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DETERMINATION OF THE STABILITY CONSTANTS FOR THE OMPLEXES OF RARE EARTH ELEMENTS AND TETRACYCLINE

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Stability constants for the lanthanide elements complexes with tetracycline were determined by the methods of average number of ligands, the two parameters and by weighted least squares. The technique of solvent extraction was applied to obtain the values of the parameters required for the determination of the constants.

Introduction

t has been shown that rare-earth elements and the antibiotic tetracycline hydro-ride (TC) form complex compounds extractable into benzyl alcohol.[1–3] Separa- procedures for the lanthanides, uranium, thorium and scandium were devised g TC dissolved in benzyl alcohol, as extractant agent.[2,3] In this paper the de-ination of the stability constants for the rare-earth elements and TC was car- out for the 15 lanthanide elements (except promethium) using solvent extrac- technique and labelled radioisotopes solutions for the determination of distri-ion ratios D. The constants were calculated by the methods of average number igands, two parameters and weighted least squares.[4]

lost of the works on complexes of tetracycline have been carried out along the of devising separation procedures for some metallic elements, preparation of plexes of radioelements for clinical applications and for determination of sta- constants of tetracycline and some metals in order to correlate these values the biological activity of the ligand used as antibiotic.[5]

OLUISIO and MARTIN,[6] favoured the explanation that the biologically active atives form 2 : 1 complexes, i.e., two ligands for each metal ion of copper, el and zinc. The inactive derivatives would form 1 : 1 complexes. However,

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BENET and GOYAN[7] when determining the stability constants of tetracycline and the derivatives chlorotetracycline, dimethylchlorotetracycline, 4-epichlorotetracycline and 4-epianhydrotetracycline with copper ions, concluded that the biological inactive tetracyclines form complexes with two ligand molecules for each copper ion.

Stability constants for the complexes of the various tetracycline and bivalent ions of Mg, Ca, Sr, Ba, Mn, Co, Ni, Cu, Zn and Cd were determined by SILVA and DIAS[5,8] who have shown that the bacteriostatic action of tetracycline is correlated with complex formation capability.

ALBERT and REES[9] determined the stability constants for tetracycline and the trivalent ions Fe and Al and for the bivalent ions Cu, Ni, Fe, Co, Zn and Mn. SAKAGUCHI et al.[10] determined the constants for the ions Fe^{3+}, Zr^{4+}, Th^{4+}, UO_2^{2+}, Al^{3+} and Mg^{2+}.

Complexes of tetracycline and the lanthanide elements have been used by TUBIS and MORRISON[11] for the examination of brain tumors. Such complexes allow the use of various radioisotopes with similar chemical and biochemical properties but with rather different nuclear characteristics such as half-lives and energy of emitted radiations.

Theory

To calculate stability constants the following correlation[4] was used

$$D = I_0/I_a = K_D\ \beta_3\ [A]^3 / \sum_{n=0}^{3} \beta_n\ [A]^n \qquad (1)$$

where
- D – the distribution ratio of the lanthanide;
- I_0 and I_a – the activities of the radioelements in the organic and aqueous phases, respectively;
- K_D – the distribution constant of the complex MA_3;
- $[A]$ – the concentration of the ligand ion in the aqueous phase;
- β_n $(n = 1, 2, 3)$ – the formation constants for the complexes MA, MA_2, MA_3 (charges are omitted for simplicity).

By using labelled radioelements the concentrations of the metal can be made much smaller than the initial concentration of the ligand. The amount of ligand in the complex molecule can thus be ignored and the following mass balance correlation will prevail

$$V_0\ C_0 = [HA]_0\ V_0 + ([HA] + [A])\ V \qquad (2)$$

V_0 and V – the volumes of organic and aqueous phases, respectively;
C_0 – the initial concentration of tetracycline in the organic phase;
$[HA]_0$ – the concentration of tetracycline in the organic phase, after equilibrium;
$[HA]$ and $[A]$ – the concentrations of the ligand in the aqueous phase, after equilibrium;
(organic phase is indicated by sub-index o; no sub-indexes in the concentration formulae indicate aqueous phase).

r the pH values used in the present work (smaller than 5.50) tetracycline is as a monoacid,[1,2] that is the dissociation of the second and third hydrogen sidered as very small.
(2) can be rearranged to give

$$V_0\ C_0 = [A]\ [H]\ (1 + K_a/[H])\ (V_0\ D'/V + 1)\ V/K_a \qquad (3)$$

D' – the distribution ratio for the ligand;
K_a – the first ionization constant, i.e.,

$$D' = [HA]_0/([HA] + [A])$$

$$K_a = [H]\ [A]/[HA]$$

m Eq. (3) one has

$$pA = pK_a - pH - \lg\ C_0/(1 + K_a\,[H]^{-1})\ (1 + D'\ V_0\ V^{-1})\ V/V_0 \qquad (4)$$

lation *of the stability constants*

erage number method. The application of the average number method or m's method, was made through the use of the equations[4]

$$\bar{n} = 3 + d\ \lg\ D/dpA \qquad (5)$$

$$\bar{n} + \beta_1\ [A]\ (\bar{n} - 1) + \beta_2\,[A]^2\ (\bar{n} - 2) + \beta_3\,[A]^3\ (\bar{n} - 3) = 0 \qquad (6)$$

$\bar{n}$ is the average number of ligands. Experimental values of $\bar{n}$ and [A] substituted in Eq. (6) will give a linear system of equations through which the values of the constants β_1, β_2 and β_3 can be determined.

Two parameters method. The Dyrssen-Sillén method of two parameters was applied by using the following equations[4]

$$\lg \beta_n = a\ n + b\ n\ (3 - n) \tag{7}$$

The parameters a and b are defined by

$$\lg \beta_3 = 3\ a$$

$$\lg k_n - \lg k_{n+1} = 2\ b = 2 \lg \alpha \tag{8}$$

k_n (n = 1, 2, 3) are the consecutive stability constants. The graph of $(\lg D - \lg K_D)$ versus $\lg y = \lg [A] + a$ was prepared using the following equation for various values of b:

$$\lg D = \lg K_D + 3 \lg y - \lg \sum_{n=0}^{3} y^n\ \alpha^{n(3-n)} \tag{9}$$

By placing the templet so obtained over the experimental curve of lg D versus pA, the value of b is determined from the best curve in the templet that coincides with the experimental curve. a is equal to pA for $\lg y = 0$, for the best curve indicated previously by using the templet. The values of b and a are then used in Eq. (7) for calculation of β_n.

Least squares method. Eq. (1) can be rearranged to give

$$Z = \sum_{n=0}^{3} a_n\ [A]^n \tag{10}$$

where $$Z = [A]^3\ D^{-1} \qquad \text{and} \qquad a_n = \beta_n / K_D\ \beta_3 \tag{11}$$

Eq. (10) is solved for the a_n values by the method of weighted least squares using digital computers. In this method the parameters a_n are calculated in such a way as to minimize R in

$$R = \sum_{i=0}^{I} w_i \left(\sum_{n=0}^{3} a_n\ [A]_i^n - Z_i \right)^2 \tag{12}$$

The weight w_i is taken as being

$$w_i = 1/\sigma_i^2 \tag{13}$$

which σ_i^2 is the variance of the measurement Z_i. For calculation of the variance, e errors taken into account are the ones in the values of the distribution ratio nd in the values of the concentration of free ligand [A]. This last error was en as being equal to the error in the measurement of the pH of the aqueous se.[13] Errors in the determination of the distribution ratio D were calculated by ns of the standard deviations of counting of organic and aqueous phase, taken the square root of the accumulated number of counts divided by the counting e.

To solve Eq. (10) by the least squares method a program for the IBM/370 Mod-155 computer was prepared.[14] When the parameters a_n occur with negative es or when their standard deviations are larger than the corresponding a_n values, e computer program discards such values for a_n and recalculates a new set of es for the remaining a_n. In these cases the corresponding values of β_n are not orted, but only the product of the consecutive constants are registered. The values β_n and k_n as function of a_n are

$$\beta_n = a_n/a_0 \tag{14}$$

$$k_n = a_n/a_{n-1} \tag{15}$$

Experimental

paration of solutions

Tetracycline solutions. Fresh TC (Laborterápica Bristol) solutions were prepared ry day since the ligand molecules decompose in aqueous solution at room tem-rature. Solutions were used within six hours after preparation. Analytical grade nzyl alcohol (Carlo Erba) was used as organic phase for dissolution of TC. The ganic solvent was previously equilibrated with distilled water from a quartz appa-us and vice-versa, aqueous phase was previously equilibrated with benzyl alcohol.

Lanthanide solutions. The lanthanide oxides (La and Ce from the Britis Drug use Ltd and the other lanthanides from Johnson Matthey Chemicals Ltd) were diated in a thermal neutron flux corresponding to $5 \cdot 10^{12}$ n · cm^{-2} · sec^{-1} for ime from half an hour to eight hours, depending of the radioelement to be ob-ned. After irradiation the oxides were dissolved with drops of analytical grade

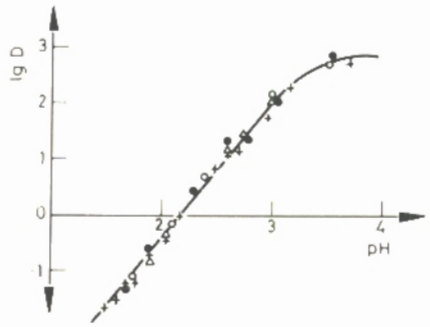


Fig. 1. Distribution ratio of Tb versus pH. [TC] : $C_0 = 0.010$M; [Tb]: △ – $1.0 \cdot 10^{-5}$ M; + 2.0·1
○ – $4.0 \cdot 10^{-5}$ M; ● – $1.0 \cdot 10^{-4}$ M

perchloric acid (Merck) at 20%, with gentle heating and then diluted to obtain a final concentration corresponding to $2.0 \cdot 10^{-4}$ M in the lanthanide elements. Dissolution of cerium oxide required some drops of hydrogen peroxide (Baker P. A.) besides the perchloric acid.

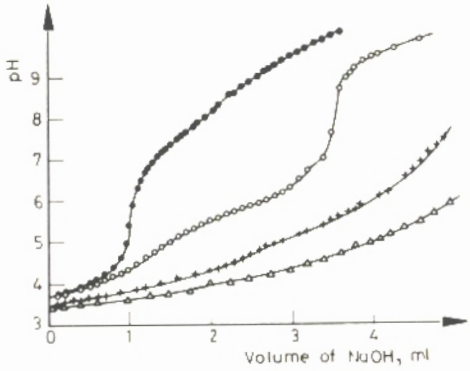
Sodium perchlorate stock solutions. They were prepared by adding perchloric acid to sodium hydroxide (Carlo Erba P. A.) solutions.

Buffer solutions for pH standardization. The buffer solutions were prepared in accordance with LANGE,[15] using potassium biphthlate (Baker P. A.) and potassium chloride (Baker P. A.).

Complex formation and extraction

To show that the metal extracted into the organic phase is bonded to the tetracycline molecule, the radioactive lanthanide solution at ionic strenght corresponding to 0.10M in $NaClO_4$ was contacted with pure benzyl alcohol at various pH values. No activity was detected in the organic phase (benzyl alcohol only) showing that the extractable species was the lanthanide-tetracycline complex.

Type of complexes formed. In order to check if polynuclear complexes would be formed, the distribution ratios D were determined for various concentrations of the lanthanide element (terbium). Concentration of TC was maintained constant and the one for the lanthanide element was made to vary as function of pH. Temperature was maintained at 25 °C±0.5 °C and ionic strenght corresponded to 0.10M in $NaClO_4$. Results are presented in Fig. 1. A statistical F test applied to the data showed that all curves, for the four different concentrations of terbium, are coincidents at a confidence level of 95%. This means that the distribution ratio



2. Potentiometric titration of TC 0.010M with NaOH 0.010M. Relation La–TC: • – no La; ○ – 1 : 1; + – 1 : 2; △ – 1 : 3

re independent of the concentration of the metallic element in the interval range 10^{-5} to 10^{-4} M and that only mononuclear complexes are formed.[4]

The ionization constants for TC, required for the calculation of pA values by mula (4), were determined by potentiometry at 25 °C ± 0.5 °C and ionic strength responding to 0.10M in $NaClO_4$, Fig. 2. In Table 1 are presented the results ob- ed as well as literature values. D′ values, also required for the calculation of pA es, were determined by spectrophotometric measurements of the distribution of between benzyl alcohol and aqueous solution of $NaClO_4$, 0.10M, Fig. 3.

Eventual formation of complexes with the formula $MA_n(OH)_p$ and $MA_n(OH)_p(HA)$ negatively charged complexes besides the mononuclear species MA_n, was checked

Table 1
Macroscopic ionization constants for tetracycline

pK_{a1}	pK_{a2}	pK_{a3}	Ionic strength, μ	Temperature, °C	References
3.35	7.82	9.57	0.01M	20	(7)
3.30	7.68	9.69	0	25	(16)
3.33	7.75	9.61	*	25	(16)
3.42	7.52	9.07	0.1M KNO_3	25	(8)
3.69	7.63	9.24	0.01M	30	(6)
3.33	7.70	9.50	0.01M	25	(7)
3.39	7.44	8.85	0.10M $NaClO_4$	25	*(this work)*

*Not indicated.

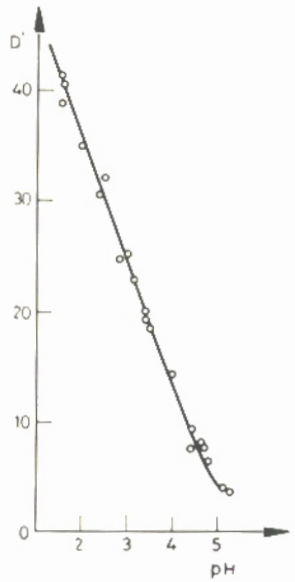


Fig. 3. Distribution ratio of TC versus pH

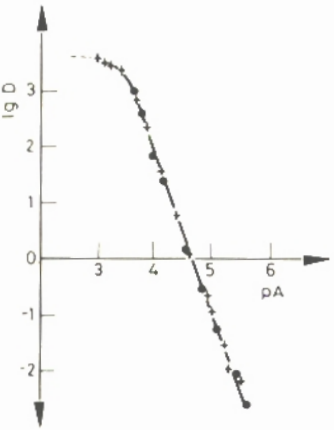
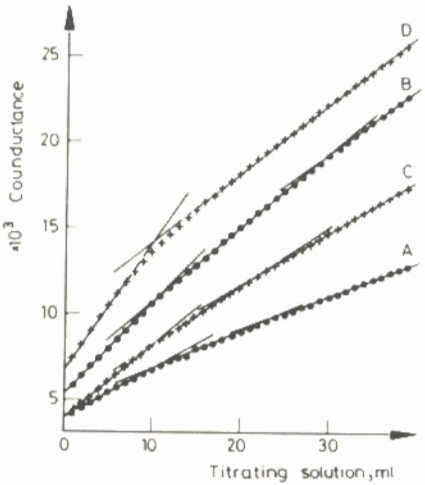


Fig. 4. Distribution ratio of Tb versus pA. [Tb] = $2.0 \cdot 10^{-5}$ M; [TC] : C_o = 0.010M (+);(

by determining the distribution ratios D for terbium as function of pA for t ferent concentrations of TC. Results are presented in Fig. 4. From Fig. 4 it *that the distribution ratio D varies with pA and it is independent of the initi* concentrations, that is, the distribution follows Eq. (1), indicating non-existen



5. Conductimetric titrations of TC and ATC. Curves A and C – 10 ml $LaCl_3$, 0.010M + 20 ml of water. Titrating solutions: TC 0.010M (A) and ATC 0.010M (C). Curves B and D – 30 ml of TC solution 0.010M (B); 30 ml of ATC solution 0.010M (D). Titrating solution: $LaCl_3$ 0.010M

droxycomplexes, negatively charged complexes or complexes of the type $A_n(OH)_p(HA)_r$.[4] The same set of experiments were carried out for europium d thullium with the same results indicating the formation of complexes of the A_n type. In fact hydroxycomplexes should not be formed, as verified, since drolysis of rare-earths ions does not occur at pH values smaller than 5.50.[17,18] The formation of the MA_n type of complexes was crosschecked by conductitric titrations of tetracycline and lanthanum. Experiments were carried out at e temperature of 25 °C ± 0.5 °C. Total volume of solution to be titrated was ual to 30 ml. The titrating solution was added in volume fractions equal to 1 ml. sults are indicated in Fig. 5 for the element lanthanum. Curve A shows the foration of 1 : 1 species (MA) and 1 : 2 (MA_2). In curve B it is shown the formaon of 1 : 1 and 1 : 3 species.

Complexation position in the tetracycline molecule. TC has three ionizable hydrogens corresponding to the tricarbonylmethane group, $pK_{a1} = 3.30$; phenolic dike-, $pK_{a2} = 7.68$; and dimethylamino, $pK_{a3} = 9.63$.[16]

Complexation position for the lanthanide ions was determined by potentiometric d conductimetric titrations, as well as by infrared absorption spectrophotometry. sults for TC potentiometric titration with sodium hydroxide solutions, in presence d in absence of lanthanum ions are shown in Fig. 2. It can be seen that the in-

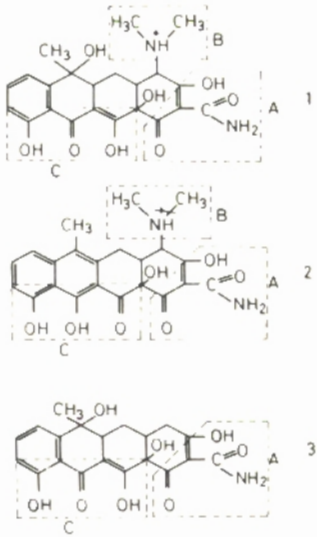


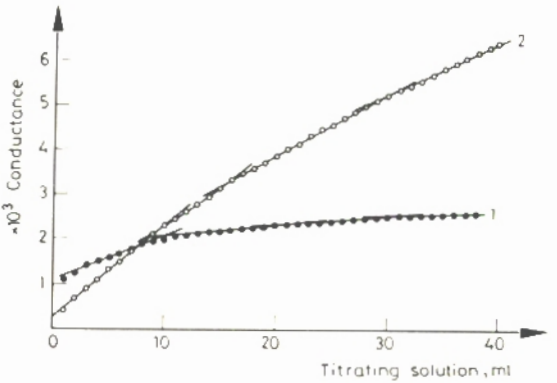
Fig. 6. Formulae: 1 – TC; 2 – ATC; 3 – DTC

crease of pH on titrating TC–La is less pronounced than when titration is carried out in absence of lanthanum. This indicates formation of the complex by the tricarbonylmethane group, since this group is the one that dissociates at pH values smaller than 5.50.

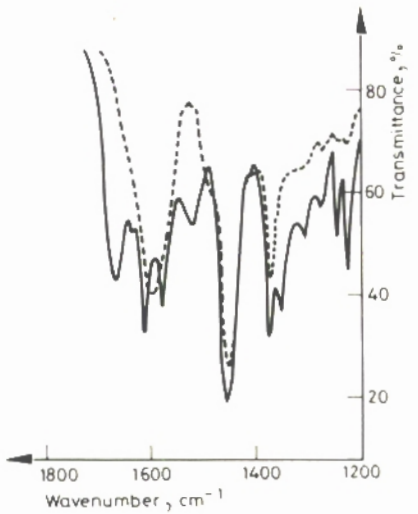
For conductimetric titrations, two tetracycline derivatives (anhydrotetracycline ATC and dedimethylamine-tetracycline DTC, Fig. 6 were used as well as the TC ligand. TC and ATC were titrated in aqueous solutions and DTC in methanol since its solubility in water is rather small. Formation of complexes with a relation metal: ligand equal to 1 : 1, 1 : 2 and 1 : 3 was thus confirmed, Figs 5 and 7. It is thus seen that the lanthanide is not coordinated through the nitrogen of group B (dimethylamino) since this group is not present in the DTC. The same conclusion was reached by solvent extraction technique since the compounds formed with ATC and DTC are both extractable into benzyl alcohol.

Absorption infrared spectra of TC and of La–TC were made. Both compounds were emulsified in mineral oil (Nujol). The La–TC solid compound was prepared in accordance with BAKER and BROWN.[19] The spectra showed the following characteristics:

(a) TC and La–TC have the same absorption bands in the interval from 200 to 1500 cm^{-1}.



7. Conductimetric titration of DTC. Curves: 1 – 10 ml of $LaCl_3$ 0.010M + 20 ml methanol. Titration with DTC 0.010M. 2 – 30 ml DTC 0.010M. Titration with $LaCl_3$ 0.010M



8. Infrared absorption spectrum of TC and La – TC. Curves: TC – full line, La – TC – dotted line

b) The compound La–TC obtained at pH = 3.0 and the one obtained at 4.5 are the same and both have water molecules in their structures.

c) TC presents three absorption bands at 1580, 1610 and 1670 cm^{-1} which not present in the spectrum of La–TC; instead a large band, at approximately 0 cm^{-1}, is presented by La–TC (Fig. 8). Since the absorption corresponding

to the value at 1600 cm^{-1} is due to the vibration of the group –C=O it is seen that lanthanum is linked to the TC molecule by the tricarbonyl methane group.

Based on all information obtained from potentiometric and conductimetric titrations for TC, ATC and DTC, as well as the information from the absoption spectra in the infrared region for the solid compound La–TC, it is seen that the complexation of the lanthanide is through the hydrogen position of the tricarbonylmethane group in the TC molecule and whose termodynamic ionization constant is $10^{-3.30}$, that is $pK_a = 3.30$, at 25 °C.

WILLIAMSON and EVERETT[20] have also shown, by nuclear magnetic ressonance that the trivalent ions of Nd, Tb, La, V and the bivalent ones Cu, Mn, Co, Ca and Mg are linked to the TC molecule by the tricarbonylmethane group.

Determination of distribution ratios. The extraction systems consisted of 5 ml of benzyl alcohol and 5 ml of aqueous labelled lanthanide solution with ionic strength corresponding to 0.10M sodium perchlorate. Concentration of TC in the organic solvent varied from 10^{-3} to 10^{-2} M and of the metal ion in the aqueous phase from 10^{-5} to 10^{-4} M. pH of the aqueous phase was adjusted by adding diluted solutions of perchloric acid or sodium hydroxide. pH measurements were carried out with a scale reading of 0.05 units. pH values in which extractions were made were always smaller than 5.50.

The phases were equilibrated at 25 °C ± 0.5 °C by shaking in a mechanical stirrer for the desired time. Results were reproducible for a shaking time from a few minutes up to 10 hrs, which was the maximum time at which equilibrium conditions were examined. A standard 30 min shaking time was adopted. After equilibration the phases were separated by centrifugation at 3500 rpm for 5 min. Aliquots of each phase were taken and counted using a well-type NaI(Tl) scintillation counter 7 X 7 cm, coupled to a multichannel analyser. The area under the main peaks for each radioisotope were evaluated by using a minicomputer on line with the analyser. Background counting was subtracted in each case and the net counting rate and the corresponding standard deviation were calculated by using a program in BASIC language. Each counting was reported to zero time.

Results and discussion

The curve of lg D versus the atomic number of the lanthanide for a pH equal to 2.45 and initial TC concentration equal to 0.010M is presented in Fig. 9.

From the graph of lg D versus atomic number of the lanthanide elements presented in Fig. 9, it is seen that, also for this system, the double-double effect (FIDELIS and SIEKIERSKI[21]) or tetrad effect (PEPPARD et al.[22]) is present.

e sets of curves have, as usual, an intercept between neodymium and promethium; e second intercept is at gadolinium, which is a common point for the second d third part of the curves; the third intercepts lies between holmium and erbium. e positions of these intercepts are the same as for other ligands and the lantha-ides.[21,22]

Values for the stability constants are presented in Tables 2, 3 and 4. In these bles β_n are the stability constants and k_n the consecutive equilibrium constants

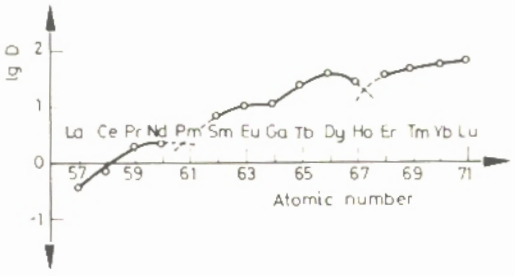


Fig. 9. Lg D versus atomic number of lanthanides

r the MA_n complexes. The constants β_n are expressed in units corresponding to itre)^n/(mol)^n and the constants k_n in units (litre)/(mol).

The calculation of lg β_2 by the least squares method, was not performed by e computer program since the value of a_2 was rejected by the program as a con-quence of a too large standard deviation for a_2 or a negative value for a_2. A new t of values for a_0, a_1 and a_3 was recalculated by the computer program and in is way instead of β_2 values the product k_2k_3 is reported. β_2 values were also not lculated by the average number of ligands since these values occurred with nega-e signs.

The omission of the a_2 parameter in the least squares calculations does not nec-sarily means that the corresponding complex does not exist, but only that the ability constant cannot be calculated because of uncertainties in the corresponding perimental data, probably because the concentration of MA_2 is not high enough influence the measurements.

The difficulty encountered in calculation β_2 by the average number of ligands ay also supports the conclusion that the calculation of this value is dubious.

The two parameters method makes the assumption that the ratio of adjacent mplexity constants is the same throughout a series of complexes of a metal ion and a ligand A. This approximation has proved helpful in systems where the

Table 2
Stability constants for the complexes of lanthanides with tetracycline determined by the average number method

Element	$\lg \beta_1$	$\lg k_2 \cdot k_3$	$\lg \beta_3$
La	2.82	6.08	8.90
Ce	3.10	6.32	9.42
Pr	3.59	6.52	10.11
Nd	3.62	6.22	9.84
Sm	3.45	6.78	10.23
Eu	3.53	6.38	9.91
Gd	3.60	6.64	10.24
Tb	3.78	6.81	10.59
Dy	3.72	6.82	10.54
Ho	3.53	6.88	10.41
Er	3.71	7.01	10.72
Tm	3.99	6.77	10.76
Yb	4.26	6.69	10.95
Lu	4.20	6.22	10.42

Table 3
Stability constants for the complexes of lanthanides with tetracycline determined by the two parameters method

Element	$\lg \beta_1$	$\lg \beta_2$	$\lg \beta_3$
La	2.95	5.90	8.85
Ce	3.10	6.20	9.30
Pr	3.25	6.50	9.75
Nd	3.20	6.40	9.60
Sm	3.30	6.60	9.90
Eu	3.35	6.70	10.05
Gd	3.35	6.70	10.05
Tb	3.45	6.90	10.35
Dy	3.45	6.90	10.35
Ho	3.50	7.00	10.50
Er	3.65	7.30	10.95
Tm	3.70	7.40	11.10
Yb	3.55	7.10	10.65
Lu	3.50	7.00	10.50

Table 4
Stability constants for the complexes of lanthanides with tetracycline determined by the least squares method

Element	$\lg \beta_1$	$\lg k_2 \cdot k_3$	$\lg \beta_3$
La	3.50 ± 0.16	5.84 ± 0.26	9.35 ± 0.22
Ce	3.31 ± 0.24	6.16 ± 0.30	9.47 ± 0.22
Pr	2.86 ± 0.12	7.45 ± 0.24	10.32 ± 0.18
Nd	2.92 ± 0.38	6.67 ± 0.41	9.59 ± 0.15
Sm	2.81 ± 0.77	7.20 ± 0.78	10.01 ± 0.14
Eu	3.97 ± 0.14	5.93 ± 0.38	9.90 ± 0.37
Gd	3.79 ± 0.14	6.53 ± 0.17	10.32 ± 0.13
Tb	3.78 ± 0.19	6.73 ± 0.23	10.52 ± 0.15
Dy	2.70 ± 0.59	7.72 ± 0.59	10.43 ± 0.06
Ho	3.53 ± 0.33	7.26 ± 0.33	10.79 ± 0.12
Er	3.73 ± 0.21	7.14 ± 0.22	10.87 ± 0.11
Tm	4.26 ± 0.10	6.78 ± 0.12	11.05 ± 0.08
Yb	3.55 ± 0.35	7.33 ± 0.44	10.88 ± 0.27
Lu	4.48 ± 0.09	6.36 ± 0.11	10.84 ± 0.11

are not accurate enough to allow a separate determination of all consecutive ilibrium constants, DYRSSEN and SILLÉN.[23] The small concentration of MA_2 ies would not give accurate enough data for application of the average number igands as well as for the application of least squares method, for β_2 determina-, but the mentioned approximation of the two parameters method will be help- for the evaluation of an approximate value for β_2.

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