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Vibrational Dynamics of the Diterpene-Neoandrographolide

P. K.SINGH, TANVEER HASAN and NEERAJ MISRA*

Department of Physics,
Lucknow University-226007, India.
neerajmisra@hotmail.com

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Abstract: A complete normal coordinate analysis was performed for neoandrographolide in terms of the calculation by using Wilson's G-F matrix method and Urey Bradley force field. Andrographis paniculata has been reported for its potent hepatoprotective. Andrographis paniculata has been reported to have antisecretory (antidiarrhoeal), immunostimulant, antimalarial, antifilarial activity. It is also reported to have anticancer, anti HIV, anti-inflammatory, hypotensive action. In addition, it has found to be effective in myocardial infraction.

Keywords: FT-IR spectra, Diterpene and Vibrational analysis.

Introduction

The proven track record of natural products and their attributes as modulators of biological activity have made them agents of choice in lead discovery in the pharmaceutical industry and molecular biology research. At the same time, their conformational and stereochemical complexity has made them often daunting from the perspective of structure/function studies. Bioactive natural products have an enormous economic importance as speciality chemicals. Apart from drugs, they can also be used as lead compounds, neutraceuticals, excipients, cosmetics *etc*. Natural products from terrestrial, microbial and marine sources have long served as sources of therapeutic drugs that are used in medicine today. More often these natural products provide lead structures that can serve as starting material for chemical modification to derive an optimal drug.

The present work on the sugar bound diterpenoid "neoandrographolide" is in continuation to our earlier work on andrographolide[1]. Since this constituent of andrographis paniculata (AP) shows significant inhibitory action on both pathways of human complement *in vitro* it was decided to study its molecular structure and vibrational spectra in detail. Andrographis paniculata has been reported to exhibit a wide spectrum of biological activity, such as anti-inflammatory[2-4], antiallergic[5-6], antiplatelet aggregation[7], hepatoprotective[8,9] and anti-human immunodeficiency virus (HIV) activity[10,11]. This compound has also been widely used for the treatment of fever, cold, diarrhea and infectious diseases and hence it has aroused the interest of researchers to probe in detail its structure and dynamics[12-14].

To the best of our knowledge no study on the normal coordinate analysis on neoandrographolide has been reported so far in the literature apart from few spectroscopic studies[15]. As a part of our ongoing research work[16,17] on vibrational analysis in a variety of macromolecules, here in the present communication we report the dynamical study carried out on the highly active constituent of andrographis paniculata, namely neoandrographolide. The purpose of this study assumes importance because of our earlier work[1] on the major constituent of AP *i.e*. andrographolide and hence a comparative study between the two diterpenes can be carried out.

Theory

The well known Wilson's G-F Matrix method[18-20] with Urey Bradley[21] force field has been used to evaluate the normal modes.

Experimental

The FTIR spectra of neoandrographolide have been recorded in CsI on a Perkin Elmer 1800 spectrophotometer. Spectroscopic preparation of sample was carried out under an atmosphere of prepurified nitrogen. Neoandrographolide was isolated from fresh plant material of andrographis paniculata to the procedure reported in literature[22]. The compound was identified by comparison with its IR, MS, NMR data with that of reported in literature[22, 23].

Isolation

Plant material (Andrographis paniculata, 2 kg) was powdered and percolated with ethanol (3x6 Lt).The ethanolic extract was concentrated in vacuo at 50^0C. This was diluted with water (750 mL) and fractionated to hexane (10 g) chloroform (15.6 g), butanol (30 g) and aqueous fractions (35 g).

The butanol fraction (25 g) was dissolved in methanol (100 mL) and kept for crystallization overnight when andrographolide was crystallized out and filtered. The filtrate was concentrated and chromatographed over a column of silica gel in chloroform .Elution was carried out with chloroform-methanol. When deoxyandrographolide followed by andrographolide was eluted, the 5% chloroform-methanol eluate containing neoandrographolide was concentrated and rechromatographed and crystallized with ethanol (50 mg), m.p.174-75 ^{0}C.

Results and Discussion

Structure

The title compound consists of a slightly modified andrographolide molecule with its C (19) atom bonded to the O (23) atom of a *β-d*-glucopyranose group. The present grapholide moiety resembles that in the structure of andrographolide[23], the most important difference being the absence (in the present structure) of the hydroxyl groups at C3 and C14 and the planarity of the five membered lactone rings in view of the C13-C14 double bond.

Vibrational investigation

Normal coordinate calculations were performed using the Shimanouchi program, which follows the Wilson's G-F matrix method. This method describes the motion in terms of the internal coordinates, which are changes in bond lengths, bond angles and those out of plane bending and dihedral angles. The force constants in terms of these coordinates can be easily visualized and have a physical meaning. We have used a Urey Bradley force field in our calculations. It incorporates intra unit interactions and interactions due to the neighboring units, in addition to the bonded interactions. It also includes the interactions between non-bonded atoms. Force constants were initially taken from the literature[18] and later modified to give the "best fit" with the observed FT-IR spectra.

The neoandrographolide has 74 atoms, however to reduce the problem to manageable dimensions CH, CH_2, CH_3 have been treated as mass points with a mass of 13, 14 and 15 respectively. This does not in any way disturb the accuracy of the results reported here. This is because the frequencies belonging to these can be well designated as group frequencies and many of them being in the higher range do not mix with other modes. With this approximation the andrographolide problem reduces to 34 atom problem with 96 normal modes of vibrations. The structural data used for neoandrographolide is reported by Spek *et al*[24]. The model molecular structure of neo-andrographolide used in normal coordinate analysis is given in Figure 1. The internal coordinates and final optimized force constant values for the corresponding modes for neoandrographolide can be obtained from the corresponding author. The frequencies along with the potential energy distribution are given in Table 1.The FT-IR spectra of neoandrographolide are given in Figure 2. The observed frequencies agree with the calculated ones within 10 cm^{-1}. In the assignment of the normal modes only the dominant potential energy distributions are given. Identification with the experimental data has been made on the basis of potential energy distribution, line profile, relative intensities, energies and the presence/absence of a given mode in similar molecules.

Although a number of spectroscopic studies[25] have been performed on andrographis paniculata but presumably, the data for the normal mode analysis on neoandrographolide is being reported for the first time and this makes it imperative to discuss all the vibrational modes with significant potential energy distribution and hence their relation with the conformation of neoandrographolide (Figure 1). All the significant vibrational modes involving the prime sites are discussed as follows:

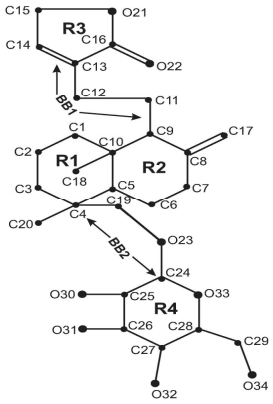

Figure 1. Model molecular structure of neoandrographolide.

Table 1. Calculated and observed vibrational modes of neoandrographolide.

Calculated Freq, cm^{-1}	Observed Freq, cm^{-1}	Assignment (% Potential energy distribution)
1749	1749	ν(C=O)adj-R3 [74] + ν(C-C)R3 [14] + ν(C=C) R3 [6] + ν(C-O)R3 adj (=O) [6]
1641	1641	ν(C=C)R3 [54] + ν(C-C)adj-R3 [25] + ν(C-C)R3 [10] + a(C-C=O)adj-R3 [9] + a(C=C-C)R3 [5] + a(O-C=O)adj-R3 [5]
1593	1594	ν(C=C)adj-R2 [57] + a(C-C-C)cmn R1&R2 [13] + ν(C-C)cmnR1&R2 [8] + ν(C-C)adj-BB1 [7]
1443	1443	ν(C-C)R4 jn BB2 [54] + ν(C-O)R4 [24] + a(C-C-C)R4 [10] + a(C-C-O)adj-R4 [8] + ν(C-O) adj-R4 [7] + ν(C-C) adj-R4 [6] + ν(C-C)R4 [6]
1384	1383	ν(C-C)cmnR1&R2 [38] + ν(C-C)adj-cmnR1&R2 [36] + ν(C-C)R1adj-BB2 [9] + ν(C-C)R2 [5] + ω(C-C)cmnR1&R2 [5]
1353	1354	ν(C-C)adj-R2 jnBB1 [45] +ν(C-C) BB1 [19] + ν(C-C)R1[12] + ν(C-C)adj-BB1 [9] + ν(C-C)adj-cmnR1&R2 [6]
1286	1287	ν(C-C)R4 [33] + ν(C-C)adj-R4 [27] + ν(C-C)adj-BB1 [16] + ν(C-O) adj-R4 [15] + a(C-C-O)adj-R4 [6]
1246	1251	ν(C-O) adj-R4 [32] + ν(C-O)R4 [30] + ν(C-C) R4 [28] + a(C-C-O)adj-R4 [7] + ν(C-C) adj-R4 [6] + a(C-C-C)R4 [6]
1177	1174	ν(C-O) R3 [67] + ν(C-O)R3 adj (=O) [18] + a(C-C-O)R3 [5]
1123	1118	ν(C-O) adj-R4 [26] + ν(C-C) R4 [20] + ν(C-C)R1 [14] + ν(C-O)BB2 [8] + + ν(C-O) BB2 jn R4 [7]
1078	1072	ν(C-O) adj-R4 [42] + ν(C-O) o/s R4 [19] + ν(C-c)R4 [14] + a(C-C-O)adj-R3 [6]+ ω(O-C)R4 [6] + a(C-C-O)R4 [6]
1027	1031	ν(C-O) o/s R4 [60] + ν(C-O) adj-R4 [13] + a(C-C-O) o/s R4 [7] + ν(C-C)R4 [6]
911	908	a(C-C-C)adj-R4 [20] + a(C-C-O)adj-R4 [19] + a(C-C-O) o/s R4 [7] + ν(C-C)R4 [6]+ ν(C-O) o/s R4 [6]
833	835	a(C-O-C)R3 [30] + a(C-C-O)R3 [24] + a(C=C-C)R3 [5] + ν(C=C)R3 [5]
657	649	a(C-C-O)o/s R4 [12] + ν(C-O) adj-R4 [10] + a(C-C-C)R2 [8] + ω(O-C)R4 [8]+ a(C-C-O)adj-R4 [7] + ν(C-C)R4 [7]
571		ω(O=C)R3 [12] + τ(C-O)R3 [12] + a(C-O-C)R3 [7] + τ(C=C)R3 [7] + τ(C-C) BB1 adj-R3 [5] + a(C-C-C)o/s cmn R1&R2 [5]
450		τ(C-C)R2 [19] + τ(C-C) BB1 adj-R3 [9] + τ(C-C)R3 [9] + a(C-C-C)R2 adj-(=O) 8]+ a(C-C-C)R2 [6] + a(C-C=C)adj-R2 [5] + a(C-O-C)R3 [5]

NOTE- Abbreviations used in the table have following meanings

R - Ring adj–Adjacent to o/s – Out side of cmn- Common to BB - Back Bone

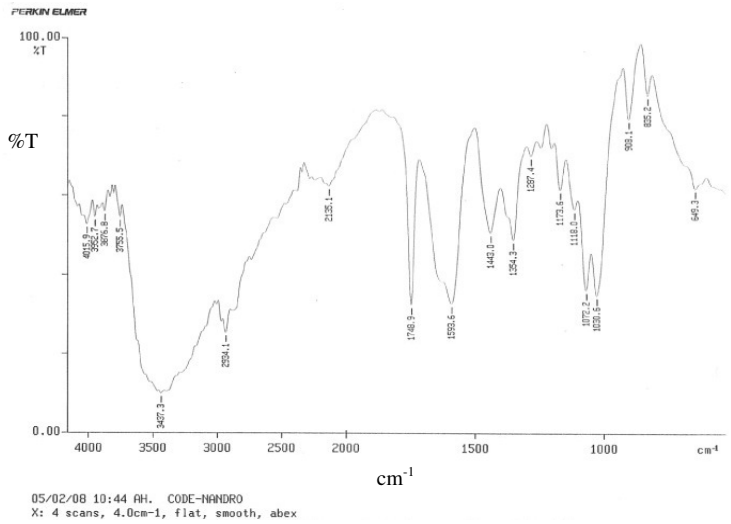

Figure 2. FI- IR spectra of neoandrographolide.

Rings R1, R2, R3 & R4

The main difference between the structure of neoandrographolide and andrographolide being in the ring R3 and ring R1.In the former case a hydroxyl group is absent at C14 and the C16 carbonyl is in conjugation with the C13=C14, whereas in the latter case a hydroxyl group was present at C14 and C16 carbonyl was in conjugation with C12=C13, which was also evidenced by our lower potential energy distribution (p.e.d) value C12-C13 (25%) in the former case and a high p.e.d value (47%) in latter case. This difference brings about the planarity of ring R3 in neoandrographolide as evidenced by *X*-ray studies[24]. A remarkable wagging of 12% at 571 cm^{-1} was also observed for C16-O22 in neoandrographolide. The common feature between the two constituents of andrographis paniculata is the appearance of C=O stretching mode which is at 1728 cm^{-1} in andrographolide as compared to 1749 cm^{-1} in neoandrographolide. Approximately, the same order of p.e.d was observed for C16-O22 (74%) in neo andrographolide as compared to andrographolide (77%). This value is very typical for similar modes in *gamma*-butyrolactone and other similar fragments. The same order of p.e.d *i.e*. 25% and 18% was observed for C15-O21-C16 angle for neo andrographolide and andrographolide, respectively.

The planar orientation of five membered ring R3 is also illustrated by low value of torsional angles C10-C9-C11-C12, C9-C11-C12-C13 and C11-C12-C13-C16, as evidenced by X-ray studies also. And this may be the reason for a slightly high p.e.d *i.e*. 45% of C9-C11 in neo andrographolide as compared to 23% in andrographolide. A lower p.e.d 25% was observed in neo andrographolide having C12-C13 single bond which was 47% in andrographolide having C12=C13.

The other difference is in the ring R4, which has a *β-d*-glucopyranoside linkage with the C4 primary carbinol group. This substitution in Neo andrographolide does not make an appreciable change in the bond angle C20-C4-C19 which is 18% in neoandrographolide whereas in andrographolide it is 12% (p.e.d).It clearly indicates that glucosidation at C4 primary carbinol group do not bring about any change in the geometry of the molecule as such. The value of p.e.d of the C24-C25 stretching mode in the R4 ring is very typical for similar mode found in the literature. This observation is further supported by NMR studies,

according to which the observed coupling constants for the glucose ring of neo-andrographolide confirm that the presence of the trans-decalin moiety has little effect on the conformation of the molecule as a whole.

Lastly, it can be said that the structural/conformational study on this highly active constituent of andrographis paniculata *i.e*., neo-andrographolide needs to be probed further, possibly by *ab-initio* and DFT methods and this is the subject of the proposed study on neo-andrographolide and shall be reported shortly.

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