

Complexation of thorium(IV) with desmethyl-desferrithiocin

By Linfeng Rao^{1,*}, Gregory R. Choppin² and Raymond J. Bergeron³

¹ Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

² Department of Chemistry, Florida State University, Tallahassee, Florida 32306, USA

³ Department of Medicinal Chemistry, Medicine, University of Florida, Gainesville, Florida 32610, USA

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Summary. The complexation of Th(IV) with desmethyl-desferrithiocin (H₂DMDFT), a derivative of the siderophore desferrithiocin (H₂DFT), was studied by potentiometry, spectrophotometry and NMR. Three protonation constants of the ligand were determined by potentiometric titrations and ¹H-NMR and assigned to the phenolate group, the nitrogen at the hydroxypyridine ring, and the carboxylate group. The formation constant of the 1:2 complex, Th(DMDFT)₂, was determined by absorption spectrophotometry with oxalate as a competing ligand. A tridentate complex with Th(IV) involving the phenolate oxygen, the thiazoline nitrogen and the carboxylate group of H₂DMDFT was proposed.

Introduction

There has been great interest in the study of the coordination chemistry of naturally occurring siderophores and their synthetic analogs with metal ions due to various reasons [1–9]. First, siderophores are highly effective iron chelators and play important roles in the transport of iron in organisms. For example, a hydroxamate bacterial siderophore, desferrioxamine B (DFO), forms a very strong 1:1 complex with Fe(III) and is the only drug approved at present for the treatment of transfusional iron overload [10–12]. Also, some siderophores form strong complexes with Pu(IV) and Th(IV) [11, 13]. As a result, they can solubilize plutonium from a hydrous Pu(IV) oxide [14], and enhance the sequestration of plutonium from laboratory animals [15, 16]. Thus, siderophores are potentially selective sequestering agents for actinides and may find applications in chemical separations, decontamination, and environmental migration of metal ions.

Though DFO remains the drug of choice for the treatment of iron overload, there are shortcomings associated with its application, such as relatively high cost and low oral effectiveness [11, 12]. As a result, there is a demand to isolate new siderophores and/or develop alternative iron chelators and, in particular, those that are orally effective. Recently, a new siderophore, desferrithiocin (H₂DFT,

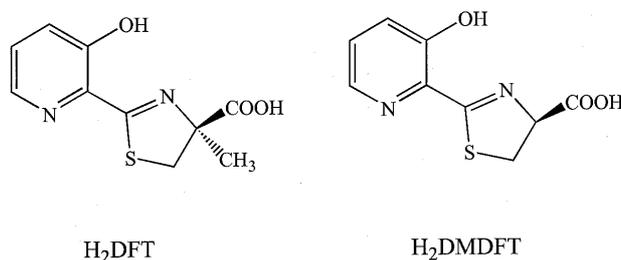


Fig. 1. H₂DFT and H₂DMDFT.

Fig. 1), has received much attention since its first isolation from *Streptomyces antibioticus* [17]. Comparative studies of H₂DFT and DFO have demonstrated that H₂DFT, like DFO, is a very strong iron chelator and is highly effective when administered orally [18, 19]. Several ligands structurally related to H₂DFT were also found to form strong complexes with Fe(III) and other tri- and divalent metal ions [5].

To identify the structural features of H₂DFT that make this ligand an orally effective iron chelator and to develop a structure-reactivity relationship as guidelines in search for new drugs, Bergeron *et al.* [6, 10, 12, 20] synthesized a series of ligands by systematically varying the functionality on the hydroxypyridine and/or the thiazoline rings. Among these ligands, desmethyl-desferrithiocin (H₂DMDFT, Fig. 1), resulting from the replacement of the methyl group of H₂DFT with hydrogen, is of particular interest because it is more water-soluble and less toxic than H₂DFT [20]. Langemann *et al.* determined the formation constants of the complexes between H₂DMDFT and a few trivalent metal ions (Al, Ga, and Fe). To evaluate the binding strength of this siderophore-related ligand with tetravalent actinides, the coordination chemistry of H₂DMDFT with Th(IV) was studied in this work, by potentiometry, ¹H-NMR, and UV/Vis absorption spectrophotometry.

Experimental

Chemicals

All the experiments were conducted at an ionic strength of 0.1 M (NaClO₄) and 25 °C. Purified water from a MilliQ system was used for the preparation of all aqueous solutions.

* Author for correspondence (E-mail: LRao@lbl.gov).

Desmethyl-desferrithiocin (H_2DMDFT) was synthesized as its sodium salt ($NaHDMDFT$) at the University of Florida and used without further purification. The procedures for the synthesis of this compound have been described previously [12]. It has been reported that the thiazoline ring of H_2DMDFT slowly decomposes to cysteine in strong acid [5, 11] so, in the present study, all the solutions of H_2DMDFT were prepared immediately prior to use. In addition, the UV/Vis absorption spectrum of H_2DMDFT in acidic solutions was followed to make sure that no identifiable decomposition occurred over the period of the experiment.

Thorium nitrate (reagent grade, Alfa Chemical Co.) was converted to thorium perchlorate by repeated evaporations in perchloric acid. All the other chemicals used in this work are reagent grade or higher.

Potentiometry

Potentiometric titrations were performed in a glass vessel jacketed to allow the temperature to be maintained at $25.0 \pm 0.1^\circ C$. The solution in the vessel was protected by an inert atmosphere (N_2) during the titration. The hydrogen ion concentration was measured with a Fisher 950 pH meter equipped with a combination pH electrode. The titrations were conducted in two ways: 1) a solution of 25 ml containing $NaHDMDFT$ ($6 \times 10^{-3} M$) and $HClO_4$ ($6 \times 10^{-3} M$) was titrated with 0.1 M NaOH; 2) a solution of 25.0 ml containing $NaHDMDFT$ ($6 \times 10^{-3} M$) and NaOH ($1.2 \times 10^{-2} M$) was titrated with 0.1 M $HClO_4$. A pH range between 2.3 and 12 was covered in the titrations. Two protonation constants of H_2DMDFT were calculated from the titration data by the data analysis procedure outlined in previous literature [21].

1H -NMR

NMR measurements were performed on the SUNS 300 MHz NMR spectrometer in the Department of Chemistry, the Florida State University. Samples were prepared by dissolving weighed amounts of the sodium salt of H_2DMDFT in D_2O . The acidity of the solution, $[D^+]$, was adjusted with fresh D_2O solutions of 20% DCl or 10% NaOD. Sodium 3-(trimethylsilyl)-1-propane-sulfonate was used as an internal standard.

UV/Vis spectrophotometry

A computer-controlled Cary-14 spectrophotometer (modified by On-Line Instrument Systems, Inc.) was used for the spectrophotometric experiments. Three milliliters of solution were placed in a quartz cell with an optical path of 1.0 cm. The absorption spectra of the solutions of H_2DMDFT , $H_2DMDFT + Th(IV)$, $H_2DMDFT + Th(IV) + EDTA$, and $H_2DMDFT + Th(IV) + oxalate$ were collected in the wavelength range between 250 nm and 450 nm. The pH of the solutions was maintained at 4.7 with sodium acetate buffer (0.01 M).

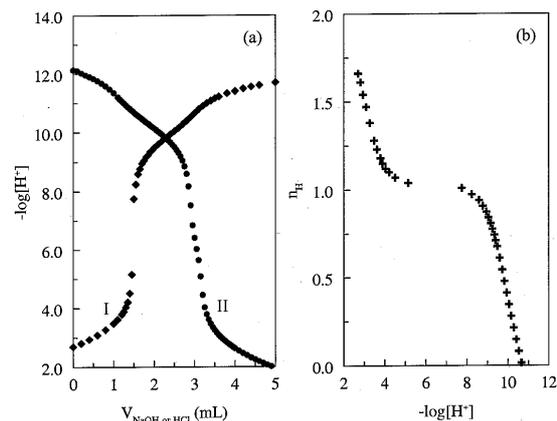


Fig. 2. Potentiometric titrations of H_2DMDFT . (a) $-\log[H^+]$ as a function of the volume of titrant. Initial cup solution: 25.0 mL. Curve I: $6.045 \times 10^{-3} M$ $NaHDMDFT$, $6.00 \times 10^{-3} M$ $HClO_4$; titrant: 0.10 M NaOH. Curve II: $6.045 \times 10^{-3} M$ $NaHDMDFT$, $1.20 \times 10^{-2} M$ NaOH; titrant: 0.10 M $HClO_4$. (b) \bar{n}_H as a function of $-\log[H^+]$ for titration I shown in Fig. 2a.

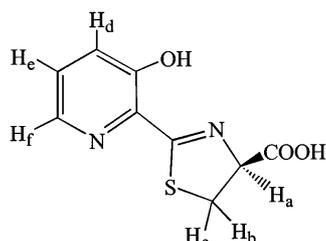
Results and discussion

Potentiometry

Potentiometric titrations were performed to determine the protonation constants of H_2DMDFT . Two titrations are shown in Fig. 2a. Curves I and II represent the titrations in opposite directions with NaOH and $HClO_4$, respectively. The average number of protons associated with the ligand, \bar{n}_H , is plotted as a function of $-\log[H^+]$ in Fig. 2b. From these data, two protonation constants (K_1 and K_2) were calculated. The protonation of the phenolate oxygen on the hydroxypyridine ring has a $\log K_1$ value of 9.81. This probably involves the formation of an intramolecular hydrogen bond between the phenolate oxygen atom on the hydroxypyridine ring and the nitrogen atom on the thiazoline ring, as suggested by X-ray structural analysis of the parent compound H_2DFT [5]. The second protonation ($\log K_2 = 3.02$) could take place either at the carboxylate oxygen atom, as suggested for the parent compound (H_2DFT) [5] or, at the nitrogen on the pyridine ring. Based on the results of 1H -NMR titrations described subsequently, we propose that the second protonation involves the nitrogen on the pyridine ring. The values are in good agreement with those previously reported for H_2DMDFT [11] and H_2DFT [5]. A third protonation, which may occur under strongly acidic conditions, was not observed because, in the potentiometric titrations, the pH did not reach a sufficiently low value to observe this protonation.

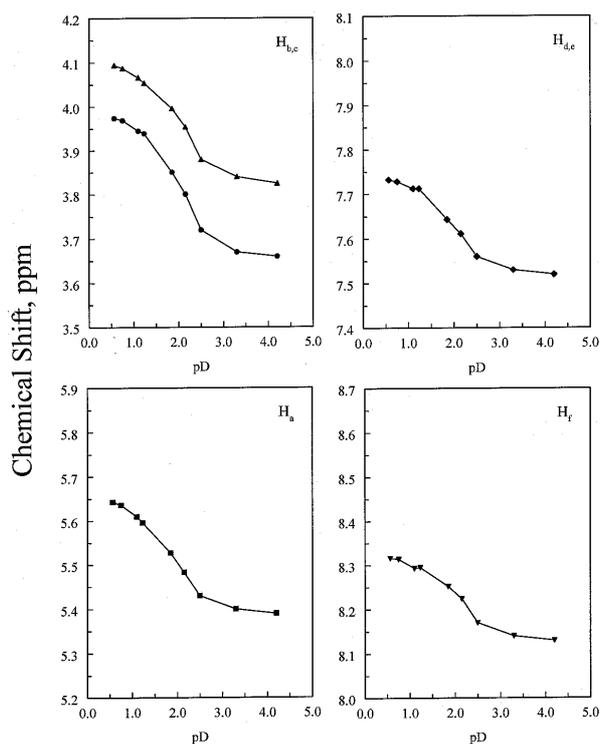
1H -NMR

1H -NMR data for H_2DMDFT and its complex with $Th(IV)$ are shown in Table 1. The chemical shifts of all the protons were influenced by the protonation and the complexation with $Th(IV)$. A series of 1H -NMR titrations were performed to determine the third protonation constant in strongly acidic region. The chemical shifts were followed as a function of pD (i.e., $-\log[D^+]$) between pD 0.56 and 7.7 with more data in the lower pD region. As shown in Fig. 3, there was a break in the region around pD of 1.9, which we

Table 1. ¹H-NMR data for desmethyl-desferrithiocin and its complex with Th(IV). (¹H-NMR spectra were recorded in D₂O at 300 MHz.)

System	Chemical shifts, ppm			
	H _a	H _{b,c}	H _{d,e}	H _f
Desmethyl-desferrithiocin pH = 7.7	5.33 (1H)	3.57 (1H) 3.74 (1H)	7.46 (2H)	8.07 (1H)
Desmethyl-desferrithiocin pH = 0.56	5.64 (1H)	3.97 (1H) 4.09 (1H)	7.73 (2H)	8.32 (1H)
Th(IV)/DMDFT pH = 4.7	5.67 (1H)	3.58 (1H) 3.78 (1H)	7.54 (1H) 7.74 (1H)	8.10 (1H)

ascibe as due to the third protonation. When the pD was raised from 0.56 to 2.15, the changes in the chemical shifts of all the protons are in the order: H_a ≈ H_b (0.16–0.17 ppm) > H_c (0.14 ppm) > H_{d,e} (0.12 ppm) > H_f (0.09 ppm). Based on these observations, the third protonation was assigned to the carboxylate group on the thiazoline ring. The relationship between pD and pH is pD = pH + 0.4 [13, 22], leading to a third protonation constant of log K₃ = 1.5.

**Fig. 3.** ¹H-NMR titrations of H₂DMDFT protons. The assignment of the protons is shown in Table 1.

The protonation constants of H₂DMDFT determined in this study are summarized in Table 2. The protonation constants of the parent compound, H₂DFT [5], are also listed for comparison. All the three protonation constants of H₂DFT are higher than corresponding values of H₂DMDFT, which can be attributed to the electron-donating nature of the methyl group in H₂DFT.

UV/Vis spectrophotometry

At pH 4.7, desmethyl-desferrithiocin has absorption bands near 309 nm and 386 nm in the UV/Vis region with molar absorptivities of 9390 M⁻¹ cm⁻¹ (309 nm) and 2940 M⁻¹ cm⁻¹ (386 nm), respectively. These bands are assigned to HDMDFT⁻¹ based on the protonation constants determined by potentiometry and ¹H-NMR. In this species, the phenolate group (pK_a = 9.81) remains protonated. When Th(IV) was added to the solution of HDMDFT⁻¹, a new band appeared near 336 nm and isobestic points were observed at 324 nm and 371 nm. Since Th(IV) does not have absorption bands in this region, the new band near 336 nm was assigned to the desmethyl-desferrithiocin ligand in the complex. Two series of spectrophotometric titrations were performed to determine the stoichiometry of the complex. In one series, the concentration of Th(IV) was constant (8.9 × 10⁻⁵ M) while the total concentration of the ligand, [H₂DMDFT]_{total}, was changed from 0 M to 3.6 × 10⁻⁴ M. In the other series, [H₂DMDFT]_{total} was constant (2.0 × 10⁻⁴ M) while the concentration of Th(IV) was changed from 0 M to 5 × 10⁻⁴ M. As shown in Fig. 4, the intensity of the band at 336 nm increased proportionally with the increase in the ratio of [H₂DMDFT]_{total}/[Th] (Fig. 4a) or [Th]/[H₂DMDFT]_{total} (Fig. 4b) until the ratios reached 2.0 (Fig. 4a) and 0.5 (Fig. 4b), respectively. These results suggest that a 1:2 Th/desmethyl-desferrithiocin complex was very strong and dominant under the experimental conditions. The spectra data alone do not suffice to answer the question whether the complex is Th(DMDFT)₂ or Th(HDMDFT)₂²⁺. However, we assign the formula Th(DMDFT)₂ to this complex based on the following arguments. 1) The strong interaction between Th⁴⁺ and HDMDFT⁻¹ would facilitate the deprotonation of the phenolate group and result in the formation of Th(DMDFT)₂. 2) The crystal structure data for the desmethyl-desferrithiocin complex with trivalent cations [11] show that the ligand in the complex is fully deprotonated (i.e., DMDFT⁻²). 3) Spectra analysis by a modified SQUAD program [24], to be described subsequently, indicate that the best fit to the experimental data is obtained by assuming the complex is Th(DMDFT)₂.

To obtain the stability constants of very strong complexes by spectrophotometry, it is necessary to use a competition technique. EDTA and oxalate were selected as the competing ligands because neither the two ligands nor their complexes with Th(IV) have significant absorption in the region of 250 nm to 450 nm that could interfere with the present study. The stability constants of the 1:1 Th-EDTA complex and the 1:1, 1:2 and 1:3 Th-oxalate complexes are available in the literature [25] and listed in Table 2.

Fig. 5 shows that when EDTA was added to a solution containing HDMDFT⁻¹ and Th(IV) (molar ratio 2:1), the

	Reactions	Ligand (L)				
		DMDFT	DFT ^c	DFO	Oxalate	EDTA
log K ₁	H ⁺ +L ²⁻ = HL ⁻	9.81 (4) ^a 9.53 (3) ^b	9.91 (4)		3.83 ^f	
log K ₂	H ⁺ +HL ⁻ = H ₂ L	3.02 (5) ^a 3.16 (6) ^b	3.31 (1)		4.93 ^f	
log K ₃	H ⁺ +H ₂ L = H ₃ L ⁺	1.5 (1) ^a 1.95 (20) ^b	1.65 (2)			
log β ₁	Th ⁴⁺ +L ²⁻ = ThL ²⁺				10.6 ^g	23.2 ^f
log β ₂	Th ⁴⁺ +2L ²⁻ = ThL ₂	26.7 (1) ^a			20.2 ^g	
	Al ³⁺ +2L ²⁻ = AlL ₂ ⁻	22.0 (1) ^b	22.2 (1)			
	Ga ³⁺ +2L ²⁻ = GaL ₂ ⁻	27.8 (2) ^b				
	Fe ³⁺ +2L ²⁻ = FeL ₂ ⁻	29.09 (3) ^b	29.6 (1)			
log β ₃	Th ⁴⁺ +3L ²⁻ = ThL ₃ ²⁻				26.4 ^g	
log β ₁	Th ⁴⁺ +HL ²⁻ = ThHL ²⁺			26.6 (1) ^d		
	Pu ⁴⁺ +HL ²⁻ = PuHL ²⁺			30.8 ^e		

a: This work, 0.1 M NaClO₄. b: Ref. [11], 0.1 M KCl. c: Ref. [5], 0.1 M KNO₃. d: Ref. [13], 0.1 M KCl. e: Ref. [13, 23]. f: Ref. [25], I = 0.1 M. g: Ref. [25], I = 0 M.

intensity of the absorption band of the complexed DMDFT²⁻ at 336 nm decreased, and the absorption bands of the free HDMDFT⁻¹ ligand at 309 nm and 386 nm appeared and increased with the increase in the concentration of EDTA. This indicates that DMDFT²⁻ in the complex was replaced by EDTA. The replacement seemed to be complete when the molar ratio of EDTA to Th(IV) reached 1:1. At this point, however, the band of the complexed DMDFT²⁻ at 336 nm was still significant, with the intensity decreased by only about 1/2 from the initial intensity. With the further increase in the concentration of EDTA, the absorption spectra did not show further change. These results

suggest that, for some reasons, EDTA was not able to replace both DMDFT²⁻ ligands in the Th(DMDFT)₂ complex. Instead, it has a strong tendency of forming a Th-DMDFT-EDTA mixed complex (molar ratio 1:1:1), in which the coordination number of Th(IV) is fully satisfied. A similar mixed complex containing Th(IV), EDTA and a derivative of desferrioxamine B (DFO-1,2-HOPO) was also reported in the literature [13].

In contrary to EDTA, oxalate was found to be able to replace both DMDFT²⁻ ligands from the Th(DMDFT)₂ complex. Representative absorption spectra of Th-desmethyl-desferrioxime-oxalate solutions were shown in Fig. 6. As the concentration of oxalate was increased, DMDFT²⁻ was gradually replaced by oxalate, resulting in the increase of the intensity of the free HDMDFT⁻¹ bands (309 and 386 nm) and the decrease of the intensity of the band of complexed DMDFT²⁻ (336 nm). The latter band disap-

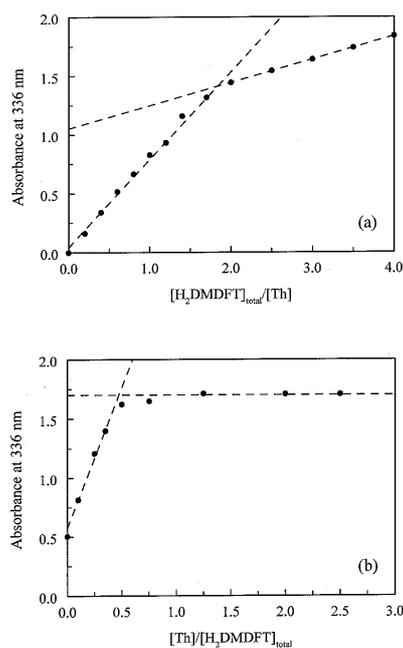


Fig. 4. The absorption at 336 nm (assigned to the DMDFT²⁻ ligand in the Th(DMDFT)₂ complex) as a function of the ligand/metal ratio. pH = 4.7. (a) [Th] = 8.9 × 10⁻⁵ M, [H₂DMDFT]_{total} ranges from 0 M to 3.6 × 10⁻⁴ M; (b) [H₂DMDFT]_{total} = 2.0 × 10⁻⁴ M, [Th] ranges from 0 M to 5.0 × 10⁻⁴ M.

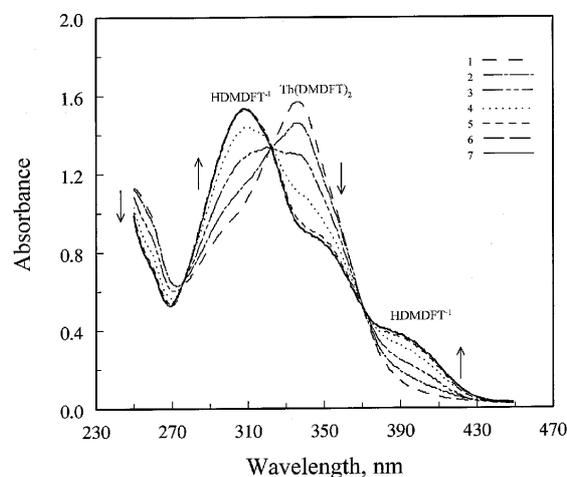


Fig. 5. Absorption spectra of the system of Th(IV) + H₂DMDFT + EDTA. pH = 4.7. Optical path: 1.0 cm. [Th] = 9.1 × 10⁻⁵ M; [H₂DMDFT]_{total} = 1.82 × 10⁻⁴ M; [EDTA] = 0 M (1), 1.82 × 10⁻⁵ M (2), 3.64 × 10⁻⁵ M (3), 5.46 × 10⁻⁵ M (4), 1.09 × 10⁻⁴ M (5), 2.18 × 10⁻⁴ M (6), 3.27 × 10⁻⁴ M (7).

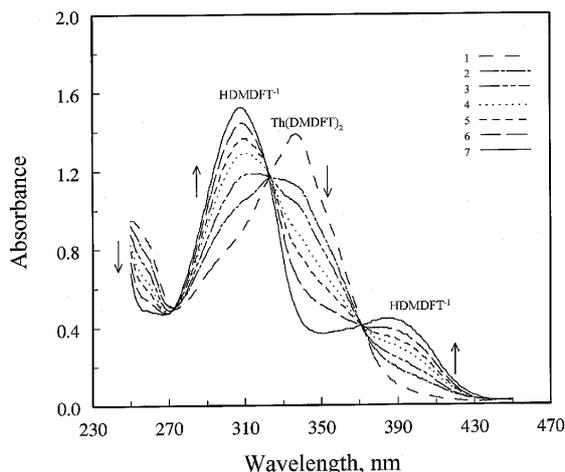


Fig. 6. Absorption spectra of the system of Th(IV) + H₂DMDFT + oxalate. pH = 4.7. Optical path: 1.0 cm. [Th] = 8.9×10^{-5} M; [H₂DMDFT]_{total} = 1.78×10^{-4} M; [oxalate] = 0 M (1), 4.5×10^{-4} M (2), 9.0×10^{-4} M (3), 1.35×10^{-3} M (4), 1.8×10^{-3} M (5), 2.7×10^{-3} M (6), 5.4×10^{-3} M (7).

peared almost completely when the molar ratio of Th(IV):DMDFT:oxalate was about 1:2:10. With these spectral data and the formation constants of Th/oxalate complexes from the literature [25], the formation constant of the Th(DMDFT)₂ complex ($\log \beta_2$) was calculated to be 26.7 ± 0.1 by the modified SQUAD program [24]. In the calculations, corrections were made for the complexation of Th(IV) with acetate (the pH buffer). The hydrolysis constants of Th(IV) [25] were also included in the calculation. However, it was found that the concentrations of the hydrolyzed Th(IV) species were negligible, suggesting that the complexation of Th(IV) with DMDFT²⁻ effectively suppressed the hydrolysis at pH 4.7.

Attempts were also made to fit the spectral data with the formation of Th(HDMDFT)₂²⁺ or the co-existence of Th(DMDFT)₂²⁺ and Th(DMDFT)₂. However, the inclusion of Th(HDMDFT)₂²⁺ gave very poor fit while the inclusion of Th(DMDFT)₂²⁺ had little effect on the $\log \beta_2$ for Th(DMDFT)₂ (the value of $\log \beta_2$ changed from 26.7 to 26.6). The calculated $\log \beta_1$ for Th(DMDFT)₂²⁺ was small (around 9.0) with large uncertainties. In addition, the calculated concentration of the 1:1 complex, if it did form, was much lower than that of the 1:2 complex. This is consistent with the results shown in Fig. 4 and supports the assumption that the 1:2 complex is dominant. As a result, only a value for the formation constant of the 1:2 complex, Th(DMDFT)₂, is reported in Table 2.

Langemann *et al.* [11] studied the complexation of desmethyl-desferrioxamine with a few trivalent metal ions (Al³⁺, Ga³⁺ and Fe³⁺). The chemical shifts of the protons of the ligand changed upon metal complexation in a similar fashion as in the Th(DMDFT)₂ complex. The formation constants of the complexes (ranging from 10^{22} to 10^{29}) are comparable with that of Th(DMDFT)₂ obtained in this work ($10^{26.7}$) (Table 2). This is not surprising as the charge densities of the cations are similar. The formation constants of the complexes of Th⁴⁺ and Pu⁴⁺ with desferrioxamine B (DFO) are also listed in Table 2 for comparison. The 1:1 (metal:ligand) complex of DFO with Th⁴⁺ and Pu⁴⁺ is as

strong as or slightly stronger than the Th(DMDFT)₂ complex. This probably results from the higher denticity of the DFO ligand [13].

No attempts were made to obtain crystals of the Th(DMDFT)₂ complex in this study. However, the crystal structure of K[Al(DMDFT)₂] · 1.166 H₂O · MeOH obtained from wet methanol by Langemann *et al.* [11] can provide insight into the structure of Th(DMDFT)₂. In K[Al(DMDFT)₂] · 1.166 H₂O · MeOH, the two DMDFT²⁻ ligands coordinate to Al with the phenolate oxygen atom, the nitrogen atom on the thiazoline ring, and the carboxylate oxygen atom. Both ligands are planar due to a delocalized π system involving the hydroxypyridine ring, the double bond in the thiazoline ring, and the sulfur atom, resulting in a distorted octahedral coordination geometry for Al(III) in the complex. Based on the similarities in the change of chemical shifts of the ligand proton upon metal complexation, it is reasonable to assume that DMDFT forms similar tridentate complex with Th(IV) involving the phenolate oxygen, the thiazoline nitrogen, and the carboxylate oxygen.

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