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4,5,6,7-Tetrahydroindazol-3-one Carboxylic Acids. IV. Acid Dissociation Constants and Complex Formation with Calcium, Strontium and Barium

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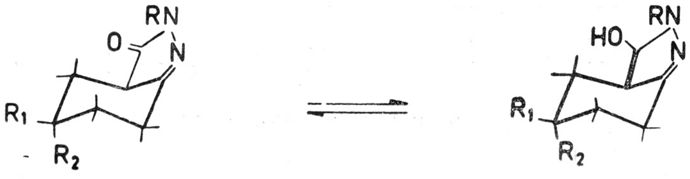
The dissociation constants of 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (I, FIDA) and its stability constants with alkaline earth ions are reported. FIDA was first tested for toxicity by the »up-and down« method.

In connection with the determination and the interpretation of *p*K values of tetrahydroindazolone carboxylic acids and their ethyl esters I — VII the potentiometric titration procedure is described. The same procedure and apparatus were used for the potentiometric titration in the presence of metals.

FIDA was shown to be an excellent reagent for the separation of barium from strontium.

In previous papers of this series[1-3] the preparation and some properties of indazol-3-one carboxylic acids have been described. The same compounds were shown to be useful for sterically controlled synthesis of cyclohexylamines. 2-Phenyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylic acid (I, FIDA) having one axial carboxy group also indicated a tendency for forming complexes. The present investigation is dealing with the property of this compound to form complexes with calcium, strontium and barium ions.



I. $R_1 = R_2 =$ COOET, R = Ph
II. $R_1 = R_2 =$ COOET, R = Ph
III. $R_1 =$ COOH, $R_2 =$ H, R = Ph
IV. $R_1 =$ COOEt, $R_2 =$ H, R = Ph
V. $R_1 = R_2 =$ COOEt, R = H
VI. $R_1 =$ COOH, $R_2 =$ R = H
VII. $R_1 =$ COOEt, $R_2 =$ R = H

In order to estimate the relative effects of functional groups in the molecule of indazolone carboxylic acid we found it convenient to study their proton dissociation constants and stability constants of their metal chelates. Furthermore, the significance and possible biological application of these compounds for sequestering of metals prompted us to test their toxicity.

The »up-and down« method[4] was adopted to test the toxicity of the disodium salt of FIDA (hydrate form). The lethal dose (LD_{50}) was 3.48 ± 0.1 g./kg.

In order to determine the true dissociation constants[5] of indazolone carboxylic acids I, III, VI and corresponding ethyl esters II, IV, V, VII the potentiometric method was very applicable resulting strictly comparable and characteristic data for all dissociable groups (Table I). The obtained values can be compared with apparent dissociation constants extrapolated to zero ionic strength, since the ionic strengths of the dioxane — water solutions at the end of the titration were less than 0.002. Calculation of all pK values followed the well known relation[6,7]:

$$pK = pH + \log [HA] - \log [A] \qquad (1)$$

where [HA] and [A] are the concentrations of titrated indazolones and its conjugate base respectively. The results are given in Table I.

TABLE I

Compound	*e*-COOH (pK_1)	*a*-COOH (pK_2)	enol (pK_3)	C $10^{-3}M$	H_2O to $O(CH_2CH_2)_2O$
I	5.05	7.66	9.84	1.87	1 : 1
II	—	—	8.31	2.47	1 : 1
	—	—	7.49	2.44	4 : 1
III	6.15	—	9.15	1.55	1 : 1
	5.07	—	8.33	1.77	4 : 1
IV	—	—	8.61	2.41	1 : 1
	—	—	7.93	2.41	3 : 1
V	—	—	9.69	2.27	1 : 1
	—	—	8.85	2.43	3 : 1
VI	6.45	—	10.44	2.96	1 : 1
	5.31	—	9.64	2.34	3 : 1
	4.48	—	9.06	3.12	H_2O only
VII	—	—	9.89	1.85	1 : 1
Malonic acid	(4.16)	(8.20)	—	1.04	1 : 1
	(2.99)	(5.62)	—	3.99	H_2O only

The dissociation constants listed in the Table I revealed the contribution of the heterocyclic ring to the pK values of carboxy groups and vice versa. Namely, the difference between the first and the second dissociation constant of the malonic acid ($\Delta\, pK_{1-2} = 4.04$) in the lower pH range is larger than the difference in the corresponding constants of I ($\Delta\, pK_{1-2} = 2.61$). Due to greater hindrance to solvation in the axial ions, the equatorial carboxy group of FIDA (I) might be expected to be more acidic having a larger dissociation constant (pK = 5.05) than the axial one (pK = 7.66).

Since the conformational equilibria of polar ring compounds are functions of temperature and polarity of solvents the alicyclic ring of 4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (VI, IMA) could exist partly in the boat conformation. Consequently, the quasi axial 5-carboxy group in the boat conformation trends to be very close to the heterocyclic ring causing deformation of its nonbonding electron cloud. The more restricted puckering of the alicyclic ring of 2-phenyl-4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (III, FIMA) as well as the marked change in the electronic configuration of its heterocyclic ring could influence the extent of this susceptibility. This is expressed by the larger difference of pK values in VI ($\Delta\, pK = 3.99$) than in III ($\Delta\, pK = 3.0$). In addition, the dissociation constants of the enols of ethyl indazolone carboxylates II and IV, compared with those of free acids I and III, varied by up to 1.53 and 0.54 pK units respectively reflecting, especially in compound I, exceptional long-range interactions of free carboxy group.

The higher dissociation constants of 2-phenyl derivatives II (pK 8.31) and IV (pK 8.61) than of the 2-unsubstituted indazolones V (pK 9.69) and VII (pK 9.89) results also from a double-tracked enolization of 2-unsubstituted compounds. The dissociation constants of the latter are between two possible limits and the considerably lower lability of the *N*-2 proton in V and in VII cause the lower acidity found.

As we could expect the acidic protons of indazolone carboxylic acids, their esters and malonic acid were more labile in water than in mixed aqueous systems especially when large percentages of dioxane were used (Table I).

The fact that Cu^{++} became appreciably complexed with **FIDA** (I) (Fig. 1) and the promising high LD_{50} value stimulated us to study the interactions of alkaline earth ions with this compound. The results were obtained by a

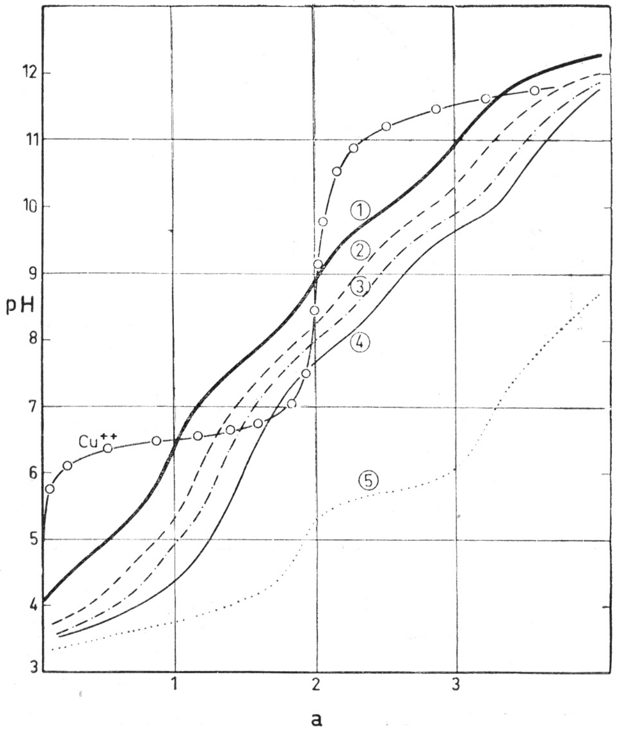


Fig. 1. Potentiometric titration of 1) FIDA, 2) FIDA — Ca^{++} system at molar ratios 5:1, 3) 3:1, 4) 2:1, 5) 1:1.5. Abscissa a = moles of NaOH added per mole of FIDA.

potentiometric titration method and compared with those from potentiometric titrations of malonic acid in the presence of alkaline earth metals. The more marked complexing effects with FIDA than with malonic acid were found mostly at the physiological *p*H range. Although the investigations concerning the interactions of malonic acid with alkaline earth ions have been already described[8,9] for comparison with FIDA (I) we also tested this ligand under appropriate conditions. The titration curves of malonic acid in the absence and in the presence of equimolar amounts of alkaline earth ions indicated small and negligible interactions. FIDA, however, titrated in the absence and in the presence of Ca^{++} (Fig. 2) and Sr^{++} (Fig. 3) clearly demonstrated the formation of metal-ligand species. The titration curves for the 2:1 molar ratio of the ligand to the metal ions showed similarities to that for 1:1 ratio suggesting the simultaneous formation of at least two metal-ligand species.

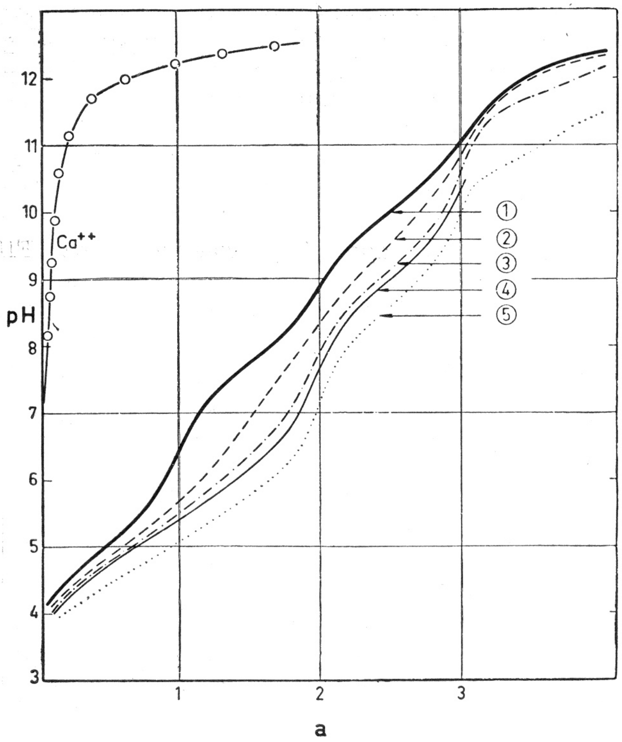


Fig. 2. Potentiometric titration of 1) FIDA, 2) FIDA — Ca^{++} system at molar ratios 2:1, 3) 1:1, 4) 1:1.5, 5) 1:10. Abscissa *a* = moles of NaOH added per mole of FIDA

In order to underline the complexing meaning of FIDA (I) having one carboxy group axially situated FIMA (III) with equatorial carboxy group was subjected also to the potentiometric titrations in the presence of Ca^{++} or Sr^{++}. The titration curves showed a very slight depression when compared with the curves presented in Figs. 2 and 3, thus confirming the complexing property of I.

The calculations of the stability constants $\log K_2^{Me}$ for the 2:1 molar ratio of FIDA to the metals were carried out by the graphical method [10] at $\tilde{n} = 0.5$. The graphical method described by Schwarzenbach and Ackermann[11] was followed for the 1:10 molar ratio. The results are given in Table II. Although the concentration of admixed FIDA was 20 times higher in the first approach both treatments gave reasonably close values for the stability constants. On the other hand, very close values of the K_{k2}^{Ca} and K_{k2}^{Sr} are the most striking aspects of FIDA-alkaline earth metal interactions. The present data are insufficient for an explanation of these very similar stability constants.

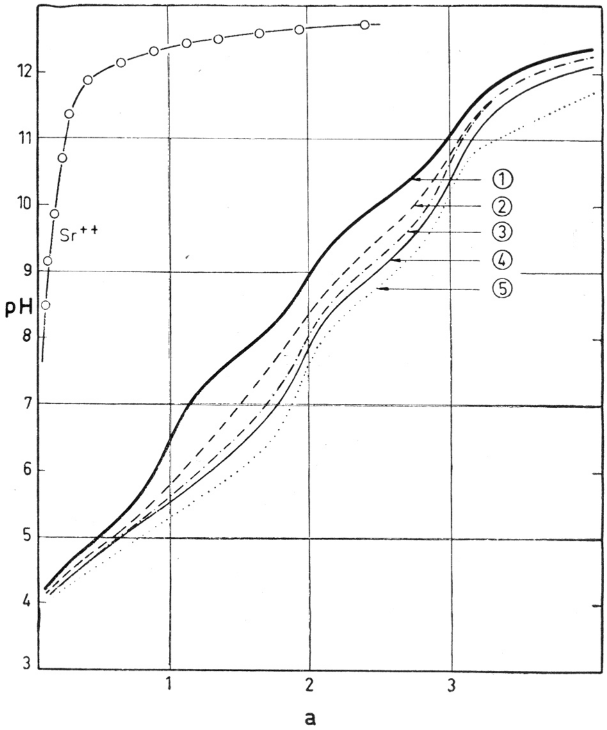
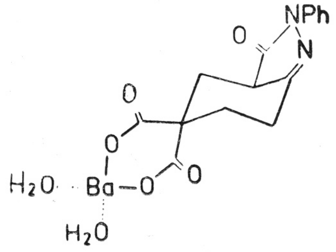


Fig. 3. Potentiometric titration of 1) FIDA, 2) FIDA — Sr++ system at molar ratios 2:1, 3) 1:1, 4) 1:1.5, 5) 1:10. Abscissa a = moles of NaOH added per mole of FIDA

TABLE II

	FIDA to earth alkali metals, molar ratio 2 : 1	FIDA to earth alkali metals, molar ratio 1 : 10
$\log K_{k2}^{Ca}$	4.8	4.6
$\log K_{k2}^{Sr}$	4.5	4.3
$\log K_{k2}^{Ba}$	4.6	4.3

An analogous interaction of FIDA with Ba^{++} was shown in the addition of up to about two moles of base (Fig. 4). At this point a crystalline precipitate appeared and remained until the addition of about three moles of the base (at about *p*H 10.5). The elemental analysis of the dihydrate form of the precipitate confirmed the 1:1 ratio of Ba^{++} to ligand. The structure of the crystalline precipitate is most probably VIII. The formation of VIII made it possible to separate quantitatively Ba^{++} from Sr^{++} or Ca^{++} in water-dioxane solutions. The precipitate was decomposed with dilute hydrochloric acid and separated from reprecipitated crystalline starting FIDA which can then be used for further separations.



VIII.

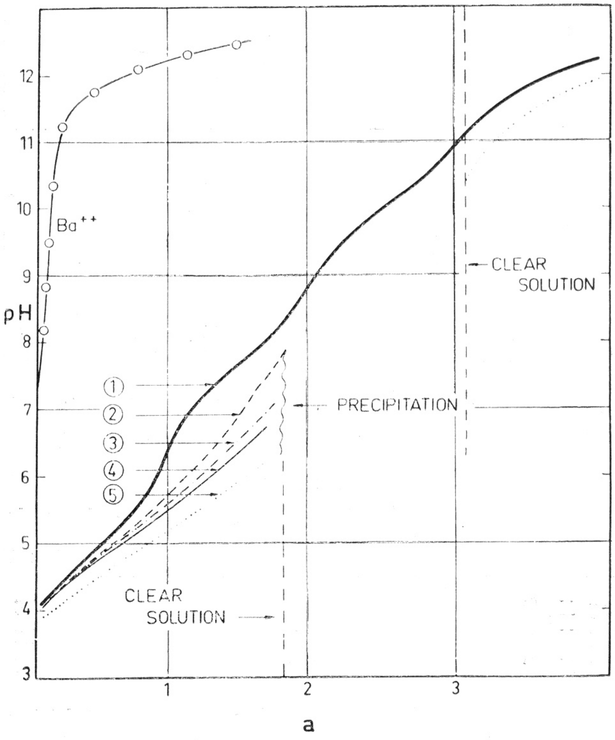


Fig. 4. Potentiometric titration of 1) FIDA, 2) FIDA — Ba^{++} system at molar ratios 2:1, 3) 1:1, 4) 1:1.5, 5) 1:10. Abscisa *a* = moles of NaOH added per mole of FIDA

Titration of malonic acid in the presence of Ba^{++} afforded a gelatinous precipitate not convenient for separation of metals. Different from the precipitate described above it had a 2:1 ratio of Ba^{++} to ligand.

EXPERIMENTAL

Conditions and Apparatus for the Determination Dissociation and Stability Constants

The instrument used for the potentiometric titration was a Radiometer *p*H-meter and mV-meter (type PHM4C) with a universal glass electrode (type G200C) and a micro-calomel reference electrode (type K 1301) with wick-type liquid junction. The *p*H-meter was standardized against Beckman buffers at *p*H 4.01, 6.5 and 9.15. Measurements were carried out at 25.0 ± 0.02^0 in a jacketed titration cell fitted with a stirrrer, nitrogen inlet and outlet tube, microburet »Misco« and electrodes. The titration cell was protected by a Faraday's cage. All solutions were kept under a nitrogen atmosphere purified by means of a KOH--pyrogallol-$Ba(OH)_2$ mixture and stirred throughout the titrations. Standard CO_2-free 0.1 *N* NaOH according to Pregl[12] was employed as the titrant. The solutions (10 ml.) of indazolone used for *p*K determinations were about $2—3 \cdot 10^{-3}$ *M* as listed in Table I. Dioxane was freed from peroxide and freshly distilled. Water was redistilled. Addition of base was made from a 0.4 ml. »Misco« microburet. The tip of the buret was kept below the surface of the titrated solutions.

The titration conditions for the stability constants determination were same as those described for the dissociation constants. The total volume of ligand and metal salt solutions did not exceed 10 ml. All solution were about $10^{-3}M$ in indazolones. After equilibrium *p*H readings had been attained, increments of standardized hydroxide were added. Measurements were carried out in solutions without neutral electrolyte, except when performed in presence of Cu^{++}.

Materials

The indazolone carboxylic acids and their corresponding ethyl esters were prepared in this laboratory[1-3]. The purities of the indazolones were found to be at least 99 percent by potentiometric titration and elemental analysis.

Cupric nitrate (0.05 *M*, 10 ml.) was standardized by an electrogravimetric method[13]. The solution was stabilized with $10^{-5}M$ perchloric acid. An ordinary 100 ml. beaker was used as the cell. The anode (stout platinum) was constructed to fit inside of a concentric platinum gauze cathode 3 cm high with diameter 1 cm. The electrodeposition of copper lasted 90 minutes at a current strength of 140 *m*A.

Analytical grade $Ca(NO_3)_2 \cdot 4\,H_2O$ and $Ba(NO_3)_2$ purchased from Merck and $Sr(NO_3)_2$ from Hopkin and Williams were used to make up stock solutions. The solutions (about 0.1 *M*) in redistilled water were standardized by an ion exchange method[14]. The hydrogen form of Dowex 50-X with a particle size of 100—200 mesh was used as a cation exchanger in a column (6 × 0.8 cm.). The filtrate and washings of salt solutions (10 ml.) containing HNO_3 were titrated with 0.1 *N* NaOH against methyl red.

Interaction of FIDA (I) and FIMA (III) with metals

Complexing with Cu^{++}. — The apparent depression of titration curves of FIDA when interacted with Cu^{++} at 5:1, 3:1, 2:1 and 1:1.5 molar ratios of ligand to metal ion are represented in Fig. 1. The colour of titrating solutions was brown and it deepened slightly with increasing *p*H. Above *p*H 8, where precipitation was observed, the solution did not reach equilibrium immediately at the mentioned ratios. For the 1:1.5 ratio the disturbances appeared at about *p*H 6. FIMA and its corresponding ester interacting with Cu^{++} at the same molar ratios as described above showed no depression when below *p*H 6.

Complexing with Ca^{++} and Sr^{++}. — The interaction of Ca^{++} and Sr^{++} with FIDA at 2:1, 1:1, 1:1.5 and 1:10 molar ratios of the ligand to the metals ions resulted in an evident release of hydrogen ions (Figs. 2 and 3). A slightly smaller depression was evident when Sr^{++} instead of Ca^{++} was used. Precipitation did not occur throughout the titration. The titration curves for 1:1 and 1:10 molar ratios of FIMA to Ca^{++} od Sr^{++} did not show significant depressions.

Complexing and Precipitation of Ba^{++} with FIDA

The depression of titration curves (Fig. 4) resulting from the interaction of Ba^{++} and FIDA at the same molar ratios of the ligand to the metal ion as described in the previous experiment was of the same order of magnitude as for Sr^{++} and Ca^{++}. The appearance of a precipitate did not affect the calculation of the stability constants (at lower *p*H range).

To a solution of FIDA (12 mg., 0.039 *m*mole) in 20 ml. of dioxane (heating may be required in order to effect complete solution) and water (5 ml.) a solution of $Ba(NO_3)_2$ ($4 \cdot 10^{-3} M$, 15 ml.) was added. The mixture was treated with 0.1 *N* NaOH (0.39 ml., 0.039 mmole). The crystalline product separated quantitatively as colourless glistenning needless and was filtered and dried. It decomposed above 300°. The analysis indicated a dihydrate od Ba^{++} to ligand in a 1 to 1 molar ratio.

Anal. $C_{15}H_{16}O_7N_2Ba$ (473.66) calc'd.: C 35.50; H 3.40; N 5.92%
found: C 35.57; H 3.43; N 6.06%

The precipitated crystals treated with 10% hydrochloric acid gave FIDA in quantitative yield, m.p. 254—256°, undepressed on admixture with an autentic sample. IR spectra of both sample were superimposable.

Evaluation of Stability Constants for Alkaline Earth Metals-FIDA Complexes

The stability constants for Ca^{++}, Sr^{++} and Ba^{++} - FIDA complexes in water -dioxane mixtures were calculated from the complexometric titration curves (Figs. 2, 3 and 4).

The stability constants for the interaction of FIDA with alkaline earth ions at molar ratio 2:1 (curves 2) were calculated by the graphical method[10] at $\tilde{n} = 0.5$. Assuming that metal species existed in two forms Me^{++} and MeHA only, the equilibrium in the solution may be expressed by the following equations:

$$H_3A \rightleftarrows H_2A^- + H^+ \qquad K_1^A = \frac{[H_2A^-][H^+]}{[H_3A]} \tag{2}$$

$$H_2A^- \rightleftarrows HA^{2-} + H^+ \qquad K_2^A = \frac{[HA^{2-}][H^+]}{[H_2A^-]} \tag{3}$$

$$Me^{2+} + HA^{2-} \rightleftarrows MeHA \qquad K_{k2}^{MeHA} = \frac{[MeHA]}{[Me^{2+}][HA^{2-}]} \tag{4}$$

In the *p*H range covered the last step of dissociation of FIDA was neglected giving:

$$T_A = [H_3A] + [H_2A^-] + [HA^{2-}] + [MeHA] \tag{5}$$

$$T_{Me} = [Me^{++}] + [MeHA] \tag{6}$$

where T_A and T_{Me} are the total concentrations of the ligand ions species and the metal species respectively.

While the $\tilde{n}$ is the average number of bounded ligand per metal it follows:

$$[MeHA] = \tilde{n}\, T_{Me} \tag{7}$$

$$[Me^{2+}] = (1 - \tilde{n})\, T_{Me} \tag{8}$$

From eqs. (2), (3), (5) and (7) the concentration of ligand species when both carboxy groups are dissociated is:

$$[HA_2^-] = \frac{T_A - \tilde{n}\, T_{Me}}{1 + \frac{[H^+]}{K_2^A} + \frac{[H^+]^2}{K_1^A K_2^A}} \tag{9}$$

On the basis of potentiometric titration data $\tilde{n}$ is calcluated from:

$$\tilde{n} = \frac{T_A}{T_{Me}} - \frac{T_H - [H^+] + [OH^-]}{\tilde{n}_H\, T_{Me}} \tag{10}$$

where T_H is total concentration of hydrogen and $\tilde{n}_H$ the average number of hydrogen bound to ligand. These parameters are defined as:

$$T_H = 2\,T_A - C_{NaOH} \qquad (11)$$

$$\tilde{n}_H = \frac{\dfrac{[H^+]}{K_2^A} + 2\dfrac{[H^+]^2}{K_1^A\,K_2^A}}{1 + \dfrac{[H^+]}{K_2^A} + \dfrac{[H^+]^2}{K_1^A\,K_2^A}} \qquad (12)$$

where C_{NaOH} is the concentration of sodium hydroxide.

The stability constant of the metal complex could be defined then from eqs. (4), (7), and (8) as:

$$K_{k2}^{MeHA} = \frac{\tilde{n}}{1-\tilde{n}}\;\frac{1}{[HA^{2-}]} \qquad (13)$$

It is evident from eq. (13) when $\tilde{n} = 0.5$ the logarithm of stability constant is equal to *-log* HA^{2-}. Thus, the following values were obtained from titration curves of FIDA —Ca^{++}, —Sr^{++} and —Ba^{++} complexes at a molar ratio of 2:1:

$$\log K_{k2}^{Ca} = 4.8$$

$$\log K_{k2}^{Sr} = 4.5$$

$$\log K_{k2}^{Ba} = 4.6$$

Stability constants for complexes of alkaline earth ions with **FIDA** were also evaluated by a different method from potentiometric titration data in dioxane-water (1:1) solutions containing FIDA to metals in 1:10 molar ratio (curve 5 in Figs. 2, 3 and 4). The graphical method used was described by Schwarzenbach and Ackermann[11]. The obtained values for stability constants and the reactions involved are:

$$Ca^{2+} + H_3A \rightleftarrows CaH_2A^+ + H^+$$

$$K_{ac.k1}^{Ca} = \frac{[H^+][CaH_2A^+]}{[Ca^{++}][H_3A]} = 2.3 \times 10^{-3} \qquad (14)$$

$$Ca^{2+} + H_2A^- \rightleftarrows CaH_2A^+$$

$$K_{k1}^{Ca} = \frac{[CaH_2A^+]}{[Ca^{2+}][H_2A^-]} = 2.6 \times 10^{2} \qquad (15)$$

$$CaH_2A^+ \rightleftarrows CaHA + H^+$$

$$K_{ac.k2}^{Ca} = \frac{[CaHA][H^+]}{[CaH_2A^+]} = 2.6 \times 10^{-6} \qquad (16)$$

$$Ca^{2+} + HA^{2-} \rightleftarrows CaHA$$

$$K_{k2}^{Ca} = \frac{[CaHA]}{[Ca^{2+}][HA^{2-}]} = 4.21 \times 10^{4} \qquad (17)$$

In the same way the constants were obtained for Sr^{++} — and Ba^{++} — FIDA complexes:

$K_{ac.k1}^{Sr} = 1.3 \times 10^{-3}$ $\qquad$ $K_{ac.k1}^{Ba} = 1.8 \times 10^{-3}$

$K_{k1}^{Sr} = 1.5 \times 10^{2}$ $\qquad$ $K_{k1}^{Ba} = 2.0 \times 10^{2}$

$K^{Sr}_{ac.k2} = 1.5 \times 10^{-6}$ $K^{Ba}_{ac.k2} = 1.7 \times 10^{-6}$

$K^{Sr}_{k2} = 1.4 \times 10^{4}$ $K^{Ba}_{k2} = 2.1 \times 10^{4}$

Separation of Ba^{++} in mixtures with Sr^{++} or Ca^{++}

To a solution of FIDA (48.45 mg.) in dioxane-water (2.5:1, 28 ml.) $2.5 \cdot 10^{-2}M$ solution of $Ba(NO_3)_2$ (5 ml.) or $Sr(NO_3)_2$ were added.

A) In separate runs the mixtures a) 2:1, b) 1:1, c) 0.5:1, d) 0.25:1 molar ratios of Sr^{++} to Ba^{++}, with volume and concentration of barium nitrate solution always equal, were treated with 0.1 *N* sodium hydroxide (3.2 ml.). The total volume of the solution did not exceed 40 ml. At the ratios c) and d) a crystalline product separated immediately, whihe at a) and b) this occurred after standing. In all experiments the same quantitative amounts of crystals were collected and analyzed as barium-ligand complex.

B) Mixtures of Ca^{++} and Sr^{++} in the same molar ratios as described above were separated quantitatively giving the same amounts of crystalline Ba^{++} — ligand complex.

Precipitation of Ba^{++} with Malonic Acid

To a solution of malonic acid (31.8 mg.) in 30 ml. of dioxane-water (2:1) a $2.5 \cdot 10^{-2}M$ solution of barium nitrate (10 ml.) and 0.1 *N* sodium hydroxide (4.5 ml.) was added. The gelatinous precipitate was separated by suction and dried. Yield 38.1 mg.

Anal. $C_3H_4O_6Ba_2$ (470.78) calc'd.: C 8.77; H 0.98%
found: C 8.32; H 1.24%

Toxicity test

The disodium salt of FIDA dissolved in water was injected intravenously. Experience with this class of compounds has shown that if the animal does not die or develops convulsions within 30 minutes, it will survive. The test was done in CBA ♀ strain at age of 6 month and provided $LD_{50} = 52.3$ mg. per mouse weighing 15 g. The result was obtained within error of ± 3 percent.

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IZVOD

4,5,6,7-Tetrahidroindazol-3-on karbonske kiseline IV. Konstante disocijacija i stvaranje kompleksa sa kalcijem, stroncijem i barijem

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Određene su konstante disocijacije 2-fenil-4,5,6,7-tetrahidroindazol-3-on-5,5-dikarbonske kiseline (I, FIDA) kao i njene konstante stabiliteta sa zemno alkalijskim ionima. Konstante stabiliteta su istoga reda veličine s napomenom da ona koja se dobiva sa barijem neznatno, ali neočekivano prelazi vrijednost konstante sa stroncijem. Ista dikiselina (FIDA) pokazuje izvanredna svojstva kao reagens kod odvajanja barija od stroncija.

FIDA je predhodno testirana na toksičnost i daje povoljne vrijednosti za letalnu dozu.

Metodom potenciometrijske titracije određene su *p*K vrijednosti 4,5,6,7-tetrahidroindazol-3-on-5-karbonske kiseline VI, odgovarajućeg estera VII kao i diestera 5,5-dikiseline V. Isto tako određene su i interpretirane *p*K vrijednosti 2-fenil derivata mono- (III), dikiseline I kao i njihovih etilnih estera IV i II.

INSTITUT »RUĐER BOŠKOVIĆ«
ZAGREB

Primljeno 16. listopada 1964.