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DETERMINATION OF DRUG POLYMORPHS BY LASER RAMAN SPECTROSCOPY. I. AMPICILLIN AND GRISEOFULVIN

James C. Bellows, Freeman P. Chen

and

Paras N. Prasad

Department of Chemistry

State University of New York at Buffalo

Buffalo, New York 14214

ABSTRACT

Raman spectroscopy of the lattice vibrations (phonons) is used to distinguish among various crystal forms of ampicillin and griseofulvin. The two anhydrous polymorphs of ampicillin and the trihydrate are all distinguishable. Griseofulvin solvates with benzene and chloroform were studied. The spectra suggest that the griseofulvin lattice structure expands to accept chloroform, but that the benzene solvate has a different crystal structure.

The various crystalline forms of a drug may differ significantly in their physical properties. These differences can cause serious problems pertaining to bioavailability and dosage form manufacturing[1,2]. Hence, it is important to be able to determine the particular form of an individual drug sample quickly and easily. It has been customary to use X-ray diffraction procedures, optical and electron microscopy, thermal methods (DTA, DSC, and TGA), and infrared spectroscopy of the internal vibration region as methods of characterizing solid pharmaceuticals.

In this communication we show that laser Raman spectra of lattice vibrations can be used to characterize and identify the solid states of a material and study their stabilities under various conditions. The lattice vibrations (phonons) correspond to librations and translations of the entire molecule. They are of low frequency (10 to 150 cm^{-1}), and are easily accessible only by Raman spectroscopy. From our previous studies of phase transitions in several organic solids[3-5], we find that the lattice vibration Raman spectrum is extremely sensitive to structural changes in the solid state. In contrast, the internal vibrations which are observed in infrared spectroscopy are only weakly sensitive to the environmental change caused by a change in crystal structure. In a Raman investigation one can obtain two types of information. First, the spectral pattern defined by the observed structures (peaks

corresponding to various lattice vibrations) is characteristic of the crystal structure. Second, the frequencies of these observed lattice vibrations are a function of the intermolecular interactions.

EXPERIMENTAL

From the experimental point of view, Raman spectroscopy offers several advantages over other methods used in the past to examine the solid state. (i) No special sample preparation is required. The grinding required for X-ray powder diffraction or the pressing for IR absorption is thus eliminated. (ii) As the incident laser radiation can be focussed into a very small spot, extremely small amounts of material can be used. (iii) The Raman spectra of lattice vibrations can be obtained easily in a short time. (iv) The temperature of the sample can be accurately controlled, allowing thermal studies of the various forms. (v) The internal vibration region is easily examined in the same experiment.

We report here the results of our studies of ampicillin, in which the two anhydrous polymorphs and the trihydrate are characterized, and on griseofulvin and its solvates with chloroform and benzene. The Raman spectra were observed photoelectrically with a Spex model 14018 double monochromater equipped with holographic gratings. Excitation was provided by a Coherent Radiation CR-5 argon ion laser at 0.2 W on the 5145Å line.

Direct current detection was used. Spectra were observed with a 1.0 to 2.0 cm^{-1} bandpass. Samples were sealed in capillaries and, as a precaution, were cooled to -50°C to minimize thermal effects due to the laser. However, no thermal degradation was observed in room temperature studies of several samples.

RESULTS AND DISCUSSION

The Raman spectra of three forms[6] of ampicillin in the 20 to 130 cm^{-1} region are shown in Figure 1. The two anhydrous polymorphic forms (I & II, chosen to conform to the nomenclature

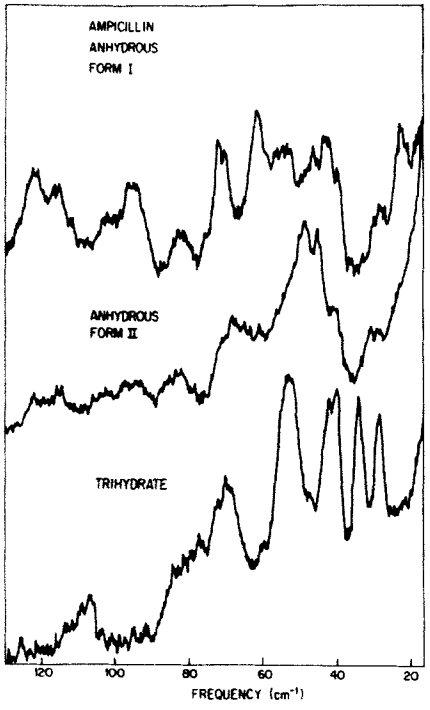

Fig. 1. Raman spectra of three crystalline forms of ampicillin in the 20 to 120 cm^{-1} region.

of reference 7) exhibit broad bands with considerable structure. The relative intensities of the peaks vary considerably between spectra of the same sample due to polarization (orientation) effects. Nonetheless, the spectral patterns are always distinguishable. The lines at 23 and 61 cm^{-1} are characteristic of form I. Form II does not have any specific lines which distinguish it from form I, but the broad band in the 50 cm^{-1} region is always present and significantly stronger than the neighboring structures. The trihydrate exhibits considerably sharper peaks than the anhydrous forms. The line at 28 cm^{-1} clearly distinguishes the trihydrate from the two anhydrous forms. Unsuccessful attempts were made to observe a Raman spectrum from the amorphous form obtained by heating the trihydrate. Amorphous solids are not expected to show structures in lattice vibration regions, so this result is not unexpected. In this study, each crystalline form could be identified. Studies of mixtures were complicated by polarization effects. However, spinning the sample in the laser beam will minimize the polarization effects by averaging over all orientations and thereby enhance the possibility of quantitative analysis.

Solvated crystals of griseofulvin[8] were prepared from solutions in chloroform[9] and benzene[10]. The crystals were removed from the mother liquor and sealed in capillaries. The Raman spectra of the lattice vibration region of the powder sample (unsolvated) and the solvated griseofulvin crystals are shown in Figure 2. Two new bands near 150 cm^{-1} were observed

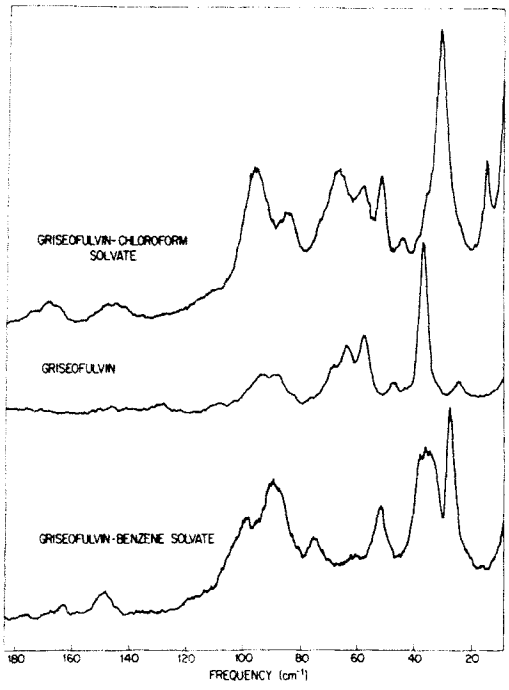

Fig. 2. Raman spectra of griseofulvin and its solvates with chloroform and benzene in the 20 to 180 cm^{-1} region.

only in the solvated crystal spectra. The presence of the solvating molecules was confirmed by observing their characteristic internal vibrations.

There is a good correlation between the spectral patterns of the griseofulvin and of the griseofulvin-chloroform solvate. The correlation implies that the crystal structure of the griseofulvin-chloroform solvate is similar to that of griseofulvin. However, the lattice vibration frequencies in the chloroform solvate are lower than those in the unsolvated form. The entire spectral pattern has shifted to lower frequency as

a result of solvation by chloroform. This result can be explained if it is assumed that the lattice simply expands to accommodate the chloroform molecules. This expansion reduces the interactions between griseofulvin molecules, leading to the decrease in frequency of the lattice vibrations. No correlation could be made between the spectral patterns of griseofulvin and the griseofulvin-benzene solvate, indicating that the two crystal structures are quite different. It was noted that extended exposure of the griseofulvin-benzene crystal to the atmosphere resulted in the crystal losing its transparency[10]. An unsealed sample left standing for 24 hours exhibited a spectrum identical to that of unsolvated griseofulvin. No internal vibrations of benzene were found in this case. The griseofulvin-chloroform solvate, however, showed no degradation on standing for several days. This result was verified by the presence of internal vibrations of chloroform.

It is shown that the various crystalline forms of drugs can be distinguished by Raman spectroscopy of the lattice vibrations. In favorable cases, such as griseofulvin, a large amount of crystal information may be obtained from the spectrum. We plan additional exploration into Raman spectroscopy as a tool for the study of crystalline states of materials of pharmaceutical interest.

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