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Evaluation of Formation Constants of Complexes of a Biologically Active Compound (*LAMI*) with Lanthanons

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The proton-ligand formation constant of 2-(2′-lepidylazo)-N-methylisatin (*LAMI*) and metal-ligand formation constants of its complexes with lanthanons(III) have been determined potentiometrically at different ionic strengths (0.02, 0.05, 0.1 and 0.15 *M* $NaClO_4$) in 75% aqueous dioxan medium. The method of *Bjerrum* and *Calvin*, as modified by *Irving* and *Rossotti*, has been used to find values of $\bar{n}$ and pL. The stability constants and the values of S_{min} have been calculated. The formation constants $\log \beta_n$ for the complexes have been found to increase with the increase in atomic number of the lanthanon. The order was found to be: La < Pr < Nd < Sm < Y < Tb < Dy < Ho.

(Keywords: Potentiometric evaluation; Formation constants; 2-(2′-Lepidylazo)-N-methylisatin; Lanthanons)

Komplexbildungskonstanten einer biologisch aktiven Verbindung (LAMI) mit Lanthaniden

Es wurden die Proton-Ligand-Bildungskonstanten von 2-(2′-lepidylazo)-N-methylisatin (*LAMI*) und die Metall-Ligand-Bildungskonstanten der Komplexe mit Lanthanid(III)ionen potentiometrisch bei verschiedenen Ionenstärken (0.02, 0.05, 0.1 und 0.15 *M* $NaClO_4$) in 75% wäßrigem Dioxan bestimmt. Die Methode nach *Bjerrum* und *Calvin* in der Modifikation nach *Irving* und *Rossotti* wurde zur Bestimmung der Werte für $\bar{n}$ und pL benutzt. Es wurden die Stabilitätskonstanten und die Werte von S_{min} berechnet. Dabei wurde festgestellt, daß die Bildungskonstanten $\log \beta_n$ der Komplexe mit steigender Ordnungszahl der Lanthaniden größer werden. Es wurde die Ordnung La < Pr < Nd < Sm < Y < Tb < Dy < Ho gefunden.

Introduction

N-Methylisatin and its derivatives are well known for their chelating and biological properties. *Knotz* and *Wendelin* [1] have reported the antiviral and antimicrobial activity of isatin derivatives. *Maysinger* et al. [2–4] have studied the antimicrobial activity of structural analogues of isatin. Derivatives of isatin and N-methylisatin have been found to act as central nervous system depressants and are used for prevention of small pox etc. [5]. The antimicrobial, antineoplastic, analgesic, antiinflammatory and cysticidal activity of isatin derivatives are well known [6]. Literature survey reveals that no work has been done on the lanthanon complexes of 2-(2′-lepidylazo)-N-methylisatin. So the present study was undertaken to determine the stability constants of lanthanons with *LAMI* at various ionic strengths in 75% dioxan-water medium.

Materials and Methods

A digital *pH*-meter (ECIL model PH 5652) with a glass electrode (0–14 *pH* range) was used for *pH*-measurements. The *pH*-meter was standardised with potassium hydrogen phthalate and phosphate buffers before performing the titrations.

N-Methylisatin (1.61 g) was dissolved in aqueous ethanol. To this saturated solution of N-methylisatin a saturated solution of 2-hydrazinolepidine (1.73 g) in ethanol was added and the mixture was refluxed for 3 h on a water bath. After completion of reaction, the mixture was cooled and the product was filtered. The colour of the final product is reddish orange. It was recrystallised from ethanol-benzene (3 : 1). Its purity was checked by NMR, elemental analysis and TLC.

The solution of ligand (*LAMI*) was prepared in freshly distilled 75% (*v*/*v*) aqueous dioxan. All the metal ion solutions were prepared and standardised by conventional procedures. Sodium perchlorate (Riedel) was used to keep the ionic strength constant for different sets. A solution of tetramethylammonium hydroxide (*TMAH*) (Merck) in 75% (*v*/*v*) aqueous dioxan was used as the titrant. It was standardised with a standard solution of oxalic acid. The dioxan used was purified by refluxing with sodium metal for 24 h and was freshly distilled over sodium before use. All other chemicals used were of reagent grade. The titrations were carried out in an atmosphere of nitrogen, which was presaturated with 75% (*v*/*v*) aqueous dioxan. All measurements were made at a definite temperature (± 0.5 °C) which was kept constant by using a MLW (Federal Republic of Germany) (NBE type) thermostat.

The method of *Bjerrum* and *Calvin* as modified by *Irving* and *Rossotti* [7], has been used to determine $\bar{n}$ and *pL* values. The experimental procedure involved the potentiometric titrations of the following solutions (total volume = 19.67 ml instead of 20 ml, due to contraction in volume on mixing dioxan and water) against standard 0.04 *M TMAH* in 75% aqueous dioxan (*v*/*v*) to determine $\bar{n}$ and *pL* values of the complexes.

(i) 3 ml $HClO_4$ (0.02 *M*) + 1 ml $NaClO_4$ (2 *M*) + 1 ml H_2O + 15 ml dioxan.

(ii) 3 ml $HClO_4$ (0.02 *M*) + 1 ml $NaClO_4$ (2 *M*) + 1 ml H_2O + 10 ml ligand (0.01 *M*) + 5 ml dioxan.

(iii) 3 ml $HClO_4$ (0.02 *M*) + 1 ml $NaClO_4$ (2 *M*) + 0.5 ml H_2O + 0.5 ml metal solution (0.02 *M*) + 10 ml ligand (0.01 *M*) + 5 ml dioxan.

In other sets a requisite amount of $NaClO_4$ was added to maintain the ionic strength at $\mu = 0.15\ M$, 0.05 *M* and 0.02 *M*. From the titration curves of solutions (i), (ii) and (iii) the values of $\bar{n}$ and pL have been calculated using an IBM 360 computer (Fortran-IV). The corresponding values of stability constants have been calculated using the weighted least-squares method of *Sullivan* et al. [8]. The weighted least squares treatment determines that the set of β_n values which makes the function

$$U\left[U = \sum_{n=0}^{N} (y - x - nz)\,\beta_n x^n\right] \tag{1}$$

nearest to zero by minimizing

$$S\left[S = \sum_{i=1}^{I} U^2(x_i y_i z_i)\right] \tag{2}$$

with respect to the variation in β_n.

The function (2) minimized, designated "S_{min}", has the same statistical distribution as "χ^2" with *K* degrees of freedom and with weights defined in accordance with *Rydberg* and *Sullivan* [9]. It can be equated to "χ^2". We report the S_{min} values for the different metal complexes. The *pKa* values and metal-ligand formation constants thus calculated are given in Tables 1–4.

Results and Discussion

Complexes of lanthanons with *LAMI* show an increase in stability from lanthanum(III) to holmium(III) in agreement with increasing acidity of the metal ion. The order of stability constants for the first and second steps in the formation of lanthanide complexes with *LAMI* has been found to be:

$$La < Pr < Nd < Sm < Y < Tb < Dy < Ho$$

Table 1. *Stability constants of lanthanon complexes with LAMI in 75% (v/v) dioxan-water media at* $\mu = 0.15\ M$ $NaClO_4$ *and* $T = 30 \pm 0.5\,°C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	12.53	—	—	—
La(III)	9.11	8.28	17.39	0.0453
Pr(III)	9.63	9.12	18.75	0.0174
Nd(III)	9.67	9.27	18.94	0.0021
Sm(III)	9.72	9.40	19.12	0.0112
Y(III)	9.87	9.32	19.19	0.0192
Tb(III)	10.26	8.96	19.22	0.0152
Dy(III)	10.37	8.81	19.18	0.0400
Ho(III)	10.35	9.39	19.74	0.3058

Table 2. *Stability constants of lanthanon complexes with LAMI in 75% (v/v) dioxan-water media at* $\mu = 0.1\ M$ $NaClO_4$ *and* $T = 30 \pm 0.5\,°C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	12.78	—	—	—
La(III)	9.55	8.29	17.84	0.0770
Pr(III)	10.07	8.75	18.82	0.0138
Nd(III)	10.12	8.82	18.94	0.0175
Sm(III)	10.18	8.99	19.17	0.0037
Y(III)	10.20	9.25	19.45	0.0040
Tb(III)	10.43	9.44	19.87	0.0038
Dy(III)	10.45	9.86	20.31	0.0040
Ho(III)	10.64	9.87	20.51	1.7655

Table 3. *Stability constants of lanthanon complexes with LAMI in 75% (v/v) dioxan-water media at* $\mu = 0.05\ M$ $NaClO_4$ *and* $T = 30 \pm 0.5\,°C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	13.10	—	—	—
La(III)	9.80	7.98	17.78	0.0264
Pr(III)	10.09	7.92	18.01	0.0165
Nd(III)	10.26	8.62	18.88	0.0122
Sm(III)	10.28	8.62	18.90	0.1228
Y(III)	10.53	8.63	19.16	0.0386
Tb(III)	10.69	9.08	19.77	0.1615
Dy(III)	10.83	9.25	20.08	0.4493
Ho(III)	10.94	9.50	20.44	0.7924

Table 4. *Stability constants of lanthanon complexes with LAMI in 75% (v/v) dioxan-water media at* $\mu = 0.02\ M$ $NaClO_4$ *and* $T = 30 \pm 0.5\,°C$

Metal ion	Weighted least-squares method			S_{min}
	$\log K_1$	$\log K_2$	$\log \beta_2$	
H^+	13.36	—	—	—
La(III)	9.92	8.97	18.89	0.0017
Pr(III)	10.13	9.28	19.41	0.0021
Nd(III)	10.34	9.70	20.04	0.0060
Sm(III)	10.45	9.73	20.18	0.1105
Y(III)	10.55	9.45	20.00	0.1471
Tb(III)	10.70	9.51	20.21	1.1350
Dy(III)	10.88	9.72	20.60	0.1770
Ho(III)	11.12	9.64	20.76	0.2895

The same trend has also been noticed in the complexes of α-imino-diacetic acid, α-hydroxy-isobutyric acid, nitrilotriacetic acid, ethylenediamine-N,N,N′,N′-tetraacetic acid, tropolone, β-isopropyltropolone [10], *cis*-1,2,3,4-cyclopentane-tetracarboxylic acid [11] and 4,5-dimethyl-2-hydroxy-acetophenone [12].

The log K_1 values for yttrium lie near to terbium because of the lack of ligand field stabilization. The stability constants of the complexes are found to decrease with increasing ionic strengths of the medium which is in agreement with the *Debye-Hückel* equation [13].

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