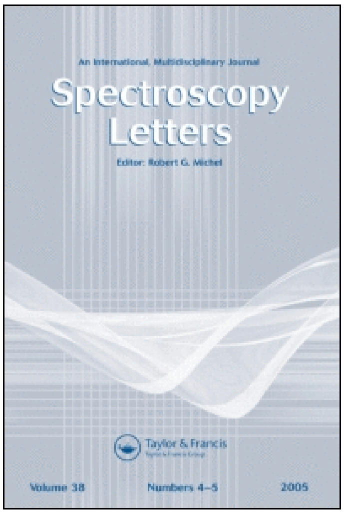

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Determination of the Protonation Constants of Gadolinium(Iii) Diethyltriaminepentaacetic Acid by Solvent Extraction and Icp-Aes

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DETERMINATION OF THE PROTONATION CONSTANTS OF GADOLINIUM(III) DIETHYLTRIAMINEPENTAACETIC ACID BY SOLVENT EXTRACTION and ICP-AES

Keywords: magnetic resonance imaging, contrast reagent, protonation, gadolinium, DTPA

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Abstract

The first and second protonation constant ($log\beta_{111}$, $log\beta_{121}$) of the metal-ligand complex Gadolinium(III)-diethyltriamine-pentaacetic acid (DTPA) have been determined to be 2.27 and 1.52 at 25 °C and I = 0.1. A technique in which the three complexes (H_2Gd-DTPA, HGd-DTPA^{-1}, Gd-DTPA^{-2}) are separated according to their relative polarity is utilized. An inductively coupled plasma-atomic emission spectrometer (ICP-AES) is used to determine the relative concentrations of each species by monitoring the gadolinium concentration.

Introduction

The thermodynamic parameters (ΔG, ΔH, ΔS) of lanthanide-aminocarboxylate complexes such as NTA, EDTA, HEDTA, and DTPA have been studied for several decades[1,2,3]. The lanthanide-aminocarboxylate complex [Gd(DPTA)$^{-2}$] has drawn attention from the medical community because of its role as a contrast reagent in magnetic resonance imaging (MRI)[4,5]. The

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stability constant (log[ML]/[M][L]) of the complex [Gd(DPTA)(H_2O)$^{-2}$] is measured in aqueous solutions to be 22.4[6,7]. The free DTPA complex has five carboxylates and three amine groups capable of being protonated. When complexed to Gd^{+3}, protonation of the complex is possible and will cause the complex to become unstable in very acidic mediums. Research has shown that there exists a strong correlation between the number of amines incorporated in the aminocarboxylate and the enthalpy of the metal ligand complexation[8]. Other studies have shown that the carboxylate arms on molecules such as EDTA and DTPA exchange rapidly between free and bound states when complexed to cations[9]. These data would indicate that the carboxylates are being protonated when the metal-ligand system complexes H$^+$. The first protonation ($log\beta 1_{111}$) of the [Gd(DPTA)$^{-2}$] has been measured to be 2.35[6] at 37°C and I=0.15.

In this work, we utilized a solvent extraction approach that differentiated between the relatively nonpolar H_2GdDTPA, and the progressively more polar HGdDTPA$^-$ and GdDTPA^{-2}. We used atomic emission spectroscopy to measure the concentration of Gd. We were able to measure both $\log\beta_{010}$ and $\log\beta_{020}$ for this important complex.

EXPERIMENTAL

A 0.01 M solution of Gadolinium (III) DTPA (Aldrich, Diethylenetriamine-pentaacetic acid, gadolinium (III) dihydrogen salt hydrate) had the pH adjusted with 0.1 M HCl. An Accumet pH meter was used to measure the [H$^+$] and a 0.1 M NaOH solution was used in the titration. After each addition of NaOH a 1-ml aliquot was removed and mixed with 10 mls of butanol. The solutions were shaken and allowed to sit for 3 days, with 25 aliquots extracted over the described pH range. A Perkin-Elmer Optima 3000 DV ICP-AES was used to measure the relative Gd concentrations. The gadolinium wavelengths monitored were 342.247 and 335.047 nm.

RESULTS

Measuring the first two protonation constants of aqueous phase GdDTPA^{-2} involves three species; GdDTPA^{-2}, HGdDTPA^{-1}, H_2GdDTPA. The first species, with a -2 charge, is relatively polar. The second species, with a -1 charge, is less polar than the first species but more polar than the last species, which is neutral.

$$\mathbf{GdDTPA^{-2} \overset{B_{010}}{\leftrightarrow} HGdDTPA^{-1} \overset{B_{020}}{\leftrightarrow} H_2GdDTPA}$$

polar **nonpolar**

In this experiment, we acidify the solution (pH = 1.5), which gives $H_2GdDTPA$. Sodium hydroxide is then added in small increments, slowly making the solution less acidic and transforming the complex from a charged to an uncharged species. At each titration interval, a 1 milliliter aliquot of the solution is drawn off and mixed with 10 milliliters of n-butanol resulting in two layers. Calculations of the [GdDTPA] in solution are adjusted accordingly.

The n-butanol has the alcohol functional group that provides 1enough polarity to attract any of the three forms of the water-soluble Gd-DTPA complex. The alcohol also has the nonpolar butyl group that offers some discrimination between the metal-ligand complexes of different polarities. *We postulated that the less polar $H_2GdDTPA$ should extract at a higher rate* from the aqueous solution to the butanol while the charged $GdDTPA^{-2}$ will extract less efficiently. Titration intervals are small enough (≈0.1 pH units) to allow for a meaningful titration curve consisting of the concentration of GdDTPA versus the pH plot to be constructed.

We should note that the cation (Na^+) is extracted into the alcohol at an inverse level to the Gd extraction. We assume that the sodium ion forms a weak, outer sphere electrostatic attraction with the charged GdDTPA complexes (i.e. $Na_2{\cdot}Gd{\cdot}DTPA$, $Na{\cdot}H{\cdot}Gd{\cdot}DTPA$). When the titration was rerun with K^+ the Gd levels shifted slightly but the trends remained the same.

In the butanol we measure the total concentration of Gadolinium by inductively coupled plasma-atomic emission spectroscopy (ICP-AES). The changes in concentration of gadolinium in the butanol can be correlated to the protonation of the Gd·DTPA complex.

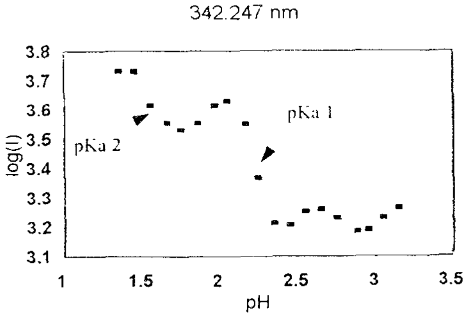

Figure 1a. Intensity of Gadolinium emission from ICP is correlated with the pH of the solution.

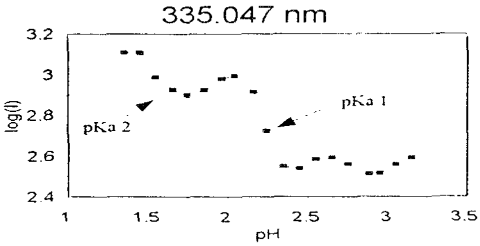

Figure 1b. The emission intensity (log(Intensity)) of trivalent gadolinium extracted into the n-butanol as a function of different aqueous phase pH's.

Figure 1a,b show the [Gd^{+3}] measured by ICP-AES as the pH increases. The two different Gd emission wavelengths monitored (335, 342 nm) are illustrated above. The y-axis is in relative log(Gd emission intensity) units. The two pKa's measured are

indicated by arrows. Recall that the pK_a = pH when the ratio of the protonated to deprotonated species is 1.0. A first derivative operation was performed and the pKa's were determined to be 2.15 (+/- 0.1) and 1.55 (+/- 0.1), respectively in an ionic strength of 0.1 (NaCl) and at a temperature of 25°C.

CONCLUSION

The protonation constants of a biomedically important molecule were measured using a solvent extraction and atomic emission technique. Using strictly potentiometric data to determine protonation constants of multiprotic molecules and complexes often results in the need for detailed statistical analysis. The results of statistical analysis, which involve various approaches to best fits, can vary from computer program to computer program and from lab to lab.

The method utilized here minimizes data treatment and interpretation. We are currently using this technique to measure the protonation constants of the amino acid cystine at high ionic strength (I>1) by monitoring its sulfur emission from n-butanol at different pH's.

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