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QUANTUM CHEMICAL AND EXPERIMENTAL STUDIES ON THE STRUCTURE AND VIBRATIONAL SPECTRA OF SUBSTITUTED 2-PYRANONES

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A systematic study on the structural characteristics of the 2-pyranone ring containing molecules with bromine, nitrile, and amide substituents at the C-3 position in the ring is conducted in the electronic ground (S_0) state by DFT calculations using the B3LYP/6-311++G** method. The geometrical structure of the bromine substituted compound, which shows potent hepatoprotective activity, is studied both in the ground (S_0) and first excited singlet (S_1) states using RHF/6-311++G** and CIS/6-311++G** methods respectively. The molecules are found to exist in two isomeric forms *gauche* and *trans* that have the enthalpy difference of less than 3.32 kcal/mol; the latter is the preferred orientation in the gaseous phase. The S_1 state is a $^1(\pi,\pi^*)$ state that arises π-electron transfer from the region of a double bond in the pyranone ring to the region of the internuclear bond connecting the 2-pyranone and benzene rings. A complete vibrational analysis is conducted for the 3-bromo-6-(4-Chlorophenyl)-4-thiomethyl-2H-pyran-2-one molecule based on the experimental infrared spectra in the 50—4000 cm^{-1} region and DFT/6-311++G** computations of vibrational frequencies for the *gauche* and *trans* isomeric forms. Spectral assignments based on the potential energy distribution along the internal coordinates confirm the non-planar structure of the molecule.

K e y w o r d s: 2-pyranone, molecular conformation, infrared spectra, DFT.

INTRODUCTION

Several classes of natural products [1, 2] display pronounced hepatoprotective activity and many of these possess pyran-2 or 4-one moieties either in a rigid or flexible form. Ram et al. [3] studied the structural requirements for the activity of substituted pyran -2-ones and concluded that substituents at C-3 and C-6 positions in the pyran ring play a pivotal role in expressing significant hepatic protection. A 4-chlorophenyl substituent at the C-6 position of the ring showed the maximum activity. Among the various substituents at C-3, a bromo group showed the maximum activity, followed by a nitrile substituent, against thioacetamide induced hepatic damage in rats. Together with the hepatoprotective activity, the importance of pyran -2-one derivatives as building blocks in the field of synthetic and medicinal chemistry has been well established and is a consequence of their interesting structural features and diverse pharmacological properties [4]. The structural features of a few substituted pyrones have been reported from X-ray diffraction studies [5—7]. A significant difference, however, exists in these studies in the geometrical parameters of the pyran ring. Woods [8] reported the characteristic absorption peaks of 3-bezoyl-2-pyrones in the infrared and UV spectra. In an earlier study [9], we have reported the results of quantum chemical, vibrational (infrared and Raman), and electronic spectroscopic studies on 6-phenyl-4-methylsulfonyl-2-oxo-2H-pyran and 6-phenyl-4-methylsulfonyl-2-oxo-2H-pyran-3-carbonitrile. Information was obtained about the geometrical structure and isomeric conformation of these molecules in the electronic ground and first excited states based on the theoretical and

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experimental studies. No quantum chemical or vibrational spectroscopic study on the geometrical and electronic structure in the ground and first excited electronic states has so far been reported for these molecules. The presence of a thiomethyl group may also result in isomeric conformations for these molecules, which together with the substituent at the C-3 position in the pyran-2-one ring can affect the electronic charge distribution and give rise to intramolecular hydrogen bonding. In the present communication, we are reporting the results of quantum chemical calculations and infrared spectroscopic studies, which provide information about the geometrical and electronic structure and isomeric conformations of these molecules in the ground and first excited electronic states as well as the presence of intramolecular hydrogen bonds. A complete vibrational analysis has also been attempted for the molecule 6-(4-chlorophenyl)-3-bromo-4-thiomethyl-2*H*-pyran-2-one based on the potential energy distribution (PED) over internal coordinates to get information about its spectral characteristics.

METHODOLOGY

Experimental. Substituted 2*H*-pyranones were synthesized by Ram et al. [3] through a sequence of reactions. The infrared spectra of high purity solid sample of 3-bromo-6-(4-chlorophenyl)-4-thiomethyl-2H-pyran-2-ones in the 600—50 cm^{-1} range were recorded in a polyethylene pellet on a Nicolett MAGNA 550 FT-IR spectrophotometer and the spectrum in the 4000—400 cm^{-1} range was recorded in KBr pellets on a Bruker TENSOR 27 FT-IR spectrometer with a spectral resolution of 4 cm^{-1}.

Computational. The molecular geometries of 3-bromo-6-(4-chlorophenyl)-4-thiomethyl-2H-pyran-2-one (molecule **1**, Fig. 1, *a*), 6-(4-chlorophenyl)-3-cyano-4-thiomethyl-2H-pyran-2-one (molecule **2**, Fig. 1, *b*), and 6-(4-chlorophenyl)-3-amide-4-thiomethyl-2H-pyran-2-one (molecule **3**, Fig. 1, *c*) in the electronic ground (S_0) were optimized by density functional theory (DFT) using the 6-311++G** basis set with polarization and diffuse functions. Becke′s three parameter hybrid exchange functional with Lee—Yang—Parr correlational functionals (B3LYP) were used for these calculations. Optimization of the geometry of molecule **1** was also carried out in the ground (S_0) and first excited singlet state (S_1) by RHF/6-311++G** and CI-Singles (CIS) method CIS/6-311++G**, as implemented in the Gaussian 03W computer software [13]. Vibrational frequencies and infrared intensities for molecule **1** were calculated in the harmonic approximation by the B3LYP/ 6-311++G** method using the optimized geometry at the same level of theory. Since the DFT frequencies are known to be higher than the experimental frequencies, they were scaled down by the wave-number linear scaling procedure (WLS) of Yoshida et al. [12] by the expression

$$\nu_{obs} = (1.0087 - 0.0000163\nu_{calc})\nu_{calc}\ cm^{-1}.$$

All the calculations were performed using the G03W computer software [13]. Potential energy distributions (PEDs) along the internal coordinates were calculated by the GAR2PED computer software [14]. The internal coordinate system with localized symmetry, as recommended by Pulay et al. [15], was used for the assignment of vibrational modes.

RESULTS AND DISCUSSION

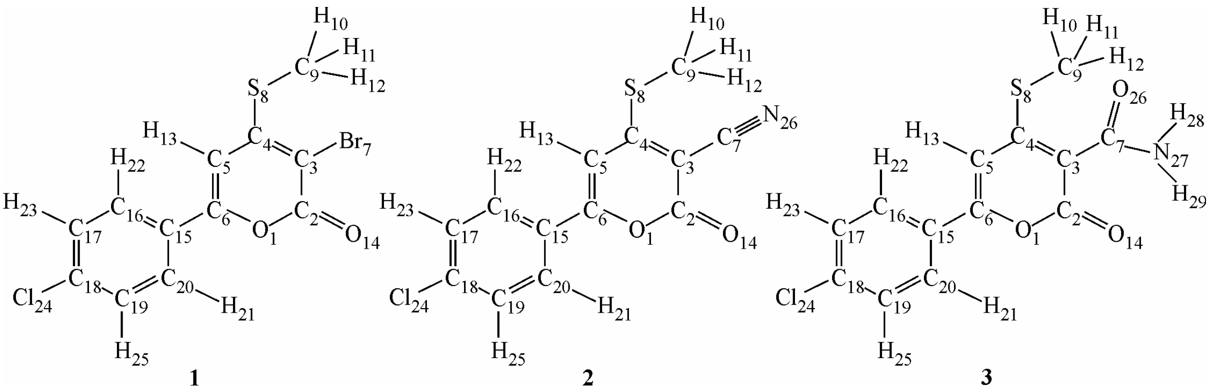
Molecular structure. The thiomethyl (SCH_3) group in the presently studied molecules **1**, **2**, and **3** may either have a *cis* (D(3,4,8,9) = 0°), *gauche* (D(3,4,8,9) ≠ 0°), or *trans* (D(3,4,8,9) = 180°) orientation relative to the C3=C4 bond and may either lie within the pyran-2-one ring plane or outside it. The possibility of the existence of conformational isomerism in the present set of molecules was explored by optimizing the geometries of molecules **1**, **2**, and **3** in the electronic ground state (S_0) by B3LYP/6-311++G**. The geometry of molecule **1** was also optimized by the RHF/6-311++G** and CIS/6-311++G** methods for the S_0 and S_1 states respectively. The results of the calculations are given in Table 1, which contains the optimized geometries and energies of the molecules. The Table has been simplified by ignoring the hydrogen atom containing parameters except those needed to understand hydrogen bonding.

It follows from Table 1 that each of the three molecules have two energy minima corresponding to the *gauche* and *trans* isomeric forms. In order to verify that these isomeric structures in each case

Table 1

Optimized geometries of molecules **1**, **2** *and* **3** *in the electronic ground* (S_0) *and molecule* **1** *in the excited* (S_1) *states using* 6-311++G** *basis set*

	Ground State (S_0)							Excited State (S_1)
	Molecule **1**			Molecule **2**		Molecule **3**		Molecule **1**
	gauche		*trans*	*gauche*	*trans*	*gauche*	*trans*	*gauche*
	RHF	B3LYP	B3LYP	B3LYP	B3LYP	B3LYP	B3LYP	CIS
Bond Length								
R(1,2)	1.355	1.406	1.415	1.409	1.419	1.399	1.405	1.377
R(2,14)	1.195	1.199	1.199	1.198	1.197	1.212	1.213	1.179
R(3,4)	1.342	1.372	1.375	1.387	1.391	1.390	1.399	1.412
R(3,7)	1.881	1.896	1.896	1.420	1.420	1.504	1.494	1.863
R(4,5)	1.449	1.433	1.432	1.429	1.423	1.432	1.430	1.384
R(4,8)	1.786	1.784	1.765	1.759	1.757	1.76	1.762	1.771
R(5,6)	1.333	1.359	1.360	1.360	1.365	1.356	1.359	1.412
R(6,15)	1.477	1.470	1.472	1.470	1.471	1.469	1.471	1.419
R(8,9)	1.82	1.833	1.826	1.828	1.824	1.822	1.836	1.820
R(15,16)	1.392	1.404	1.404	1.404	1.404	1.404	1.404	1.417
R(15,20)	1.390	1.404	1.403	1.404	1.404	1.403	1.404	1.417
R(16,17)	1.381	1.388	1.388	1.387	1.387	1.388	1.388	1.372
R(19,20)	1.383	1.390	1.390	1.390	1.389	1.390	1.390	1.372
R(7,26)	–	–	–	1.156	1.157	1.226	1.231	–
R(7,27)	–	–	–	–	–	1.361	1.354	–
R(27,28)	–	–	–	–	–	1.009	1.007	–
R(14,29)	–	–	–	–	–	1.945	1.918	–
R(10,26)	–	–	–	2.645	5.831	2.185	4.959	–
Bond angle								
A(2,3,7)	114.8	114.12	115.67	114.68	116.97	118.29	120.12	115.71
A(3,4,8)	124.7	126.60	119.15	128.88	118.02	129.59	121.35	124.64
A(1,6,15)	112.78	113.2	113.08	113.15	113.11	113.30	113.13	115.18
A(4,8,9)	101.37	104.69	103.9	108.54	104.25	108.85	102.98	102.22
A(6,15,16)	120.94	121.36	121.55	121.41	121.57	121.20	121.52	122.00
A(3,7,26)	–	–	–	179.33	181.65	120.88	119.80	–
A(3,7,27)	–	–	–	177.14	179.99	116.97	118.12	–
A(26,7,27)	–	–	–	–	–	122.15	122.08	–
A(7,27,28)	–	–	–	–	–	117.13	115.67	–
A(7,27,29)	–	–	–	–	–	120.88	118.80	–
Dihedral angle								
D(6,1,2,14)	177.71	–179.92	179.01	179.62	179.15	174.65	178.99	–163.93
D(1,2,3,7)	–176.17	–174.05	–179.27	–173.53	–179.34	–162.14	–179.22	–178.24
D(14,2,3,7)	3.39	5.13	0.51	5.80	0.48	16.93	0.59	3.18
D(7,3,4,5)	177.73	173.51	–179.81	173.23	–179.89	163.76	–179.79	168.39
D(7,3,4,8)	–0.30	–3.05	–0.18	–5.33	–0.26	–17.53	–0.14	–6.47
D(3,4,8,9)	–53.07	–54.50	179.68	–21.12	179.79	–24.57	–179.73	–71.56
D(1,6,15,20)	22.78	6.83	13.04	9.15	11.38	12.19	12.21	–0.94
D(5,6,15,20)	–155.88	–171.91	–166.06	–169.56	–167.84	–165.61	–166.95	–175.41
D(2,3,7,26)	–	–	–	68.18	179.8	149.88	179.91	–
D(2,3,7,27)	–	–	–	–108.41	–0.601	–29.52	–0.07	–
D(3,7,27,28)	–	–	–	–	–	168.61	179.91	–
D(3,7,27,29)	–	–	–	–	–	16.71	–0.21	–
Energy (a.u.)	–4038.337839	–4045.276802	–4045.281884	–1564.6846	–1564.7923	–1640.503799	–1640.509090	–4038.316182



1 2 3

Fig. 1. Atom numbering of in molecules **1**, **2** and **3**

correspond to stable isomeric forms, frequency calculations were performed using the same method and basis set. The frequency calculations provided all positive frequencies and confirmed that two energy minima in each case correspond to a stable conformation. It follows from Table 1 that the *trans* conformers in molecules **1**, **2**, and **3** have lower energies, and hence, are more stable than the *gauche* conformers; the enthalpy difference between the *gauche* and *trans* conformers in molecules **1**, **2**, and **3** are 3.19, 0.68, and 3.32 kcal/mol respectively. In contrast to this observation, based on the quantum chemical calculations at the G2 level of theory, Abramov et al. [17] report that in the case of methyl vinyl sulfide, the two stable isomeric conformations are *cis* and *gauche* and they have an enthalpy difference of about 6.92 kJ/mol; the former is more stable than the latter. As reported previously [9], the 6-phenyl-4-thiomethyl-2-pyranone molecule, which is similar to the presently studied molecules, but has no substituent at the C-3 position in the pyranone ring, has a more stable *cis* conformation.

A larger deviation from the *cis* conformation in these molecules, in contrast to 6-phenyl-4-thiomethyl-2-pyranone [9] that has a more stable *cis* conformation, may be attributed to the substitution at the C-3 position in the pyranone ring. It is thus seen that the dihedral angle D(3,4,8,9) in molecules **1**, **2**, and **3** with Br, CN, and $CONH_2$ substituents at the C-3 position are 54.50°, 21.12°, and 24.57° respectively, as against –0.11° in 6-phenyl-4-thiomethyl-2-pyranone [9]. The substituent size also affects the C4S8C9 angle that has values of 104.69°, 108.54°, and 108.85° in molecules **1**, **2**, and **3**. Neither the nature of the substituent at the C-3 position nor the change in conformation have any significant effect on the bond lengths of the aromatic or pyranone rings. In the case of the amide substituent (molecule **3**), however, the C2—O14 bond length is 1.212 Å as against 1.199 Å in molecule **1** and 1.198 Å in molecule **2**. A larger C2—O14 bond length in molecule **3** may be attributed to the presence of the intramolecular hydrogen bond between O14 and H29 atoms (Fig. 1). The internuclear O14…H29 distance in molecule **3** is 1.945 Å in the *gauche* conformation and 1.918 Å in the *trans* conformation, and is indicative of the presence of a strong hydrogen bond in both conformers.

It also follows from Table 1 that in molecule **3**, the amino group is planar in the *trans* conformer with dihedral angles D(3,7,27,28) and D(3,7,27,29) of 179.91° and –0.21° respectively, but it is twisted in the *gauche* conformer. The two dihedral angles in the *gauche* conformer are 168.61° and 16.71° respectively.

Effect of electronic excitation on molecular structure. CI-Singles (CIS) [10, 11] quantum chemical calculations are able to provide some general information about the structure of molecules in the excited electronic states. In the present case, CIS calculations were performed for molecule **1** in the first excited singlet state (S_1) using the 6-311++G** basis set. The calculations show that in the S_1 state, the molecule can exist only in one stable conformation with the thiomethyl group in *gauche* orientation to the carbonyl group (Table 1). A study of the electronic transitions by CIS show that the S_1 state of molecule **1** is a $^1(\pi,\pi^*)$ state. A similar observation has been made by Thul et al. [9] in analogous molecules of 6-phenyl-4-thiomethyl-2-oxo-2H-pyran and 6-phenyl-4-thiomethyl-2-oxo-2H-pyran-3-carbonitrile. A plot of the highest occupied molecular orbital (HOMO) (Fig. 2, *a*) and the

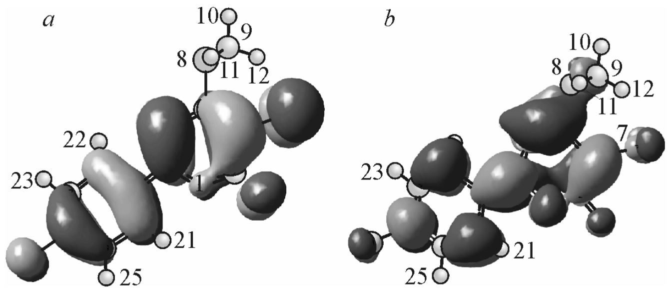


Fig. 2. Highest occupied (*a*) and lowest unoccupied (*b*) molecular orbitals of molecule **1**

lowest unoccupied molecular orbital (LUMO) (Fig. 2, *b*) shows that the S_1 state arises π-electron transfer from the region of the C3—C4 bond to C6—C15 followed by the electron charge redistribution. This may explain an increase in the C3—C4 bond length and a decrease in the C6—C15 bond length on electronic excitation (Table 1). It is seen from Table 1 that in the S_1 state, the lengths of C4—C5, C6—C15, C16—C17, and C19—C20 bonds are shorter, while those of C3—C4, C5—C6, C15—C16, and C15—C20 bonds are longer by as much as 0.05 Å than the corresponding bonds in the S_0 state. It is also noted that electronic excitation causes a reduction in the C2=O14 bond length from 1.195 Å (S_0) to 1.179 Å (S_1) (Table 1), possibly due to its reduced conjugation with the neighboring bonds in the S_1 state. This also follows from the shape of molecular orbitals in the highest occupied and lowest unoccupied states (Fig. 2); the size of the π-electron lobe on the oxygen atom of the carbonyl group in LUMO gets localized and slightly reduced in size as compared to the HOMO, where it is broad and close to the π-electron lobe of the conjugated atoms. The dihedral angles C1C6C15C20 and C5C6C15C20 between the phenyl and pyranone rings change from 6.83° and –171.91° in the S_0 state to –0.94° and –175.41° respectively in the S_1 state, making the two rings almost coplanar in this excited electronic state. It is also seen from Table 1 that the SCH_3 group further moves out of the molecular plane by about 18° in the S_1 state as compared to the S_0 state and reduces crowding around the bromine atom; the dihedral angles D(3,4,8,9) in the S_0 and S_1 states are 53.07° and –71.56°, respectively.

Mulliken Population Analysis and hydrogen bonding. Total atomic charges on the various atoms of the *gauche* and *trans* conformers of molecule **1**, **2** and **3** in the electronic ground state was obtained by Mulliken population analysis using B3LYP/6-311++G** method. These are given in Table 2, which also contains the dipole moments and ionization potentials obtained on the basis of the optimized molecular geometries. In order to understand the spatial distribution of electronic charge, three-dimensional plots of total electron densities for the three molecules were also obtained using computer program GaussView ver.3 [16]. It is found that there are some significant differences in electron charge distributions (Table 2) in molecules **1**, **2** and **3** which may affect their physicochemical properties. In all cases, the oxygen atoms O1 and O14 have large negative charge (Table 2) and behave as electron acceptor whereas the sulphur atom S8 of the these molecules acts as electron donor with large positive charge.

Using compiled data for a large number of CH…O and CH…N contacts, Desiraju and Steiner [18] find significant directionality even as far as 3.0 Å and conclude that these contacts are to be legitimately viewed as 'weak' hydrogen bonds. In the case of the gauche conformer of molecule **2**, a large negative charge on nitrogen atom N26 and a large positive charge on the hydrogen atom H10 together with a favorable interatomic distance of 2.645 Å may thus give rise to a weak hydrogen bonding between these atoms. Likewise, in the case of molecule **3**, a large positive charge on hydrogen atoms H28 and H29 and large negative charge on atom O14 together with very small internuclear distances of 1.945 Å and 1.918 Å between atoms O14 and H29 in the *gauche* and *trans* conformers, respectively, is indicative of the presence of a strong intramolecular hydrogen bond in both the conformers.

It also follows from Table 2 that the dipole moment of the *trans* conformer in all the molecules is larger than that of the *gauche* conformer. According to Koopmann's theorem [19], the energy of the highest occupied molecular orbital of a molecule may be taken as its ionization potential. These values

Table 2

Charge densities, dipole moment, and ionization potential of molecules **1**, **2** *and* **3** *in the electronic ground* (S_0) *state. Atom numbers are as in Fig. 1*

	Ground state (S_0)					
	Molecule **1**		Molecule **2**		Molecule **3**	
	gauche	*trans*	*gauche*	*trans*	*gauche*	*trans*
	DFT	DFT	DFT	DFT	DFT	DFT
1 O	–0.505	–0.509	–0.506	–0.507	–0.498	–0.504
2 C	0.601	0.597	0.605	0.596	0.585	0.586
3 C	–0.047	–0.072	–0.02	–0.005	–0.065	–0.053
4 C	–0.1	–0.082	–0.052	–0.074	–0.086	–0.128
5 C	–0.147	–0.145	–0.165	–0.155	–0.151	–0.139
6 C	0.34	0.338	0.351	0.355	0.333	0.335
7 Br/C	–0.052	–0.051	0.284	0.277	0.537	0.582
8 S	0.145	0.218	0.187	0.244	0.187	0.293
9 C	–0.47	–0.495	–0.486	–0.497	–0.48	–0.515
10 H	0.152	0.16	0.191	0.16	0.202	0.147
11 H	0.152	0.154	0.169	0.158	0.144	0.154
12 H	0.168	0.156	0.156	0.167	0.15	0.144
13 H	0.124	0.103	0.125	0.106	0.123	0.103
14 O	–0.445	–0.452	–0.442	–0.443	–0.499	–0.507
15 C	0.054	0.055	0.047	0.049	0.053	0.054
16 C	–0.105	–0.106	–0.102	–0.102	–0.105	–0.105
17 C	–0.08	–0.08	–0.08	–0.08	–0.08	–0.08
18 C	–0.089	–0.089	–0.088	–0.088	–0.089	–0.089
19 C	–0.074	–0.075	–0.075	–0.075	–0.075	–0.075
20 C	–0.098	–0.096	–0.094	–0.092	–0.096	–0.095
21 H	0.135	0.136	0.138	0.14	0.134	0.135
22 H	0.104	0.097	0.106	0.1	0.106	0.102
23 H	0.119	0.118	0.122	0.121	0.12	0.12
24 Cl	–0.003	–0.003	0.004	0.005	–0.002	–0.001
25 H	0.122	0.122	0.125	0.126	0.122	0.123
26 H/N/O	–	–	–0.501	–0.486	–0.527	–0.532
27N	–	–	–	–	–0.614	–0.634
28H	–	–	–	–	0.27	0.273
29H	–	–	–	–	0.301	0.304
μ (Debye)	4.01	6.05	6.15	8.8	2.25	3.84
I.P., eV	6.20	6.15	6.56	6.48	6.37	6.31

for molecules **1**, **2** and **3** are given in Table 2. Based on DFT calculations, the *gauche* conformers have ionization potentials of 6.20, 6.56 and 6.37 eV whereas the *trans* conformers have ionization potentials of 6.15, 6.48 and 6.31 eV.

VIBRATIONAL ANALYSIS

A complete analysis of 69 vibrational fundamental modes of 3-bromo-6-(4-chlorophenyl)-4-thiomethyl-2H-pyran-2-ones (molecule **1**) is being reported based on the experimental infrared spectrum in the 50-4000 cm^{-1} region and B3LYP /6-311++G** quantum chemical frequency calculations. As seen above, the molecule may exist in two isomeric forms *gauche* and *trans*, both of which have

Table 3

Experimental and calculated infrared frequencies, intensities, and vibrational assignments for gauche and trans conformers of 3-bromo-6-(4-chlorophenyl)-4-thiomethyl-2H-pyran-2-ones (molecule **1**)

gauche conformer			Assignments [a] [PED][b]	*trans* conformer	
Calculated Frequency (cm^{-1})	Intensity, (km/mol)	Experimental		Calculated Frequency (cm^{-1})	Intensity, (km/mol)
1	2	3	4	5	6
48	0.13	56 (w)	τ C6—C15 [86], τ asym′A [4]	33	0.01
69	2.57	60 (w)	τ C4—S8 [56], δ C—S—C [21]	61	0.04
80	1.18	88 (w)	τ puck A [21], δ O—C—C Inter-ring [15]	82	2.7
151	0.1	150 (w)	τ asym A [37], τ puck A [29]	139	0.86
181	0.87	180 (vw)	τ S8—C9 [58], τ asym A [13]	192	0.08
193	0.16	198 (w)	δ asym′A [26], υ C3—Br7 [18]	197	0.3
233	0.93	232 (w)	δ C—S—C [24], τ asym A [11]	250	0.11
285	0.67	285 (w)	γ C3—Br7 [28], δ C—C—Cl24 [22]	286	3.7
330	0.97	361 (vw)	γ C18—Cl24 [24], γ C3—Br7 [20]	329	0.31
419	0.19	405 (w)	τ asym′ B [83], γ C17—H23 [5]	415	0.23
496	7.57	479 (w)	τ asym B [37], γ C18—H24 [25]	492	9.1
521	14.2	522 (w)	υ C18—Cl24 [23], δ asym A [22]	520	11.6
571	6.01	570 (w)	υ C3—Br7 [20]	577	7.5
595	14.97	589 (w)	γ C4—S8 [37], τ asym A [20]	589	2.9
634	2.16	640 (vw)	δ C—C—O & O—C—O A [25], δ asym′B [25]	634	2.4
646	3.62	654 (vw)	δ asym′B [50], δ C—C—O & O—C—O A [10]	646	3.4
670	1.88	671 (vw)	γ C6—C15 [29], τ puck A [22]	665	2.5
683	1.91	710 (w)	υ S8—C9 [83]	700	1.1
719	15.74	718 (w)	δ asym B [39], υ C18—Cl24 [16]	718	23.4
744	14.44	738 (w)	γ C2=O14 [41], τ puck A [33]	729	17.3
817	31.91	816 (ms)	υ C4—S8 [26], δ asym A [12]	803	28.1
838	54.19	825 (s)	γ C5—H13 [53], γ C17—H23 [12]	826	11.1
857	9.49	840 (w)	γ C19—H25 [25], γ C5—H13 [22]	849	24.7
896	85.76	932 (m)	υ O1—C2 [55], δ C—C—O & O—C—O A [10]	880	93.3
976	10.53	975 (vw)	CH3 Rock′ [91], δ asym CH3 [3]	964	2.6
985	13.82	990 (w)	δ trig.A [28], γ C20—H21 [20]	983	0.3
1017	24.4	1009 (w)	δ trig. B [58], υ C15—C16 [7]	1019	28.5
1032	24.04	1058 (w)	υ O1—C6 [23], υ O1—C2 [18]	1048	17.5
1091	96.6	1094 (m)	υ C18—Cl24 [25], υ C17—C18 [22]	1095	92.6
1198	13.88	1209 (w)	δ C—C—H21 [20], δ C—C—H22 [17]	1199	27.1
1297	45.27	1304 (w)	υ C6—C15 [30], υ C4—C5 [12]	1305	75.3
1341	3.9	1327 (vw)	δ sym CH3 [78], δ C—C—H13 [5]	1347	0.75
1412	21.55	1406 (vw)	υ C16—C17 [21], υ C19—C20 [19]	1416	2.2
1442	7.83	1428 (vw)	δ asym CH3 [85], δ asym′ CH3 [10]	1450	12.2
1464	55.28	1452 (vw)	δ asym′ CH3 [66], υC3=C4 [11]	1461	42.3
1472	164.17	1475 (s)	υ C3=C4 [43], υ C4—C5 [14]	1477	168.2
1562	30.64	1566 (w)	υ C17—C18 [20], υ C15—C16 [15]	1571	28.8
1595	283.26	1606 (s)	υ C5=C6 [23], υ C15—C20 [9]	1602	89.9

Table 3 (continued)

1	2	3	4	5	6
1736	602.95	1696 (vs)	υ C2=O14 [81], υ C2—C3 [9]	1770	71.9
2917	23.83	2923 (w)	υ C9—H11 [38] , υ C9—H10 [36]	2921	14.6
2993	3.76	2990 (w)	υ C9—H10 [54], υ C9—H11 [46]	3001	3.6
3036	4.11	3045 (vw)	υ C16—H22 [78], υ C17—H23 [19]	3050	5.3
3053	1.66	3061 (vw)	υ C17—H23 [79], υ C16—H22 [19]	3066	2
3062	0.85	3088 (vw)	υ C20—H21 [82], υ C19—H25 [10]	3075	0.89
3081	6.35	3108 (w)	υ C5—H13 [98]	3113	6.91

[a] Abbreviations : τ, torsion; puck, Puckering; tri, triagonal; υ, stretching; δ, in-plane deformation; γ, out-of-plane deformation; w, weak; vw, very weak; mw, medium weak; m, medium; ms, medium strong; s, strong; vs, very strong.

[b] PED values are for the *gauche* conformer.

a non-planar structure and belong to the C_1 symmetry group. The calculated fundamental frequencies scaled by the WLS method [12], intensities and potential energy distribution (PED) for the *gauche* conformer along the internal coordinates together with the experimental frequencies and intensities of the infrared bands are given in Table 3. The Table also contains detailed vibrational assignments. Calculations were also used to plot the infrared spectra for the molecule. The experimental and theoretically predicted infrared spectra in the 400—2000 cm^{-1} and 50—450 cm^{-1} regions are given in Fig. 3, *a* and *b*, respectively. A close agreement between the calculated and experimental frequencies and intensities of the infrared bands may be noticed from Fig. 3, *a*, *b* and Table 3.

The lack of symmetry in the molecule results in mixing of the in-plane and out-Of-plane deformation modes as well as removal of degeneracy in the vibrational modes of the methyl group. The twelve vibrational modes of the pyranone ring (ring A) have been assigned based on their PED values (Table 3). Some of the prominent bands of the pyranone ring appear at 932(m) cm^{-1}, 1475(s) cm^{-1}, and 1606(s) cm^{-1} and correspond to the theoretically predicted bands at 896 (85.76) cm^{-1}, 1472 (164.17) cm^{-1} and 1595 (283.26) cm^{-1}, where the figure in parentheses refers to the intensity of the band in km/mol. These may be assigned to O1—C2 (PED 55), C3=C4 (PED 43), and C5=C6 (PED 33) stretch modes. A very strong absorption band at 1696 cm^{-1}, corresponding to the calculated value of 1736 (602.95) cm^{-1} may be assigned to the carbonyl stretch mode C2=O14 (PED 81). Usually, this band appears as a doublet in the 1720—1740 cm^{-1} range, as reported by Yamada [21] and Nakanishi

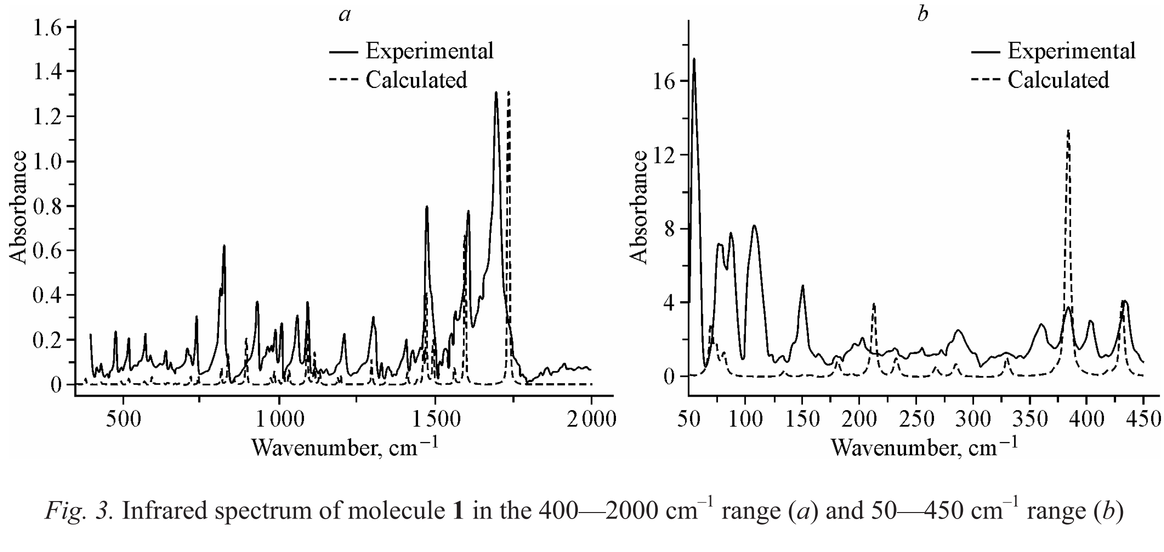


Fig. 3. Infrared spectrum of molecule **1** in the 400—2000 cm^{-1} range (*a*) and 50—450 cm^{-1} range (*b*)

[22], in substituted 2-pyranones. In a similar 6-phenyl-4-thiomethyl-2-oxo-2H-pyran-3-carbonitrile molecule, this band appears as a strong doublet at 1714 cm^{-1} and 1731 cm^{-1}, which has been explained by us [9] in terms of the Fermi resonance between the overtone of the vibrational band at 862 cm^{-1} (ms) and the carbonyl stretch band at about 1720 cm^{-1}. The higher frequency shift of the 862 cm^{-1} band corresponding to the O1—C2 stretch mode to 932 (m) cm^{-1} in the present case and the mismatch of its overtone with the carbonyl stretch mode at ~1700 cm^{-1} may, therefore, explain the absence of the Fermi resonance, and hence, the absence of a doublet.

The absorption bands at 405 cm^{-1}, 479 cm^{-1}, 640 cm^{-1}, 654 cm^{-1}, 718 cm^{-1}, 1009 cm^{-1}, 1406 cm^{-1}, 1566 cm^{-1}, and 1606 cm^{-1} (Table 3) may be assigned to the ring modes of the disubstituted aromatic ring (ring B). It may be seen that the vibrational frequencies of the aromatic ring appear at almost the same position as in 1,4-disubstituted benzenes [22, 23]. Some of these frequencies overlap with those of the pyranone ring. Thus, the strong vibrational band at 1606 cm^{-1} may be associated both with the benzene and pyranone rings with calculated values of 1597 cm^{-1} and 1595 cm^{-1}, respectively. The experimental bands at 840 (w) cm^{-1}, 1009 (w) cm^{-1}, 1094 (m) cm^{-1}, 1209 (w) cm^{-1}, 1406 (w) cm^{-1}, and 1566 (w) cm^{-1} may be assigned to the disubstituted aromatic ring of molecule **1**. These correspond to the calculated bands at 857 cm^{-1}, 1017 cm^{-1}, 1091 cm^{-1}, 1198 cm^{-1}, 1412 cm^{-1}, and 1562 cm^{-1}, respectively.

The experimental band at 710 (w) cm^{-1}, having a calculated value of 683 cm^{-1} (PED 83), may be assigned to the S8—C9 stretch mode of the thiomethyl group. In alkyl mercaptans [23], this band is reported to appear in the 685-705 cm^{-1} range. The absorption bands at 710 cm^{-1}, 975 cm^{-1}, 1327 cm^{-1}, 1428 cm^{-1}, 1452 cm^{-1}, 2923 cm^{-1}, and 2990 cm^{-1} may be assigned to the thiomethyl group (Table 3). As in the case of 6-phenyl-4-thiomethyl-2-oxo-2H-pyran-3-carbonitrile [9], the torsional modes about C4—S8 and S8—C9 and the out-of-plane deformation modes of the SCH_3 group appear in the low frequency region of 50—450 cm^{-1} region at 60 $cm^{-1}$and 198 cm^{-1} (Table 3). This region also contains torsional and puckering modes of the benzene and pyranone rings as well as the deformational modes involving the two rings.

The calculated frequencies of the *trans* conformer are close to those of the *gauche* conformer with a maximum difference of about 20 cm^{-1} between them. Most of the assignments for the two conformers are almost identical.

CONCLUSIONS

A systematic study has been conducted on the structural characteristics of three 2-pyranone rings containing molecules **1**, **2** and **3**, with different levels of hepatoprotective activity, by the experimental methods of infrared absorption spectroscopy in the far and mid IR regions and quantum chemical calculations. Conformational studies based on density functional theory computations using large basis sets and diffuse and polarization functions show that the thiomethyl group in these molecules may have two possible orientations: one facing the carbonyl group (*gauche*) of the pyranone ring and the other away from it (*trans*), resulting in two rotational isomers. In each case, the molecule has a more stable *trans* orientation, which may be attributed to steric hindrance offered by the substituent at the C-3 position in the pyranone ring: the larger is the size of the substituent, the greater is the deviation from the *cis* conformation. In the absence of a substituent, the molecule may have *cis* orientation as in the case of 6-phenyl-4-thiomethyl-2-pyranone [9]. The maximum enthalpy difference between the two isomeric forms is, however, less than 3.32 kcal/mol. Results of *ab initio* calculations and the plot of the highest occupied and lowest unoccupied molecular orbitals for molecule **1** show that the S_1 state is a $^1(\pi,\pi^*)$ state, which arises out of a π-electron transfer from the region of the double C3—C4 bond in the 2-pyranone ring to the internuclear C6—C15 bond, and is followed by electron charge redistribution. This explains the increased π-bond character, and hence, a decrease in the in-ring C6—C15 bond length resulting in a greater coplanarity of the two six-membered rings on electronic excitation. An amide substituent at the C-3 position in the pyranone ring in molecule **3** gives rise to the possibility of intramolecular hydrogen bond formation both with the carbonyl and thiomethyl groups. The presence of strong hydrogen bonds in both conformers is confirmed by small internuclear distances of 1.945 Å and 1.918 Å between the O14 and H29 atoms in the *gauche* and *trans* conformations respectively, as well as by a distance of 2.185 Å between O26 and H10 atoms in the *gauche* conformation. The presence of strong intramolecular hydrogen bonds in molecule **3** as compared to molecule **2** (weak hydrogen bond) and molecule **1** (no hydrogen bond) may be responsible for its low activity as a hepatoprotective agent. A complete vibrational analysis based on the experimental spectra in the far and mid infrared regions and DFT/6-311++G** computations of the fundamental frequencies, intensities, and potential energy distribution along the internal coordinates confirm the non-planar structure of molecule **1**. The experimental and theoretically predicted infrared spectra in the 50—4000 cm^{-1} range show a close agreement both in terms of frequencies and intensities of the infrared bands. The calculated frequencies of the *trans* conformer are close to those of the *gauche* conformer and the assignments for the two conformers are almost identical.

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