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High-pressure infrared and Raman studies of polymorphism in pharmaceutical compounds: Spironolactone, Forms **I** and **II**

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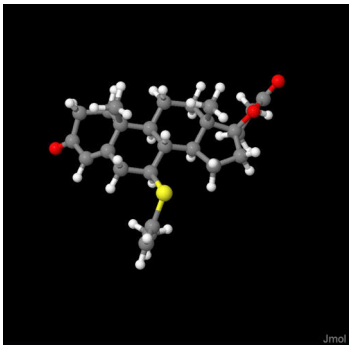
HIGHLIGHTS

- Pressure-tuning IR and Raman spectra of the two polymorphic forms of spironolactone have been examined for the first time.
- Both forms undergo structural transformations under pressure but over different pressure ranges.
- No interconversion of the two forms under high pressures.

GRAPHICAL ABSTRACT



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ABSTRACT

The infrared and Raman spectra of the two polymorphic forms, **I** and **II**, of the synthetic steroid spironolactone ($C_{24}H_{32}O_4S$) have been examined under high pressures up to about 50 kbar with the aid of a diamond-anvil cell. While the differences in peak wavenumbers between the two polymorphs are small, the difference in the pressure dependence is dramatic. Both forms undergo structural transformations under pressure, but over different pressure ranges.

1. Introduction

Polymorphism of pharmaceutical compounds is a subject of considerable importance as different lattice energies lead to different solubilities and hence alter the bio-availability. Furthermore, different polymorphs can be separately patented, a matter of commercial (and legal) interest. During processing, a drug compound can be ground, milled and incorporated into tablets. Each of these processes subjects the compound to pressure and, therefore, the effects of high pressure on polymorphic change is important [1,2]. It is sometimes possible to discriminate among organic polymorphic crystals by Raman spectroscopy and a study with this aspect in mind has recently been published on the industrially important compounds, methylacrylamide, piracetam and 2-thiobarbituric acid [3]. This comprehensive investigation involved detailed comparisons of both experimental and computer simulated Raman spectra of the three compounds. We ourselves have done some infrared and Raman spectroscopic work at high pressures on the two polymorphic forms of crystalline progesterone in an effort to distinguish between the two polymorphs [4]. In the present paper, we describe the results of a similar high-pressure vibrational spectroscopic investigation of the two polymorphic forms, **I** and **II**, of spironolactone ($C_{24}H_{32}O_4S$), a synthetic steroid that was first introduced clinically

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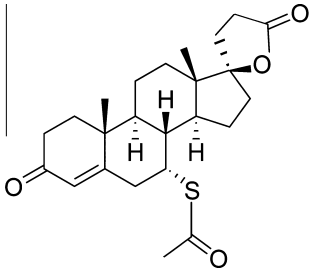
as a drug in 1959 and is widely used as a diuretic, particularly in cases of hypertension, and as an antiandrogen. The polymorphic behavior of spironolactone was discovered in 1983 when El-Dash and co-workers [5] reported the formation of different polymorphs by recrystallization from acetonitrile, ethanol, chloroform and ethyl acetate. The IR spectra of the different polymorphs in KBr were not useful in differentiating among them. Two years later, Salole and Al-Sarraj [6,7] isolated three polymorphs and five solvates, which they were able to distinguish from one another by IR spectroscopy using Nujol mulls and by TG and DTA techniques. However, these researchers did not report the degree of solvation of the solvates nor did they index the powder X-ray diffraction patterns. Crystal structures were reported earlier by Didiberg and Dupont [8,9] and Agafonov and co-workers [10–12] characterized definitively two polymorphs and five solvates using single crystal X-ray crystallographic techniques. The two distinct polymorphs of non-solvated spironolactone, Forms **I** and **II**, are both orthorhombic ($P2_12_12_1$, $Z = 4$) but differ in the conformations of the steroidal rings. These differences suggested that vibrational spectroscopy might be useful in distinguishing between the two non-solvated polymorphs. Consequently, a series of bulk pharmaceutical preparations of spironolactone and its solvates were examined by FT-Raman and diffuse reflectance Fourier transform spectroscopy (DRIFTS) by Neville and co-workers [13,14]. These authors were particularly interested in using the overtone/combination mode region (3200–3600 cm^{-1}) associated with the fundamental modes of the thioacetyl group, for diagnostic purposes. Form **II** is the thermodynamically more stable form of spironolactone [9,15,16]. The unit cell volume of Form **I** is slightly smaller than that of Form **II** and the application of high pressure might cause a transition from Form **II** to the denser Form **I**.



2. Experimental

2.1. Preparation of spironolactone (Forms *I* and *II*)

Form **I** was prepared by dissolving commercial spironolactone (Aldrich Chemical Co.) in boiling acetone and cooling the solution gradually to 0 °C over a period of a few hours to produce long, flat transparent crystals [10]. Form **II** was also prepared from solution in acetone but by slow evaporation of the solvent at room temperature. The crystals obtained were prismatic and clear. Cell parameters for the single crystals were obtained with a Rigaku AFC6S diffractometer using Mo Kα radiation and the values matched those in the literature [10] Infrared spectra were obtained using a Bruker IFS-48 FT-IR spectrometer (1000 scans at 1.0 cm^{-1} resolution) and Raman spectra with a Bruker IFS-88 spectrometer with a Nd:YAG laser, 1064.1 nm wavelength (5000 scans at 2.6 cm^{-1} resolution). The IR and Raman spectra were fitted using the Bruker OPUS software and a linear least-squares-analysis used to fit the wavenumbers versus pressure results. If the R^2 value exceeded 0.95, two significant figures are given in Tables 1–3. If R^2 was between 0.8 and 0.5, only one significant figure is listed.

For the high-pressure studies, the powdered samples, obtained after crushing of the crystals in a mortar and pestle, were con-

Table 1
Infrared spectra peak positions (cm^{-1}) and dν/dP values (cm^{-1} $kbar^{-1}$) for the two phases of Form **I** of spironolactone.

Wavenumbers (cm^{-1})	Low-pressure phase, dν/dP (cm^{-1} $kbar^{-1}$)	Wavenumbers (cm^{-1})	High-pressure phase, dν/dP (cm^{-1} $kbar^{-1}$)
763	0.26	770	0.27
781	0.42	790	0.34
810	0.27	819	0.60
–	–	813	0.14
834	0.22	845	0.13
848	0.01	–	
864	0.1	868	0.37
–		881	
912	0.2	915	0.48
918	0.68	932	0.1
946	0.1	951	0.4
957	0.25	961	0.18
970	0.35	977	0.16
982	0.39	990	0.40
1011	0.23	1014	0.32
1027	0.23	1031	0.22
1041	0.29	1048	0.01
1061	0.40	1070	0.31
1114	0.24	1117	0.98
1129	0.16	1137	0.43
1145	0.28	1151	0.22
–	–	1163	0.28
1173	0.27	1179	0.45
1189	−0.02	–	–
1198	−1.0	1200	0.27
1205	0.27	1211	0.18
1221	0.19	1227	0.47
1240	0.10	1243	0.20
1252	0.16	1256	0.20
1266	0.25	1273	0.36
1286	0.18	1290	0.12
1304	0.17	1308	0.11
1317	0.1	1320	−0.01
1331	0.20	1334	0.1
1350	0.20	1355	0.37
1377	0.10	1380	0.12

Table 2
Infrared spectra peak positions (cm^{-1}) and dν/dP values (cm^{-1} $kbar^{-1}$) for the two phases of Form **II** of spironolactone.

Wavenumbers (cm^{-1})	Low-pressure phase, dν/dP (cm^{-1} $kbar^{-1}$)	Wavenumbers (cm^{-1})	High-pressure phase, dν/dP (cm^{-1} $kbar^{-1}$)
766	0.44	770	0.2
783	0.2	790	0.19
815	0.33	822	0.45
835	0.1	–	–
850	0.2	853	0.08
871	0.46	877	0.46
907	0.31	911	0.5
918	0.46	925	0.25
948	0.05	950	0.2
975	0.23	976	0.4
1019	0.69	1031	0.37
1043	0.41	1049	0.24
1060	0.51	1066	0.27
1112	0.73	1122	0.2
1142	0.71	1151	0.11
1177	−0.03	1177	0.39
1210	0.3	1212	0.1
–	–	1228	0.17
1238	0.22	1243	0.24
1273	0.30	1277	0.2
1295	0.19	1298	0.48
1310	0.6	1320	−0.80
1331	0.17	1333	0.02
1354	0.20	1356	0.1
1379	0.28	1383	0.22