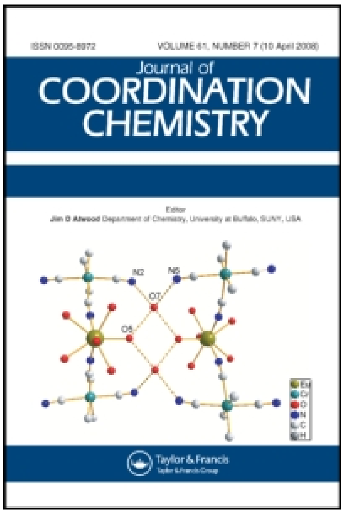

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# SEVERAL COORDINATION MODES OF 5-AMINO-1,3,4-THIADIAZOLE-2-SULFONAMIDE (HATS) WITH Cu(II), Ni(II) AND Zn(II): MIMETIC TERNARY COMPLEXES OF CARBONIC ANHYDRASE-INHIBITOR

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# SEVERAL COORDINATION MODES OF 5-AMINO-1,3,4-THIADIAZOLE-2-SULFONAMIDE (HATS) WITH Cu(II), Ni(II) AND Zn(II): MIMETIC TERNARY COMPLEXES OF CARBONIC ANHYDRASE-INHIBITOR

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The coordination properties of 5-amino-1,3,4-thiadiazole-2-sulfonamide (Hats) with Cu(II), Ni(II) and Zn(II) ions, are analyzed. Although the ligand presents several donor atoms, we have only observed three coordination behaviors: (i) as a monodentate ligand through the $N_{sulfonamido}$ atom, (ii) as a bridging ligand linking the metal ions through the $N_{sulfonamido}$ and $N_{thiadiazole}$ atoms and (iii) as a bridging ligand linking metal ions through the N and O atoms of the sulfonamidate group. It is noteworthy that coordination mode (iii) is observed for the first time in heterocyclic sulfonamides complexes. In addition, the conformation of the Hats as counter-ion is analyzed and compared with the conformations that the ligand adopts in metal complexes.

*Keywords*: 5-amino-1,3,4-thiadiazole-2-sulfonamide; Metal complexes; Zinc(II); Copper(II); Nickel(II); Carbonic anhydrase

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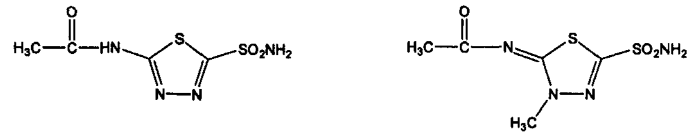
## INTRODUCTION

Carbonic anhydrase (CA) is a zinc metalloenzyme that catalyzes the reversible hydration of carbon dioxide to bicarbonate. One of the most potent inhibitors against this enzyme is acetazolamide ($H_2$acm), 5-acetamido-1,3,4-thiadiazole-2-sulfonamide (see Fig. 1) [1], which has been used clinically from 1954 [2]. Knowledge of the interactions of acetazolamide and other sulfonamide inhibitors with the enzyme is of inmense pharmacological and therapeutic interest [3–8].

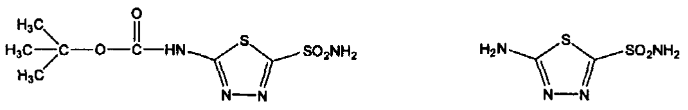
The synthesis of model compounds of enzyme active sites and inhibitor-enzyme complexes represents a new objective in the investigation of the structure-function relationship of catalytically active molecules [9]. The ligation of the zinc ion in the carbonic anhydrase active center has been modelled by tridentate ligands with nitrogen donors, but only a few model sulfonamide-metal complexes have been reported [10]. These need to be further explored.

Studies on coordination behavior have shown that acetazolamide presents a variety of coordination modes, depending on the nature of the metal ion and the deprotonation of the ligand [11–16].

As part of a research program devoted to the synthesis of structural derivatives of acetazolamide to study the effects of these changes on its inhibitory activity, pharmacological potency, acid-base behavior and metal coordination properties, we have studied some acetazolamide analogues which were modified in the electronic and structural characteristic of the substituent at the five position whereas the



Acetazolamide ($H_2$acm) Methazolamide (mHacm)



B-$H_2$ats Hats

FIGURE 1 Acetazolamide and related compounds.

thiadiazole ring and/or the sulfonamide moiety were kept unchanged [17–25] (see Fig. 1).

In this paper, we report the analysis of the coordination properties of 5-amino-1,3,4-thiadiazole-2-sulfonamide, Hats (see Fig. 1), one of these analogues, which is a poor carbonic anhydrase inhibitor (against isozyme II)[2] but its anticonvulsant activity in mice is three times greater than acetazolamide [26]. Our analysis is on a basis of zinc(II), copper(II), and nickel(II) complexes synthesized by us and their structures determined by single crystal x-ray diffraction.

## EXPERIMENTAL

### Reagents

Acetazolamide was provided by Sigma, St. Louis, MO. All reagents used were of analytical grade.

## SYNTHESIS OF THE COMPOUNDS

### Synthesis of the Ligand

5-amino-1,3,4-thiadiazole-2-sulfonamide (Hats) was prepared by acidic hydrolysis of acetazolamide and recrystallized from methanol : water (1 : 1) [27].

### Synthesis of $[Zn(ats)_2(NH_3)] \cdot H_2O$

The synthesis and crystal structure of this complex was reported in our previous work [28].

### Synthesis of $[Cu(ats)_2(dipn)]$

This complex was prepared by mixing copper(II) acetate hydrate (1 mmol), dipropylenetriamine (2 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (2 mmol) in ethanol (50 mL), at room temperature. Single crystals were obtained after five days from the resulting blue solution. The size of the selected crystal for x-ray diffraction was $0.23 \times 0.20 \times 0.10\,mm^3$.

### Synthesis of [Ni(dien)$_2$](ats)Cl • H$_2$O

This complex was prepared by mixing nickel(II) chloride hexahydrate (1 mmol), diethylenetriamine (2 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (2 mmol) in ethanol (50 mL), at room temperature. Single crystals were obtained after one month from the resulting pale purple solution. The size of the selected crystal for x-ray diffraction was $0.10 \times 0.15 \times 0.15\,mm^3$.

### X-ray Crystallography

X-ray measurements were carried out for [Cu(ats)$_2$(dipn)] and [Ni(dien)$_2$](ats)Cl · H$_2$O at 293 K on an Enraf-Nonius CAD-4 Single-crystal Diffractometer using Mo K$\alpha$ radiation with a graphite crystal monochromator ($\lambda = 0.7173$ Å). The unit cell dimensions were determined from the angular settings of 25 reflections (with $\theta$ between 0° and 26° for Cu(II) complex and between 1.79° and 24.98° for Ni(II)). Data were collected with the $\omega$-$2\theta$ scan technique and a variable scan rate, with a maximum scan time of 60 s per reflection. On all reflections, profile analysis was performed [29, 30]. Lorentz and polarization corrections were applied and the data were reduced to $F_o$ values.

The structure was solved by direct methods using the program SHELXS97 [31] and expanded by DIRDIF [32]. Isotropic full-matrix least-squares refinement on $F^2$ was accomplished using SHELX97 [33]. At this stage an empirical absorption correction was performed using XABS2. Atomic scattering factors were taken from International Tables for x-ray Crystallography [34]. Geometrical calculations were made with PARST [35].

## RESULTS AND DISCUSSION

Figures 2, 3 and 4 show the molecular structures of [Zn(ats)$_2$(NH$_3$)] · H$_2$O, [Cu(ats)$_2$(dipn)] and [Ni(dien)$_2$](ats)Cl · H$_2$O complexes, respectively.

The [Zn(ats)$_2$(NH$_3$)] · H$_2$O structure was described in previous work [28]. In this complex the coordination about the zinc ions is tetrahedral with the metal ion surrounded by four nitrogen atoms, three from the sulfonamide ligands and the other from the ammonia molecule, see Figure 2. The Zn—N$_{\text{sulfonamido}}$ and Zn—N$_{\text{ammonia}}$ bond distances are the same while the Zn—N$_{\text{thiadiazole}}$ is slightly larger (see Tab. I).

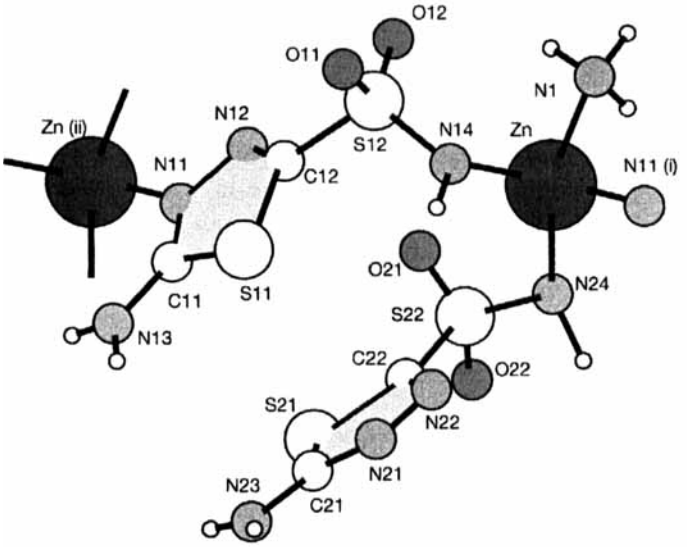


FIGURE 2 Molecular structure of $[Zn(ats)_2(NH_3)] \cdot H_2O$.

In the $[Cu(ats)_2(dipn)]$ structure, the copper ion shows a tetragonally elongated octahedral geometry, the four basal donor atoms being one sulfonamidate nitrogen atom from an $ats^{1-}$ ligand and three nitrogen atoms from dipropylenetriamine (dipn), which is positioned meridional (see Fig. 3). The axial sites are occupied by a sulfonamidate nitrogen atom from a second $ats^{1-}$ ligand and a sulfonamidate oxygen atom from a third $ats^{1-}$ ligand. The $Cu—N_{sulfonamido}$ distance of the equatorial plane, Cu1—N4 (see Tab. I) is comparable to those of the copper coordination compounds of related ligands [13, 17, 20, 36]. In contrast, the $Cu—N_{sulfonamido}$ distance of the apical ligand is quite long and observed for the first time for copper complexes with heterocyclic sulfonamides; this fact is related to the energetic preference of the elongated coordination mode in Jahn-Teller distorted octahedral copper complexes [37].

In the zinc and copper complexes, the sulfonamide ligand presents three coordination behaviors:

(i) as a monodentate ligand through the $N_{sulfonamido}$ atom, in both complexes. This coordination mode is normal for aromatic and heterocyclic sulfonamide ligands [6, 11, 17–19].

(ii) as a bridging ligand linking the metal ions through the $N_{sulfonamido}$ and $N_{thiadiazole}$ atoms, in the zinc complex. This is the unique case in which a thiadiazole sulfonamide derivative binds the zinc ion through the

$N_{thiadiazole}$ atom, although coordination through this atom has been observed in copper and nickel complexes [12, 13, 16, 20].

(iii) as a bridging ligand linking the metal ions through the nitrogen and oxygen atoms of the sulfonamidate group, in the copper complex. Some years ago, Ferrer *et al.* [16] synthesized a copper complex with acetazolamide and ethylenediamine in which the complexation of the metal ion is achieved through an oxygen atom of the sulfonamidate group. But this bridging coordination mode is observed for the first time in metal complexes with thiadiazole sulfonamide ligands.

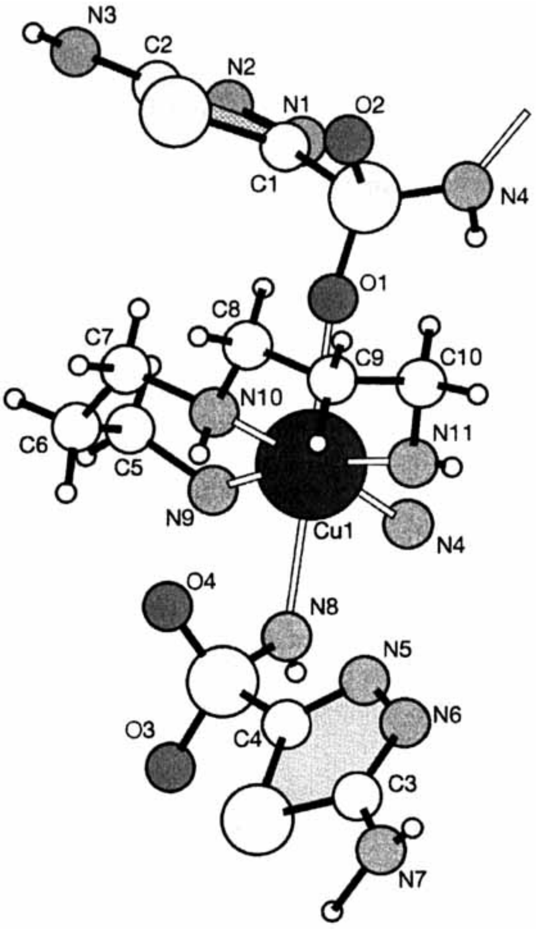


FIGURE 3 Molecular structure of $[Cu(ats)_2(dipn)]$.

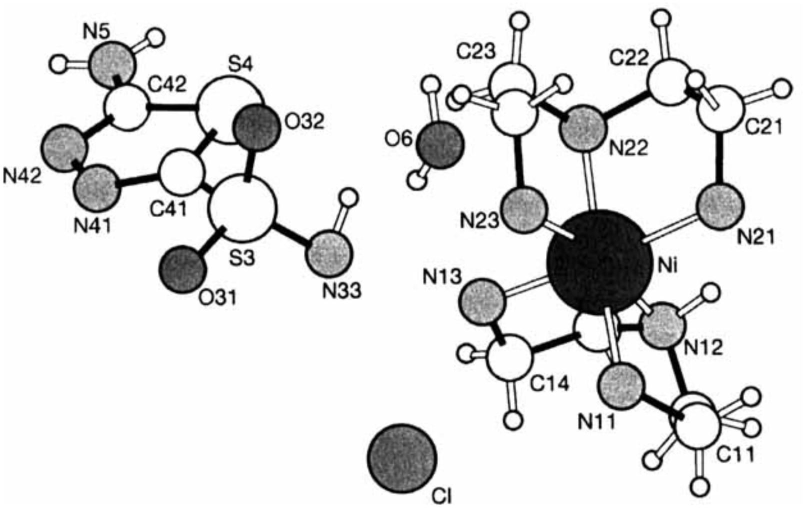


FIGURE 4 Molecular structure of $[Ni(dien)_2](ats)Cl \cdot H_2O$.

TABLE I Geometry and bond distances (Å) of the coordination polyhedra

| $[Zn(ats)_2(NH_3)] \cdot H_2O$[†] | | $[Cu(ats)_2(dipn)]$ | | $[Ni(dien)_2](ats)Cl \cdot H_2O$[‡] | |
|---|---|---|---|---|---|
| *Distorted tetrahedral* | | *Tetragonally elongated octahedral* | | *Octahedral* | |
| Zn—N1 | 1.989 (3) | Cu1—N9 | 2.003 (8) | Ni—N11 | 2.13 (2) |
| Zn—N14 | 1.989 (4) | Cu1—N10 | 2.087 (6) | Ni—N12 | 2.134 (5) |
| Zn—N24 | 1.987 (3) | Cu1—N11 | 1.995 (8) | Ni—N13 | 2.129 (6) |
| Zn—N11(i) | 2.045 (4) | Cu1—N4 | 2.074 (7) | Ni—N21 | 2.131 (5) |
| | | Cu1—N8 | 2.595 (7) | Ni—N22 | 2.13 (2) |
| | | Cu1—O1 | 2.431 (5) | Ni—N23 | 2.105 (5) |

[†] Reference [28].

[‡] The sulfonamide acts as counter-ion instead ligand.

The tridentate bridging coordination mode exhibited in the copper complexes of acetazolamide and B-$H_2$ats [13,20] is not observed for the Hats ligand. This is related with the substitution of the methylcarbonyl group (or tertbutyloxycarbonyl) by hydrogen in Hats molecule. The double bond of the carbonyl group is conjugated with the thiadiazole ring; thus, its absence modifies the electronic and coordination properties of the ring in Hats moiety. This is supported by several failures in the attempt to synthesize the ternary copper complex with Hats and ammonia.

For $[Ni(dien)_2](ats)Cl \cdot H_2O$, the coordination polyhedron consists of non-centrosymmetric unit of $[Ni(dien)_2]^{2+}$, in which the diethylenetriamine coordinates to the metal as a tridentate ligand in an unsymmetrical-facial position [38]. The Ni(II) ions are linked to six nitrogen atoms, forming $NiN_6$ chromophores with octahedral geometry slightly compressed in one axis (see Tab. I). If we compare the dimensions of this coordination polyhedron with that of the $[Cu(ats)_2(dipn)]$, we can observe the $Ni—N_{triamine}$ bond are longer than the $Cu—N_{triamine}$ ones. This fact is usually observed in $M—N_{ammonia}$ and $M—N_{pyridine}$ when nickel(II) and copper(II) complexes are compared [13, 17].

It is worth mentioning that the $[Cu(ats)_2(dipn)]$ complex was synthesized with the same metal : triamine : sulfonamide molar ratio (1 : 2 : 2) and similar experimental conditions to the $[Ni(dien)_2](ats)Cl \cdot H_2O$. The reason the bis(triamine) is not formed for the copper(II) complex, is related to the fact that the copper(II) ion is subject to the Jahn-Teller effect [39].

In the nickel complex, $[Ni(dien)_2(ats)Cl \cdot H_2O$, the sulfonamide behaves as a counter-ion instead of a ligand. As far as we know, this is the unique metal complex structure where the thiadiazole sulfonamide acts as counter-ion.

The main structural difference between the sulfonamidate anion and the free sulfonamide is the shortening of the N—S bond (see Tab. II). This is due to deprotonation of the sulfonamido group and subsequent delocalization of the negative charge through the N—S bond. This phenomenon is present for complexes in which Hats acts as a monodeprotonated ligand. Another structural feature of the counter-ion sulfonamidate is the slight increasing of the S(3)—O(31) bond due to electron transfer from the negatively charged N atom to the sulfonyl oxygen atom, resulting in S—O partial single bond character. This is also observed for $[Cu(ats)_2(dipn)]$, in which the two S—O bonds of the bridging ligand are increased, including one that is involved in the coordination to the metal ion. On the other hand, in

TABLE II Relevant bond distances (Å) of the Hats in different environments

| | *Free Hats*‡ | (i) | (ii) | (iii) | *Counter-ion* |
|---|---|---|---|---|---|
| *S—N* | 1.569 (2) | 1.542 (5)†<br>1.508 (7)* | 1.544 (5) | 1.517 (6) | 1.528 (6) |
| *S—O1* | 1.427 (1) | 1.435 (5)†<br>1.439 (6)* | 1.437 (4) | 1.456 (5) | 1.453 (7) |
| *S—O2* | 1.432 (1) | 1.444 (3)†<br>1.444 (6)* | 1.438 (3) | 1.451 (6) | 1.434 (6) |
| *N—N* | 1.375 (2) | 1.384 (4)†<br>1.383 (9)* | 1.389 (5) | 1.379 (8) | 1.384 (11) |

* In $[Cu(ats)_2(dipn)]$.
† In $[Zn(ats)_2(NH_3)] \cdot H_2O$.
‡ Reference [21].

(i) Monodentate ligand.
(ii) Bridging bidentate ligand through $N_{sulfonamido}$ and $N_{thiadiazole}$ atoms.
(iii) Bridging bidentate ligand through $N_{sulfonamido}$ and $O_{sulfonamido}$ atoms.

$[Zn(ats)_2(NH_3)] \cdot H_2O$ and other complexes like $[Ni(Hacm)_2(NH_3)_4]$ [12], the coordination through the $N_{thiadiazole}$ atom does not involve modification of the N—N bond length. These facts show that structural properties are more affected by deprotonation than by coordination, as was concluded by vibrational spectroscopy for similar metal complexes [24].

In conclusion, Hats ligand exhibits different coordination modes which involve the nitrogen and oxygen atoms of the sulfonamidate group and the ring nitrogen atom closest to the amino group. It seems reasonable to assume that the variable coordination behavior of Hats in mixed-ligand complexes with mono- or tri-amines depends on the nature of the metal ion and the limited steric requirements imposed by these auxiliary ligands.

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