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Review

Coordination chemistry of acrylamide

K.B. Girma, Volker Lorenz, Steffen Blaurock, Frank T. Edelmann *

Chemisches Institut der Otto-von-Guericke-Universität Magdeburg, Universitätsplatz 2, D-39106 Magdeburg, Germany

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Dedicated to Professor Heinrich Vahrenkamp on the occasion of his 65th birthday.

Contents

Abstract

This review provides a literature survey of the coordination chemistry of acrylamide, CH_2=CHC(O)NH_2 (also known as 2-propenamide, =AAm), with a variety of transition metals. First, a general overview of the structure and possible modes of coordination of acrylamide are discussed. This is followed by a summary of the published data on the syntheses and structures of acrylamide complexes. Despite the potential versatility of acrylamide as a ligand, only few complexes that coordinate exclusively through the carbonyl oxygen, $[Co(AAm)_4(H_2O)_2](NO_3)_2$, $[Cu(AAm)_4(NO_3)_2]$, $[Co(AAm)_4Cl_2]$, and $[Co(AAm)_6][CoCl_4]$ have been fully characterized by spectroscopic and X-ray diffraction studies. Finally, some reactions involving acrylamide or acrylamide-based ligands coordinated with less acidic biologically relevant transition metals are considered in order to form a notion of the potential role of such interactions in acrylamide reactivity in biological systems. With regard to acrylamide in food and its health effects, the solution and solid-state chemistry of acrylamide or acrylamide-based ligands (metabolites) with less acidic biologically relevant metal ions may be of a great relevance in elucidating the mechanism of acrylamide metabolism and its health effects.

Keywords: Acrylamide; Acrylamide complexes; Coordination compounds

1. Introduction

The coordination chemistry of acrylamide with transition metals is of interest due to the biological relevance of the

* Corresponding author. Tel.: +49 391 6718327; fax: +49 391 6712933.
E-mail address: frank.edelmann@vst.uni-magdeburg.de (F.T. Edelmann).

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amide group in peptides and proteins [1–3] and in the context of the recent public concerns on acrylamide exposure from food and its health effects. From the industrial point of view, metal complexes of acrylamide are employed in the production of water-soluble polymers and copolymers that are used in many commercial and scientific applications [4,5].

Acrylamide is toxic and probably carcinogenic to animals and human beings [6–8]. The monomer used in the industry and the release of the monomer residues from polyacrylamide [9] used in water treatment and construction had been considered as the two major sources of acrylamide exposure. In 2002, Tareke et al. [10] reported the presence of acrylamide in fried and oven cooked foods suggesting another wide spread public exposure concern. In an integrated review [11], Friedman showed that neurotoxicity is a documented effect in human epidemiological studies, whereas reproductive toxicity, genotoxicity, and carcinogenicity are potential health risks only on the basis of animal studies. Recently [12], an assessment of published data based on biochemical and physiological mechanisms with regard to acrylamide suggests that the risk from dietary exposure or other sources of exposure may be lower than previously anticipated.

To evaluate fully the health effects and risks associated with acrylamide exposure, it is important to elucidate the mechanism of acrylamide metabolism [13,14]. Acrylamide is a polyfunctional molecule, which contains a vinylic carbon–carbon double bond and an amide group. The electron deficient double bond of acrylamide is susceptible to a wide range of chemical reactions including nucleophilic additions, Diels-Alder, and free radical reactions [15]. Thus, alkylation of protein and non-protein SH groups (cysteine, homocysteine, and glutathione), N-terminal NH_2 groups of the valine residue of hemoglobin and NH_2 groups of guanine and other nucleic acids occur via the double bond [16]. The reactions of the amide residue that include hydrolysis, dehydration, alcholysis, and condensation with aldehydes [17] have also been under discussion in an attempt to elucidate the mechanism of acrylamide metabolism and its health effects.

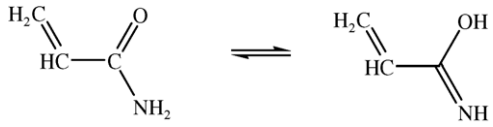
Acrylamide is also capable of coordinating with less acidic metal ions through the carbonyl oxygen atom, the nitrogen atom, or the olefin in η^2-mode [2,18–30]. It could be a neutral or negatively charged ligand acting as a monodentate or bidentate chelating ligand to one metal or bridging ligand to two or three metals [31–33]. Polydentate ligands such as acrylamide are both commercially and biologically important, because they can yield complexes that readily provide additional coordination or binding sites for incoming substrates. The ease with which an organic substrate can enter the coordination sphere of a metal ion is thought to be a key factor in determining the ability of such an ion to catalyze the reactions of the substrate [34]. Biologically, relevant ligands based on acrylamide (as in ligands in drugs and toxic ligands) can bind to metals that are available in biological systems [35–38].

However, the coordination of metal ions to acrylamide or to the amide residue of an acrylamide adduct which may play a catalytic role in activating or deactivating biochemical reactions has not been considered in prior reviews and in many other discussions on the mechanism of acrylamide metabolism and its health effects. Thus, to stimulate further research towards a better understanding of acrylamide's coordination and bioinorganic chemistry, we have reviewed the literature on the coordination chemistry of acrylamide with a variety of Lewis acids where applications can be in biocatalysts, biology, medicine, environmental science and technology. We have also included a brief overview of the literature on the structure of free acrylamide since the experimental results for free acrylamide are often used for comparison in predicting the structures of metal complexes of acrylamide. Particular attention has been given to some reactions involving acrylamide or acrylamide-carrying ligands and less acidic biologically relevant transition metal ions to form a notion of the potential role of such interactions in biological systems. The solution and solid-state chemistry of acrylamide and acrylamide-based ligands or metabolites with less acidic biologically relevant metal ions may be of a great relevance in elucidating the mechanism of acrylamide metabolism and its health effects.

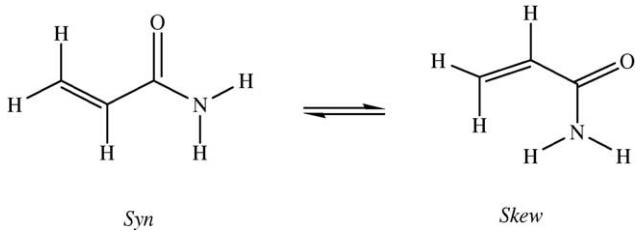
2. The free acrylamide structure

Acrylamide is a white crystalline compound, which is soluble in water, alcohol and acetone but insoluble in benzene and heptane [39]. The crystals of a free acrylamide are monoclinic belonging to the space group of $P2_1/c$ [$C_{2h}{}^5$] with four molecules in the unit cell [40]. In the crystal, the molecular skeleton is planar to a good approximation, although the hydrogen atoms were not determined in the X-ray analysis. Infrared, far IR-vapor phase and Raman spectroscopic studies [41–43] suggest that the entire acrylamide molecule is planar and the structure of acrylamide is consistent with the amide structure. No evidence for a possible tautomeric form (Scheme 1) was found in the IR and Raman spectroscopic studies.

The microwave spectrum investigated in the 20.0–60.5 GHz spectral region at room temperature showed that gaseous acrylamide exists in the heavy-atom *syn* and *skew* conformations [44] (Scheme 2). The *syn* form is the more stable conformation being 6.5(6) kJ mol^{-1} more stable than the *skew* form. The *syn* rotamer has a planar heavy atom skeleton and a nearly planar amide group, whereas the *skew* rotamer, which is obtained by twisting approximately 150° around the central C–C bond, may exhibit a decrease in the overall conjugacy and excessive repulsion between the terminal



Scheme 1. Tautomeric forms of acrylamide.



Scheme 2. Two conformations of acrylamide.

vinyl and the amino hydrogens rendering $-NH_2$ pyramidality. However, less information is available for the *skew* rotamer.

Thermodynamic functions (heat capacity, enthalpy, entropy, and free energy) for acrylamide in the ideal gas state from 273.15 K to 1400 K at 1 atm pressure have been calculated by statistical mechanical means [45]. The magnitude of error introduced in this calculation due to the uncertainties in spectroscopic and microwave data or the discrepancies in the vibration assignments for acrylamide in the earlier reports can be reduced in the present availability of both spectroscopic [43] and microwave data [44] for acrylamide.

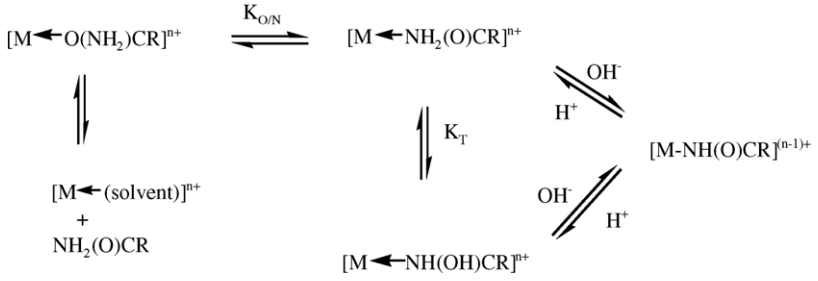
3. Structure of metal–acrylamide complexes

Metal complexes of acrylamide are generally prepared by direct reaction of metal ions with acrylamide [2,5d,18–33] and by base catalyzed hydrolysis of a coordinated acrylonitrile, $[M{-}N{\equiv}C{-}CH{=}CH_2]^{n+}$ (where $M^{n+} = Co^{3+}$) [31]. The first route usually gives complexes in which the metal is coordinated through oxygen, although coordination through nitrogen or the olefin has been reported in some cases. The latter forms a more stable deprotonated *N*-amidate, $[M{-}NHC(O)CH{=}CH_2]^{(n-1)+}$, which protonates instantaneously in acidic conditions to give *N*- or *O*-coordinated complexes.

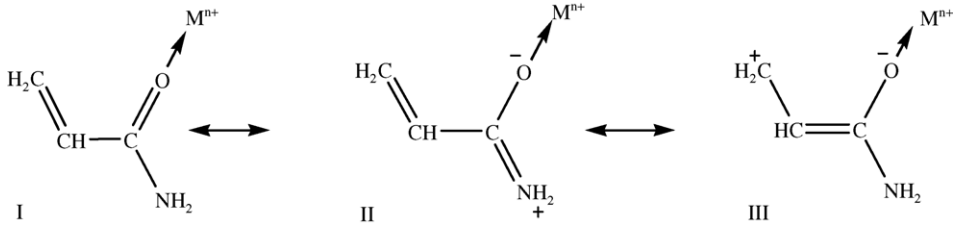
The most basic site in acrylamide is oxygen, where protonation or metallation occurs in neutral conditions. However, the basicity of the amide nitrogen may also make protonation or complexation at this site a possibility, where the amide oxygen then becomes the most basic center calling for additional rapid protonation or complexation at the oxygen [2,3]. Thus, the O- to N-linkage isomerization or the vise versa, tautomerization, solvolysis and hydrolysis to the corresponding *N*-amidate complexes in solutions are typical characteristics in metal–amide complexes. These factors have frequently complicated the stabilization and characterization of metal–amide complexes. Complexation in amides can be summarized as shown in Scheme 3 [46,47]. In general, changes in the acidity and oxidation states of the metal center, substituent group, temperature, and solvent system influence the stability and mode of coordination in metal–amide complexes [46–48]. Comparisons of enthalpies of formation of the complexes of acrylamide with formamide complexes of the same metals showed that acrylamide forms less stable bonds than formamide [49].

3.1. Possible coordination modes of acrylamide

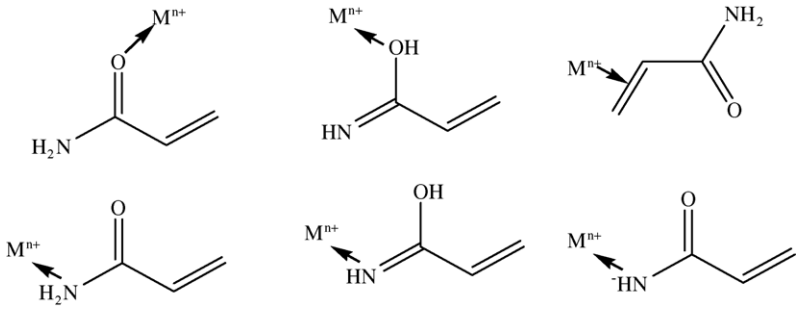
Assuming the resonance of the C=C and C=O groups with the participation of the $-NH_2$ function, the resonance structures suggest complexing of metal ions at the carbonyl oxygen and/or nitrogen (Scheme 4) [18,25]. The presence of the conjugate double bond and a predominant resonance structure in the molecule causes an increase in the basicity of the amide group rendering easiness to protonate or metallate at the carbonyl oxygen and/or nitrogen. The mode



Scheme 3. The chemistry of amide complexes.



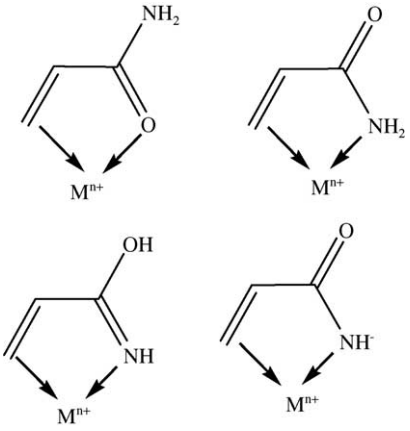
Scheme 4. Delocalized resonance structures of O-bonded acrylamide.



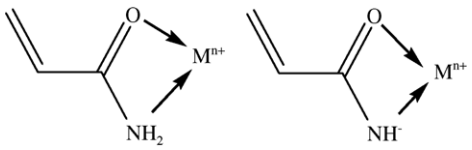
Scheme 5. Possible monodentate coordination modes of acrylamide.

of coordination being at either oxygen or nitrogen has been debated. Stronger coordination via the carbonyl oxygen is feasible. Metal ions that are considered to be "hard" (e.g. Cr(III), Co(III), Ru(III), Rh(III), etc.) and those that are on the "borderline" (Cu(II), Co(II), Fe(II), etc.) favor O-bonded amide complexation. Although the stronger basicity of the amide nitrogen in acrylamide as compared to simple amides seems to make protonation or complexation at this site more a possibility than in simple amides, there is no strong evidence that supports N-coordination modes for acrylamide complexes [28]. However, metal ions, which have strong affinity for N- over O-donor ligands may favor the formation of amide complexes either in the *N*-amide, *N*-iminol, or *N*-amidate forms. Acrylamide, which is also an unsaturated hydrocarbon, can act as a π-acceptor ligand bonding strongly to metals in low oxidation states via back donation in a η^2-mode [29,30]. Possible monodentate coordination modes of acrylamide are summarized in Scheme 5.

O-bonded interactions are more favored in the presence of a primary anchoring group capable of forming five membered chelate rings with a metal ion and the carbonyl oxygen in metal amide complexes [3]. However, chelation between a very weakly activated double bond and the carbonyl oxygen [32] or the amide nitrogen to form a five-membered ring in acrylamide is only probable. A much stronger chelate coordination between the olefin and the amide nitrogen can be formed by metal ion substitution of the nitrogen bound hydrogen [33]. Possible bidentate chelate rings in acrylamide complexes are summarized in Scheme 6. Chelation between the carbonyl oxygen and the amine nitrogen or the deprotonated nitrogen resulting in a rare four member chelate



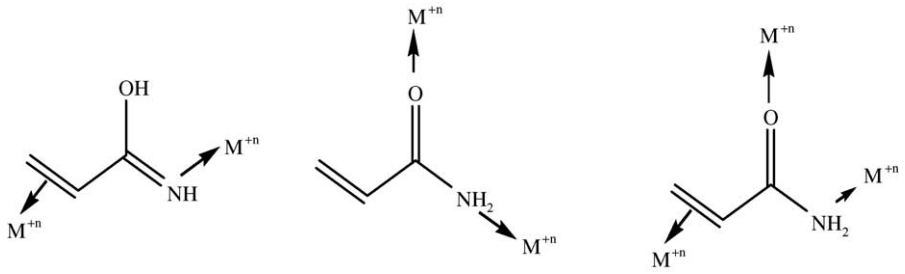
Scheme 6. Possible chelate rings in acrylamide complexes.



Scheme 7. Possible four-membered chelate rings in acrylamide complexes.

rings is an unlikely but an imaginable structural possibility (Scheme 7).

Another possibility is the simultaneous coordination of two or all donor sites in acrylamide where the ligand acts as a bridge between two or more metal atoms (Scheme 8). Bridging complexes with molybdenum and copper are known for acrylonitrile through its multiple donor sites [50].



Scheme 8. Possible bridging coordination modes of neutral acrylamide.

The structures of acrylamide complexes reported to support O-bonding, N-bonding, chelating or bridging modes are discussed in the following sections. Where available, emphasis is given to structures that are fully characterized using modern methods.

3.2. Oxygen-bound metal–acrylamide complexes

Fairlie and co-workers [2] reported the solution structure by NMR and reactivity of an O-bonded acrylamide complex of cobalt(III), $[(NH_3)_5Co(acrylamide\text{-}O)]^{3+}$, synthesized from the labile precursor $[(NH_3)_5CoOSO_2CF_3]^{3+}$ and acrylamide in poorly coordinating solvents (acetone or sulfolane). The complex solvolyzes to free acrylamide and hydroxopentaamminecobalt(III) complex in basic and coordinating neutral solutions. No amide O- to N-bonded linkage isomerization was detected for the complex in basic solution. The solid-state crystal structure of the complex has not been confirmed by X-ray diffraction.

The solid-state structures of acrylamide complexes of transition [18–23] and rare earth [24] metals in which the oxygen of the carbonyl group coordinates to the metal ion are well characterized using several physical methods.

Savost'yanov et al. [18] synthesized and characterized O-bonded acrylamide complexes of chlorides and nitrates of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), and Zn(II) by elemental and X-ray diffraction analysis, IR and electronic spectroscopy, and magnetic measurements. In this work only the X-ray structures of $[Co\ (AAm)_4(H_2O)_2](NO_3)_2$ were reported as an example. The molecular structure of the crystals consists of octahedral $[Co(AAm)_4(H_2O)_2]^{2+}$ cations and NO_3^- anions (Scheme 9). The Co(II) ion is coordinated by the O atoms of four AAm ligands and two H_2O molecules, and the structural framework is formed by a three-dimensional system of hydrogen bonds between the NH_2 and NO_3^- groups and between the coordinated H_2O molecules and NO_3^- anions.

Evstratova et al. [19] reported the synthesis and crystal structure of $[Cu(AAm)_4(NO_3)_2]$. The structure of the complex is composed of neutral centrosymmetric molecules united by a system of hydrogen bonds (Fig. 1). The Cu(II) polyhedron includes four acrylamide-O atoms coplanar with the Cu atom and two nitro-O atoms. The latter extend the copper polyhedron into a distorted (by the Jahn–Teller effect) octahedron (4+2). The coordinated AAm molecules are planar.

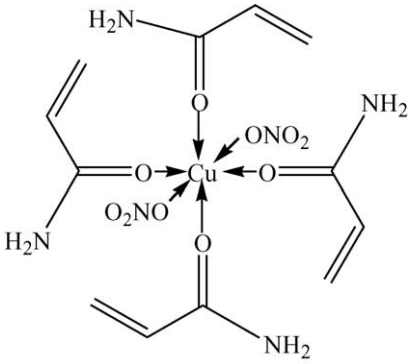
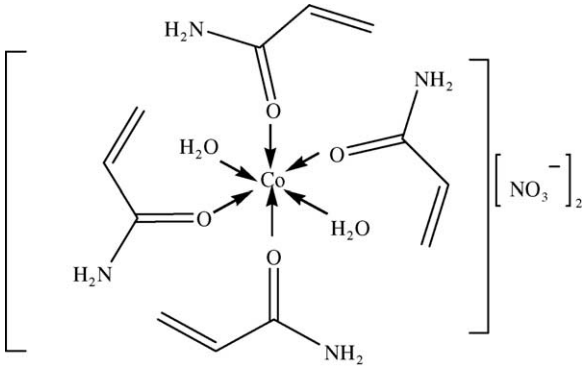


Fig. 1. Crystal structure of $[Cu(AAm)_4(NO_3)_2]$.

In our laboratory O-bonded tetragonally-distorted octahedral blue, $[Co(AAm)_4Cl_2]$ (Fig. 2), and violet, $[Co(AAm)_6][CoCl_4]$ (Fig. 3), crystals have been synthesized and characterized by single crystal X-ray diffraction [20]. The coordination geometry of Co(II) in the first complex involves four O-donor atoms of acrylamide in the equatorial positions and two chlorides in the apical positions. The complex $[Co(AAm)_6][CoCl_4]$ contains Co^{2+} cations surrounded by an octahedral array of acrylamide ligands, accompanied by the $[CoCl_4]^{2-}$ anion. In the counter ion $[CoCl_4]^{2-}$ the metal ion is tetrahedrally surrounded by four chlorine atoms.

Previously [21], the characterization of the $[Co(AAm)_4Cl_2]$ complex and its single crystals by diffuse reflectance spectra suggested a tetragonally distorted octahedral structure which is consistent to our present work. In this report, it was suggested that $[Co(AAm)_4Cl_2]$ changes its structure from a tetragonally distorted octahedron in



Scheme 9. Structure of $[Co(AAm)_4(H_2O)_2](NO_3)_2$.

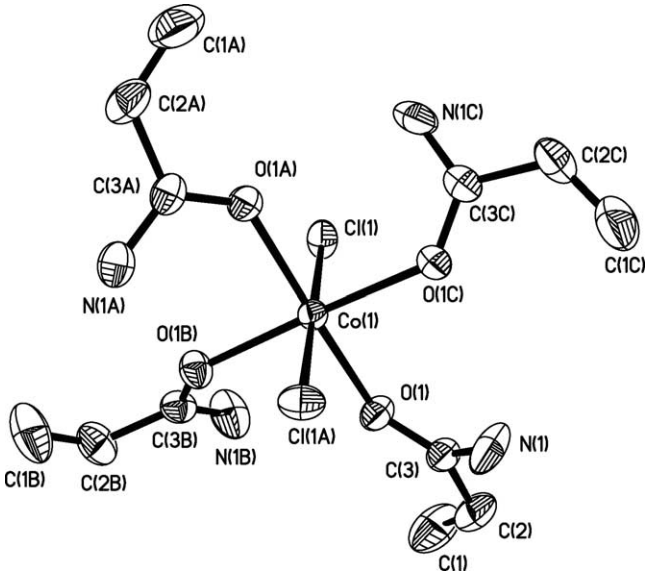


Fig. 2. Crystal structure of $[Co(AAm)_4Cl_2]$.

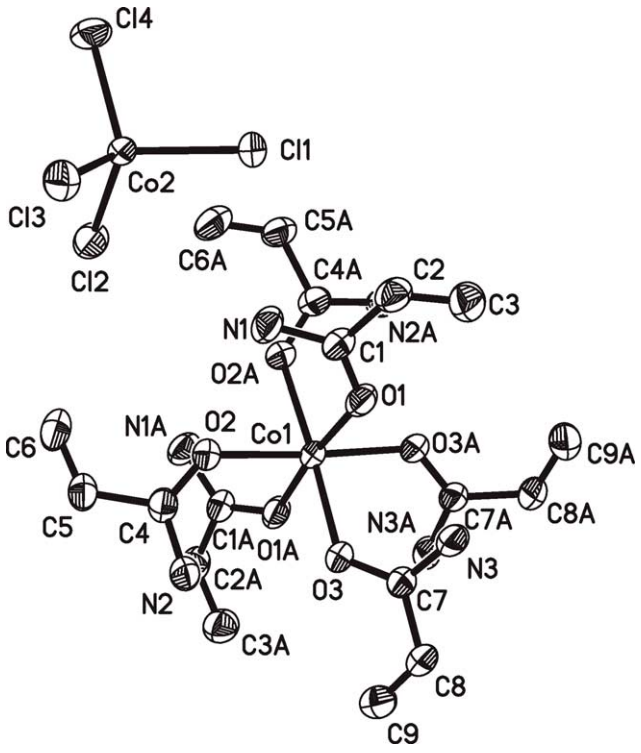


Fig. 3. Crystal structure of $[Co(AAm)_6][CoCl_4]$.

crystal to a tetrahedron in solution. The crystal structures of tetragonally distorted octahedral $[Co(AAm)_6][CoCl_4]$ rather suggest that the changes from the violet to blue and the vice versa in solution may be due to equilibria between the blue $[Co(AAm)_4Cl_2]$ and the violet $[Co(AAm)_6][CoCl_4]$ forms.

3.3. Nitrogen-bound metal–acrylamide complexes

In case of *N*-coordination, amides can adopt *N*-amide $[M\text{-}NH_2C(O)CH{=}CH_2]^{n+}$, *N*-amidate, $[M{-}NHCOCH{=}CH_2]^{(n-1)+}$ or *N*-iminol tautomeric forms $[M{-}NHC(OH)CH{=}CH_2]^{n+}$ (where M^{n+} = metal ion) [1,2,31,45]. Farona et al. [25,26] reported acrylamide complexes of tin(IV) halides, $SnX_4{\cdot}2AAm$ (X = Cl, Br), that exhibit coordination through *N*-amide nitrogen. However, the primary evidence for *N*-coordination in this work that comes from peaks of fragments of the composition SnN^+, $SnNH^+$ and $SnNH_2{}^+$ in the mass spectra is not conclusive, and an attempt to reinvestigate the mass spectrum of $SnCl_4{\cdot}2AAm$ did not show the above peaks in [22]. The exact structure of the complex remained unknown until now.

Barvinok and Mashkov [27] reported complexes with the general composition $MCl_2{\cdot}4AAm$, where M = Mn(II), Co(II), Ni(II), or Cu(II), and characterized them using IR spectroscopy to assume coordination through the nitrogen atom. The same authors published O-bonded complexes for M(II) nitrate acrylamide complexes [23]. In another study, Allan et al. [28] reported chloro complexes of copper, $[Cu(AAm)_2]Cl_2$, cobalt, $[Co(AAm)_2]Cl_2$, and nickel, $[Ni(AAm)_2]Cl_2$, with acrylamide characterized by electronic spectra, IR spectra and magnetic moments suggesting coordination through the amide nitrogen atom. On the contrary, the single crystal X-ray structure [20] and the spectroscopic data [18,21] for $[Co(AAm)_4Cl_2]$ suggest coordination through the carbonyl oxygen.

Metallation with less acidic transition metals at the amide nitrogen via deprotonation of the amide nitrogen in neutral or basic solutions has not been feasible due to the very weak acidity of the amide nitrogen [46–48]. Hydrogen distraction from the trigonal nitrogen in acrylamide and as a consequence metal ion substitution of amide hydrogen could be difficult even when using non-coordinating solvents and non-coordinating sterically hindered bases to avoid solvolysis. The solution structures of cobalt(III) complexes in which acrylamide adopts deprotonated *N*-amidate, $[M{-}NHCOCH{=}CH_2]^{(n-1)+}$ and *N*-iminol tautomeric forms $[M{-}NHC(OH)CH{=}CH_2]^{n+}$ (where $M = Co^{III}$, $n = 2$ or 3) characterized by NMR spectroscopy were deduced indirectly from the hydrolysis of coordinated acrylonitrile [31]. The *N*-iminol product was isolated pure by adding $HClO_4$ to an aqueous solution of $[(NH_3)_5CoNHC(O)CH{=}CH_2](ClO_4)_2$ prepared from the base catalyzed hydrolysis of $[(NH_3)_5CoN{\equiv}CCH{=}CH_2]^{3+}$.

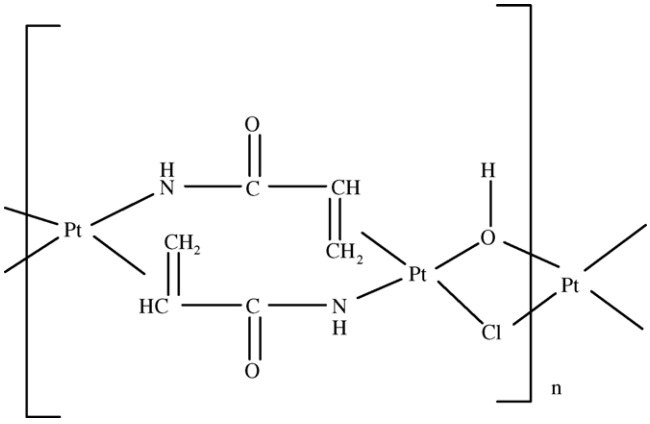
Generally, there is no strong evidence, especially from single X-ray diffraction, for *N*-amide, *N*-iminol or *N*-amidate metal–acrylamide species. In most cases an ambiguous interpretation of the IR spectra of acrylamide and acrylamide complexes demonstrated *N*-coordination. Previous results from mass spectrometry, theoretical calculations, spectroscopic and magnetic data are not conclusive and need to be reinvestigated by modern methods.

3.4. Complexes containing chelating or bridging acrylamide

The presence of an anchoring group capable of forming a chelate ring with a metal ion and the carbonyl oxygen stabilizes weak interactions between metal ions and the ligand. Yoichiro et al. [32] reported reactions of $CoH(N_2)(PPh_3)_3$ and $CoCH_3(PPh_3)_3$ with acrylamide that lead to displacement of all triphenylphosphine ligands to give chelate complexes of formulas $CoH(AAm)_3$ and $Co(AAm)_3$, respectively. Structural assignments based on ligand displacement equilibria and IR measurements suggest coordination of acrylamide through both the double bond and the carbonyl oxygen of substituted acrylamide.

By the substitution of the nitrogen bound hydrogen, metal ions can form bridging interactions on the amidate nitrogen and the olefin in acrylamide. Schmuckler and Limoni [33] prepared a polymeric platinum acrylamide complex, which exhibit bridging interactions (Eq. (1)).

$$H_2O + 2K_2PtCl_4 + 2CH_2{=}CHCONH_2 \rightarrow Pt_2(CH_2{=}CHCONH)_2(OH)Cl + 4KCl + 3HCl \quad (1)$$



Scheme 10. Proposed structure for the platinum acrylamide complex $Pt_2(CH_2{=}CHCONH)_2(OH)Cl$.

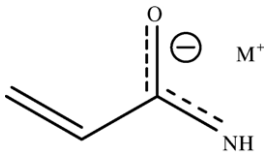
The IR spectrum of the platinum acrylamide complex suggests coordination through both the double bond and nitrogen presumably resulting in structure shown in Scheme 10. The experimental evidence from the IR spectra for the proposed structure includes a decisive weakening of the C=C vibration (a negative shift of 140 cm^{-1}) and consequent increase in CN vibration, weakened bending and rocking NH_2 vibrations and unchanged CO vibrations. Various authors have reported a negative shift of this magnitude when the metal coordinates to double or triple bonds [51].

4. Some reactions involving metal ions and coordinated acrylamide

Acrylamide is a weakly acidic and basic conjugated amide capable of coordinating to metal ions. The coordination of metal ions to the free acrylamide or to the amide residue of an acrylamide adduct may play a catalytic role in prompting biochemical reactions, that either the vinylic group or the amide residue can undergo. It is clear that metal atoms coordinated to an organic substrate affect the reactivity of the substrate [52].

The knowledge about the coordination compounds of acrylamide has been exploited to a certain degree and will continue to be in the focus of the polymer industry in searching for catalytic activity for polymerization and in building coordination polymers and special materials. Acrylamide complexes of transition metal nitrates, for example, are known for their unique property to undergo frontal polymerization under the mildest possible conditions that are known for such processes [4]. The following references are given without trying to be comprehensive for Lewis acid prompted polymerization reactions [4,5].

In this review, only some coordinated acrylamide or acrylamide-based ligands and metal ion prompted reactions are discussed. Emphasis is given to reactions that may give a hint in searching and identifying the potential role of coordination of acrylamide or adducts of acrylamide with metals or metal-containing biomolecules in biological systems.



Scheme 11. The structure of alkali metal salts of acrylamide.

4.1. Proton exchange reactions

The alkali metal salts of acrylamide C_3H_4NOM (M = Li, Na, and K) were synthesized by metallation of acrylamide with alkali metals in ammonia or especially from their alkyl derivatives and hydrides capable of influencing the deprotonation [53] (Scheme 11). Based on spectroscopic studies, ionic structures were proposed for the salts of acrylamide, C_3H_4NOM (M = Li, Na, and K).

N-Potassium acrylamide is obtained by treating acrylamide with potassium *t*-butoxide in *t*-BuOH at room temperature (Eq. (2)). The corresponding *N*-sodium acrylamide is more readily prepared by metallation of acrylamide with sodium amide in liquid ammonia [39].

$$CH_2{=}CHCONH_2 + KOC(CH_3)_3 \rightarrow CH_2{=}CHCONHK + (CH_3)_3COH \quad (2)$$

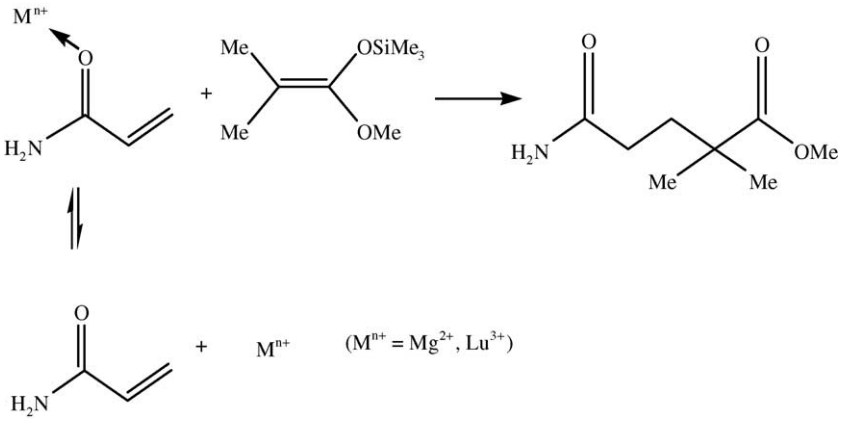
In the presence of coordinated metal ions, synthesis of the amido *N*-complexes under nonaqueous solution conditions from the parent amide are predicted on the assumption that the O-bonded isomer forms first and isomerizes to the stable nitrogen bonded species with the loss of an amide proton.

4.2. Metal ion prompted Michael addition of acrylamide

The Michael addition of β,β-dimethyl-substituted ketene silyl acetals with acrylamide occurs in the presence of magnesium perchlorate or lutetium trifluoromethanesulfonate in acetonitrile at 298 K via the 1:1 complexes between acrylamide and the metal ion in which the coordination of the metal ion enhances the electrophilicity of the acrylamide to accelerate the reaction rate [54] (Scheme 12).

4.3. Metal ion prompted conversion of acrylamide to ethylacrylate

The conjugation between the double bond and the amide group in acrylamide inhibits hydrolysis of the amide group by nucleophilic attack on the carbonyl carbon. However, some bacteria (e.g. *Pseudomonas chlororaphis* B-23, *Klebsiella pneumonia*, *Xanthomanos maltophilia*, and *Rhodococcus rhodochrous* J1) are known to efficiently metabolize acrylamide to ammonium acrylate using amidase [55]. This activity has already managed its way to industrial applications



Scheme 12. Metal ion prompted addition of acrylamide to ketene silyl acetal.

in biotechnology [56a]. Ciskanik et al. [56b] and Kotlova et al. [56c] reported chelating using EDTA does not influence enzymatic activity. Metal ion involvement in the mechanism has not been reported to the best of our knowledge, but the use of metal containing enzymes, which break amide linkages under conditions of physiological temperature and pH, have evolved an efficient method of converting carboxamides to carboxylic esters or acids in biological systems [57,58].

Czarnik [36] reported a model reaction of the mechanism in the biological system, where a nickel(II) ion coordinated to a Diels-Alder adduct of acrylamide and 2-pyridylanthracene promotes ethanolysis of acrylamide to ethyl acrylate simply by refluxing in ethanol (Scheme 13). Alcoholysis of acrylamide with methanol leading to ethyl acrylate catalyzed by Pr and Nd complexes has also been published recently [59].

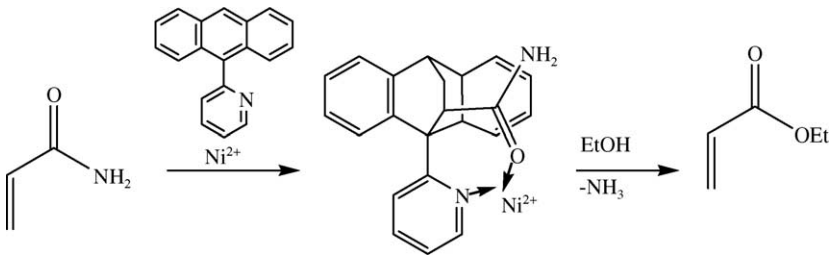
One such mechanism, in biological systems, utilizes bound zinc metal ions in amidase to polarize the amide carbonyl group via *O*-coordination, thereby increasing the rate of productive attack by oxygen nucleophiles at the carbonyl carbon to hydrolyze amides in biological systems [34,57,58]. A similar situation where metal ions in enzymes are involved with the hydrolysis of urea and acrylonitrile by nickel metalloenzyme jack bean urease and by iron- and cobalt-containing nitrile hydratases, respectively, are fairly known [60,61]. Higher animals are also capable of metabolizing compounds such as acrylamide via suitable metal containing enzymes [62].

4.4. Metal complexes of acrylamide-based macrocyclic ligands

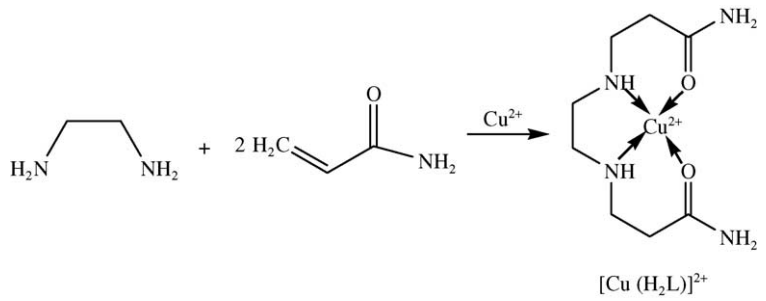
Hay et al. [37] reported the synthesis and structures of macrocyclic diamide ligand, *N*,*N*′-bis(2-carbamoylethyl) ethylenediamine (H_2L) from ethylenediamine and acrylamide by Michael addition, and their complexes of copper(II), nickel(II), palladium(II) (Scheme 14). The crystal structure of the carbonyl–oxygen bonded copper(II) complex, $[Cu(H_2L)]ClO_4$, have been determined by X-ray diffraction. Deprotonation of the complex occurs in two consecutive steps to give $[Cu(HL)]^+$ and $[Cu(HL)]$.

Kong and Xie [38] and Morrow et al. [63] reported octadentate macrocyclic ligands, *N*,*N*′,*N*″,*N*‴-tetrakis(2-carbamoylethyl)-*N*,*N*′,*N*″,*N*(-tetraazacyclotetradecane and *N*,*N*′,*N*″,*N*(-tetrakis(2-carbamoylethyl)-*N*,*N*′,*N*″,*N*(-tetraazacyclododecane and their cobalt(II), nickel(II), copper(II), zinc(II) [38] and lanthanum(III) [62]complexes (Scheme 15). The crystal structures of the cyclen-based macro cyclic cobalt(II), nickel(II), copper(II) and lanthanum(III) complexes have been determined by X-ray diffraction.

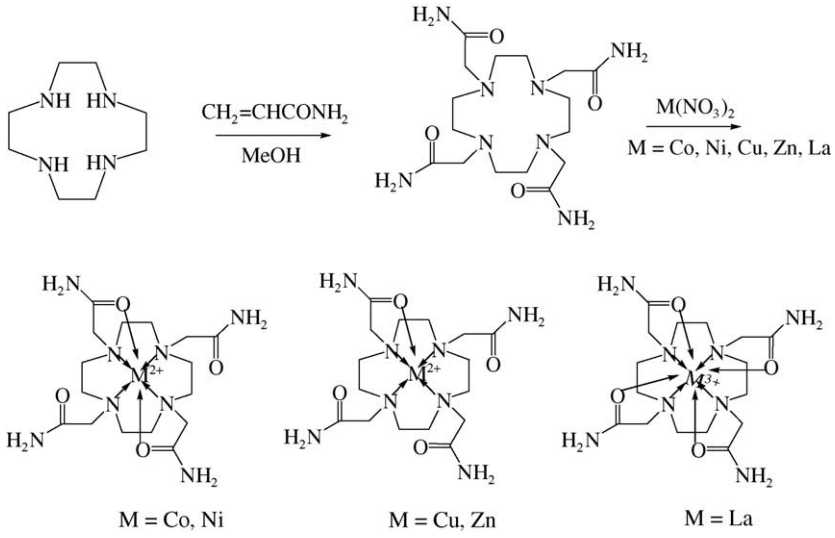
These structures demonstrate the possibility of acrylamide to bind to prosthetic groups such as in metalloporphyrins and metallocorrins and subsequently coordinate to a metal center via the amide moiety. Metal complexes of cyclen-based macrocyclic ligands containing bound acrylamide are known for their RNA and DNA cleavage ability and for their



Scheme 13. Metal ion prompted conversion of acrylamide to ethyl acrylate.



Scheme 14. Metal complex of diamide ligands based on acrylamide.



Scheme 15. Metal complexes of a macrocyclic ligand based on acrylamide.

antitumor and anti-HIV biological activities [38,62–64]. Recently, Sakano et al. [65] reported a mechanism of metal-mediated DNA damage induced by a metabolite of analogous carcinogenic acetamide treated with amidase in the presence of Cu(II).

5. Conclusions and future outlook

As a ligand, acrylamide can be monodentate *O*- or *N*-bonded, or exhibit a bidentate chelate rings or bridging complexes. It can be in the amide or the hydroxyimine tautomeric forms, and may be neutral or deprotonated. Which of these coordination possibilities are realized depends on the "hard" and "soft" nature and oxidation state of the metal center, counter ions, ligands to be substituted, solvent system, role of oxygen and moisture, and temperature during complexation [46–48].

Different types of modes, *O*-bound [18–24], *N*-bound [25–28], and chelating or bridging [32,33] coordinations of acrylamide with Lewis acids, were suggested in the previous solid-state structure studies; most of them based on spectroscopic experiments. Coordination of acrylamide to Ru(II) [29] and Os(II) [30] in η^2-mode, and linkages isomerizations of acrylamide complexes of $Ru(NH_3)_5^{2+/3+}$ from η^2 to η^1 when changing the oxidation states of the metal have been reported. The synthesis and solution structure by H^1 NMR spectra, and isomerization between different forms, $[(NH_3)_5CoOC(NH_2)CH{=}CH_2]^{3+}$, $[(NH_3)_5CoNHCOCH{=}CH_2](ClO_4)_2$ and $[(NH_3)_5CoNHC(OH)CH{=}CH_2](ClO_4)_3$, were reported together with a series of pentaamminecobalt(III) complexes of some other amides [2,31].

Despite the potential versatility of acrylamide as a ligand only few *O*-bonded complexes have been fully characterized by spectroscopic and single crystal X-ray crystal diffraction studies. The single X-ray crystal structures of $[Co(AAm)_4(H_2O)_2](NO_3)_2$ [18], $[Cu(AAm)_4(NO_3)_2]$ [19], $[Co(AAm)_4Cl_2]$ and $[Co(AAm)_6][CoCl_4]$ [20] show monodentate coordination exclusively through the carbonyl oxygen. No single crystals of the other compounds were isolated which means that no complete structure determination has been carried out until now for most acrylamide complexes.

Metal ion coordination in acrylamide enhances the electrophilicity of the acrylamide and increases its reactivity. Nickel-containing 2-pyridylanthracene, which models the

activity of metal containing enzymes that are involved in the conversion of carboxamides to carboxylic esters or acids, is known to catalyze the conversion of acrylamide to ethyl acrylate [34]. Alcoholysis of acrylamide with methanol was also reported in the presence of rare earth transition metal complexes [59]. Acrylamide and few biologically relevant adducts of acrylamide with ethylenediamine [59] and cyclen [60,62] are able to coordinate to biologically relevant metal ions such as Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+} and La^{3+}.

Although the presence of such reports on the coordination behavior of acrylamide and acrylamide adducts in non-physiological environment may not directly represent their behavior in biological systems, where many stronger ligands can compete for coordination, excluding the relevance of the coordination of metal ions and the interaction of bioinorganic molecules with acrylamide or its adducts from our efforts to understand and evaluate the health effects of acrylamide is unacceptable. This is especially true, when there are no studies on the coordination behavior of acrylamide or adducts of acrylamide with bioinorganic molecules in the physiological media.

How much do we know whether or not bound metal ions, metal ions in metalloproteins or metal-containing nucleic acids are involved in the metabolism, toxicity and carcinogenicity mechanism of acrylamide in biological systems? The possibility of biologically relevant metal ions to coordinate with acrylamide or its metabolites, thus activating or deactivating the reactions of the substrates and/or dysfunctioning of a metal ion due to coordination with acrylamide or its metabolites deserves much more attention in elucidating the mechanism of acrylamide metabolism and its health effects in future studies.

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