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Synthesis of Complexing Agents Derived from Ammonia and Ethylene Diamine and Containing Carboxyl and Secondary Amino Groups

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Abstract—The synthesis of carboxyl-containing complexing agents derived from secondary amines as highly efficient reagents for solving specific problems in science, engineering, medicine, agriculture, and other fields is an urgent task in organic chemistry. Published data on the synthesis of such practically valuable compounds as ethylenediamine-*N,N'*-diacetic (sym.EDDA), ethylenediamine-*N,N'*-di-β-propionic acids (sym.EDDP), iminodiacetic (IDA), and iminodi-β-propionic (IDP) acids are symmarized. The latest achievements in the synthetic chemistry of carboxyl-containing complexing agents—ethylenediamine-*N,N*-di-β-propionic (as.EDDP) and a previously unknown new ethylenediamine-*N*-β-propionic (βEDMP) EDMP) acids—are presented.

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Targeted synthesis of compounds with desired properties for solving specific tasks of science and modern industry is a challenging problem of organic chemistry. Among such compounds, a prominent place belongs to complexing agents, the role of which as promising polydentate ligands can hardly be overestimated.

In this connection, search for technologically feasible synthetic approaches to novel complexing agents and improvement of synthetic procedures for already known ligands take on particular significance.

One of the major modern approaches to carboxyl-containing complexing agents consists in the introduction of carboxyl groups into reactive primary and secondary amines. Carboxylation of amines by, as a rule, monochloroacetic acid (MCAA) is still quite a common and sufficiently practical method of synthesis of complexing agents containing aminoacetate moieties, which allows wide variation of the starting amines. This method is used for commercial production of such practically valuable complexing agents as ethylenediamine-*N,N,N',N'*-tetraacetic acid (EDTA), nitrilotriacetic acid (NTA), diethylenetriamine-*N,N,N',N'',N''*-pentaacetic acid (DTPA), and other acids.

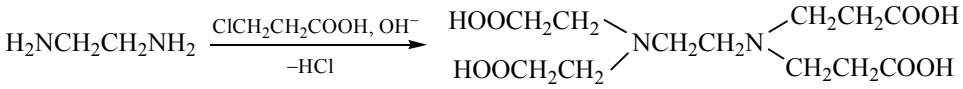
In spite of being widely used, the carboxyalkylation method is not free of certain disadvantages associated with the fact that the mandatory starting material in this synthesis is the monohaloacetic acid. This compound is sensitive to hydrolysis and should be added in excess to stoichiometry, which adversely affects the profitability of the process [1].

Furthermore, the presence in the starting amine other functional groups capable of reacting with the carboxyalkylating agent makes complexing agents containing such functionalities impossible to obtain.

The carboxyalkylation of amines with MCAA generally involves exhaustive substitution of amino protons, the limiting stage of process is reaction of the starting amine with the first MCAA molecule, whereas further stages occur at high rates. Amine derivatives containing secondary amino groups could not be prepared, even if an excess of the starting amine was used [2–4].

The same reaction pathway was observed, when MCAA was replaced by β-monochloropropionic acid (βMCPA) with the aim to obtain complexing agents containing β-carboxyethyl groups [5] (Scheme 1).

Scheme 1.



In all the cases the classical carboxylation of ammonia and aliphatic amines with MCAA or βMCPA in an alkaline medium could not be stopped at the intermediate stage to obtain aminocarboxylic acids containing secondary amino groups.

At the same time, aminocarboxylic acids with the amino protons only partially substituted by carboxyalkyl groups present interest as chelants, as well as synthons for complex- and polycomplex-forming agents with a more complicated structure.

Special place among complexing agents with secondary amino groups belongs to ethylenediamine derivatives: ethylenediamine-*N*,*N*'-diacetic acid (sym.EDDA) and ethylenediamine-*N*,*N*'-di-β-propionic (sym.βEDDP).

The interest of researchers in sym.EDDA is explained by its optimal molecular structure which makes this acid a highly efficient complexing agent. At present sym.EDDA is widely used in practice [6–11].

Not considering in detail the entire range of practical applications of sym.EDDA, we would like to mention here only two of them: diagnosis and treatment of cancer and nanotechnologies. For example, Pt(IV) complexes of dialkyl esters of sym.EDDA were found to exhibit antitumor activity [12]. Similar activity was also reported for mixed-ligand complexes of divalent Cu, Co, and Zn with sym.EDDA, 1,10-phenanthroline, and dinicotineamide [13].

Babaei et al. [14] reported successful preclinical testing of some conjugates of a ^{99m}Tc sym.EDDA chelate with antibody fragments for cancer diagnosis [14].

The publication of Matsuoka et al. [15] who synthesized nanocage aggregates composed of bilayer sheets formed by derivatives of sym.EDDA deserves mentioning. In view of the development of nanotechnology research, we expect that these results will serve to extend the range of potential applications of sym.EDDA and its derivatives.

Along with sym.EDDA, its analog sym. βEDDP is used to success in solving certain analytical and medical problems [16].

As known, the complexes of sym.βEDDP are appreciably less stable that complexes of sym.EDDA, except for the Cu^{2+} complex of sym.βEDDP, which compares in stability with the corresponding sym.EDDA complex [17]. This circumstance explains that sym.βEDDP is preferred over sym.EDDA in solving various problems, including determination of copper ions in or their extraction from complex composite materials containing, along with Cu(II), other transition metal ions [17–19].

The antitumor activity of *cis* and *trans* Pt(II) and Pt(IV), as well as Ru(III) complexes of sym.βEDDP and its dialkyl esters, cisplatin analogs, was studied [20, 21]. Encouraging results were obtained [22, 23].

Due to the presence of reactive secondary amino groups, sym.EDDA and sym.βEDDP present interest for modification with the aim of targeted synthesis of polydentate ligands with desired properties [24–30].

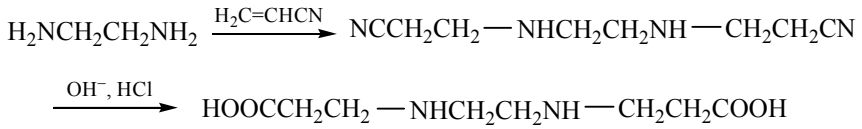
Along with carboxyl derivatives of ethylenediamine, containing two secondary amino groups, of interest are also complexing agents containing one secondary amino group, the best known of which are iminodiacetic (IDA) and iminodi-β-propionic acids (βIDP).

Unlike sym.EDDA and sym.βEDDP, the monosubstituted chelants IDA snd βIDP should be primarily considered as complexing fragments for the synthesis on their basis of polyfunctional ligands to be used as metal indicators (IDA), synthetic resins, etc. Noteworthy is the use of βIDP as a scaffold for dendrimers, specifically, monodisperse polymers for the synthesis of dimers and tetramers of biologically active molecules for their subsequent application in new biomedical technologies, in particular, gene therapy [31].

Thus, the above-described applications of carboxylated complexing agents containing secondary amino groups clearly demonstrate the necessity in developing synthetic approaches to such ligands. However, at present this issue is not being given sufficient attention.

Up to now carboxylated complexing agents containing secondary amino groups (IDA, sym.EDDA) have always been synthesized by the procedure proposed by Strecker in 1850 [32] and improved by

Scheme 2.



Kendall and Mc Kenzie [33]. The procedure was based on the reaction of aldehydes and cyanides with ammonia or amines and subsequent conversion of the nitrile that formed into an aminocarboxylic acid containing one carbon atom more than the starting aldehyde. Thus, sym.βEDDP is prepared by the reaction of ethylenediamine with acrylonitrile [34] (Scheme 2).

The reactions are generally performed in an alkaline medium, and the resulting nitriles are concurrently hydrolyzed to corresponding acids with evolution of ammonia.

The side reaction of cyanoalkylation of ammonia evolved in the course of the reaction is suppressed by periodic addition of cyanoalkylating agents followed by repeated vacuum evacuation of ammonia, which leads to a considerable prolongation of the process.

Cyanoalkylation, like direct carboxyalkylation of amines, is studied in sufficient detail and applied for preparative synthesis of complexing agents containing secondary amino groups. In spite of its limited possibility for commercial realization because of the high toxicity of the starting materials (hydrogen cyanide and its salts, organic nitriles), cyanoalkylation still attracts researchers' attention. Thus, Korean researches in 2013 patented the method of synthesis of IDA by cyanomethylation of glycine [35]. Concurrently, the search for an environmentally friendly method of synthesis of IDA is being continued: In 2012 Chinese researches patented a catalytic synthesis of IDA by oxidation of diethanolamine in the presence of a CuO_2/ZrO_2 catalyst [36].

In 1950s [37], Lur'e and Chaman detected βIDP as a by-product in the synthesis of β-alanine by a large excess of ammonium (ammonia water) with βMCPA (molar ratio 28 : 1). The acid further recirculated to form β-alanine. Mathematical simulation of the process gave evidence showing that βIDP recirculated according to the scheme below until it was consumed completely.

$$HN(CH_2CH_2COOH)_2 + NH_3 \leftrightarrow 2H_2NCH_2CH_2COOH.$$

From the alcoholic solution of β-alanine hydrochloride, obtained by treatment of an ammonium solution of βMCPA, after it has kept for 10–12 days, with charcoal, evaporated until dry, and acidification of the dry residue with HCl, removal of excess HCl by distillation, and extraction with alcohol, the authors of the cited work could isolate an oily material which was found to contain βIDP. The latter was identified as its diethyl ether isolated after esterification of the oily product. Thus, the nucleophilic substitution of chlorine in βMCPA by the amino group in the synthesis of β-alanine (containing a primary amino group) also gave βIDP, a secondary amine derivative. Unlike this reaction, in the case of the reaction of ammonia with acrylic acid, βIDP was not detected in the reaction mixture [38].

Note also that in late 1980s Poznyak et al. [39] proposed to replace the classical synthesis of sym.βEDDP by cyanoalkylation of ethylenediamine by alkaline hydrolysis of *N,N'*-bis(2-carbamoylethyl)ethylenediamine followed by acidification of the alkaline solution with HC to isolate the acid as dihydrochloride [39]. Such method does not use cyano derivations but is complicated by the necessity of preliminary synthesis of *N,N'*-bis(2-carbamoylethyl)ethylenediamine.

Kawaguchi [40] described the reaction of trimethylenediamine with presynthesized ethyl acrylate to form *N,N'*-diethyl trimethylenediamine-*N,N'*-di-β-propionate followed by acid hydrolysis to isolate trimethylenediamine-*N,N'*-di-β-propionic acid dihydrochloride [40]. Probably, the same method with ethylenediamine instead of trimethylenediamine was used to synthesize sym.βEDDP.

Thus, as seen from the aforesaid, known synthetic approaches to complexing agents containing carboxyl and secondary amino groups, are hardly technologically feasible in view of the necessity to use highly toxic starting materials and also to perform, in some cases, additional chemical reactions.

Consequently, the potential of such methods for the production of practically valuable polyfunctional ligands in quantities required for solving specific tasks of science and modern industry, as well as for using as synthons is quite limited for them to be able to satisfy

the demand of the national economy for such chelants. In this connection, search for and development of routine, high-performance, cost-efficient, environmentally friendly, and low-waste production technologies for complexing agents of this type still remains an urgent task of synthetic organic chemistry, even though some progress in this direction has already been made.

Among recent promising results we would like to dwell on the optimal method for the production of complexing agents containing secondary amino groups by template carboxyalkylation of ammonia and aliphatic amines with MCAA in the presence of CaO, which we proposed and developed in late 1990s [41–43].

Research on the reactivity of coordinated nitrogen-containing ligands (including amines) revealed the possibility of synthesis of many organic compounds and their complexes in the presence of metal ions in cases when in the absence of metal ions such synthesis either does not occur at all or occurs with low yields and is accompanied by by-product formation. The coordination of various organic ligands to a central atom makes possible stereospecific halogenation, nitration, thiocyanation, and other reactions [44].

The mechanism of such reactions depends on the nature of the metal ion or its compounds, geometric orientation of the reaction components, arising after their coordination, ordering and binding role of the metal ion, as well as change in the electronic state of the entire system and its separate functional groups [44].

Template reactions offer great scope for the synthesis of complexing agents containing secondary amino groups. Actually, the carboxyalkylation of amines with MCAA in the presence of CaO or MgO results in direct formation of incompletely carboxylated secondary amines [43].

This is an optimal synthetic approach because it allows reactive chelants to be prepared in fairly high yields (up to 70%) by direct nucleophilic substitution of chlorine in MCAA with ammonia or aliphatic amines. The intermediate reaction products, aminoacetic acid hydrochlorides, present interest, because they can be esterified and used to synthesize polyfunctional complexing agents, including chelating resins.

The template reaction of ethylenediamine with β-chloropropionic acid in the presence of CaO gave sym.βEDDP (Scheme 3) [45].

Under the same conditions, ethylenediamine was reacted with monochloro-α-propionic acid (αMCPA) to obtain a calcium complex of ethylenediamine-*N*,*N*'-di-α-propionic acid. The latter was destroyed with HCl, and the resulting hydrochloride was treated with triethylamine to obtain ethylenediamine-*N*,*N*'-di-α-propionic acid (sym.αEDDP) in 55% yield (Scheme 3) [46].

It should be noted that in the synthesis of sym.αEDDP by the reaction of ethylene bromide with α-alanine in an alkaline medium under reflux followed by neutralization of the reaction solution to pH 5, proposed by Leonard et al. [47], the yield of the target acid was as low as 11.6% (mp 256–258°C). It is quite obvious that sym.αEDDP could hardly be prepared in a high yield under the conditions in [47], because one of the main reaction pathways here would without any doubt involve exhaustive carboxyalkylation to form ethylenediamine-*N,N,N',N'*-tetra-α-propionic acid (αEDTP).

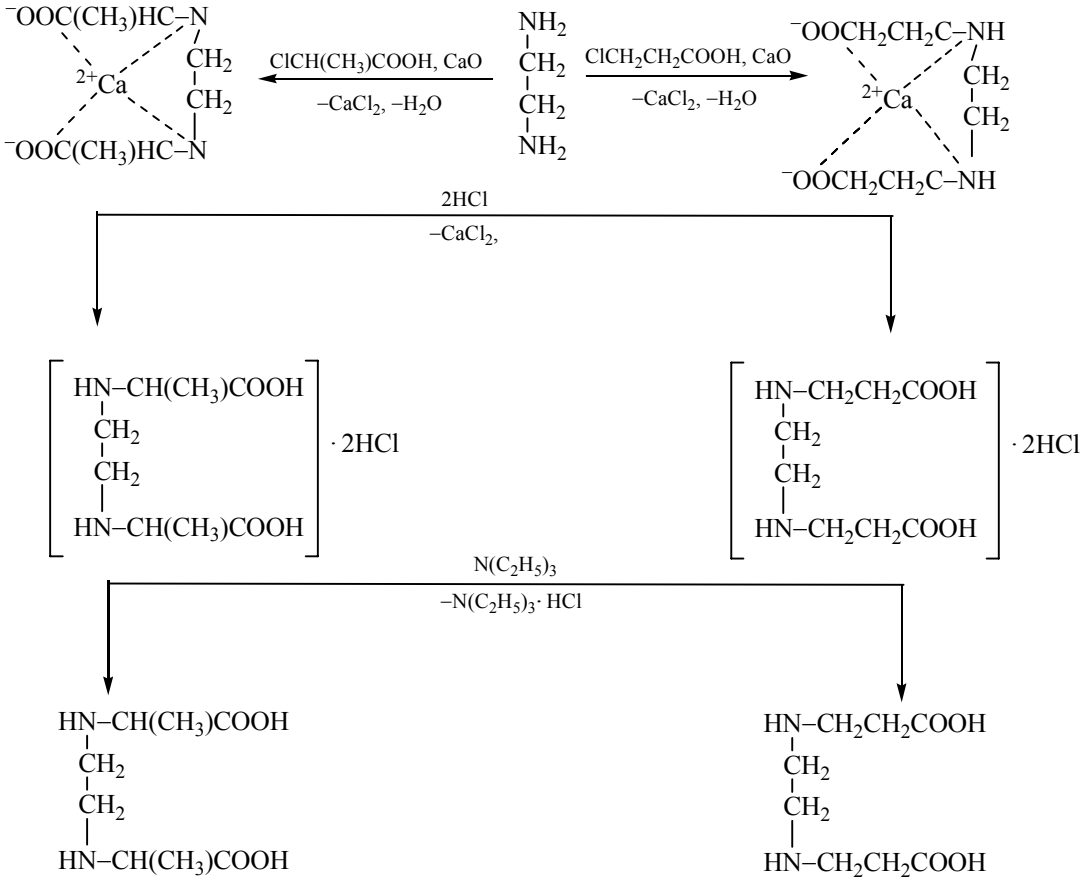
At the same time, αEDTP was synthesized in a low yield (15%) by the reaction of ethylenediamine with αMCPA in an alkaline medium at 85ºC [48]. We suggested that the reason for the low yields of sym.αEDDP and αEDTP (≥15%) is that under alkaline conditions at a high temperature the main reaction with αMCPA is accompanied by side reactions, specifically, hydrolysis of and HCl elimination from the latter to form acrylic acid. Actually, the reduction of the reaction temperature to 65ºC allowed the yields of sym.αEDDP and αEDTP to be increased to 55% and 30%, respectively [46].

The results of carboxyalkylation of aliphatic amines, in particular, ethylenediamine, with monochloropropionic acid in the presence of CaO can be explained, like with MCAA, in terms of mixed complex formation.

Thus, the calcium monochloropropionate–amine complex serves as a convenient matrix for reaction of the amine with αMCPA or βMCPA and "assembling" aminopropionic acid containing a secondary amino group. The secondary nitrogen atom in the coordinated aminocarboxylic acid has a lower basicity compared with that in a free, uncoordinated acid, and this prevents further carboxyalkylation. Under such conditions, the main reaction products are complexing agents containing secondary amino groups.

The moderate (40%) yield of sym.βEDDP is likely to be explained by the occurrence of two side reactions

Scheme 3. Synthesis of ethylenediamine-*N*,*N*'-di-α-propionic acid (sym.αEDDP) and ethylenediamine-*N*,*N*'-di-β-propionic acid (sym.βEDDP).



involving βMCPA: its hydrolysis to β-oxopropionic acid and elimination of HCl to form acrylic acid:

$$ClCH_2CH_2COOH \rightarrow HCl + H_2C{=}CHCOOH$$
$$ClCH_2CH_2COOH \rightarrow OHCH_2CH_2COOH + HCl$$

Acrylic acid is known to enter the aza-Michael reaction with the amino group to form the target amino-β-propionic acids. Apparently, under the synthesis conditions, the result of the reaction of ethylene diamine with βMCPA will depend on the relative rates of the main and side reactions, including the reaction of the amine with acrylic acid:

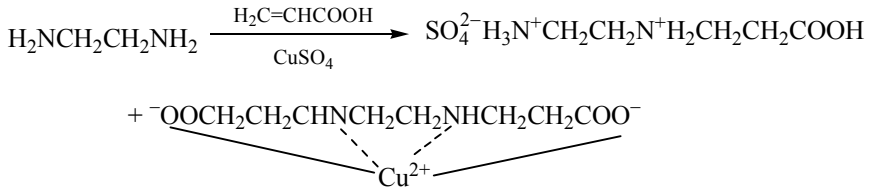
$$ClCH_2CH_2COOH \xrightarrow[-NaCl]{} H_2NCH_2CH_2NH_2 \xrightarrow{H_2C{=}CHCOOH} (HOOCH_2CH_2C)_2NCH_2CH_2N(CH_2CH_2COOH)_2$$

The tendencies of acrylic acid for polymerization at high temperatures and of monochloropropionic acid for hydrolysis should also be taken into account. In view of the data of Kaluderovic et al. [49], who observed an interesting regularity in reactions of halides with alkalis, specifically, CH_3CH_2Br was less reactive than CH_3Br, we can suggest with some assurance that βMCAA is more resistant to hydrolysis than MCAA.

Previously we showed [50] that Ca(II) ions have almost no effect on MCAA hydrolysis. At pH 9–11 and temperature 50–55ºC the degree of MCAA hydrolysis is low (5%) and, therefore, in template carboxyalkylation we need no more than a 7–10% excess of MCAA.

At temperatures lower than 55ºC, alkaline hydrolysis of βMCPA which is more stable than MCAA can be neglected. At temperatures higher than 55ºC, the contribution of βMCPA hydrolysis with concurrent HCl elimination to form acrylic acid should be higher. In a blank experiment under the carboxyalkylation reaction conditions (pH = 9–11) at a temperature higher than 55°C the conversion of βMCPA was higher than 50% [51]. Therewith, the main side

Scheme 4. Reaction of acrylic acid with ethylenediamine in the presence of $CuSO_4$.



reaction was HCl elimination from βMCPA, resulting in the formation of acrylic acid.

Taking account of the ability of acrylic acid to enter the aza-Michael reaction with amines, we undertook an attempt to prepare ethylenediamine derivatives containing secondary amino and β-carboxyethyl groups by template synthesis [52].

Badea et al. [53] made use of the aza-Michael reaction of ethylenediamine with acrylic acid in the presence of a basic nickel(II) salt (molar ratio 1 : 4 : 2, respectively) to obtain for the first time a binuclear complex of ethylenediamine-*N,N*-di-β-propionic acid (as.βEDDP), containing a secondary and a tertiary amino groups [53]. According to the X-ray diffraction (XRD) analysis, the binuclear complex was assigned the structure $[Ni_2(as.\beta EDDP)_2(H_2O)]\cdot 2H_2O$, with the nickel(II) ion coordinated to two carboxylato groups each acting as a monoatomic bridge. We chose Cu(II) as a complexing ion in view of the known selectivity of ethylenediaminepropionic acids to this ion (Scheme 4).

The result of the first performed reaction of acrylic acid with ethylenediamine in the presence of $CuSO_4$ (molar ratio 4 : 2 : 1, respectively) proved unexpected: As the final products we isolated a previously unknown ethylenediamine-*N*-β-propionic acid (βEDMP) as its sulfate and a copper sym.βEDDP complex whose structure was established by XRD analysis [54]. This is the first precedent when two products of different nature were formed by a single reaction.

Note that the main reaction product was βEDMP sulfate (yield 55%), and, therefore, we found it impractical to use the resulting copper complex of sym.βEDDP for isolation of free sym.βEDDP. Therefore, in terms of the potential for comercialization, preference should be given to the above-described template carboxyalkylation of ethylenediamine with βMCPA in the presence of CaO, which provides a higher yield of the target product [45].

Unlike the results with Cu(II), assembly of carboxyl-containing complexing agents derived from secondary amines on a Zn(II) matrix did not meet with success. Template reaction of acrylic acid with ethylenediamine in the presence of $ZnCl_2$ instead of $CuSO_4$ gave a previously unknown complex zinc ethylenediamine-*N,N*-di-β-propionic acid dichloride $[Zn(as.\beta EDDP)Cl_2]$ whose structure was established by XRD analysis [55]. This complex is an example of a coordination compound with an ethylenediamine-

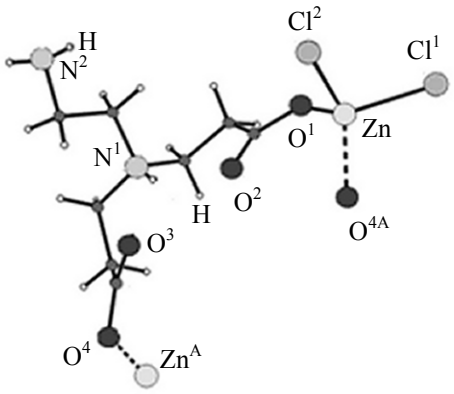


Fig. 1. Fragment of the crystal structure of Zn(II) ethylenediamine-*N,N*-di-β-propionic acid dichloride $[Zn(as.\beta EDDP)Cl_2]$.

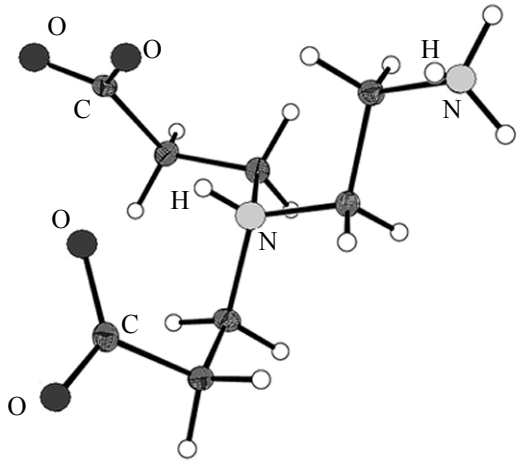


Fig. 2. Structure of ethylenediamine-*N,N*-di-β-propionic acid (as.βEDDP).

carboxylato ligand, which, unlike traditional complexing agents, contains no ethylenediamine chelate ring; as.βEDDP is present as a double betaine (Fig. 1).

The complex was destroyed to isolate free as.βEDDP, its structure was confirmed by XRD analysis (Fig. 2) [56].

The synthesis of as.βEDDP by destroying its zinc complex dichloride is preferred over the method in [57], which involves carboxylation of *N*-acetylethylenediamine by the aza-Michael reaction followed by removal of the protective group in an alkaline medium to obtain disodium salt of as.βEDDP, and acidification of the latter to isolate as.βEDDP as dihydrochloride.

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