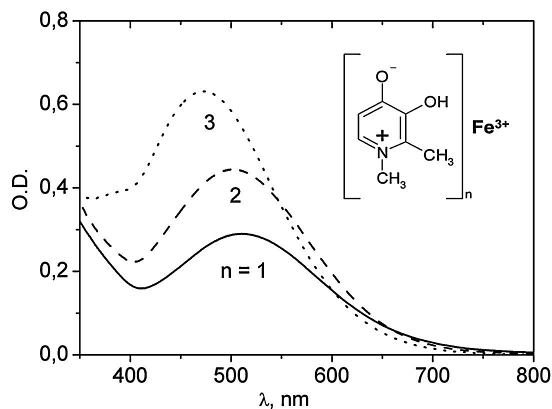


Fig. 1. Absorption spectrum of the L1-Fe^{3+} complex in water at different L1/Fe^{3+} ratios and pH = 5.5; [$Fe(ClO_4)_3$] = 0.2 mM; [L1] = 0.2, 0.4 and 0.6 mM respectively. Pure L1 has no absorption at this region (see Fig. 2).

The study of the photochemical behavior of L1 and its iron complexes was carried out using UV–vis and CIDNP techniques [21]. The CIDNP method was applied for detection and identification of free paramagnetic intermediates of L1. In the present study we have investigated the electron accepting and electron donating ability of L1 in a model of photochemical reactions with electron donors (NADH and aromatic amino acids) and acceptors (quinones).

For the CIDNP experiments, samples in standard 5 mm Pyrex NMR tubes were irradiated directly in the probe of an NMR spectrometer at room temperature. An EMG 101 MSC Lambda Physik excimer laser was used as the light source for CIDNP experiments (λ = 308 nm, pulse duration 15 ns, average pulse energy 100 mJ). During the photochemical reaction, the CIDNP spectra were detected using the DPX 200 Bruker NMR spectrometer (200 MHz ^{1}H operating frequency). During the time-resolved (TR) CIDNP experiments [22], standard presaturation techniques were used to suppress the equilibrium signals that occurred with the following pulse sequences: (i) saturating radiofrequency pulse; (ii) laser pulse; (iii) time delay; (iv) the detecting radiofrequency pulse; and (v) free induction decay. In the TR CIDNP experiments, a 1 μs detecting radiofrequency pulse was used, which is approximately equivalent to a 15° pulse. Quasi Steady State (QSS) CIDNP experiments were performed using the special presaturation technique: saturation – 180° pulse – a number of laser pulses – evolution time – detection pulse – free induction decay. Since the background (equilibrium) NMR signals in the pulse CIDNP experiments were suppressed, only the signals of the products demonstrating nuclear polarization could be observed [23]. It should be noted that in the CIDNP experiments laser irradiation is mainly absorbed by partner molecules (quinone, tryptophan, NADH), but not L1 itself due to low extinction coefficient at 308 nm.

The analysis of mass spectra was performed using a MALDI-TOF/TOF spectrometer Ultraflex III (Bruker Daltonics) in the International Tomography Center, Novosibirsk. The mass spectra of L1 products were recorded in reflective positive ion mode in the 0–1000 *m*/*z* range.

3. Results and discussion

3.1. Optical absorption study of deferiprone–iron complex formation

In the first instance the interaction of L1 with Fe(III) and Fe(II) ions by optical absorption technique have been studied. The formation of L1 complexes with Fe(III) can be easily detected from

Download English Version:

https://daneshyari.com/en/article/26560

Download Persian Version:

https://daneshyari.com/article/26560

Daneshyari.com