Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 123 (2014) 447–454

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Analysis of the molecular structure and vibrational spectra of the indole based analgesic drug indomethacin

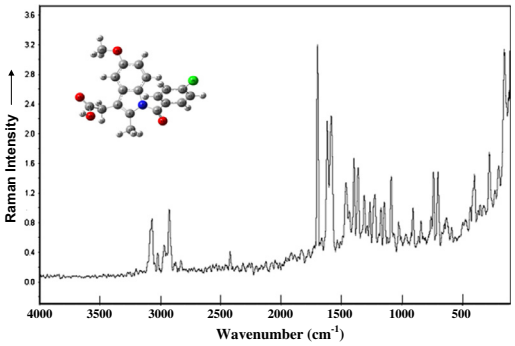
Hassan M. Badawi *, Wolfgang Förner

Department of Chemistry, King Fahd University of Petroleum & Minerals (KFUPM), Dhahran 31261, Saudi Arabia

HIGHLIGHTS

- The structure of indomethacin is optimized at the DFT and MP2 levels.
- The vibrational wavenumbers of the drug were calculated at the DFT level.
- Vibrational assignments were provided by combining experimental and theoretical data.
- The vibrational analysis is consistent with the presence of a single conformer in the spectra of solid indomethacin.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 4 October 2013
Received in revised form 1 December 2013
Accepted 4 December 2013
Available online 18 December 2013

Keywords:
Molecular structure
Vibrational spectra and assignments
Indomethacin
2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid
Non-steroidal anti-inflammatory drug

ABSTRACT

The stability of the *syn* and *anti* structures of the non-steroidal anti-inflammatory drug indomethacin were investigated by the DFT-B3LYP and ab initio MP2 calculations with the 6-311G** basis set. The molecule was predicted at the DFT and MP2 levels of calculation to have the *syn* ($C_1N_7C_{10}C_{18} \sim 40°$) form being about 1.7 and 1.5 kcal/mol, respectively lower in energy than the *anti* ($C_1N_7C_{10}C_{18} \sim 140°$) structure. The calculated CNCC torsional angles for the chlorobenzene and indole rings *syn-anti* conformational interconversion was in a good qualitative agreement with the reported X-ray angles ($C_1N_7C_{10}C_{18} \sim 29$ and 155°) for the *syn* and *anti* conformers, respectively). Indomethacin was estimated from the calculated Gibb's free energies to have an equilibrium mixture of 95% *syn* and 5% *anti* structures at 298.15 K. The vibrational wavenumbers were computed at the B3LYP level of theory and complete vibrational assignments were provided on the basis of theoretical and normal coordinate calculations combined with experimental infrared and Raman data of the molecule. The analysis of the observed spectra supports the presence of indomethacin in only one conformation at room temperature.

Introduction

The conformational profiles and vibrational spectra of a series of biologically active phenyl- and phenoxyacetic acids [1–8] were thoroughly investigated and analyzed in recent studies [9–11]. For the phenoxyacetic acid and its 2,4-dichloro derivative contradicting results were obtained by the DFT and the Møller–Plesset levels about the nature of the lowest and the next higher stable structures. The planar structure with a *transoid* O=C—O—H moiety was predicted by the DFT-B3LYP level to be the lowest energy form. At the MP2 level and the MP4(SDQ) levels the *non-planar* form with *cisoid* O=C—O—H moiety was predicted to be the most favorable structure of the molecules [9,10]. The *planar* form was expected to be the low energy form as a result of stabilizing 5-membered H-bonding between the phenoxy O atom and the hydroxyl H atom. However, on the assumption that the Møller–Plesset calculations are known to account for non-bonding O—H interactions better than the DFT calculations, the non-planar structures were adopted as the low energy structures of phenoxyacetic

* Corresponding author. Tel.: +966 3 8604208; fax: +966 3 8604277.
E-mail address: hbadawi@kfupm.edu.sa (H.M. Badawi).

1386-1425/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2013.12.044

acids [9,10]. It was reported that the stability of the non-planar conformers imply that steric forces play a major role in governing the ground state structure of phenoxyacetic acids. The prediction of a significant change in the calculated total dipole moment as going from one conformer to another was reported to be an indication of the comparable role of both the dipolar interactions and the steric forces in determining the relative stability of the low energy conformations of phenoxyacetic acids [9,10].

The phenylacetic acid and its 2-hydroxy derivative (mandelic acid) were also predicted to exist predominantly in a non-planar structure as a result of hyperconjugation effects [11]. It was reported that in the non-planar structures the π systems of the carboxylic and of the phenyl groups are close enough to lead to stabilizing hyperconjugation interactions. In the case of the planar structures no conjugation between the π system of the carboxylic group and that of the phenyl ring could occur, because they are separated by an aliphatic methylene group. Thus a *planar* structure would not have any stabilizing effects due to the two π systems. It was reported that the sharpness of the methylenic O—H stretching mode in the IR spectrum of mandelic acid suggests the absence of intermolecular dimerization in the acid which is supported by the observation of no splitting of its C═O stretching mode [11]. In both the phenoxyacetic [10,11] and phenylacetic [11] acids the optimized lowest energy forms were reported to adopt a structure where the phenyl rings similar to the phenoxy groups are in near perpendicular (about 90 degrees) configurations with respect to the acetic —CH_2COOH molecular frames.

As a continuation of the interest in bioactive acetic acid derivatives the structural stability and vibrational spectra of indomethacin (2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid) were investigated at the DFT-B3LYP/6-311G**, MP2/6-311G** and MP4/6-311G** levels of theory. The vibrational frequencies were computed at the B3LYP level for the molecule in its low energy structures. The vibrational assignments of the normal modes were made on the basis of normal coordinate analysis and the calculated and observed infrared and Raman spectra of the molecule. The results of the work are presented herein.

Experimental infrared and Raman spectra

The sample of indomethacin (Fig. 1) with about 98% purity was purchased from Aldrich Chemical Company. The KBr mid-infrared spectrum (4000–500 cm^{-1}) of the molecule was obtained with a Perkin Elmer 16F PC FTIR spectrometer as shown in Fig. 2. The Raman Spectrum (4000–100 cm^{-1}) of the pure solid of indomethacin at 2 cm^{-1} resolution was recorded on a Nicolet 6700 FTIR NXR Raman Module (Fig. 2).

Computational details

The GAUSSIAN 03 program [12], running on a 128 node High performance e-1350 IBM Cluster to carry out the DFT-B3LYP and MP2 calculations with the 6-311G** basis set. The *syn* and *anti* structures of indomethacin (Fig. 1) were optimized and the energies and dipole moments were predicted at the two levels of calculations. The optimized structural parameters of the *syn* and *anti* forms at the DFT-B3LYP level of theory are listed in Tables S1 and S2. The optimized energies of the molecule at the DFT-B3LYP and MP2 levels are listed in Tables 1 and S3. The theoretical spectra of the molecule are constructed by using the *Gauss-View*-5 graphical animation [13]. The calculated (DFT) and experimental infrared and Raman spectra of indomethacin are combined and presented in Figs. S1 and S2.

Vibrational frequencies and normal coordinate analysis

The optimized structural parameters of indomethacin in its *low energy* conformations were used to calculate their vibrational frequencies at the B3LYP/6-311G** level of theory. Complete assignments of the normal vibrational modes were proposed on the basis of normal coordinate calculations [14] and the calculated infrared band intensities, Raman line activities, depolarization ratios and experimental infrared and Raman spectra of the molecule (Fig. 2).

To construct the complex symmetry coordinates for the fused indole ring in indomethacin we first tested the normal coordinate definitions for the parent indole molecule. In the previous work on indole the ring modes of the benzene and the pyrrole rings of the indole moiety were defined separately [15]. In our work it turned out that the ring breathing in particular and the other stretching deformation coordinates had to be delocalized over the whole ring system, while most other group coordinates can be taken as localized on either the five or the six ring subsystem. The ring stretching deformations and ring breathings were set up at first in analogy to the separated ring systems, and then the combined ones were used to obtain the final form of the group coordinates. The coefficients for those linear combinations were completely determined by the requirement of orthogonality. The stretching of the C—C bond common to both rings had to be taken as associated with the pyrrole subsystem, not with the phenyl subsystem. In this way two indole ring breathing coordinates and eight indole ring stretching deformations were set up. Another completely delocalized group coordinate describes the ring flapping motion, however, in this case with wagging movements. In this indole ring flapping motion the two rings are flapping like bird wings in flight. The complete sets of the internal and the symmetry coordinates of indomethacin are listed in Tables S4 and S5. The vibrational assignments of all the normal modes of the two conformers are listed in S6 and S7.

Discussion

The activity of indomethacin as a non-steroidal anti-inflammatory drug is reported to be a result of its ability to bind to a wide range of enzymes in different conformations [16]. It was reported that the chlorobenzene and indole rings in indomethacin adopt different conformations depending on the nature of the binding sites in different enzymes [16]. It has been shown that indomethacin binds to certain enzymes in the *anti* configuration (CCNC ~ 150°) [16], while to bind to other enzymes in the *syn* form (CCNC ~ 30°) [16–18]. These interesting structural [16,19,20] and biological [21–24] properties of indomethacin have prompted us to investigate its structure stability, infrared and Raman spectra in the present study.

From the calculations at the DFT-B3LYP and MP2 levels of theory the *syn* ($C_1N_7C_{10}C_{18}$ ~ 40°) form is predicted to be 1.7 and 1.5 kcal/mol, respectively lower in energy than the *anti* ($C_1N_7C_{10}C_{18}$ ~ 140°) structure (Table 1). The calculated CNCC torsional angles for the chlorobenzene and the indole rings *syn-anti* conformational interconversion was in good qualitative agreement with the reported X-ray angles ($C_1N_7C_{10}C_{18}$ ~ 29 and 155° for the *syn* and *anti*, respectively). As shown in Fig. 1 the atoms of the chlorobenzene ring come very close to the methyl group at the indole ring in the *anti* form. Therefore, the repulsive interaction between the chlorobenzene ring and the methyl pyrrole moiety relatively destabilizes the *anti* form as compared to the *syn* conformation of indomethacin. The relative energy difference of 1.5 kcal/mol is not very large, because of the fact that there is also some degree of sterical hindrance in the *syn* form between the benzene and the indole ring that seems to be less than that between the