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Irbesartan: FTIR and Raman spectra. Density functional study on vibrational and NMR spectra

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Arterial hypertension is a very common disease, which is treated with different medications such as Irbesartan. This compound is a nonpeptide antagonist of the receptor of the enzyme angiotensin II. The infrared and Raman spectra of this compound were recorded and discussed assisted with density functional theory using the 6-31G basis set and animated pictures. Irbesartan exists in two tautomeric forms which can be isolated in the solid state. The vibrational study has been recorded using a mixture of both forms. ^{13}C, ^{15}N and ^{1}H NMR theoretical studies have been performed and compared with previously reported experimental data. Theoretical calculations allowed the determination of the main features of the A and B tautomers of Irbesartan both in the vibrational studies and in the NMR spectroscopy.**

Supporting information may be found in the online version of this article.

Keywords: Irbesartan; FTIR spectra; Raman spectra; NMR; density functional theory

Introduction

Irbesartan is an angiotensin II receptor (AT_1 subtype) antagonist used mainly for the treatment of hypertension. It belongs to the group of angiotensin receptor blockers (ARBs) with pharmaceutical properties involved in the renin-angiotensin-aldosterone system.[1] The drug is an effective therapy for patients with mild to moderate hypertension and had an adverse event profile similar to that of placebo in clinical trials. On this basis it would appear to be an effective therapeutic option.[2] It is a nonpeptide compound, chemically described as 2-butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (Fig. 1) that exists in the solid state as two distinct forms: form A and form B which differ in the tetrazol ring protonation. They have been characterized by high-resolution NMR methods to define the solution-state and solid-state ^{13}C and ^{15}N to establish the tautomeric nature of the two different crystal forms A and B.[3] The crystal structure of Irbesartan form B (the 2-H tautomer) has been previously determined.[4]

The aim of the present study is to thoroughly investigate the room temperature vibrational spectra [Fourier Transform Infrared (FTIR) and Raman][3] of the supplied sample of Irbesartan (which is a mixture of forms A and B). Theoretical calculations are performed on both forms of Irbesartan. Geometry optimizations and the calculation of vibrational wavenumbers and ^{1}H, ^{13}C and ^{15}N chemical shifts are accomplished using tools from the density functional theory. Calculated infrared (IR) and NMR spectra are used to aid in the assignment of experimental information.

Experimental

Irbesartan was generously supplied by Sanofi-Aventis Group, Bristol-Myers Squibb Argentina S.R.L. The infrared spectrum was recorded in the spectral range between 4000 and 400 cm^{-1} using the KBr pellet technique with a Bruker IFS 66 FTIR instrument. A total of 60 scans were accumulated. Spectral resolution was ± 4 cm^{-1}. Raman spectrum was obtained with the FRA 106 Raman accessory of the mentioned spectrophotometer, using the 1064-nm line of a solid-state Nd : Yag laser for excitation. Spectral resolution was ± 4 cm^{-1}.

Computational details

The conformational space of A and B forms of Irbesartan was investigated using molecular dynamics simulations and the MM+ force field,[5] both available in the HyperChem package.[6]

Optimized starting geometries of both forms were heated from 0 to 900 K in 0.1 ps, and temperature was then kept constant by coupling the system to a thermal bath with a bath relaxation time of 0.5 ps. A 500-ps long simulation was performed after an equilibration period of 10 ps, saving molecular Cartesian coordinates every 10 ps. The time step for the simulations was 0.1 fs. Outcome geometries were then optimized using the AM1 semiempirical method[7] as implemented in the HyperChem package. The lowest-energy geometries of the two forms obtained according to the above-mentioned methodology were further optimized using tools from the density functional theory[8–10] as implemented in the Gaussian 03 package.[11] The optimizations were accomplished using the Becke's three parameters hybrid

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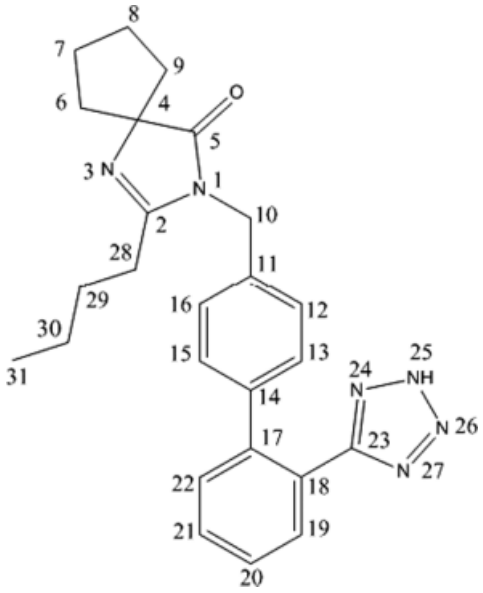

Figure 1. Molecular structure and atomic numbering for Irbesartan.

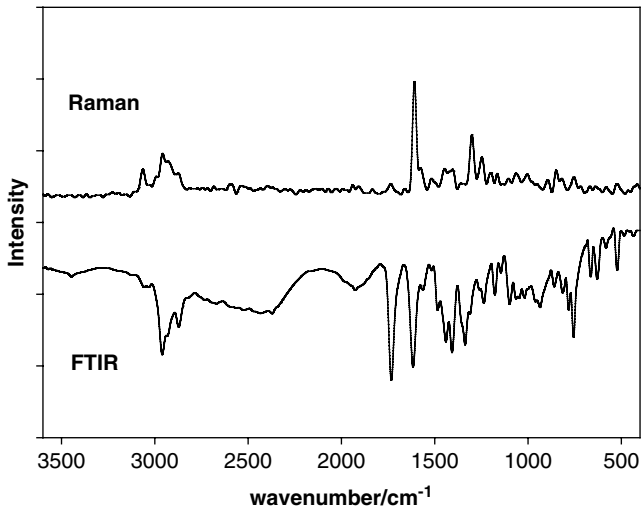

Figure 2. Irbesartan FTIR spectrum and FT-Raman spectrum in the spectral range 3600–400 cm^{-1}.

density functional[12] with the gradient-corrected correlation functional due to Lee, Yang and Parr,[13] a combination that gave rise to the well-known B3LYP method. The 6-31G** basis set was used for all atoms. All optimizations were carried out in gas phase.

A vibrational analysis at the B3LYP/6-31G** level of theory was accomplished for the optimized conformers to verify whether they were local minima or saddle points on the molecular potential energy surface. Calculations were also performed with the Gaussian 03 package. Nuclear magnetic resonance properties of Irbesartan were calculated at the B3LYP/6-311++G** level of theory suggested by Cheeseman *et al.*[14] using the gauge-including atomic orbital method[15,16] as implemented in the Gaussian 03 package. Isotropic shielding tensors of ^{13}C were turned into chemical shifts using a linear relationship suggested by van Eikema Hommes and Clark.[17] A similar relationship proposed by Franca *et al.*[18] was used to obtain chemical shifts for ^{15}N. Isotropic shielding tensors of ^{1}H were turned into chemical shifts by least TMS shielding.

Results and Discussion

Vibrational study

The main characteristic experimental vibrations obtained from FTIR and Raman spectra are shown in Table 1 and Fig. 2. Detailed assignments of the vibrational modes are made assisted with animated pictures. In the FTIR spectrum, a weak broad band was observed with a maximum at 3447 cm^{-1}. This band was also predicted at 3519 and 3511 cm^{-1} for the A and B forms, respectively, in density functional theory (DFT) calculation of Irbesartan for NH stretching vibrations. In the Raman spectrum, the band observed at 3063 cm^{-1} could be attributed without ambiguity to the CH stretching mode of the aromatic ring. The peaks observed in the 3000–2870 cm^{-1} range were due to asymmetric and symmetric CH stretching modes.

Table 1. Wavenumbers (in cm^{-1}) of the vibrational Raman and IR spectra and calculated harmonic wavenumbers of Irbesartan. The proposed assignment is also given

Raman exp	FTIR exp	Calculated wavenumber form A	Calculated wavenumber form B	Assignments
	3446.92 (w)	3519.47 (82)	3510.68 (112)	υ N–H
3063.33 (m)	3059.93 (w)	3088.28 (18)	3081.98 (18)	υ CH arom iph
	3032.93 (w)	3072.19 (17)	3072.56 (14)	υ CH arom oph
2994.48 (w)	2960.93 (s)	2920.32 (41)	2991.66 (55)	υ CH as CH_3
2962.16 (m)	2932.65 (sh)	2933.15 (15)	2922.14 (21)	υ CH s CH_3
2879.26 (w)	2873.51 (m)	2912.90 (28)	2905.98 (34)	υ CH s CH_2
1731.27 (w)	1731.82 (vs)	1737.64 (214)	1736.56 (216)	υ C=O
1607.62 (vs)	1616.11 (vs)	1631.25 (195)	1631.99 (193)	υ C_2=N_3
1579.52 (m)	1563.39 (m)	1590.62 (12)	1590.86 (4)	υ C=C
1509.26 (w)	1517.11 (w)	1525.33 (31)		δ CNH ip aromatic ring + υ C_{23}–C_{18}
			1502.11 (6)	δ CCH ip aromatic ring + υ C_{23}–C_{18}
1490.99 (w)	1484.97 (m)		1491.98 (21)	δ NNH + υ C_{23}–C_{18} + δ CCH ip + υ CN
1444.62 (w)	1439.97 (s)		1466.33 (31)	δ NNH + δ CCH ip + υ CN
		1461.77 (53)		δ CCH ip + υ CN
1399.66 (w)	1406.54 (s)	1424.07 (11)		δ NNH + δ CCH ip
			1407.38 (17)	δ NNH + υ C_{23}–C_{18} + δ CCH ip
	1337.11 (s)	1314.50 (126)	1311.27 (158)	CH_2 wag
1298.49 (s)	1311.4 (sh)	1282.42 (14)	1279.89 (11)	CH_2 wag + CH_2 rock
	1256.11 (sh)	1253.33 (15)	1269.24 (15)	υ C–C bridge bond biphenyl
1243.69 (m)	1236.83 (m)		1268.24 (24)	δ NNH + υ NN + υ C–C bridge bond biphenyl
		1214.22 (13)		δ NNH + υ NN
1163.60 (m)	1177.69 (m)	1164.41 (19)	1157.28 (43)	δ CCH ip aromatic ring + CH_2 rock and wag
1100.37 (w)	1145.55 (w)	1131.05 (–)	1161.81 (26)	δ NNH + υ NN
	1099.26 (m)	1078.45 (24)	1093.39 (9)	CH_2 rock + δ CCH ip aromatic ring
1066.65 (w)	1064.55 (m)	1051.18 (8)	1048.05 (12)	υ CN (imidazolic ring) + CH_2 rock and wag
	1047.83 (m)	1019.18 (47)		δ NNH + υ NN
			1008.13 (11)	υ NN + δ CCH ip aromatic ring + ring breath
993.58 (w)	1018.26 (m)		1005.55 (15)	δ NNN
		979.9 (10)		υ NN
888.20 (w)	935.98 (m)	933.99 (18)	923.88 (18)	δ CCH op aromatic ring + CH_2 twist
846.04 (m)	858.84 (w)	841.76 (12)	844.98 (11)	δ CCH op aromatic ring
819.34 (w)	815.12 (m)	819.25 (9)	824.71 (11)	δ CCH op aromatic ring
	782.98 (m)	755.94 (26)	748.59 (19)	δ CCH op aromatic ring
749.09 (w)	755.98 (s)	729.20 (13)	702.40 (41)	γ NH
661.97 (w)	664.7 (w)	666.75 (1)	693.83 (3)	CH_2 rock
635.27 (w)	628.7 (w)	629.95 (4)	632.63 (9)	Biphenyl, cyclopropyl ring breathing
	582.42 (vw)	581.74 (1)	585.77 (2)	Biphenyl, cyclopropyl ring breathing
	521.99 (w)	523.72 (2)	528.05 (2)	see text
514.43 (w)	520.7 (w)	507.13 (6)	505.9 (1)	see text
	484.7 (vw)	466.26 (1)	446.76 (2)	see text
	483.42 (vw)	449.74 (2)	410.35 (3)	see text
	435.85 (vw)	401.54 (1)	404.12 (1)	see text

The intensities for the calculated wavenumbers are given in parenthesis.
s, strong; m, medium; w, weak; sh, shoulder; vw, very weak; ip, in plane; op, out of plane; iph, in phase; oph, out of phase.

The vast majority of compounds containing a carbonyl group exhibit ν(C=O) in the region 1800–1600 cm^{-1}, and these modes have strong IR and low Raman band intensities.[19–21] For Irbesartan, this band is located at 1731 cm^{-1} with the expected intensities. The calculated wavenumbers of C=O stretching concur satisfactorily well with the experimental determinations. The bands of medium intensity observed at 1563 and 1580 cm^{-1} in the FTIR spectra and Raman spectra were ascribed to the C=C stretching mode. These vibrations were predicted at 1590 cm^{-1} (both forms) by our DFT calculations in good agreement with the experimental values.

A desmotropic substance has individual tautomers that can be isolated in the solid state as a unique and stable form. Irbesartan exists as a mixture of A and B tautomers in the liquid state. These forms differ in the protonation of the tetrazole ring (Fig. 3) and can be isolated in solid state. Each form may have different physical properties, for instance, different patterns in their vibrational spectra. The position of the bands associated to the ring vibration modes of the imidazol and tetrazol moieties are difficult to assign unambiguously because they are superimposed.[22–25] Billes *et al.*[26] studied the vibrational spectra of the triazoles and tetrazoles and established that the difficulty in the interpretation

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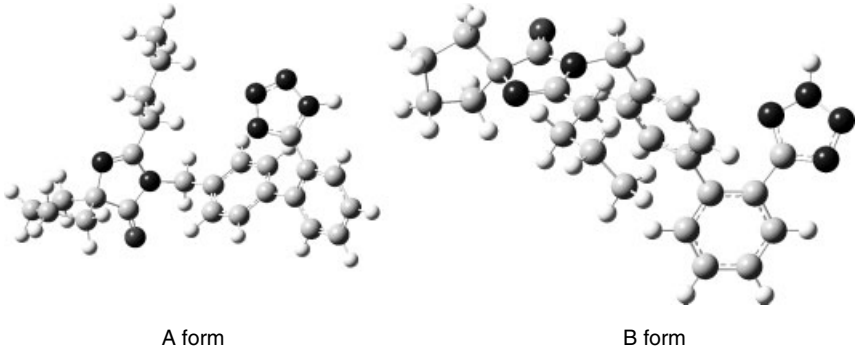

Figure 3. Tautomeric forms of Irbesartan.

arises from the very strong associations in condensed state. They assigned bands at 1002, 1015, 1159 and 1384 cm^{-1} to the in-plane bending NH for 1H-tetrazole and 1329 and 1453 cm^{-1} to the same mode in 2H-tetrazole. The out-of-plane NH bending modes were measured between 500 and 939 cm^{-1} (1H-tetrazole) and at 571 and 675 cm^{-1} (2H-tetrazole).[26] In a recent work,[24] IR bands of three series of substituted tetrazole ligands were established. The NN stretching modes were reported from 968 to 1075 cm^{-1}, 1167 to 1183 cm^{-1} and from 1481 to 1492 cm^{-1}, and NCN and NNN bends were placed at 925 cm^{-1}. The strong coupling of these modes for Irbesartan is shown in Table 1. The protonation of the tetrazol moiety produces the localization of the electronic density generating a double bond between nitrogen atoms causing medium absorption bands in the range 1018–1237 cm^{-1}. A complex coupling is the major characteristic of these bands, mainly in the case of the bending NNH and CCH in-plane modes. We have assigned NN stretches at 1018, 1048, 1146 and 1237 cm^{-1}. At 1406, 1440 and 1485 cm^{-1}, NNH bending vibrations appear overlapped as medium and strong IR bands. It is difficult to assign accurately the NN stretching modes, probably because of the overlapping between these bands and the NNH deformations.

Interestingly, at 1517 cm^{-1}, a band assigned by DFT calculations to the bending CNH appeared in the FTIR spectrum. The CNH moiety is only present in the A tautomer, consequently the presence of this band is an indication of the existence of this form. In this region, a NNH bending mode appeared for the B form, being the difference between both wavenumbers of *ca* 20 cm^{-1}. The strong band at 756 cm^{-1} was assigned to an NH out-of-plane bending mode in accordance to reported values.[26,27] An additional characteristic band to distinguish between both forms may be the NNN bending that appeared only in the B tautomeric form with a theoretical value of 1006 cm^{-1}.

A strong Raman band located at 1256 cm^{-1} corresponds to the biphenyl C–C bridge bond stretching.[28,29] The medium band at 815 cm^{-1}, both in FTIR and Raman spectra corresponds to a ring-breathing vibrational mode.[30]

Besides, the bands in the 620–520 cm^{-1} region corresponds to the torsion and breathing of the biphenyl and cyclopropyl cycles. On the other hand, the bands located in the 520–400 cm^{-1} range were assigned (applying DFT calculations and animated pictures) to a combination of torsion modes of different rings of Irbesartan.

NMR theoretical studies

As stated above, Irbesartan exhibits desmotropic behavior, since the isolated crystal forms are stable in the solid state but there exists a tautomeric equilibrium in solution. This tautomerism has been previously studied by high-resolution NMR spectroscopy. The crystal forms A and B of the solid state were characterized earlier by ^{13}C and ^{15}N NMR methods.[3]

Theoretical and experimental chemical shifts for ^{13}C, ^{15}N and ^{1}H are shown in Tables S2–S4 (Supporting Information), respectively. Chemical shifts for ^{13}C and ^{15}N are listed for the two forms of Irbesartan. It is important to note that the experimental ^{1}H chemical shifts were obtained in solution both using [$^{2}H_2$] dichloromethane and [$^{2}H_6$] dimethylsulfoxide as solvents.[3] It is claimed in Ref. [3] that the two forms of Irbesartan are indistinguishable.

It can be seen in Table S2 (Supporting Information) that the agreement of experimental and calculated data is quite good. Bauer *et al*.[3] indicate in their work that it is difficult to assign the ^{13}C chemical shifts in the regions between 24 and 44 ppm and between 127 and 136 ppm. Calculations in the present work provide a clear assignment in this region, contributing to clarify the difficulties stated by those authors. They also found in their experimental work an appreciable difference of 8.6 ppm between forms A and B for the chemical shift of C23. Interestingly, the present calculations predict a difference of about 11 ppm for the same nucleus.

Table S3 (Supporting Information) clearly shows that calculated ^{15}N chemical shifts present important disagreements with experimental data. However, the trends observed in the empirical chemical shifts are well reproduced by the present results for form B. Discrepancies for form A, however, are more pronounced. This fact allows us to propose an alternative assignment for ^{15}N chemical shifts in form A of Irbesartan involving atoms N24, N25 and N27. For completeness, both the original assignment proposed by Bauer *et al*.,[3] and the new one suggested in the present work are shown in Table S3 (Supporting Information). It can be seen that trends are better reproduced for form A of Irbesartan when the new assignment proposed in this work is taken into account.

Finally, it is shown in Table S4 (Supporting Information) that the agreement between experimental and theoretical chemical shifts is very good. It can be seen that the hydrogen atom bound to the nitrogen atom presents the larger error. We argue that this is mainly due to an intermolecular hydrogen bond formed with other Irbesartan molecule or with a solvent molecule. This is in line with the findings reported in Ref. [4] indicating that in solid form B the hydrogen atom attached to the nitrogen atom is involved in an intermolecular hydrogen bond. It is worth noting that despite our results it is very difficult to assign one of the forms of Irbesartan to the two species present in solution.

Conclusions

The experimental vibrational study has been performed on a commercial sample of Irbesartan. The results indicate that a powder mixture of both tautomeric forms A and B is present. When applying DFT studies, the complete vibrational assignments of both forms could be performed. The CNH moiety of the tetrazole ring of Irbesartan can only exist in the A tautomer, hence the appearence of this band is a good feature to distinguish both forms. The position of the bands corresponding to the in-plane CNH bending (A form) and the in-plane CCH bending (B form) has been assigned using DFT calculations. In addition, the precise assignment of the symmetric vibrations could be determined more accurately by means of the Raman spectrum.

On the NMR timescale, the equilibrium between the two tautomeric forms results sufficiently rapid to identify individual tautomers by NMR solution spectra studies. In this context, the theoretical approach establishes new assignments for ^{1}H chemical shifts characteristic of each form of Irbesartan. The main differences in these chemical shifts have been observed for H(NH) and it is attributed to intermolecular hydrogen bonds. Besides, an alternative assignment for ^{15}N chemical shifts in form A of Irbesartan is proposed and it is achieved a better agreement between experimental and calculated data.

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Supporting information

Supporting information may be found in the online version of this article.

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