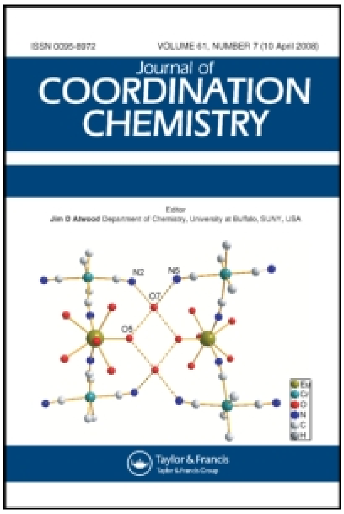


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

TRANSITION METAL COMPLEXES OF DL-AZETIDINE-2-CARBOXYLIC ACID

Carl R. White[a]; Melvin D. Joesten[a]
[a] Department of Chemistry, Vanderbilt University, Nashville, Tennessee, U.S.A.

To cite this Article White, Carl R. and Joesten, Melvin D.(1976) 'TRANSITION METAL COMPLEXES OF DL-AZETIDINE-2-CARBOXYLIC ACID', Journal of Coordination Chemistry, 6: 1, 53 — 57
To link to this Article: DOI: 10.1080/00958977608079883
URL: http://dx.doi.org/10.1080/00958977608079883

J. Coord. Chem.
1976, vol. 6, pp. 53–57

TRANSITION METAL COMPLEXES OF DL-AZETIDINE-2-CARBOXYLIC ACID

CARL R. WHITE[1] and MELVIN D. JOESTEN

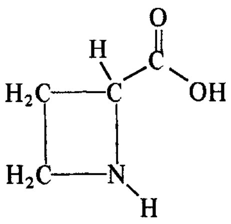
Contribution from the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, U.S.A.

(Received February 23, 1976; in final form April 12, 1976)

Azetidine-2-carboxylic acid and proline are unique among amino acids in that the amino group is part of a ring. In the present study several transition metal complexes of azetidine-2-carboxylic acid (AzCOOH) have been prepared. They include $Cu(DL\text{-}AzCOO)_2(H_2O)_2$, $Zn(DL\text{-}AzCO_2)_2(H_2O)_2$, $Ni(DL\text{-}AzCO_2)_2(H_2O)_{2.5}$, $Co(DL\text{-}AzCO_2)_3 \cdot 3H_2O$, and $Pt(DL\text{-}AzCO_2)_2$. These complexes are similar to the corresponding metal complexes of proline. Azetidine-2-carboxylic acid acts as a bidentate ligand with coordination to the metal ions through the amino and carboxyl groups.

INTRODUCTION

L-Azetidine-2-carboxylic acid is a homologue of L-proline, a major building stone of collagen, the protein of connective tissue, differing from L-proline by the loss of one methylene group from the ring. It has the structure shown below.



Most of the interest in azetidine-2-carboxylic acid (AzCOOH) has been concerned with the effects produced when it is substituted for proline in proteins. L-AzCOOH has been shown to inhibit growth of plant seedlings[2] and to produce deformation of limbs in chick embryos.[3] Other studies have shown that L-AzCOOH prevents viral RNA synthesis[4] and growth of Japanese encephalitis virus.[5]

The growth inhibiting properties of L-AzCOOH suggest its possible use as an anti-cancer agent. We are synthesizing sufficient quantities of DL-azetidine-2-carboxylic acid, L-azetidine-2-carboxylic acid, and metal complexes of both the racemic amino acid, and the L-isomer for screening as anti-tumor agents by the National Cancer Institute.

The present report describes the synthesis and characterization of several transition metal complexes of DL-azetidine-2-carboxylic acid. The only previous report of complexes of azetidine-2-carboxylic acid is that of Lin and Douglas, who isolated $Co(S\text{-}AzCO_2)_3$.[6]

EXPERIMENTAL

Preparation of DL-Azetidine-2-carboxylic acid

DL-Azetidine-2-carboxylic acid was prepared by the method of Phillips and Cromwell.[7] It was purified by fractional recrystallization from 92-93% methanol.

Preparation of $Cu(DL\text{-}AzCO_2)_2(H_2O)_2$

$Cu(OH)_2$ was prepared according to a previously published procedure.[8] DL-AzCOOH (0.43 g, 4.20 mmoles) was added to the stirred suspension of $Cu(OH)_2$ (0.4 g, 2.35 mmoles in 5 ml H_2O) causing the formation of a very dark blue solution. The mixture was stirred for one hour and filtered to remove a small amount of unreacted $Cu(OH)_2$. Acetone was added to the filtrate until precipitation was complete. The blue precipitate was filtered via suction, washed with acetone, and recrystallized from acetone-water. Yield = 0.30 g (47.8%).

Preparation of $Ni(DL\text{-}AzCO_2)_2(H_2O)_{2.5}$

$Ni(OH)_2$ was freshly prepared by adding KOH (0.24 g, 4.32 mmoles) in 50 ml of water to $NiSO_4 \cdot 6H_2O$ (0.57 g, 2.16 mmoles) in about 200 ml of water. The precipitated $Ni(OH)_2$ was filtered via suction and washed with water. The $Ni(OH)_2$ was transferred quantitatively to a beaker and suspended by stirring in 15 ml of water. DL-AzCOOH (0.44 g, 4.32 mmoles) was added to the mixture which was stirred for about four hours. The solution was filtered and the filtrate was concentrated to a small volume. Acetone was added to the solution until precipitation was complete. The light blue precipitate was filtered via suction and recrystallized from acetone-water by cooling at 0°C overnight. Yield = 0.10 g (15.6%).

Preparation of $Zn(DL\text{-}AzCO_2)_2(H_2O)_2$.

$Zn(OH)_2$ was prepared by the method of Dietrich and Johnston.[9] $Zn(OH)_2$ (0.20 g, 2.0 mmoles), DL-AzCOOH (0.40 g, 4.0 mmoles) and 15 ml of water stirred at 70-80°C for four hours. The mixture was filtered and the filtrate was evaporated to near dryness. It was cooled in a refrigerator to produce crystallization. The white product was collected by suction filtration and recrystallized from acetone-water. Yield = 0.29 g (54.7%).

Preparation of $Pt(DL\text{-}AzCO_2)_2$.

K_2PtCl_4 (0.20 g, 0.48 mmoles) and DL-AzCOOH (0.24 g, 2.40 mmoles) were dissolved in 2 ml of water in a small erlenmeyer flask. This mixture was heated on a water bath for about three hours. The solution was cooled and placed in the refrigerator overnight. White crystals were filtered and washed thoroughly with hot water. The product is insoluble in all common solvents. Yield = 0.02 g (10.5%).

Preparation of $Co(DL\text{-}AzCO_2)_3 \cdot 3H_2O$

$[Co(NH_3)_5(H_2O)](NO_3)_3$ (0.16 g, 0.5 mmoles) and DL-AzCOOH (0.16 g, 1.6 mmoles) were dissolved in about 5 ml of water and refluxed overnight at which time the generation of ammonia could not be detected with moist litmus paper. The solution was evaporated to dryness at room temperature and the residue was extracted with methanol. The methanol was evaporated and the remaining solid was recrystallized from acetone-water. A flaky pink precipitate formed after sitting at 0°C overnight. Yield = 0.015 g (8.3%).

Analyzes and Measurements

All compounds were dried under vacuum at 25°C before analysis. Carbon, hydrogen and nitrogen analyses were performed either by Galbraith Laboratories, Knoxville, Tennessee or PCR, inc., Gainesville, Florida.

Infrared spectra were recorded on a Perkin-Elmer 727 infrared spectrometer. All of the spectra were obtained by means of potassium bromide disks. The visible and near-infrared spectra were obtained for aqueous solutions. The spectra were recorded on a Cary Model 14 Recording Spectrophotometer using matched 1 cm silica cells.

Magnetic susceptibility measurements were obtained for powdered samples by the Faraday method. The measurements were recorded at 25°C using mercury(II) tetrathiocyanatocobaltate(II) as the reference. The magnetic susceptibility of $Zn(DL\text{-}AzCO_2)_2(H_2O)_2$ was used as the diamagnetic correction for paramagnetic complexes.

Proton NMR spectra were recorded on a JEOL MH-100 spectrometer. The spectrum of the ligand was measured in approximately 10% solution in deuterium oxide. The complexes were measured as saturated solutions (2–3%) in deuterium oxide. Measurements were made at ambient temperature using acetone as an internal standard.

The acid dissociation constants for DL-AzCOOH were calculated by the method developed by Irving and Rossotti.[10] The techniques of Irving and Pettit were employed in collecting the experimental data.[11] Carbonate free 3.4792 M NaOH solution was prepared and standardized by titrating accurately weighed samples of potassium hydrogen phthalate. 0.0609 M HCl solution was standardized with the standard base solution. The acid dissociation constants were calculated from data obtained by titrating 100 ml of the standard acid solution in the absence of and in the presence of DL-AzCOOH. The concentration of DL-AzCOOH was 0.0600 M. The titrations were followed by means of pH measurements read on an Orion model 801 digital pH meter which had been standarized at pH 4 and 10. The pH of the solution was measured with a saturated calomel reference electrode and a glass electrode. The ionic strength of both solutions was adjusted to 0.15 M with KCl. The titrations were performed at 20± 0.1°C in a double-walled glass vessel through which water from a thermostat-bath was circulated. The MaOH solution was delivered by means of a 10 ml buret calibrated to 0.01 ml.

RESULTS AND DISCUSSION.

The complexes of DL-azetidine-2-carboxylic (DL-AzCOOH) have properties similar to the

TABLE I
Analytical data for DL–azetidine–2-carboxylic acid complexes

		% Carbon		% Hydrogen		% Nitrogen	
Compound	Color	Calc	Found	Calc	Found	Calc	Found
DL–AzCOOH	White	47.47	47.47	6.98	6.97	13.86	13.82
$Cu(DL–AzCO_2)_2(H_2O)_2$	Blue	32.02	32.15	5.38	5.18	9.35	9.37
$Zn(DL–AzCO_2)_2(H_2O)_2$	White	31.83	31.78	5.35	5.54	9.29	9.16
$Ni(DL–AzCO_2)_2(H_2O)_{2.5}$	Light Blue	31.58	31.64	5.63	6.01	9.22	9.61
$Pt(DL–AzCO_2)_2$	White	24.28	24.26	3.06	2.94	7.09	6.96
$Co(DL–AzCO_2)_3 \cdot 3H_2O$	Pink	34.64	34.84	5.85	5.41	10.16	9.91

corresponding complexes of proline and other commonly studied amino acids. DL-AzCOOH acts as a bidentate ligand by forming five-membered chelate rings with the metal ions. The ligand coordinates to the metal ions through the amino and carboxyl groups.

The stoichiometries of the complexes were determined by carbon, hydrogen and nitrogen analyses. The analytical data and colors of the complexes are listed in Table I. The complexes with Ni(II) and Co(III) were isolated with varying amounts of water present. After repeated recrystallizations, the number of water molecules was 2.5 for the Ni(II) complex and 3 for the Co(III) complex.

Infrared and Electronic Spectral Data

The infrared and electronic spectral data are listed in Table II. The most important absorption band in the infrared spectra of the complexes of DL-AzCOOH is the asymmetric stretching band of the carboxylate group. This band occurs at 1580 cm^{-1} for the uncoordinated DL-AzCOOH. A shift to higher frequency is observed for the asymmetric carboxylate stretching mode for each of the complexes investigated. This indicates that the carboxyl group acts as a donor group in each of the complexes. The shift in frequency, $\Delta\nu$, varies from 17 cm^{-1} for the Ni(II) complex to 75 cm^{-1} for the Pt(II) complex. A peak at approximately 3400 cm^{-1} which is attributed to water absorption is found in the spectrum of every metal complex which has water included in its formula in Table II. The only complex which does not contain water is $Pt(DL\text{-}AzCO_2)_2$.

The electronic spectrum of $Cu(DL\text{-}AzCO_2)_2(H_2O)_2$ shows a single absorption peak centered at 625 nm. All of the complexes of the type *bis*(amino-acidate) copper(II) have a similar visible spectrum, with one broad band at approximately 620 nm due to d-d transitions.[12] $Cu(proline)_2(H_2O)_2$ absorbs at about 610 nm with a molar absorptivity, ϵ, of about 70. These spectra are characteristic of an octahedral configuration about the Cu(II) ion with the two water molecules occupying axial positions and with the amino acid ligands occupying equatorial positions where the N atoms are coordinated *trans* to one

TABLE II
Infrared and electronic spectral data for DL–azetidine–2-carboxylic acid complexes[a]

Compound	λ_{max}[b] nm (cm^{-1})	ϵ	$\nu(COO_{asy})$, cm^{-1}
DL–AzCOOH			1580
$Cu(DL–AzCO_2)_2(H_2O)_2$	625 (16,000)	60.5	1605
$Zn(DL–AzCO_2)_2(H_2O)_2$			1602
$Ni(DL–AzCO_2)_2(H_2O)_{2.5}$	1033 (9,681)	5.5	1597
	632 (15,823)	4.9	
	372 (26,882)	8.8	
$Pt(DL–AzCO_2)_2$			1655
$Co(DL–AzCO_2)_3 \cdot 3H_2O$	528 (18,939)	160	1640
	380 (26,316)	152	

[a] As KBr disks.
[b] Determined as aqueous solutions of 10^{-2}–10^{-3}M.

another.[13] The crystal structure has been determined for Cu(L-proline)$_2$ confirming this *trans*-N configuration.[14] The absorption spectra of the solid state and the solution are very similar which indicates that the structure of Cu(DL-proline)$_2$ is probably *trans* in solution. The similarity of the spectra of Cu(DL-proline)$_2 \cdot 2H_2O$ and Cu(DL-AzCO$_2$)$_2$(H$_2$O)$_2$ indicate the latter is probably a *trans* isomer with water molecules occupying the axial positions.

The electronic spectrum of Ni(DL-AzCO$_2$)$_2$(H$_2$O)$_{2.5}$ contains three peaks at 1033, 632 and 372 nm. They are assigned to the d-d transitions $^3T_{2g} \leftarrow {}^3A_{2g}$, $^3T_{1g}(F) \leftarrow {}^3A_{2g}$ and $^3T_{1g}(P) \leftarrow {}^3A_{2g}$, respectively. The three absorption peaks are of low intensity as shown by the molar absorptivities listed in Table II. This spectrum is similar to the electronic spectrum determined for the corresponding proline complex.[15] The Dq value for Ni(DL-AzCO$_2$)$_2$(H$_2$O)$_{2.5}$ is 968 cm^{-1}. The Dq values for the corresponding complexes of proline, alanine, valine and aspartic acid are 999, 990, 988 and 964 cm^{-1}, respectively.[15] The decrease in the Racah parameter, as defined by β, is 0.86 for Ni(DL-AzCO$_2$)$_2$(H$_2$O)$_{2.5}$. This compares to 0.93 for Ni(H$_2$O)$_6^{2+}$ and 0.82 for Ni(proline)$_2 \cdot 2H_2O$.

The electronic spectrum of Co(DL-AzCO$_2$)$_3 \cdot 3H_2O$ consists of two absorption peaks at 528 and 380 nm which are the same as those observed by Lin and Douglas for Co(S-AzCO$_2$)$_3$.[6] The relative intensities of the peaks and the lack of splitting of the 528 nm peak is characteristic of the facial isomers of most amino acids. The meridional isomers of Co(III) amino acid complexes show a splitting of the first peak into two peaks. The spectral data indicate that Co(DL-AzCO$_2$)$_3 \cdot 3H_2O$ exists in a facial configuration.

NMR Spectral Data

Azetidine-2-carboxylic acid and proline are unique among amino acids in that the amino group is contained within a ring. The data reported herein (Table III) are the first NMR spectral data recorded for complexes of these ligands. The spectra were determined as D$_2$O solutions which contained acetone as an internal standard.

A shift to higher frequency was observed for the proton absorptions of the anionic ligand as compared to the free ligand. This shift is about 30 Hz for the α-proton, 5 – 20 Hz for the β-protons, and 20 Hz for the γ-protons. A shift in electron density toward the four-membered ring of the amino acid occurs upon losing the acidic proton. This produces greater shielding about the ring protons which results in the upfield chemical shift. The NMR spectrum of Zn(DL-AzCO$_2$)$_2$ (H$_2$O)$_2$ is similar to the spectrum of the anionic ligand.

Magnetic Susceptibility Results

The Co(III), Zn(II), and Pt(II) complexes are diamagnetic. The corrected molar susceptibility for Cu(DL-AzCOO)$_2$(H$_2$O)$_2$ was 1503 x 10^{-6} cgs at 25°C which gives a magnetic moment of 1.90 BM. For Ni(DL-AzCO$_2$)$_2$(H$_2$O)$_{2.5}$ the corrected molar susceptibility was 3966 x 10^{-6} cgs at 25°C which gives a magnetic moment of 3.08 BM. These magnetic moments are within the ranges expected for octahedral complexes (1.70–2.20 BM for Cu(II) and 2.80–3.50 BM for Ni(II)). The diamagnetic susceptibility of the Co(III) complex indicates a strong-field d^6 configuration.

Acid Dissociation Constants

The average pKa$_1$ value is 1.83; the average pKa$_2$

TABLE III
Proton magnetic resonance data

Compound	Proton environment	δ, ppm (relative to TMS)
DL–AzCOOH[a]	CHCO	4.62, triplet
	CH$_2$N	4.16–3.55, multiplet
	CH$_2$CHCO	2.88–2.14, multiplet
DL–AzCOO$^{\theta}$[b]	CHCO	4.35, triplet
	CH$_2$N	3.85–3.39, multiplet
	CH$_2$CHCO	2.87–2.11, multiplet
Zn(DL–AzCO$_2$)$_2$(H$_2$O)$_2$[c]	CHCO	4.33, triplet
	CH$_2$O	3.84–3.19, multiplet
	CH$_2$CHCO	2.72–1.90, multiplet

[a] In 10% D$_2$O solutions with acetone internal standard.
[b] For a 5% D$_2$O solution at pH of 12.
[c] For a saturated D$_2$O solution (2–3%).

value is 10.46. Both values were determined at 20 ± 0.1°C. These values compare to 1.95 and 10.63, respectively, for L-proline. The pKa_2 value determined herein supports the previously recognised trend that secondary amino acids have higher dissociation constants than the acids with a primary amino group. This trend is attributed to an increased inductive effect on the nitrogen of the NH group, making removal of the second proton more difficult.[12]

REFERENCES

1. Taken from the Ph. D. Dissertation of C. R. White, Vanderbilt University, 1976. We wish to acknowledge the support of this research by Vanderbilt University.
2. L. Fowden, *J. Exp. Botany,* **14**, 387 (1963).
3. T. V. Zamaraeva and V. I. Mazurev, *Vop. Med. Khim.,* **18**, 430 (1972).
4. F. D. Collins and W. K. Roberts, *J. Virol.,* **10**, 969 (1972).
5. A. Izarashi, F. Sasao, and K. Fukai, *Biken. J.,* **17**, 35 (1974).
6. C. Lin and B. E. Douglas, *J. Coord. Chem.,* **2**, 117 (1972).
7. B. A. Phillips and N. H. Cromwell, *J. Hetero. Chem.,* **10**, 795 (1973).
8. A. Lepore, *Anales asoc. quim y farm. Uruguay,* **48**, 5 (1946); *Chem. Abs.,* **43**, 7361h (1949).
9. H. G. Dietrich and J. Johnston, *J. Am. Chem. Soc.,* **49**, 1419 (1927).
10. H. M. Irving and M. S. Rossotti, *J. Chem. Soc.,* **1954**, 2904.
11. H. Irving and L. D. Pettit, *J. Chem. Soc.,* **1954**, 1546.
12. R. D. Gillard, H. M. Irving, R. M. Parkins, N. C. Payne, and L. D. Pettit, *J. Chem. Soc. (A),* **1966**, 1159.
13. D. P. Graddon and L. Munday, *J. Inorg. Nuclear Chem.,* **23**, 231 (1961).
14. A. A. Mathieson and H. K. Welsh, *Acta Cryst.,* **5**, 599 (1952).
15. R. A. Haines and M. Reimer, *Inorg. Chem.,* **12**, 1482 (1973).