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Vibrational Spectra of Captopril (SQ 14,225: 1-(D-3-Mercapto-2-methylpropionyl)-L-proline) and the Synthesis of the 1:1 Coordination Compound of Captopril with Zn(II) and its Characterization by Vibrational Spectra

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Abstract

Infrared and Raman spectra of captopril (SQ 14,225) are published for the first time and their tentative assignment proposed. A new 1:1 coordination compound of Zn(II) and captopril has been synthesized. Changes in infrared and Raman spectra show coordination of captopril through both carboxylate oxygens, carbonyl oxygen and through sulphur, with captopril presumably acting as a link in a polymer chain between four coordinated Zn^{2+} ions.

Introduction

Captopril (SQ 14,225) was first synthesized in 1975 [1, 2] in an attempt to find an inhibitor of the angiotensin-converting enzyme, ACE, which could be used for treating hypertension [1, 3]. The synthesis was conceived from the fact that the Zn^{2+} ion is the active site of ACE, and an inhibitor should coordinate to it. Side effects appearing in captopril treatment, especially in the case of overdosing [4], are presumably also caused by interactions with metal ions, particularly Zn^{2+} [5]. Therefore the question of the role of the two acidic hydrogens is interesting and also which of the possible coordination sites of captopril (carboxylate, amino, carbonyl or mercapto groups) are used in forming coordination bonds to this metal. We synthesized the complex of captopril with zinc, and used the changes in the infrared and Raman spectra to obtain information about this problem. The preparation of monocrystals for X-ray structure determination has been unsuccessful so far.

Experimental

We are grateful to Lek Pharmaceutical Industries for the donation of a sample of captopril.

Synthesis

3 ml of 1 M NaOH (3 mmol) were added to 0.65 g (3 mmol) of captopril dissolved in 10 ml of water. A solution of zinc acetate (0.279 g, 1.5 mmol in 4 ml of water) was added at 50 °C. A white precipitate was formed and then cooled, filtered and washed with cold water. The hygroscopic product was kept over P_2O_5. *Anal.* Calc. for $Zn(C_9H_{13}NO_3S)$: Zn, 23.29; C, 38.52; H, 4.67; N, 5.00. Found: Zn, 23.5; C, 38.6; H, 4.8; N, 5.1%. Captopril was deuterated by repeated precipitation from D_2O.

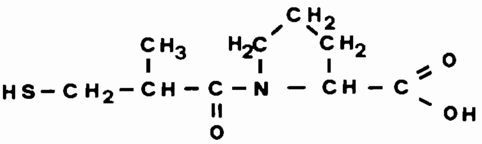
Vibrational Spectra

Infrared spectra were recorded as Nujol and perfluorobutadiene mulls on a Perkin-Elmer 521 grating spectrophotometer. For exiting Raman spectra, an Ar^+ ion laser, Coherent Radiation model CR-3 (4880, 5145 Å), was used. The spectra were recorded in reflection geometry (180°) on an instrument constructed at the Department for Fluorine Chemistry, 'Jozef Stefan' Institute, Ljubljana, using a Spex-1401 double monochromator. The samples were placed in capillary tubes.

Results and Discussion

Vibrational spectra of captopril, deuterated captopril and the coordination compound with zinc are given in Fig. 1 and in Table I.

Captopril is a mercaptoamido acid:



$$HS-CH_2-\underset{|}{\overset{CH_3}{CH}}-\underset{\|\atop O}{C}-N-CH-C\overset{\nearrow O}{\searrow OH}$$

The vibrational spectra of similar compounds have not been, so far as we are aware, thoroughly investigated [6]. Nevertheless, we hoped to find some indications of the type of coordination from the characteristic changes in the spectra.

In the solid state, captopril molecules are bonded together as infinite zigzag chains by hydrogen bonds

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TABLE I. Infrared (Nujol and Perfluorobutadiene Mull) and Rama Spectra of Captopril, Deuterated Captopril and 1:1 Coordination Compound of Zn(II) with Captopril (cm^{-1})

Captopril		D-Captopril		Zn–Captopril		Assignment[a]
IR[b]	Raman[c]	IR	Raman	IR	Raman	
	3010(22)		3013(15)		3000(16)	ν(CH)
2973s	2980(77)		2983(54)	2978m		
	2961sh	2963m	2963(15)		2966(69)	
2940s					2942(87)	
2930s	2930(73)	2922m	2931(56)	2928m	2908(100)	
2870s	2874(32)	2866w–m	2878(28)	2874w–m	2863(39)	
		2845sh				
2900s, br		2140m, br				ν(OH)(ν(OD))
	2830(2)					comb. bands
	2700(1)					
2627s, br		2140m, br				
2562m	2567(100)	1858w	1865(100)			ν(SH)(ν(SD))
1742vs	1744(22)	1734vs	1735(21)			ν(C=O)(COOH)
				1644sh	1643sh	$\nu_a(\mathrm{COO}^-)$
				1632vs	1626(20)	
	1605(6)		1603(7)			Amide I
1585vs	1585(10)	1583vs	1582(20)	1561vs		
				1590s	1589(7)	$\nu_s(\mathrm{COO}^-)$
1475s	1471(35)		1480sh			δ(CH)
1465s		1463s	1470(28)	1467m	1464(25)	
1443m–s	1447(43)	1443m–s	1447(33)	1444s	1444(43)	
1422w	1421(13)		1421(12)	1425s	1421(32)	
1375m		1369m		1369sh		
	1352(8)		1353(3)			
1344w						$\delta(\mathrm{OH}_{\text{in plane}})$ + ν(C–O)
1330m	1337(9)					
1315w						
	1317(9)	1325w	1317(6)	1322w–m	1340(3)	δ(CH)
	1305(7)	1310w	1305(4)		1313(15)	
				1295m	1296(9)	
1269w	1272(12)	1273w–m	1278(5)	1276w	1263(11)	
1247w–m	1253(12)		1250(9)	1257m	1242(15)	
		1233m	1234(4)			δ(OD) + ν(C–O)
1228m	1228(10)					ν(C–O) + $\delta(\mathrm{OH}_{\text{in plane}})$
	1219(3)					
1203m	1201(6)		1200(3)	1202m	1199(9)	δ(CH)
1192m		1190w-m			1183(17)	
1164w–m	1165(3)	1157sh	1162(4)	1157m	1158	ν(skeletal)
1125w	1124(1)	1115sh	1120		1130	
				1113vw	1113(3)	
1093w	1093(6)	1086sh	1092(4)	1097vw	1094(3)	
1081w	1080(16)			1079vw	1071(22)	
1050w–m	1049(10)		1066(11)			
1037w–m	1036(26)	1041sh	1036(22)	1049w	1048(8)	
		1030w		1033w	1030(23)	
	1001(4)	1000sh	1003(6)	998w	991(15)	
974w–m	973(6)		969(7)	979w	975(8)	

(continued)

TABLE I. *(continued)*

Captopril		D-Captopril		Zn–Captopril		Assignment[a]
IR[b]	Raman[c]	IR	Raman	IR	Raman	
	930(20		929(18)	943w	934(14)	
				925vw	921(18)	
	917(13)		914(13)		909(17)	
905w	906(10)	905vw		894w		
		982m	985(4)			ν(C–O) + δ(OD)
882w–m						δ($OH_{out\ of\ plane}$)
	869(3)	867vw	862(5)	877w	869(21)	r(CH_2)
	852(7)	855w				
843w			840(8)	846vw	844(5)	
				822w		
795w	799(61)	795w	798(36)			
787w				775w	786(13)	
	766(7)	760vw				
752w				761m	754(5)	
730w	739(15)	735w–m	739(15)			
		722w–m		713m	716(79)	
675w–m	679(6)	674w–m	678(9)	671m	677(7)	ν(CS)
650sh	652(9)	653vw	663(6)			δ(COO)
			656(6)			
		630w–m				δ($OD_{out\ of\ plane}$)
607w–m	608(3)	615w–m		610w–m		δ(CCO)
597sh		605w–m				
552w–m	552(13)	547w–m	550(10)	545m	541(6)	ν(skeletal) + lattice modes
				486w–m	488(5)	
453m	443(30)	442w–m	444(25)	435w–m		
					422(43)	
					410(37)	
				381 m	381(22)	
359vw	362(6)	355vw	360(8)			
				341m	338(9)	
	322(3)		319(8)			
	294(34)		292(30)		291(80)	
	258(12)		259(7)		223(9)	
	207(4)		198(8)			

[a] Tentative assignment according to refs. 6, 8–12. ν = stretching, a = antisymmetric, s = symmetric, δ = deformation, r = rocking.
[b] s = strong, m = medium, w = weak, v = very, br = broad, sh = shoulder. [c] Raman intensities are given in parentheses.

from the carboxylic oxygen of one molecule to the carbonyl oxygen of another [7]. This is, most probably, the explanation for the infrared spectrum, which shows some similarity to the spectra of dimeric carboxylic acids [8, 9] (Fig. 1). This similarity was the basis of our assignment of bands arising from vibrations of the carboxylic function. Shifts on deuteration are within the limits observed for carboxylic acids [8, 10]. The frequency of ν(SH) and its relative intensity in the infrared and Raman are as expected [11]. The amide I band (predominantly carbonyl stretching), which is moderate in the Raman and strong in the infrared spectra [12], is assigned in accordance with the spectra of mercapturic acids [6a].

All the bands in which acidic hydrogens of captopril participate, disappear in the zinc compound. There is no hydrogen bonding and the coordination has to occur through carboxylate and through sulphur. Of the three strong bands in the IR (at 1632, 1590 and 1561 cm^{-1}) only the first two were observed in the Raman spectra. Hence we propose the assignment shown in Table I. The consequent separation of ν_a(COO^-) and ν_s(COO^-) is very low (41

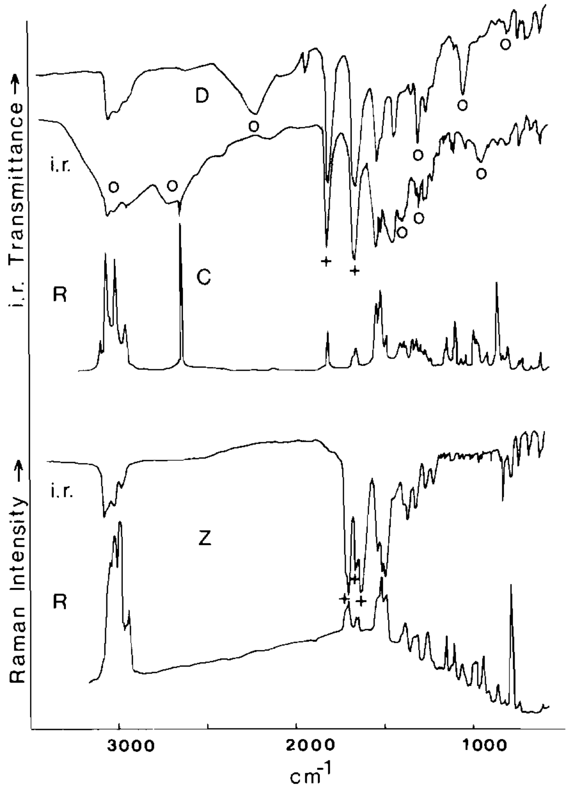

Fig. 1. Raman (R) and infrared (IR) Nujol and perfluorobutadiene mull spectra of captopril (C), deuterated captopril (D) and the 1:1 coordination compound of Zn(II) with captopril (Z): (o) for bands involving acidic H or D vibrations; (+) for carboxyl and amide I bands (see text and Table 1).

cm^{-1}), suggesting chelating or bridging carboxylate groups [13]. The amide I band should shift to higher frequencies both in the case of breaking of the hydrogen bond to the carbonyl oxygen [14] and in the case of nitrogen coordination (compare this with the influence of electron-attracting groups on the N atom [15]). The shift to lower frequencies implies an interaction with Zn^{2+} in which carbonyl oxygen is involved.

Conclusions

Vibrational spectra of the coordination compound demonstrate the absence of acidic hydrogens, no hydrogen bonding and coordination of captopril to Zn^{2+} through four sites: three oxygen atoms and the sulphur atom. A simple molecular model reveals the impossibility of all four sites coordinating to a sole Zn^{2+} ion (which would otherwise be very interesting), so we must consider polymer chains with captopril coordinating via its bidentate carboxylate group to one Zn^{2+} ion and with the carbonyl oxygen and sulphur to another, producing the usual four-coordination.

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