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Vibrational spectra and normal coordinate analysis of diazepam, phenytoin and phenobarbitone

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Abstract

Vibrational spectroscopy is an important tool for the structural investigation of the organic molecules. In the present investigation, a normal coordinate analysis has been carried out on some anti-epileptic drugs, viz. diazepam, phenytoin and phenobarbitone. Diazepam is a derivative of benzodiazepine, phenytoin is a derivative of hydanation and pheonobarbitone is a barbiturate. The infrared spectra of the compounds are recorded in the region 4000–400 cm^{-1} and Raman spectra are recorded in the region 3500–50 cm^{-1}. From the structural point of view, diazepam, phenytoin and phenobarbitone have been assumed to C_s point group. A systematic set of symmetry coordinates has been constructed for these compounds and Wilson's *FG* matrix method has been applied for the normal coordinate analysis using general quadratic valance force field. The potential energy distribution is also calculated to check the vibrational band assignments.

Keywords: FTIR spectra; FTRaman spectra; Normal coordinate analysis; Diazepam; Phenytoin; Phenobarbitone

1. Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of population, second only to stroke. In the present work, the anti-epileptic drugs diazepam (valium), phenytoin and phenobarbitone have been chosen for the normal coordinate analysis since they are pharmaceutically related compounds. The molecular formula of diazepam is $C_{16}H_{13}ClN_2O$. Diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one. Phenytoin is 5,5-diphenyl-2,4-imidazolidinedione and its molecular formula is $C_{15}H_{11}N_2O_2$. The molecular formula of phenobaribitone is $C_{12}H_{12}N_2O_3$. Phenobarbitone is 5-ethyl-5-phenylbarbituric acid. Diazepam is effective in calming people who experience mild to moderate levels of anxiety, which could trigger epileptic seizures. Phenytoin, often administered as its sodium salt, has been widely used as an anticonvulsant in the treatment of epilepsy and to a lesser extent and more recently, in the treatment of certain cardiac arrhythmias. Phenobarbitone, a barbiturate, is used to control epilepsy and as a sedative to relieve anxiety. The molecular structure and other related parameters of diazepam were reported by Arthur Camerman and Norman Camerman [1]. Fourier transform Raman and infrared vibrational study of diazepam and four closely related 1,4 benzodiazepines have reported by Neville and Shurvell [2]. The relationship between the molecular structure and activity has been thoroughly studied for phenytoin and its derivatives [3–6]. A general model compound with anticonvulsant activity proposed in Ref. [4] comprises two aromatic rings or their equivalents in a suitable orientation and a third, heterocyclic region, usually a cyclic imid. Williams [7] has reported the crystal structure of phenobarbitone. Recent spectroscopic studies of benzene and its derivatives have been motivated, by their biological and pharmaceutical importance [8,9]. The vibrational spectroscopic studies on benzene ring fused to five-membered received considerable attention recently [10–12]. The results obtained from these studies reveal that the change of simple constituents on a constant ring system produces only little changes in the spectrum. Also a small variation in the spectral panorama follows the replacement of atom in the five membered rings. But so far no work is done on vibrational spectra and normal

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coordinate analysis of the anti-epileptic drugs because of their high complexity and low symmetry and it is also very difficult to interpret the spectra of these molecules. By keeping this in mind, the FTIR and FTRaman spectra are recorded for these molecules and complete vibrational band assignments have been made. A normal coordinate analysis has also been carried out with a set of symmetry coordinates for these molecules using Wilson's *FG* matrix method. Further to check whether the chosen set of vibrational frequencies contribute maximum to the potential energy associated with the normal coordinates of the molecule, the potential energy distribution is also calculated.

2. Experimental

Spectroscopic grade pure samples of diazepam, phenytoin and phenobarbitone have been procured from Sigma–Aldrich Company, USA and used as such without further purification. The FTIR spectra of the samples are recorded in the region 4000–400 cm^{-1} on Perkin-Elmer Spectrum One Spectrometer using KBr pellet technique. The FTRaman spectra are recorded using 1064 nm line of Nd:YAG laser operating at 200 mW on Bruker FRA106/Bruker RSS 100 spectrometer in the region 3500–50 cm^{-1} at Sophisticated Analytical Instrumentation Facility, IIT, Chennai, India. The frequencies of all the sharp bands are accurate to $\pm 1\ cm^{-1}$. A spectral width of 4.29 cm^{-1} was used and spectra were measured with a scanning speed of 1.87 cm^{-1} min^{-1}. The FTIR and FTRaman spectra of the chosen drugs are presented in Figs. 1–3.

3. Kinetic constants and potential energy distribution

The elements of inverse kinetic energy matrix have been derived from the relation $G = B\mu B'$, where B is the matrix formulated using the vectors which have been evaluated from the expression of the symmetry coordinates in terms of Cartesian displacement coordinates. B' is the transpose of B matrix and μ is the diagonal matrix of the reciprocal masses of the atoms in the molecule. In order to evaluate force constants (potential constants) the secular equation $|FG - E\lambda| = 0$ has to be solved. Here E is the unit matrix and λ's are the roots of the secular equation related to the fundamentals. The method of kinetic constants relates the off-diagonal elements of the F matrix to its diagonal elements through the relation, $F_{ij}/F_{jj} = K_{ij}/K_{jj}$ ($i < j$, $i = j = 1, 2, 3, \ldots$). In the present study, only the diagonal force constants have been calculated and the initial set of force constants has been taken from the related molecules and they are subsequently refined using successive approximation technique. The potential energy distribution (PED) is calculated using the relation, PED $= F_{ij}L_{ij}^2/\lambda_j$, where L_{ij} is the linear transformation matrix.

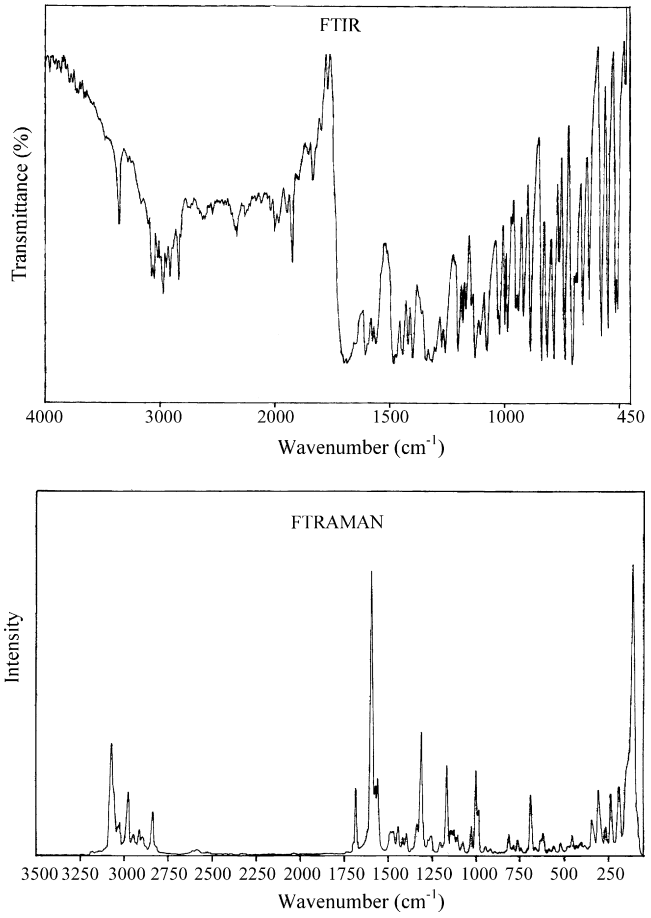

Fig. 1. Vibrational spectra of diazepam.

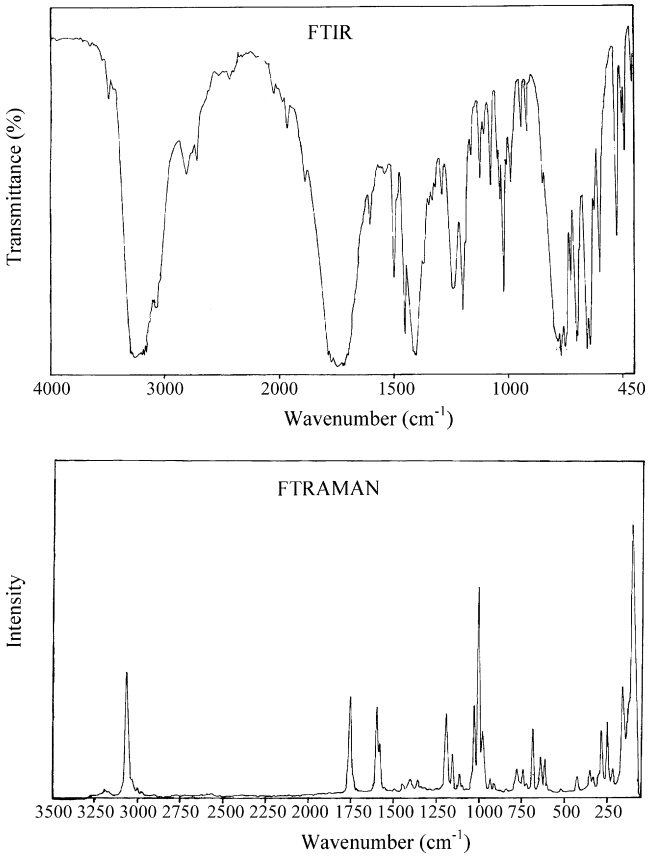

Fig. 2. Vibrational spectra of phenytoin.