Copper(II) complexes with N-(2-carboxyethyl)anthranilic acid H$_2$CEAnt. Synthesis and crystal structure of [Cu(CEAnt)(H$_2$O)] $\cdot$ H$_2$O

Yu. A. Skorik, E. V. Osintseva, N. V. Podberezskaya, A. V. Virovets, L. K. Neudachina, and A. A. Vshivkov

$^a$A. M. Gorky Ural State University, 51 prosp. Lenina, 620083 Ekaterinburg, Russian Federation. Fax: +7 (343) 266 5978. E-mail: skorik@pitt.edu

$^b$Ural Scientific Research Institute of Metrology, 4 ul. Krasnoarmeiskaya, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343) 350 2039. E-mail: ev_osinceva@mail.ru

$^c$A. V. Nikolaev Institute of Inorganic Chemistry, Siberian Branch of the Russian Academy of Sciences, 3 prosp. Akad. Lavrentieva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 9489. E-mail: podberez@che.nsk.su

Protolytic equilibria and complexation of N-(2-carboxyethyl)anthranilic acid (H$_2$CEAnt) with copper(II) ions in aqueous solutions were studied by UV spectroscopy and pH potentiometry. The H$_2$CEAnt compound has no zwitterionic structure, and the protons are localized on the carboxy groups. The acid ionization constants of H$_3$CEAnt$^+$ ($T = 25$ °C, $I = 0.1$ M KNO$_3$) are $pK_0 = 1.3 \pm 0.2$ (═NH$_2^+$), $pK_1 = 3.88 \pm 0.02$ (Alk—COOH), and $pK_2 = 5.28 \pm 0.02$ (Ar—COOH). The model of complexation of H$_2$CEAnt with copper(II) ions involves two deprotonated complexes [Cu(CEAnt)] and [Cu(CEAnt)$_2$]$^{2-}$ ($\log \beta = 6.31 \pm 0.04$ and 8.0±0.2, respectively). The [Cu(CEAnt)(H$_2$O)]$\cdot$H$_2$O complex was synthesized by the reaction of H$_2$CEAnt with (CuOH)$_2$CO$_3$, and its structure was established by X-ray diffraction. The coordination polyhedron of Cu is intermediate between the tetragonal pyramid and trigonal bipyramid. The CEAnt$^{2-}$ ligand serves as a tetradentate chelating bridging ligand (Cu—O, 1.944(3) and 1.950(3) Å; Cu—O', 2.195(4) Å; Cu—N, 2.016(5) Å), and the fifth position of the polyhedron is occupied by a water molecule (Cu—O$_w$, 1.976(4) Å).

Key words: N-(2-carboxyethyl)anthranilic acid, β-alanine, aza-Michael reaction, acid ionization constants, copper(II) complexes, crystal structure.

The present study is part of systematic investigation of the coordination ability of N-substituted aromatic β-amino acids$^1$–$^5$ and is aimed at investigating the acid-base equilibria, compositions, stability, and structures of the complexes of N-(2-carboxyethyl)anthranilic acid (H$_2$CEAnt) with copper(II) ions in aqueous solutions and in the crystalline state.

The new ligand contains anthranilic acid as the main structural fragment. This acid has long been used for the spectrophotometric$^6$–$^8$ and potentiometric$^9$ determination of various metals. Anthranilic acid by itself is not a selective agent, and selectivity of analytical reactions is achieved by performing determination under specific conditions (preseparation, masking, pH, etc.). Complexes of anthranilic acid with copper(II) ions possess biological activity. For example, although anthranilic acid exhibits no antiinflammatory activity, it acquires the ability to exhibit antiinflammatory activity due to specific binding of copper(II) ions at inflammatory sites.$^{10,11}$

Earlier,$^{1,5,12}$ the introduction of β-carboxyethyl groups into aromatic amines has been demonstrated to enhance, on the whole, the selectivity of complex formation with copper(II) ions and increase the stability of the resulting complexes. Hence, one would expect H$_2$CEAnt, which is produced by carboxyethylation of anthranilic acid, to react with copper(II) ions more selectively than the starting anthranilic acid.

**Experimental**

The $^1$H NMR spectra were recorded on an Avance DRX-400 spectrometer (DMSO—CCl$_4$) operating at 400 MHz with Me$_4$Si as the internal standard. The UV-Vis absorption spectra were measured on Shimadzu UV-3101PC and SF-46 spectrophotometers. Elemental analysis was carried out on a Carlo Erba EA 1108 automated analyzer at the Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences.

Potentiometric titration was carried out on a Crison MicropH 2002 pH-meter equipped with glass (Russel SWL/S7) and silver-chloride (Orion 90-02-00) electrodes under nitrogen (free of CO$_2$ and O$_2$) at an ionic strength $\mu = 0.1$ M KNO$_3$ and at 25±0.1 °C. The pH-meter was connected to a PC through an RS232C interface. The parameters of the system were controlled.
using a program written in QuickBasic (Microsoft Corporation, version 7.0). The electrode system was calibrated against the proton concentration using buffer solutions with an ionic strength of 0.1 (KNO₃ additive) according to recommendations. A carbonate-free 0.1 M KOH solution was used as the titrant. The acid ionization constants were determined from the titration curves of 5×10⁻³ M H₂CEAnt solutions containing an equimolar amount of nitric acid (0.1000 M HNO₃, E. Merck 9964). The stability constants were determined by titration of 5×10⁻³ M H₂CEAnt solutions, the Cu(NO₃)₂ concentration (0.1000±0.0005 M solution, Orion 942096) being varied in the CEAnt : Cu ratio range from 2 : 1 to 1 : 2. The acid ionization constants and the complexation constants were calculated using the SUPERQUAD program.¹⁴

Synthesis of the ligand.¹⁵ Anthranilic acid of analytical grade (8.22 g, 0.06 mol), acrylic acid (E. Merck 8.00181) (8.6 mL, 0.12 mol), acetonitrile of reagent grade (70 mL), and hydroquinone of analytical grade (~0.1 g) were placed in a 500 mL round-bottom flask equipped with a reflux condenser. The reaction mixture was refluxed for 12 h. After one day, a gray powdered precipitate was obtained in a yield of 6.0 g (48%). The precipitate was filtered off and twice recrystallized from water, m.p. 182 °C (DTA). According to the results of pH-metric titration, the percentage of the acid was at least 98%. Found (%): C, 57.42; H, 5.35; N, 6.71. C₁₀H₁₁NO₄. Calculated (%): C, 57.41; H, 5.30; N, 6.70. ¹H NMR (DMSO—CCl₄), δ: 2.53 (t, 2 H, —CH₂COOH, J = 7.6 Hz); 3.44 (t, 2 H, —NH—CH₂—, J = 6.7 Hz); 3.82 (s, 1 H, H(5)); 6.52 (m, 1 H, H(4)); 6.69 (d, 1 H, H(6), J = 7.9 Hz); 7.31 (m, 1 H, H(5)); 7.78 (dd, 1 H, H(3), JAB = 7.9 Hz, JAX = 1.7 Hz); 7.92 (br.s, 1 H, Ar—COOH); 12.15 (br.s, 1 H, Alk—COOH).

Synthesis of the [Cu(CEAnt)·H₂O] complex (1). A weighed sample (1 g) of H₂CEAnt was dissolved in water (30 ml) on heating, and then an excess of (CuOH)₂CO₃ was added until carbon dioxide ceased to evolve. Green crystals of Cu(CEAnt)·2H₂O precipitated from the solution. Found (%): C, 39.57; H, 4.49; N, 4.54. C₁₀H₁₃NO₄Cu. Calculated (%): C, 39.15; H, 4.27; N, 4.57.

X-ray diffraction analysis. X-ray diffraction data were collected from a single crystal of complex 1 (green platelet of dimensions 0.35×0.30×0.05 mm) on an automated four-circle Nonius CAD4 diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, 293 K, θ/2θ scanning technique). The crystallographic data and details of structure refinement are given in Table 1. No absorption correction was applied because of the low absorption coefficient. The structure was solved by direct methods and refined by the full-matrix least-squares method. The nonhydrogen atoms were refined first isotropically and then anisotropically. The H atoms were refined isotropically. The positions of the hydrogen atoms were located from difference electron density maps and refined with geometric constraints. All calculations were carried out with the use of the SHELX97 program package.¹⁶

Results and Discussion

Protolytic equilibria of H₂CEAnt in aqueous solution

N-(2-Carboxyethyl)anthranilic acid H₂CEAnt has amphoteric properties and is involved in the following equilibria in solution:

\[
\begin{align*}
\text{CEAnt}^{2-} + \text{H}_3\text{O}^+ & \rightleftharpoons \text{HCEAnt}^- + \text{H}_2\text{O}, \\
\text{HCEAnt}^- + \text{H}_3\text{O}^+ & \rightleftharpoons \text{H}_2\text{CEAnt} + \text{H}_2\text{O}, \\
\text{H}_2\text{CEAnt} + \text{H}_3\text{O}^+ & \rightleftharpoons \text{H}_3\text{CEAnt}^- + \text{H}_2\text{O}.
\end{align*}
\]

The protonation constants determined from pH-potentiometric titration are given in Table 2 in comparison with the constants of related compounds, viz., benzoate (Benz⁻),¹⁷ anthranilate (Ant⁻),¹⁰ N-(carboxymethyl)anthranilate (CMAnt⁻²⁻),¹⁸ and N-(2-carbamoylethyl)anthranilate (CmEant⁻).¹⁹

To relate these protonation constants to the corresponding constants of the functional groups of the ligand, we additionally used the UV spectrophotometric method. The characteristic spectra of CEAnt at different acidities are shown in Fig. 1. One of the pH dependences of absorbance at a fixed wavelength is presented in Fig. 2 (curve I). The presence of two steps in the latter curve allowed us to determine only two (of three possible) constants characterizing protonation of the amino and carboxylate groups directly conjugated with the benzene chromophore. The calculated protonation constants are given in Table 2.

A comparison of the constants evaluated by two methods shows that the constant K₂H₁ was not determined by spectrophotometry. Hence, this constant presumably corresponds to protonation of the aliphatic carboxylate group. Taking into account that the constant logK₂H₁ of CEAnt²⁻ is similar to the corresponding constants of benzoate, anthranilate, and N-(2-carbamoylethyl)anthranilate (see Table 2), it can be assigned to protonation of the aromatic