# SYNTHESIS AND STRUCTURE OF COMPLEXES BETWEEN ASCORBIC ACID AND AMINO ACIDS

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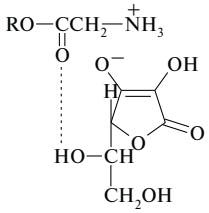
Interacting with amino acids, ascorbic acid (I) readily forms complexes of the ammonium salt type. Many of such compounds possess valuable pharmacological properties and are used as medicinal preparations [1, 2]. For example, the complexes of ascorbic acid with γ-aminobutyric acid (GABA) and cobalt or iron produce anticonvulsant action [3].

For the targeted synthesis of ascorbic acid complexes possessing therapeutic properties, it is necessary to establish relationships between the physicochemical properties and biological activity of these compounds. In particular, it was found that there is a direct correlation between redox potentials of the chelate complexes of Fe and Co with I and methylmethionine, on the one hand, and their antihypoxant activity, on the other hand [4]. However, the physicochemical properties of the complexes between ascorbic acid and amino acids are still insufficiently studied.

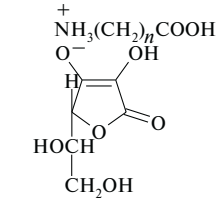
We have synthesized the complexes of I with seven amino acids containing one or two amino groups, or an amino group and a thio group (Table 1). The complexes of I with glycine (IIa), β-alanine (IIIa), GABA (IIIb), lysine (IV), methionine (Va), and acetylmethionine (Vb) were obtained by heating aqueous solutions of I with the corresponding amino acids. The complex between I and glycine ethylate (complex IIb) was obtained by etherification of complex IIa.

In order to determine the structures of the synthesized complexes, we measured their IR absorption spectra (Table 2). In the IR spectra of complexes II – IV, the absorption bands due to C=O and C=C groups in the acid I ring are shifted toward lower vibration frequencies as compared to the spectrum of pure ascorbic acid. Previously [5], we demonstrated that the conversion of I into sodium ascorbate (VI) is also accompanied by a low-frequency shift of the C=O and C=C vibration frequencies (Table 2). The low-frequency shift of $\nu_{C=O}$ and $\nu_{C=C}$ reaches maximum in the IR spectrum of salt VI, which is indicative of an increase in the degree of ionization. The shifts of bands of the spectra of complexes II – IV are proportional to the ability of their $NH_2$ groups to attach protons (i.e., to the increase in $pK_2$).



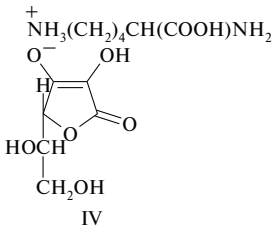
IIa, IIb

R = H (a); R = $C_2H_5$ (b)

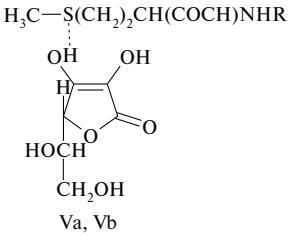


IIIa, IIIb

*n* = 2 (a), 3 (b)

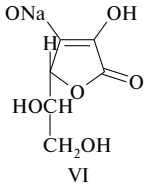


IV



Va, Vb

R = H (a); $COCH_3$ (b)



VI

The introduction of lysine leads to a change in the IR absorption spectrum analogous to the effect of GABA, which confirms that lysine is attached to I with a γ-amino group. The addition of glycine or its ethyl ether to I leads to a decrease in the frequency of C=O and C=C vibrations, which is more pronounced than might be expected taking into account the $pK_2$ value of glycine (Table 2). As is known [6], a favorable mutual spatial arrangement of the acid I ring and a substituent at C-3 may lead to the formation of an additional hydrogen bond between a COOH group of the substituent and the 5-OH group of I. We suggested that the attachment of glycine or its ethyl ether to I may also lead to the formation of an additional hydrogen bond and, hence, of complexes IIa and IIb.

The IR absorption spectra of the complexes between I and methionine or acetylmethionine (Va, Vb) exhibit no shift

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**TABLE 1.** Yields and Physicochemical Characteristics of Complexes between Ascorbic Acid and Amino Acids

| Compound | Yield, % | M.p., °C | $[\alpha]_D^{20}$ | Empirical formula |
|---|---|---|---|---|
| IIa | 85 | 137 – 138 | + 26 | $C_8H_{13}NO_8$ |
| IIb | 63 | 148 – 149 | | $C_{10}H_{17}NO_8$ |
| IIIa | 85 | 145 – 146 | + 37 | $C_9H_{15}NO_8$ |
| IIIb | 85 | 125 – 126 | + 47 | $C_{10}H_{17}NO_8$ |
| IV | 72.5 | 136.5 – 140 | + 21 | $C_{12}H_{22}N_2O_8$ |
| Va | 84 | 153 – 154 | + 12 | $C_{11}H_{19}NO_8S$ |
| Vb | 83 | 116 – 117 | + 14 | $C_{13}H_{21}NO_9S$ |

**TABLE 2.** Structural Characteristics of Complexes between Ascorbic Acid and Amino Acids

| Compound | $\nu_{C=O}$, $cm^{-1}$ | $\nu_{C=C}$, $cm^{-1}$ | $pK_2$ | Amino acid |
|---|---|---|---|---|
| I | 1753 | 1670 | – | – |
| IIa | 1725 | 1655 | 9.86 | Glycine |
| IIb | 1730 | 1655 | – | Glycine ethylate |
| IIIa | 1735 | 1660 | 10.36 | β-Alanine |
| IIIb | 1730 | 1665 | 10.43 | GABA |
| IV | 1730 | 1665 | 10.53 | Lysine |
| Va | 1755 | | 9.21 | Methionine |
| Vb | 1755 | | | Acetylmethionine |
| VI | 1702 | 1595 | – | – |

of the vibration frequencies of C=O groups in I (Table 2). The complex between I and methylmethionine described in [3] was assigned a structure containing the O–H…S bond. We suggested that methionine and acetylmethionine are attached to the 3-OH group in I also via a hydrogen bond of the O–H…S type, thus forming complexes Va and Vb. As is known [7], the greater the difference in atomic electronegativities, the higher the polarity of interatomic bonds. The electronegativities of H and S atoms are 2.1 and 2.5, respectively. This corresponds to a low polarity of the O–N…S bond and explains the absence of a shift in the $\nu_{C=O}$ frequency of the acid I ring in complexes Va and Vb (Table 1). Additional evidence for the proposed structure of these complexes is that acetylmethionine can hardly form a complex of the ammonium salt type with I, albeit methionine can, in principle, form such a complex. However, the frequencies of C=O vibrations in the IR spectra of both complexes coincide, which indicates that the two amino acids form complexes of the same structural type.

Thus, we have established that different amino acids attached to ascorbic acid may form complexes of various types.

## EXPERIMENTAL PART

The IR spectra were measured on a Perkin-Elmer model 180 spectrophotometer using samples pelletized with KBr. The data of elemental analyses (C, H, N, S) correspond to the results of calculations using empirical formulas.

**Ascorbic acid – glycine complex (IIa)**. To a solution of 1.50 g (0.02 mole) of glycine in 25 ml of distilled water was added 3.52 g (0.02 mole) of ascorbic acid. After complete dissolution of the acid, water was distilled off in a rotor-film evaporator at 80 – 85°C. The flask with a residue was cooled on ice and the obtained crystals were triturated with acetone. Finally, compound IIa was filtered and dried (Table 1).

**Ascorbic acid – β–alanine complex (IIIa)**. Compound IIIa was obtained similarly to IIa, proceeding from 1.78 g (0.02 mole) of β–alanine and 3.52 g (0.02 mole) of ascorbic acid (Table 1).

**Ascorbic acid – GABA complex (IIIb)**. Compound IIIb was obtained similarly to IIa, proceeding from 2.06 g (0.02 mole) of GABA and 3.52 g (0.02 mole) of ascorbic acid (Table 1).

**Ascorbic acid – lysine complex (IV)**. To a solution of 33 g (0.25 mole) of lysine in 300 ml of distilled water were added a solution of 44 g (0.25 mole) of ascorbic acid in 200 ml of water and 5 g of activated charcoal, after which the mixture was stirred and filtered. Then the solution was evaporated in a rotor-film evaporator at 40 – 50°C until a dense syrup was obtained. To this residue was added 50 ml of acetone and the mixture was cooled down to 0°C. The precipitate was filtered and dissolved in ethanol. Finally, ethanol was distilled off at 50°C, after which the residue of compound IV was washed with acetone and dried (Table 1).

**Ascorbic acid – methionine complex (Va)**. To a solution of 3 g (0.02 mole) of methionine in 20 ml of acetone was added a solution of 3.59 g (0.02 mole) of ascorbic acid in 20 ml of water. The solution was distilled off in a rotor-film evaporator and the residue was triturated with acetone to obtain compound Va (Table 1).

**Ascorbic acid – acetylmethionine complex (Vb)**. Compound Vb was obtained silimilarly to Va, proceeding from 3.82 g (0.02 mole) of acetylmethionine and 3.59 g (0.02 mole) of ascorbic acid (Table 1).

**Ascorbic acid – glycine ethylate complex (IIb)**. A mixture of 2.06 g (0.02 mole) of complex IIa and 15 ml of ethanol was heated until ethanol evaporated. The residue was triturated with acetone to obtain compound IIa (Table 1).

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