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Fourier transform infrared spectra and normal mode analysis of 1-[(3-methylphenyl)piperazin-1-yl]-3-[thio(4-acetamido-phenyl]propane: a potent 5-HT_2 and D_2 receptor ligand

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Abstract

1-[(3-methylphenyl)piperazin-1-yl]-3-[thio(4-acetamidophenyl]propane and its analogs have shown good hypotensive activity and the title compound has shown a profile of centrally acting anti-hypertensive agent. It also binds with the 5-HT_2 receptors. The conformation of the title compound was determined by X-ray diffraction but this is not possible for its analogs because of the difficulty in preparing their single crystals. A novel and easy approach is envisaged to determine the conformation in such cases by the application of semi-empirical molecular orbital calculations, Fourier transform infra red (FTIR) spectroscopy and normal mode analysis. As a first step in this direction the FTIR spectrum of the title compound has been recorded and its normal mode analysis carried out. The assignments of the frequencies are based on the concept of group frequencies and band intensities. The spectrally observed frequencies have been tabulated along with the theoretically calculated ones and their assignments. Good agreement has been obtained between them and a set of 101 force field constants is established.

Keywords: FTIR spectra; Vibrational frequencies; Force constants; Infra red spectral band assignments; Conformation

1. Introduction

1-[(3-methylphenyl)piperazin-1-yl]-3-[thio(4-acetamidophenyl]propane and its analogs have shown good hypotensive activity and the title compound has shown a profile of centrally acting anti-hypertensive agent [1]. It also binds with the

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5-HT_2 receptors [2]. The conformation of a drug molecule plays an important role in drug receptor interactions, which lead to its biological response. Several methods are available which predict such effects [3–6] and provide insight to active site space and binding requirements, but most of these are biased due to arbitrarily chosen molecular overlays on binding site points. The conformation of the title compound was determined by Carpy et al. [7] using X-ray diffraction, but such determinations are very difficult for several of its analogs as they can not be grown into single crystals.

Facing a similar problem in the case of the analogs of a potent anti-hypertensive agent 1-[(3-methylphenyl) piperazin-1-yl)-2-(quinolin-2-yl)ethane (centhaquin) the authors envisaged a new and simple way out [8]. In this approach, the conformation of the compound is determined using the semi-empirical molecular orbital method. Experimental support to such calculations is then provided by the application of the normal mode analysis and Fourier transform infra red (FTIR) spectroscopy which are well established techniques and are being used for variety of other applications [9–13]. For this purpose at least one compound in the series of analogs is first selected which can be conveniently studied by X-ray diffraction for the determination of its conformation. Its FTIR spectrum is recorded and the normal mode analysis is carried out using its X-ray determined conformation to establish the force field constants which give the best agreement between the spectra and the calculated frequencies. These force field constants are utilized in the normal mode analysis of the analog using its geometry calculated from the molecular orbital method. This is reasonable because the force field constants are invariant from one analog to the other, as there is not much change in the basic structural environment. If the theoretical frequencies of the analogs agree with their FTIR spectra then it is concluded that the calculated geometry is correct, otherwise it is again determined using a different conformation of the molecule. These experimentally supported conformations may then be utilized in establishing 3-D structure-activity relationships.

As a first step in the application of the above approach to the present series of analogs, the title compound has been chosen because its X-ray determined structure is available [7]. This has been utilized in carrying out its normal mode calculations. The FTIR spectrum has been recorded and a set of force field constants has been established to obtain a good agreement between the theoretical frequencies and the observed spectra. These results are presented in this paper. The work on the analogs is in progress and will be reported very soon.

2. Materials, methods and theory

The compound 1-[(3-methylphenyl)piperazin-1-yl]-3-[thio(4-acetamidophenyl]propane (**3**) was synthesized essentially by the reported method [1] starting from 4-acetamidothiophenol (**1**), which on condensation with 1-bromo-3-chloropropane yielded the key intermediate chloropropyl derivative (**2**). This on reaction with 3-methylphenyl piperazin in the presence of sodium carbonate and sodium iodide in DMF afforded the title compound (**3**) as shown in Scheme 1.

The FTIR spectra in KBr and in dilute $CHCl_3$ solution were recorded on the Impact 400 spectrophotometer, Nicolet, having a resolution of 1 cm^{-1}, using interferometer dispersing KBr beam splitter and having noise level equal to RMS 7.1. The X-ray data used for the calculations were taken from Carpy et al. [7]. The well-known Wilson's G-F matrix method [14] with Urey–Bradley force field has been used to evaluate the normal mode frequencies of vibration. These are given by the eigen values of the secular equation

$$GFL = \lambda L \tag{1}$$

as

$$\lambda = 4\pi^2 c^2 f^2 \tag{2}$$

The potential is represented as

$$v = \sum_{j,k}\left\{K'_{jk}v_{jk}(\Delta v_{jk}) + \frac{1}{2}K_{jk}(\Delta v_{jk})^2\right\} + \sum_{i,j,k}\left\{H'_{ijk}r_{ij}r_{jk}(\Delta\Phi_{ijk})^2 + \frac{1}{2}H_{ijk}r_{ij}r_{jk}(\Delta\Phi_{ijk})^2\right\} + \sum_{i,j}\left\{F'_{ik}q_{ik}(\Delta q_{ik}) + \frac{1}{2}F_{ik}q_{ik}(\Delta q_{ik})^2\right\} + \sum_{j}K_j^{\omega}(\Delta\omega_j)^2 + \sum_{j}K_j^{\tau}(\Delta\tau_j)^2 \quad (3)$$

where Δv_{jk}, $\Delta\Phi_{ijk}$, $\Delta\omega_j$, $\Delta\tau_j$ are the internal co-ordinates corresponding to bond stretch, angle bend, out of plane deformation and torsion respectively and q represents non-bonded nearest neighbor interactions. The potential energy distribution (PED) in the jth internal co-ordinate for the ith normal mode is given by

$$(\mathrm{PED})_j^i = \frac{L_{ji}^* L_{ji} F_{ji}}{\lambda_i} \quad (4)$$

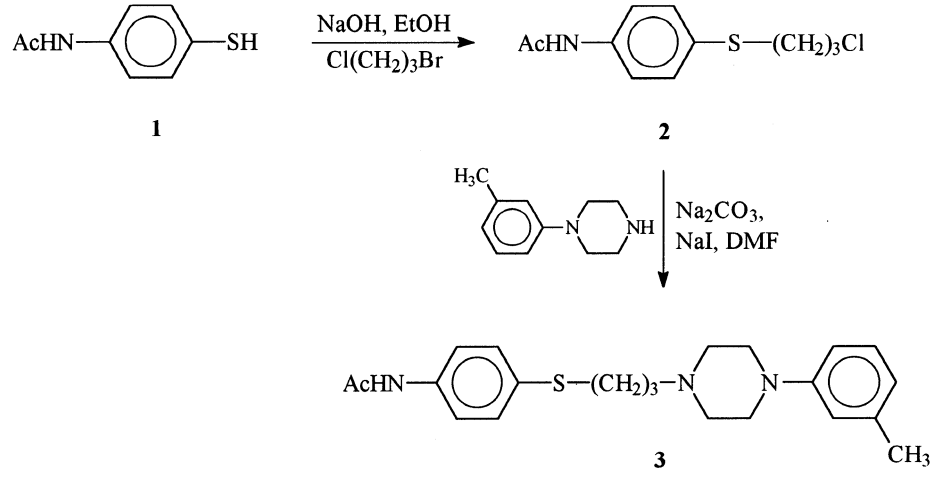
The estimates of the force constants for the force field were taken from the literature [14,15] and subsequently refined to match the observed spectra.

3. Results and discussion

The FTIR spectra of the title compound in KBr and in dilute $CHCl_3$ solution are shown in Figs. 1–3. The conformer structure diagram of the molecule is shown in Fig. 4. This is in line with the figure obtained from the X-ray diffraction [7]. The important calculated normal mode frequencies, along with the observed frequencies in the FTIR spectra in KBr, their assignments and percentage PED are tabulated in Table 1. The complete table of all the calculated frequencies is provided as supplementary material. The assignments are based on the concept of group frequencies and band intensities. The internal co-ordinates and corresponding force constants are given in Table 2.

The N–H mode vibrations along with amide I and II band-positions and their intensities are used with reasonable certainty to characterize the *cis*- or *trans*-configuration and hydrogen-bonding effects in the secondary amide group. A very strong band at 3307 cm^{-1} is assigned to N–H stretch of the amide group in the solid state. The strong intensity can be attributed to the Fermi resonance of N–H stretch with the overtone of amide I band (1659 cm^{-1}). This band is suggestive of the –N–H…O = C rather than the –N–H…N– linkage involvement, i.e. *N*-mono-substituted amide exists mainly with N–H and C = O in *trans*- rather than *cis*-configuration. The X-ray data also supports this.

In addition to the above main absorption band of N–H stretching vibration we get two associated N–H bands of medium intensity at 3155 and 3090 cm^{-1}. These bands are also observed in the spectra of polypeptides and proteins where their relative intensities vary with the transition of protein from alpha to beta folding.



Scheme 1.

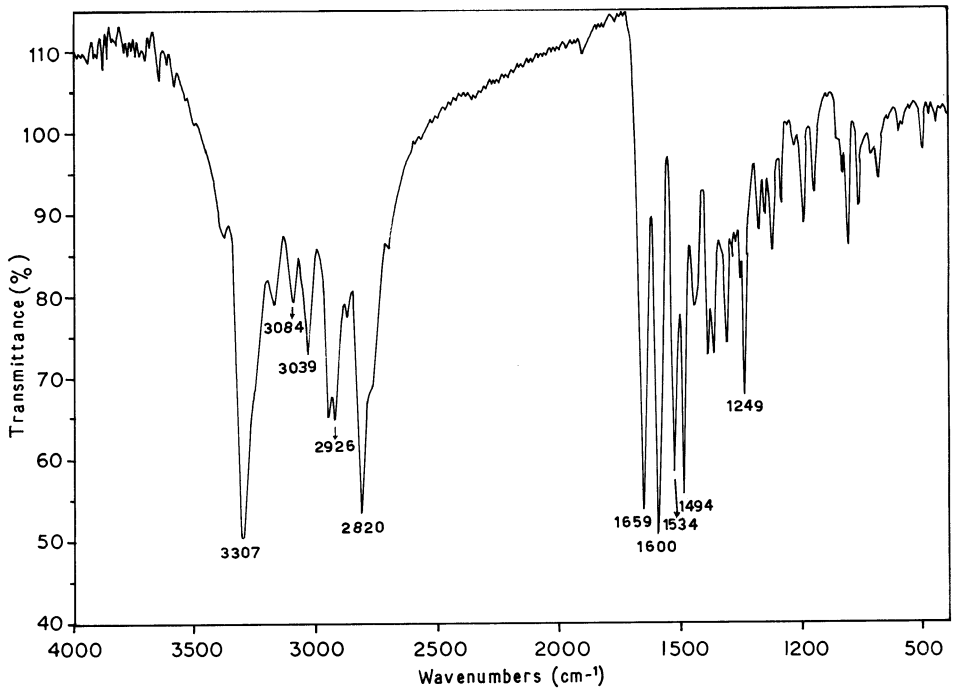


Fig. 1. The FTIR spectrum of the title compound in KBr: (400–4000 cm^{-1}).

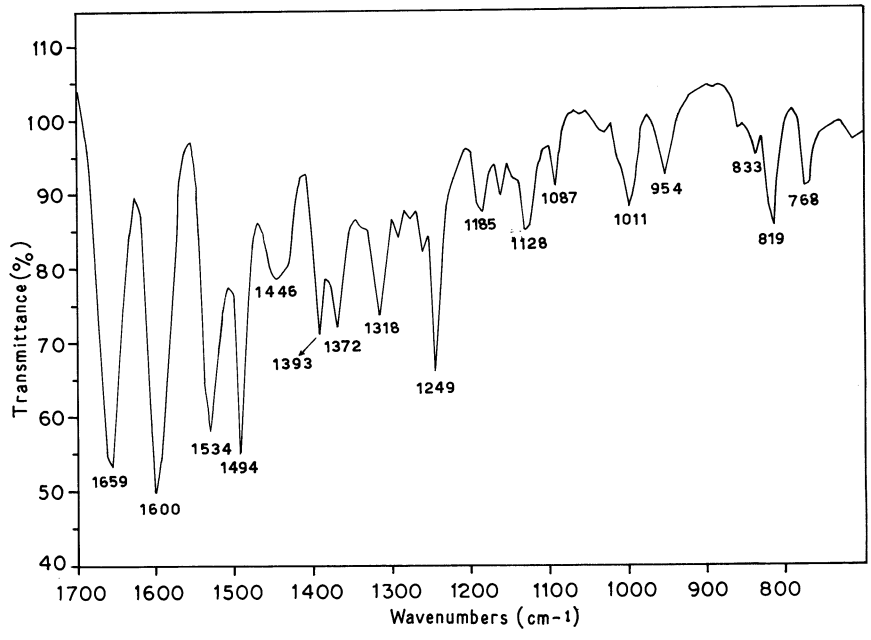


Fig. 2. The finger print region spectrum of the title compound in KBr: (700–1700 cm^{-1}).

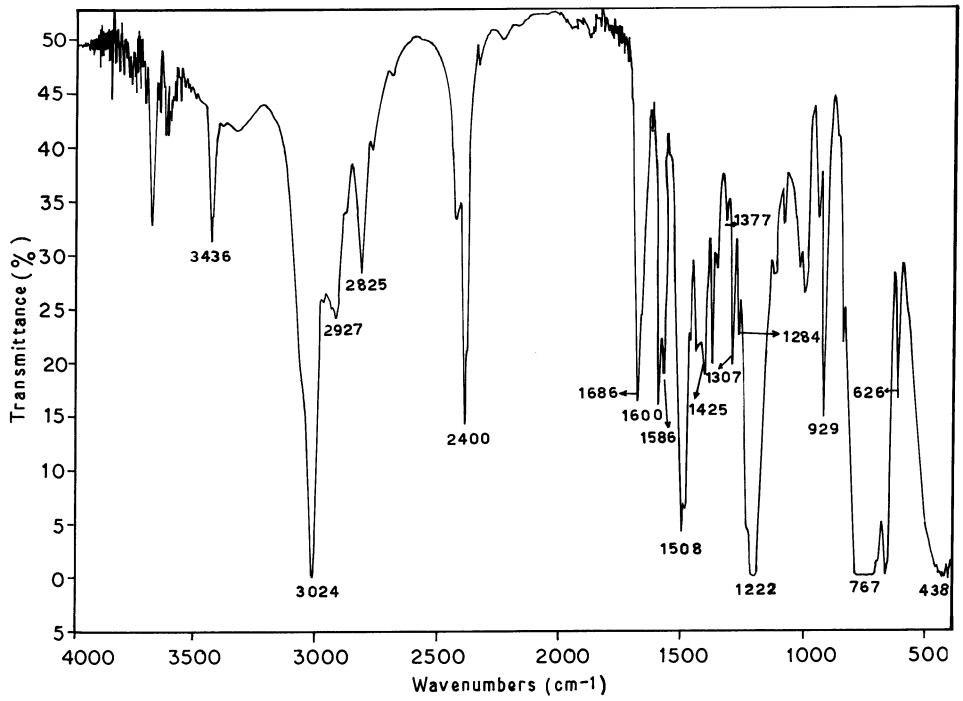


Fig. 3. The FTIR spectrum of the title compound in dilute $CHCl_3$ solution: (400–4000 cm^{-1}).

The above three bands disappear in dilute $CHCl_3$ solution and are replaced by a strong band at 3436 cm^{-1} for N–H stretching. This suggests the intra-molecular hydrogen bonding effect to be giving rise to them in the solid phase. The intensity to the band at 3155 cm^{-1} may have been provided by the overtone (2 × amide III + amide IV) and to the band at 3090cm^{-1} by (2 × amide II).

The strongest and most characteristic bands of the secondary amides, i.e. amide I and amide II lie between 1500 and 1700 cm^{-1} [16]. The amide I band occurs at 1686 cm^{-1} in the solution phase and at 1658 cm^{-1} in the solid phase. This may again suggest to the intra-molecular hydrogen bonding in the solid phase as it affects the resonance between C = O and C–N stretching causing decrease in the frequency. The frequency of 1686 cm^{-1} corresponds to Hammett σ constant equal to 0.23 and variation in intensity also follows the Thompson and Jameson correlation [17].

The strong band at 1534 cm^{-1} in the solid phase is assigned to the amide II vibration (N–H bending + aryl C–N and amide C–N stretch). X-ray data shows decreased C–N bond lengths of

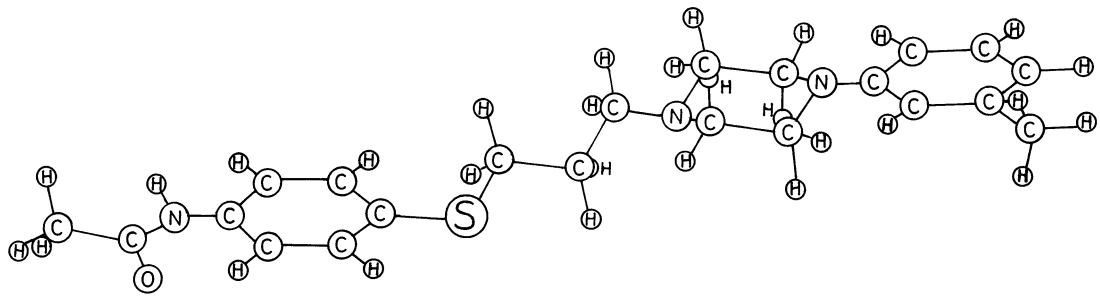


Fig. 4. The structure of the title compound.

Table 1
Normal mode frequencies and their assignments

Frequencies (in cm^{-1})		Assignments (PED is given in % within brackets and the groups are given within braces)
Calculation	Observed	
3307	3307	ν(N–H) [100]
3086	3084	ν(C–H) [100]
3084	3084	ν(C–H) [100] {phenyl_1}
3083	3084	ν(C–H) [95]
3082	3084	ν(C–H) [100]
3041	3039	ν(C–H) [100]
3037	3039	ν(C–H) [91] {phenyl_2}
3035	3039	ν(C–H) [98]
3034	3039	ν(C–H) [99]
2953	2953	ν(C–H) [100] {phenyl_2–CH_3 asymmetrical}
2917	2926	ν(C–H) [96] {O=C–CH_3 asymmetrical}
2871	2872	ν(C–H) [100] {S–CH_2 symmetrical}
2868	2872	ν(C–H) [100] {O=C–CH_3 symmetrical}
2844	2820	ν(C–H) [87] {piperazin-CH_2 symmetrical}
2841	2820	ν(C–H) [97] {piperazin-CH_2 symmetrical}
2840	2820	ν(C–H) [96] {piperazin-CH_2 symmetrical}
2836	2820	ν(C–H) [98] {piperazin-CH_2 symmetrical}
2827	2820	ν(C–H) [100] {piperazin-CH_2 symmetrical}
2822	2820	ν(C–H) [89] {piperazin-CH_2 symmetrical}
2821	2820	ν(C–H) [100] {piperazin-CH_2 symmetrical}
2820	2820	ν(C–H) [100] {piperazin-CH_2 symmetrical}
2819	2820	ν(C–H) [100] {piperazin-CH_2 symmetrical}
1659	1659	Amide I (ν(C=O) [67], ν(C=N) [23])
1600	1600	ν(C–C) [71] ϕ(C–C–H) [24] {phenyl_2}
1599	1600	ν(C–C) [64] ϕ(C–C–H) [34] {phenyl_1}
1535	1534	Amide II (ϕ(C–N–H) [48], ν(C–N) [17])
1501	1494	ν(C–C) [37] ϕ(C–C–H) [32], {phenyl_2}
	1494	ϕ(H–C–H) [20] {phenyl_2–CH_3}
1498	1494	ν(C–C) [33] ϕ(C–C–H) [33] {phenyl_1} ϕ(C–N–H) [21] {amide}
1451	1446	ϕ(H–C–H) [72] ϕ(C–C–H) [11] {Phenyl_2–CH_3 symmetrical}
1444	1446	ϕ(H–C–H) [54] {aliphatic}; CH_2 scissoring
1442	1446	ϕ(H–C–H) [52]; ϕ(C–C–H) [20] {piperazin};CH_2 scissoring
1441	1446	ϕ(H–C–H) [60] ϕ(C–C–H) [11] {piperazin};CH_2 scissoring
1433	1433	ϕ(H–C–H) [48] ϕ(C–C–H) [17] {aliphatic}; CH_2 scissoring
1398	1393	ϕ(H–C–H) [37] ϕ(N–C–H) [14] {piperazin}
1389	1393	ν(C–N) [10], ϕ(H–C–H) [24] {aliphatic} ϕ(H–C–H) [14] {piperazin}
1373	1372	ν(C–C)+ν(C–N) [21] {piperazin} ϕ(H–C–H) [20] {aliphatic}
1356	1349	ϕ(H–C–H) [65] ϕ(C–C–H) [12] {Phenyl_2-H_3 symmetrical}
1314	1318	(ν(C–C)+ν(C–N)) [23], ϕ(C–C–H) [30] {Piperazin}, ν(aryl-N) [24]
1299	1295	ϕ(C–C–H) [30] ϕ(H–C–H) [69] CH_2 wagging
1286	1290	ϕ(C–C–H) [24] ϕ(H–C–H) [42] CH_2 wagging
1262	1261	Amide III (ν(C–C) [38] ν(C–N) [24] ϕ(C–N–H) [16])
1246	1249	ϕ(S–C–H) [31] ϕ(C–C–H) [17] ν(C–C) [28] {aliphatic}
1185	1185	ν(C–N) [11] {Aryl-N} ϕ(C–C–H) [27] {piperazin} ϕ(C–C–H) [23] {phenyl_2}
1184	1185	ν(C–C)[12] ϕ(C–C–H)[34] {Phenyl_1} ν(C–N) [23] {Aryl-Amide}
1122	1128	(ν(C–C)+ ν(C–N)) [15] (ϕ(N–C–H)+ϕ(C–C–H) [46] {Piperazin}
1082	1087	ν(C–N) [12] ϕ(N–C–H) [22] {Piperazin}
1066	1066	ν(C–C) [5] ϕ(C–C–H) [50] {Piperazin}
1046	1066	ν(C–C)+ ν(C–N)+ ϕ(C–N–H) [90] {Piperazin Ring Vibrations}
1029	1033	ν(C–C) [29] ϕ(C–C–H) [35] {Aliphatic}

Table 1 (*Continued*)
Normal mode frequencies and their assignments

Frequencies (in cm^{-1})		Assignments (PED is given in % within brackets and the groups are given within braces)
Calculation	Observed	
1013	1011	ν(C–C) [38] ϕ(C–C–H) [20] {Phenyl_2}
945	954	ν(C–N) [25] (ϕ(N–C–H)+ϕ(C–C–H)) [30] {Piperazin}
934	936	ν(C–C) [37] ϕ(C–C–H) [48] {Phenyl_2}
930	936	ω(C–H) [43] {2_Adj_H} τ(C–C) [48]
923	914	(ν(C–C)+ν(C–C)) [18] {Piperazin} ν(Aryl-N) [7] ν(C–C) [32] {Phenyl_2} ϕ(C–C–H) [6] ϕ(H–C–H) [7] {Phenyl-CH_3}
865	862	ω(C–H) [48] {Lone H}, ν(S–C) [12] ν(N–C) [12] {Aliphatic}
835	833	ω(C–H) [69] {2_Adj_H} τ(C–C) [21]
767	768	Amide V {ν(C–C) [31] {Phenyl_1} ν(C–N) {Phenyl-Amide} [10] ν(C–N) {Me-Amide} [14] ω(N–H) [40]}
735	738	ω(C–H) [70] {3_Adj_H} τ(C–C) [27]
691	702	ϕ(C–C–H) [60] {Phenyl_2} ν(C–C) [38]
689	690	ν(C–C) [23] ϕ(C–C–C) [15] {Phenyl_2} ϕ(C–C–N)[13] {Piperazin}
555	554	ϕ(C–C–C) [60] ν(C–C) [08] {Phenyl_1}
514	505	ϕ(C–C–C) [15] {Aliphatic} ϕ(C–C–N) [23] (τ(C–C)+ τ(C–N)) [25] {Piperazin}
479	480	ϕ(C–C–C) [38] ν(C–C) [17] {Phenyl_2-CH_3}
460	465	ϕ(C–N–C) [11] {Piperazin} ω(C–H) {2_Adj_H} [11] τ(C–C) [19] {Phenyl_1}
436	432	ϕ(C–C–N) [15] (τ(C–C)+τ(C–N)) [28] {Piperazin}
403	405	ϕ(S–C–C)[10] {Aliphatic} τ(C–C) [18] ϕ(C–C–C) [12] {Phenyl_2}

the order of 1.34 Å which are shorter than the usual single C–N bond length of 1.38 Å. This may be ascribed to the increased bond orders of the C–N bonds due to resonance stiffening. These increased bond orders also contribute to the decrease in the frequency of N–H bending, which is caused by the increased effective mass of the hydrogen due to the effect of the hydrogen bonding. In the solution phase, this band shifts to 1560 cm^{-1}.

The medium intensity band at 1261 cm^{-1} is assigned to Amide III and has major contribution from C–C ($O=C–CH_3$) stretching with lesser contributions of C–N stretch and C–N–H in plane bending.

The strong absorption band at 596 cm^{-1} is assigned as amide VI vibration band. It seems that inductive and resonance effects play in tune to shift the frequency to higher side and to increase the intensity of the band.

3.1. Benzene ring vibrations

The band at 3090 cm^{-1} in the solid KBr spectrum has been assigned to the C–H stretching vibration of 1,4 di-substituted benzene (hereafter referred to as phenyl_1). The difference in individual bond lengths in this ring is similar to that of polycyclic structures. These differences are ne cessarily reflected in the FTIR spectrum. These along with the presence of unoxidized sulfur in this ring are suggestive of a very weak absorption band, but the interaction of this band position with the associated N–H vibration of bonded amide in the same region may be the reason for the increased intensity of the band. The band at 1600 cm^{-1} is assigned to quadrant stretching of benzene rings.

The out-of-plane bending vibrations of the hydrogen atoms in the two phenyl rings are complicated by the heavy substitutions, viz. unoxidized sulfur and acetamide at 1,4 positions in one (phenyl_1) and the piperazin ring and methyl group at 1,3 position in the other (hereafter referred to as phenyl_2). The situation becomes more so due to the presence of piperazin ring vibrations in the same region.

A strong band at 820 cm^{-1} and a medium

Table 2
Internal co-ordinates and their force constants[a]

Internal co-ordinates		Force constants* ($\times 10^5$ dynes/cm)
ν(C–C)	Phenyl_1	5.060
ν(C–N)	Phenyl_1-amide	3.830
ν(C–S)	Phenyl-sulfur	3.680
ν(C–S)	Aliphatic-sulfur	3.520
ν(C–C)	CH_2 adjacent to S	3.850
ν(C–C)	Aliphatic	3.900
ν(C–N)	Aliphatic-piperazin	3.590
ν(C–N)	Piperazin	3.620
ν(C–C)	Piperazin	3.650
ν(C–N)	Aryl-N	3.730
ν(C–C)	Phenyl_2	4.950
ν(C–C)	Phenyl-CH_3	4.750
ν(C = O)		8.840
ν(C–C)	O = C–CH_3	4.340
ν(C–N)	Amide	3.840
ν(C–H)	Phenyl_1	4.930
ν(C–H)	CH_2 adjacent to S	4.310
ν(C–H)	Aliphatic CH_2	4.280
ν(C–H)	Piperazin CH_2	4.090
ν(C–H)	Phenyl_2	4.770
ν(C–H)	CH_3 attached to phenyl_2	4.300
ν(N–H)		5.800
ν(C–H)	O = C–CH_3	4.200
ϕ(C–C–H)	Phenyl_1	0.355(0.230)
ϕ(C–C–H)	CH_2 adjacent to S	0.368(0.170)
ϕ(C–C–H)	Aliphatic CH_2	0.370(0.210)
ϕ(N–C–H)	CH_2-piperazine	0.369(0.200)
ϕ(C–C–H)	CH_2-piperazine	0.371(0.180)
ϕ(C–C–H)	Phenyl_2	0.360(0.230)
ϕ(C–C–H)	CH_3 attached to phenyl_2	0.394(0.190)
ϕ(C–C–C)	Phenyl_1	0.485(0.350)
ϕ(C–C–N)	Phenyl_1-amide	0.580(0.320)
ϕ(C–C–S)	Phenyl_1-sulfur	0.753(0.400)
ϕ(C–S–C)	Phenyl_1-thio-CH_2	0.760(0.500)
ϕ(C–C–S)	Aliphatic-sulfur	0.750(0.400)
ϕ(C–C–C)	Aliphatic chain	0.513(0.250)
ϕ(C–N–C)	Aliphatic-piperazin	0.510(0.180)
ϕ(C–C–N)	Piperazin	0.490(0.150)
ϕ(C–N–C)	Piperazin	0.491(0.230)
ϕ(N–C–C)	Piperazin-phenyl_2	0.490(0.250)
ϕ(C–C–C)	Phenyl_2	0.492(0.350)
ϕ(C–C–C)	Phenyl-CH_3	0.493(0.260)
ϕ(N–C=O)		0.570(0.260)
ϕ(C–C=O)		0.569(0.270)
ϕ(C–C–H)	(O=C–CH_3)	0.460(0.240)
ϕ(C–N–H)	(O=C–N–H)	0.419(0.240)
ϕ(C–N–H)	(Phenyl_1-N–H)	0.420(0.240)
ϕ(H–C–H)	CH_3 attached to C=O	0.300(0.220)
ϕ(H–C–H)	Aliphatic CH_2	0.320(0.210)
ϕ(H–C–H)	Piperazin ring	0.315(0.200)
ϕ(H–C–H)	CH_2 attached to phenyl_2	0.350(0.240)
ϕ(S–C–H)		0.423(0.210)
ϕ(C–N–C)	Phenyl_1-N–C	0.440(0.250)
ϕ(C–C–N)	Amide	0.425(0.230)
ω(C–H)	Phenyl_1	0.120
ω(N–H)		0.260
ω(C=O)		0.500
ω(C–H)	(Lone H) phenyl_2	0.160
ω(C–H)	Phenyl_2	0.110
τ(C–C)	Phenyl_1	0.070
τ(C–N)	Phenyl_1-amide	0.040
τ(C–C)	O=C–CH_3	0.060
τ(C–S)	Phenyl_1-S	0.080
τ(S–C)	S–CH_2	0.070
τ(C–C)	Aliphatic	0.085
τ(C–N)	Piperazin	0.072
τ(C–C)	Piperazin	0.040
τ(C–N)	Aryl-N	0.041
τ(C–C)	Phenyl_2	0.039
τ(C–C)	Phenyl_2–CH_3	0.040

band at 835 cm^{-1} are assigned to out-of-plane vibration of two adjacent hydrogen atoms in 1,4 different bond orders of benzene C–C bonds. This is also evident from the X-ray data with the standard deviation approximately equal to 0.02 Å over the mean value of 1.39 Å of the C–C bond length.

The band at 779 cm^{-1} is assigned to the wagging of the three adjacent hydrogen atoms present in 1,3 di-substituted phenyl ring, and that at 862 cm^{-1} is assigned to the wagging vibration of the isolated hydrogen atom. The intensity of the latter is rather weak due to the presence of piperazin ring adjacent to this lone hydrogen atom.

The strong absorption band at 1318 cm^{-1} is di-substituted benzene. The presence of two bands may be ascribed to the charge redistribution, giving rise to assigned to aryl-N linkage vibration. There is a striking similarity of this band with the C = O and C–C vibrations where either the compound is cyclic or one of the carbon atoms has aromatic character. The overlapping of expected piperazin ring vibration in this characteristic band is evident in the normal mode calculations.

3.2. Piperazin ring vibrations

The strong bands at 1128 and 1087 cm^{-1} are assigned to the asymmetrical and symmetrical C–N stretching vibrations in the heterocyclic piperazin ring system. This is the same region in which C–N vibrations in the non-cyclic tertiary amines have their absorption bands. The C–C and the C–N bond stretches couple with each other in this favorable environment. The strong absorption band at 1446 cm^{-1} is assigned to the CH_2 deformation frequency. This band shows the absence of ring strain in the chair conformation of the piperazin ring. The band at 1295 cm^{-1} is assigned to the CH_2 wagging vibration. This band along with the band at 1446 cm^{-1} are characteristic of the piperazin or dioxane derivative six-membered ring. These bands are useful for the detection of the ring strain, as any non-staggering of the ring bonds would have increased the frequencies of these two bands. The staggered chain conformation is evident from the X-ray data. The small lowering of the frequency of the band from aliphatic CH_2 wagging frequency at 1304 cm^{-1} is attributed to the presence of the N atom in the heterocyclic ring. This is well distinguished from S–CH_2 wagging frequency of 1249 cm^{-1}.

The band at 954 cm^{-1} is assigned to the symmetrical ring vibration of piperazin. The expected contribution of other C–C linkages in this absorption band is shown by the calculations. The interaction of the C–C–H and N–C–H in-plane bending due to the motion of the C atoms is also evident.

The intense band at 2818 cm^{-1} is characteristically absorbed in the symmetrical CH_2 stretching of the group adjacent to the N atom. The large intensity is attributed to the presence of a large number of similar CH_2 groups and to the Fermi resonance with the additive bending vibration of CH_3 group present in the vicinity of the carbonyl group (1446 cm^{-1} + 1371 cm^{-1}). This vibration along with ring breathing vibrations at 1128 and 1087 cm^{-1} have previously also been shown to confirm the presence of tertiary amines (cyclic or non-cyclic) along with the presence of CH_3 or CH_2 group conjugated by a double bond in the molecule.

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