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Synthesis, crystal structure, IR and Raman properties of 1,2-diacetamidocyclohexane and its complexes with ZnBr₂ and HBr₃

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Abstract

X-ray crystallography, infrared absorption and Raman scattering were applied to study the influence of Zn(II) or H^+ on the amidic bond. (R,R)-1,2-diacetamidocyclohexane (DAACH) was chosen as a conformationally strained chiral building block including two amide bonds; this model is hoped to be not too far from a peptide and gives easily crystalline complexes.

Crystallographic structures of DAACH molecule (1), DAACH/ZnBr₂ (2) and DAACH/HBr₃ (3) complexes were studied.

Complexation of Zn by DAACH is due to the hyperpolarization of the amidic bond. IR and Raman studies of 1–3 agree with the X-ray results. This could be a model in the study of metal/proteins interactions or acidic denaturation of polypeptides.

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Keywords: DAACH; Complexes with Zn(II) or H+; X-ray structures; IR; Raman

1. Introduction

Secondary or tertiary native structure of proteins cannot be predicted from the protein's amino-acids sequence alone whereas successive residues with identical or nearly identical main chain conformation form α helices β sheets or polyproline type II helices; adjacent residues with enantiomeric main chain conformation form so-called nests when the (ϕ , ϕ) values are close to -90.0 and $+90.0^{\circ}$. This concept sets the stage for a general approach to binding sites in proteins.

Main chain N–H groups form a binding site at the N terminal of an α helix and amidic oxygen atoms behave similarly to those of carboxylates; they can bind cations and thus are named the *catgrips* [1], performed with the help of protein structure databases [2].

Following our work concerning the crystallographic structure of amides/cations complexes [3–5], we decided to build a synthetic chiral model as close as possible to

peptides, being capable of binding metals or cations in crystalline complexes.

Our purpose was to study the influence of a metal on the tautomeric forms of the amidic bond. As tools, X-ray crystallography, infrared absorption and Raman scattering were used to study these organometallic interactions.

(R,R)-1,2-diacetamidocyclohexane (DAACH) was chosen as a chiral building block containing two amide bonds; this conformationally preorganized model is hoped to be not too far from a peptide and gives easily crystalline complexes due to its strained geometry. As a model of metal/amide interaction Zn(II) as ZnBr₂ has been chosen. The electron configuration 3d¹⁰ of Zn(II) implies that the stereochemistry of the complexes formed depend on size of the ligand or electrostatic forces.

Peptide/zinc interactions are common in biochemistry. Angiotensin Converting Enzyme is the prototype of a Zn containing peptide and many metalloproteases are Zn containing molecules. The action of hydroperbromic acid on DAACH has been studied with the crystallized DAACH/ HBr₃ complex as a model of a strong acid influence on a peptide structure.

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In this paper, crystal structures of DAACH and DAACH/ HBr₃ are reported and compared with a DAACH/ZnBr₂ complex recently described by us [5]. IR and Raman studies complete crystallographic results.

Amidification of 1,2-diacetamidocyclohexane (DAACH) give flexibility in the side chain. Changes in configuration are in relation with the interaction of Zn(II) or H^+ and the amidic bond. If crystalline DAACH is bounded as a dimmer by two conventional hydrogen bonds, DAACH dibromozinc is a catena-structure. Each DAACH is bounded with another threw a three centers atomic bond including double bounded oxygen Zn(II) and another double bounded oxygen.

DAACH hydroperbromide complex is a catena-ionized molecule. A three center atomic bond joins each DAACH to another. This bond is formed with amide oxygen, external H^+ and the amide oxygen of a second DAACH.

2. Experimental

2.1. Preparation of crystalline complexes

2.1.1. Catena-(R,R)-1,2-diacetamidocyclohexane (DAACH) (1)

This compound was synthesized by acetylation of commercial (R,R)-1,2-diaminocyclohexane using triethylamine (1/1) and acetic anhydride in excess (3/1). Suitable crystals were grown from the saturated boiling solution of **1** in the glacial acetic acid by slow cooling (mp > 240 °C).

2.1.2. Catena-poly(hydrogenato)- μ -(R,R)-1,2,diacetamido cyclohexane (3)

DAACH/HBr₃ crystals were prepared as following: an acetic solution of HBr₃ is prepared by addition of equimolecular quantities of bromine to a saturated solution of HBr in acetic acid. HBr₃ and DAACH were then reacted in stoechiometric quantity to give the complex **3**. A slow evaporation of saturated acetic acid solution leads to suitable crystals as orange needles (mp=210 °C, dec.).

2.2. X-ray crystallographic study

Data were collected on a Enraf–Nonius CAD4 diffractometer at 293 K, with graphite monochromated Mo K α radiation, with data collection and reduction using CAD4 Express Enraf–Nonius (1994) programs package [6] and XCAD4 (1995) [7]. All data were corrected for Lorentzpolarisation effects. All the structures were solved by direct methods using SIR92 [8] and refined by least-squares methods on F^2 using SHELXL97 [9]. Hydrogen atoms were inserted at calculated positions. The same isotropic thermal parameter for all H atoms is refined. Drawings of these molecules were obtained with the CAMERON program [10]. All programs used for structure refinement are incorporated

Table 1

Crystal data of R,R-1,2-diacetamidocyclohexane(1) catena-poly(h	ydrogen-
ato)- μ -(R,R)-1,2-diacetamidocyclohexane (3)	

	1	3
Formula	C ₁₀ H ₁₈ N ₂ O ₂	C ₁₀ H ₁₉ Br ₃ N ₂ O ₂
Formula weight	198.26	439.00
Crystal system	Monoclinic	Orthorhombic
a (Å)	10.113(5)	9.572(2)
<i>b</i> (Å)	4.825(5)	15.115(3)
<i>c</i> (Å)	11.533(5)	11.340(5)
β (°)	96.644(5)	
$V(Å^3)$	559.0(7)	1640.7(9)
Space group	$P2_1$	C222 ₁
Z	2	4
$Dx (g cm^{-3})$	1.178	1.777
μ (Mo K α) (mm ⁻¹)	0.82	7.37
Independent reflections	3253	2405
Reflections number $I > 2\sigma(I)$	1835	690
R	0.051	0.055
Rw	0.141	0.132
Largest diff. peak and hole (e \AA^{-3})	-0.17/0.21	-0.62/0.55

See crystal data of catena-poly[[dibromozinc(II)]- μ -(R,R)-1,2-diacetami-docyclohexane] (2) earlier published [5].

in the WINGX package [11]. The crystallographic data and refinement parameters are shown in Table 1.

2.3. Raman scattering and infrared absorption spectra

Raman scattering spectra were obtained with a resolution of 1 cm^{-1} using a Bruker IFS66+FRA106 interferometer and a continuous YAG laser (1.06 µm) for excitation. Raman spectra obtained on a Dilor Labram spectrometer with excitation at 514.5 nm have not been used, because they were of poor quality due to the fluorescence of the samples.

Infrared spectra were recorded on a Bruker IFS66 interferometer with a resolution of 1 cm^{-1} on KBr pellets or on a Bruker Vector 22 using an ATR cell (resolution 4 cm⁻¹).

Table 2 Selected geometric parameters $(\text{\AA}, ^{\circ})$ and hydrogen-bonding geometry $(\text{\AA}, ^{\circ})$ for 1–3

	1	2	3
O2–C2	1.229(3)	1.237(7)	1.247(9)
N3-C2	1.328(3)	1.339(7)	1.297(10)
011-C11	1.224(3)	1.264(7)	
N10-C11	1.333(3)	1.324(7)	
Zn–O2 ⁱ		1.974(4)	
Zn-011		1.970(4)	
O2-C2-N3	122.3(2)	118.4(5)	119.4(7)
O11-C11-N10	123.0(3)	118.6(5)	
N10 ⁱ⁻ H10 ⁱ …O11	2.864(4) 172		
N3–H3…O2 ⁱ	2.894(4) 169		
N3-H3…O11		2.864(6)	
		127	
O2…H2…O2 ⁱⁱⁱ			2.473(10)
			179(11)

i: x, y-1, z; ii; x, y+1, z; iii: 1-x, y, 5/2-z.



Fig. 1. R,R-1,2-diacetamidocyclohexane (DAACH) (a) scheme, (b) perspective view showing 20% probability displacement ellipsoids. Hydrogen atoms are omitted for clarity except for those involved in hydrogen bonding (dotted lines). Symmetry code i, x, y-1, z.

Deuterated derivatives were obtained by dissolution of the compounds in deuterium oxyde followed by evaporation of the solution under heating (DAACH, DAACH/ ZnBr₂) or by dissolution in deuterated methanol (CH₃OD) followed by evaporation of the methanol (DAACH, DAACH/HBr₃).

3. Results and discussion

3.1. Crystal structures

Selected interatomic distances, bond angles and hydrogen bonds are given in Table 2.

3.1.1. Catena-(R,R)-1,2-diacetamidocyclohexane

The two amidic bonds of this molecule are in a strained conformation due to cyclohexane with the two nitrogens at a distance close to that found in peptides. Molecules of DAACH are found in the structure as pseudopeptide backbone mimic (Fig. 1). Individual molecules are linked into chains running parallel to b axis by two intermolecular hydrogen bonds involving H3 and H10.

The intramolecular hydrogen bonds are impossible to form due to the strained conformation of DAACH [N3…O11: 3.921(3) Å or N10…O2: 3.953(3) Å].

The bond lengths within the amide portions of DAACH [1.224(3) and 1.229(3) Å for C=O; 1.328(3) and 1.333(3) Å for C–N], are in good agreement with distances found for free amide (1.24 and 1.325 Å, respectively) [12].

3.1.2. Catena-poly[[dibromozinc(II)]-µ-(R,R)-1,2diacetamidocyclohexane]

Crystallized complexes of 2 present a catena structure [5] with Zn bridging two amides belonging to two molecules (Fig. 2). It is to our knowledge the first example of such a type of bridge with Zn.

Inclusion of Zn in the structure is due to hyperpolarization of the amidic bond with subsequent changes in the conformation. DAACH is in a chair conformation with the two acetamid groups in equatorial positions. The difference between the two C=O bond lengths [C2–O2: 1.237(7) Å and C11–O11: 1.264(7) Å] can be explained by the presence of the N –H···O intramolecular hydrogen bond [N3···O11: 2.864(6) Å, 127°] which causes the stretching of



Fig. 2. Catena-poly[[dibromozinc(II)]- μ -(*R*,*R*)-1,2-diacetamidocyclohexane]. (a) Scheme, (b) perspective view showing 20% probability displacement ellipsoids. Hydrogen atoms are omitted for clarity except for those involved in hydrogen bonding (dotted lines). Symmetry codes i; *x*, *y*-1, *z*; ii: 1-*x*, -*y*, 1-*z*.



Fig. 3. Catena-poly(hydrogenato)- μ -(*R*,*R*)-1,2-diacetamidocyclohexane. (a) Scheme, (b) perspective view showing 20% probability displacement ellipsoids. Hydrogen atoms are omitted for clarity except for those involved in hydrogen bonding (dotted lines). Symmetry codes iii: 1-x, *y*, 5/2-z; iv: *x*, 1-y, 2-z.

the C11–O11 bond. Moreover, the torsion angles C4–N3–C2–O2 $(4.9(8)^{\circ})$ is slightly different from C9–N10–C11–O11 $(1.4(8)^{\circ})$ which may be compared with the values found in **1** (1.1(4) and $1.2(4)^{\circ}$, respectively).

3.1.3. Catena-poly(hydrogenato)-µ-(R,R)-1,2diacetamidocyclohexane

Individual molecules of **3** are linked into chains running parallel to *c*-axis by CO···H···OC intermolecular hydrogen bonds involving H(O2) (Fig. 3). In this bond, the proton is located on two-fold axis (4b position of $C222_1$ space group). This symmetric hydrogen bond is very short (2.473(10) Å; $179(11)^\circ$); some examples of such bonds have been described in the literature [13].

This proton comes from HBr_3 , quite differently from CO···*H*–N found in crystalline DAACH.

The C=O bond length is 1.247(9) Å which is in accordance with an increasing of the amidic bond polarization.

Table 3 Frequencies (cm^{-1}) of stretching or bending vibrations for the C=O or N–H bonds

Compounds	Raman	(Deuterated derivative)	IR	(Deuterated derivative)
(a) Stretching vibra	tion for the C	C=O bond		
DAACH	1645	1644	1643	1644
DAACH/ZnBr ₂	1616	1617	1617	1617
	1593		1592	
DAACH/HBr3	_	_	1612	1612
(b) Stretching vibra	tion for the N	I–H bond		
DAACH	3285	2444	3285	2438
		2423	3220	2400
DAACH/ZnBr ₂	3358	2495	3358	2454
		2423	3300	2503
DAACH/HBr3	3151	_	3330	2500
			3280	2310
			3145	
(c) Bending vibration	on for the N-	H bond		
DAACH		1470	1547	1471
DAACH/ZnBr2	1567	1506	1561	1504
DAACH/HBr ₃	1579	-	1578	1514

3.2. Raman and IR spectra

Comparative studies of 1 and 2 spectra show many differences among which some can be directly related to complexation.

If complexation creates a bond between the oxygen atom of the carbonyl and the zinc cation, it should lead to a diminution of the C=O stretching frequency.

In fact the comparison of the spectra is not straightforward since, in this region, deformation frequencies implying the N–H bonds should also appear. In order to resolve this ambiguity, we have deuteriated the N–H bonds and checked which peaks remained almost unchanged and which one were shifted.



Fig. 4. Correlation between the bond length C=O and the stretching vibration frequency.



Fig. 5. Raman spectra of the compounds.

3.2.1. C=O stretching vibrations

In DAACH, we have attributed this vibration to the Raman peak at 1645 cm⁻¹ (IR: 1633 cm⁻¹) which remains unshifted by deuteriation (Table 3). In the complexes, this peak is shifted down to 1616 cm⁻¹ (Raman) and 1593 cm⁻¹ (IR) for **2**, and 1612 cm⁻¹ (IR) for **3**. The values of Table 3 have been completed by some other values from literature [14] and can be reported on a graph as a function of corresponding C=O distances obtained by X-ray diffraction (Fig. 4). There is a good agreement between the two sets of data.

3.2.2. NH stretching vibrations

The study of the structure also indicates the probability of NH…O bonds. This can be checked by observing the spectra in the NH stretching and deformation vibration regions, the assignment being comforted by the effect of the ND/NH isotopic substitution (Figs. 5 and 6).

N–H stretching vibrations give a Raman peak at 3285 cm^{-1} to which correspond two IR peaks at $3285 \text{ and} 3220 \text{ cm}^{-1}$ (Table 3). Upon deuteriation, these peaks shift down 2444–2423 cm⁻¹ (Raman) and 2438, 2400 cm⁻¹ (IR, two large bands).



Fig. 6. Infrared spectra of the compounds.

On the contrary, in **2**, there is an increase of the N–H stretching frequency to 3358 cm^{-1} (Raman: 2495, 2423 for the deuteriated derivative). This is in good agreement with the fact that due to the complexation one N–H of DAACH is now free and hence stronger.

In 3, the Raman stretching frequencies are shifted down to 3151 cm^{-1} and the IR frequency to 3330, 3280 and 3145 cm^{-1} (2500 and 2310 for the deuteriated derivative) indicating an increase of the hydrogen bond strength.

3.2.3. NH deformation frequencies

Peaks corresponding to the NH deformations differ from the C=O stretching frequencies of similar values by the fact that they may be shifted upon deuteriation.

Upon complexation, there is an increase of this frequency: 1 to 2 and to 3. One can note that for 2, the shifts of the NH deformation corresponds to an increase of the NH bond strength, contrarily to what was observed for the NH stretching frequency; this could be explained by the free NH bond being visible in the stretching region and the other one in the deformation region.

In the low frequency range, we expect vibrations corresponding to Zn–O and Zn–Br stretching. In this range, by comparison with the Raman spectra of DMF, ZnBr₂ (261, 217 and 187 cm⁻¹) and with the frequency ranges mentioned in the literature for the Zn–Br stretching [15,16], the Zn–O stretching [17,18] and CH₃ torsions, we assigned the peak at 313 cm⁻¹ to this vibration the peaks at 248 and 210 to the Zn–Br stretching, and the peak at 187 cm⁻¹ for the CH₃ torsion.

4. Conclusion

X-ray crystallography, infrared and Raman spectroscopies were used to study DAACH and its complexes with $ZnBr_2$ and HBr_3 particularly about metal/ligand interactions. Complexation induces conformation modifications of **1** leading catena Zn or H bridged compounds. This could be a model in the study of metal/proteins interactions or acidic denaturation of polypeptides.

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