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DETERMINATION OF THE IONIZATION CONSTANTS OF 2,4-DIIODO-6-METHYLPHENYL CARBAMOYLMETHYL IMINODIACETIC ACID

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Abstract

The ionization constants of 2,4-diiodo-6-methylphenylcarbamoylmethyl iminodiacetic acid were determined: pK_1 1.3 (the first carboxylic group), pK_2 2.52 (the second carboxylic group), pK_3 5.86 (amino group) and pK_4 10.85 (amide group). The determination were performed at 25°C.

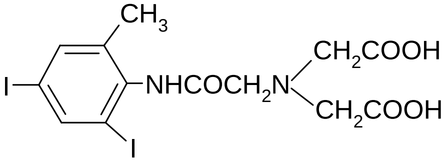
Introduction

The analogues of iminodiacetic acid (IDA) labeled with technetium-99m are used as diagnostic radiopharmaceutical for hepatobiliary imaging. In order to develop a radiopharmaceutical with better hepatobiliary properties and larger tolerance on bilirubin, a new ligand for complexation of technetium-99m, 2,4-diiodo-6-methyl phenylcarbamoylmethyl iminodiacetic acid (DIIODIDA) was synthesized [1].

The data of acid-base equilibria of DIIODIDA are important for determination of complex formation conditions. Considering the fact that DIIODIDA is newly synthesized compound it was of interest to determine its ionization constants.

Results and Disscusion

In molecule of DIIODIDA there are three acidic centers (two carboxylic groups and amide group) and one basic center (amino group).



The neutral form of DIIODIDA (H_3A) is rearranged spontaneously to the zwitter ion ($H_3A^{\pm}$) due to the protolysis of the first carboxylic group and proton acceptance of the amino group. The protolysis of the second carboxylic group, amino and amide group results in H_2A^-, HA^{2-} and A^{3-} forms. The form H_4A^+ exists in more acidic media. The corresponding ionization constants are as follows:

$$K_1 = \frac{[H_3A^{\pm}][H^+]}{[H_4A^+]} \quad (1) \qquad K_2 = \frac{[H_2A^-][H^+]}{[H_3A^{\pm}]} \quad (2)$$

$$K_3 = \frac{[HA^{2-}][H^+]}{[H_2A^-]} \quad (3) \qquad K_4 = \frac{[A^{3-}][H^+]}{[HA^{2-}]} \quad (4)$$

The ionization constants K_2, K_3 and K_4 were determined potentiometrically by application of the formation function method ($\bar{n}_H$) [2]:

$$\bar{n}_H = \frac{\sum_1^n n[H_nA]}{\sum_0^n [H_nA]} \tag{5}$$

(The charges in equation (5) were omitted due to simplicity)

The function $\bar{n}_H$ was calculated from experimental data of potentiometric titration of DIIODIDA with standard solutions of HCl (K_2) and NaOH (K_3 and K_4):

$$\bar{n}_H = \frac{3\,c_{DIODIDA} + c_{HCl} - c_{NaOH} - [H^+] + [OH^-]}{c_{DIIODIDA}} \tag{6}$$

where $c_{DIIODIDA}$, c_{HCl} and c_{NaOH} correspond to the stoichiometric concentration of DIIODIDA, HCl and NaOH; $[H^+]$ is the equilibrium concentration of protons obtained from pH measurements ($pc_H = -\log[H_3O^+] = pH - 0.05$) [3]; $[OH^-]$ is concentration of hydroxyl ions.

The ionization constants are determined in separated pH ranges where only one acid-base pair is dominant. The calculation of ionization constants was performed using equations which correspond to monoprotic acids. pH intervals for determination of ionization constants as well as obtained values are presented in Table I.

Table I. Stoichiometric equilibrium constants determined in homogeneous and heterogeneous systems of DIIODIDA; t = 25°C.

Constants	pH range of determination	Acid-base pair	pK± sd
pK_1	0 - 1.0	H_4A^+ - $H_3A^\pm$	1.3 ± 0.4*
pK_2	2.3 - 3.5	$H_3A^\pm$ - H_2A^-	2.52 ±0.02
pK_3	4.7 - 6.8	H_2A^- - HA^{2-}	5.86 ± 0.01
pK_4	9.2 - 11.0	HA^{2-} - A^{3-}	10.85 ± 0.01
pK_{s0}	0 - 1.0		5.0 ± 0.4
pK_{s1}	0 - 1.0		3.69 ± 0.04

*The great value of Sd for pK_1 could be explained by unsatisfactory reliable determination of pK in very acid medium (pH<1)

The acid-base process were the first carboxylic group of DIIODIDA participates was performed in range pH<2. As DIIODIDA in this pH range is slightly soluble in water (zwitter-ion), the constant K_1 could not be determined using pH-metrical titrations. This constant was determined indirectly, on the basis of equilibrium constants obtained in heterogeneous system. In aqueous solution at pH<1 between solid phase, $(H_3A^\pm)_s$, and ions in solution the following equilibria are possible:

$$(H_3A^\pm)_s \rightleftharpoons H_3A^\pm \qquad K_{s0} = [H_3A^\pm] \tag{7}$$

$$(H_3A^\pm)_s + H^+ \rightleftharpoons H_4A^+ \qquad K_{s1} = \frac{[H_4A^+]}{[H^+]} \tag{8}$$

The constant K_1 can be directly calculated from the equation:

$$K_1 = \frac{K_{s0}}{K_{s1}} \qquad (9)$$

Stoichiometric equilibrium constants K_{s0} and K_{s1} were determined spectrophotometrically using method of solubility [3]. The solubility (S) of DIIODIDA at pH<1 was calculated by equation:

$$S = H_3A^{\pm} + H_4A^{+} = K_{s0} + K_{s1}\,[H^{+}] \qquad (10)$$

Applying the experimentally determined solubility of DIIODIDA in solutions of HCl (0.1-1M; pc_H 0-1) and using the equation (10), the constants K_{s0} and K_{s1} were calculated from intercept and slope of linear dependance. The constant K_1 was calculated by applying equation (9).

The corresponding distribution diagram of DIIODIDA, obtained from experimental data of p*K*a values, is presented in Figure 1.

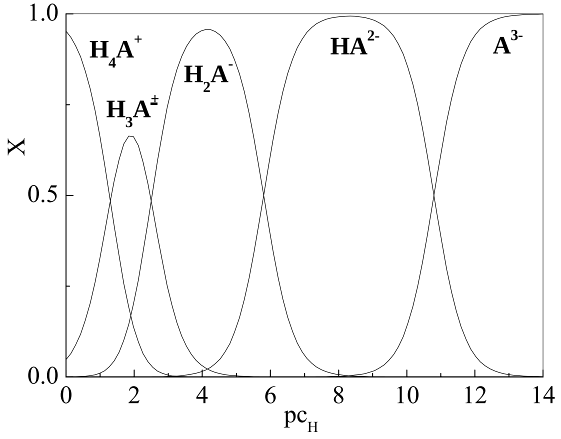


Figure 1. Distribution diagram of DIIODIDA in function of pc_H

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