Research Article

Magnetic Resonance in Chemistry

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Molecular dynamics of 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one and 6-methyl-2-(4-nitrophenyl)-2,3-dihydro-4*H*-chromen-4-one (flavanone) derivatives in a solution studied by NMR spectroscopy

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Molecular dynamics of benzoxazepin, oxime, pyrazole, and thiosemicarbazone derivatives of some flavanones have been investigated in a solution using NMR. The results confirm the formation of different O–H···O, O–H···N, N···H–N type intramolecular hydrogen bonds in the pyrazole and oxime molecules. The rotational barrier energy and energy of intramolecular hydrogen bonds have been determined. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: flavanone; benzoxazepin; oxime; thiosemicarbazone; molecular dynamics; hydrogen bond; conformers

Introduction

NMR spectroscopy plays an important role in studying various interactions in solutions including hydrogen bond formations. The NMR line shape is sensitive to temperature and chemical exchange processes and can be used successfully for the study of fast reversible reactions. Thus, NMR has become an important tool to evaluate the kinetics of reactions at equilibrium over a very large dynamic range, and its results have theoretical and practical significance for chemistry, biochemistry, and molecular physics.[1–16] We have applied these methods to benzoxazepin, pyrazole, oxime, and thiosemicarbazone derivatives of some flavanones. The flavanones are naturally occurring heterocyclic compounds, and these molecules have potential biological and pharmacological activities.[17–23] Analogues of benzoxazepin are extremely potent activators of human transient receptors.[24,25] Oxime compounds are well known as antidotes for nerve agents, analytical reagents.[26–30] Semicarbazones and thiosemicarbazones are used in medicine, especially as anticancer chemotherapeutic agents, in the treatment of tuberculosis, and others.[31–34]

Experimental

NMR Spectra

NMR experiments have been performed on a BRUKER FT NMR spectrometer AVANCE 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5-mm sample tubes using Bruker Standard software (TopSpin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal TMS; the experimental parameters for ^{1}H were as follows: digital resolution = 0.23 Hz, SW = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse length = 10 μs, and PL1 = 3 dB; and for ^{13}C: digital resolution = 0.27 Hz, SW = 17 985 Hz, TD = 64 K, SI = 32K, 90° pulse length = 9 μs, and PL1 = 1.5 dB. NMR-grade DMSO-d_6 (99.7%, containing 0.3% H_2O), acetone-d_6 (99.7%), and CCl_4 (100%, several drops of D_2O were added for the lock signal as external standard) were used for the solutions of benzoxazepin, oxime, pyrazole, and thiosemicarbazones.

The rate constants for the two-center exchange processes at the coalescence temperature calculated by the formula $k_c = 2.22\delta\nu$ ($\delta\nu$, difference of resonance frequency).[2]

The intramolecular hydrogen bond energies have been calculated with T. Schaefer's formula.

$$\Delta\delta = -0.4 \pm 0.2 + E$$

where $\Delta\delta$ is given in parts per million relative to phenol (4.29 ppm)[35] and E in kilocalorie per mole.

The calculation errors for two exchange sites were ±5% and for hydrogen bond energies ±0.2 kcal/mol.

Synthesis

The (4*Z*)-6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one oxime (**II**, T^{II}_{mp} = 193 °C, yield ~89%), 7-methyl-2-phenyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**III**, the compound has high viscosity and red color, yield ~69%), 3-(2-hydroxy-5-methylphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**IV**, T^{IV}_{mp} = 238–240 °C, yield ~43%), and (4*E*)-[(4-aminocarbonothioyl)hydrazono]-3,

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4-dihydro-6-methyl-2-phenyl-2*H*-1-benzopyran (**V**, T^{V}_{mp} = 240–242 °C, yield ~78%) have been prepared by the known literature methods[36–38] (**II–V** are known compounds in the literature) (Scheme 1).

The new compounds (*Z*)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (**VII**) and (*E*)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (**VIII**) were obtained by the reaction of 0.1 mol 6-methyl-2-(4-nitrophenyl-2,3-dihydro-4*H*-chromen-4-one (**VI**) with 0.2 mol hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) in 130 ml ethanol at temperature 78 °C, reaction time 3 h[36] (T^{VII}_{mp} = 162 °C and T^{VIII}_{mp} = 178 °C, yield ~85%) (Scheme 1).

The purity and structure of the synthesized compounds are confirmed by layer chromatography (Silufol UV-254, 0.1-mm silica gel plates, using iodine vapor as visualizing agent, eluent hexane/ethyl acetate, 7:2), ^{1}H NMR, ^{13}C NMR, DEPT, COSY, NOESY, HMBC, and HMQC. The ^{1}H and ^{13}C NMR data of compounds (**II–V**, **VII**, and **VIII**) are given in Table 1.

Results and Discussion

In the present work, we have decided an investigation of the molecular dynamics of benzoxazepine, oxime, thiosemicarbazone, and pyrazole derivatives of some flavanones (**I** and **VI**) in a solution using NMR spectroscopy.

Initially, we have investigated the (4*Z*)-6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one oxime (**II**). Detailed NMR investigations confirmed that pyrone ring in the 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one (**I**) has not opened and only (*Z*)-oxime (**II**) has been obtained.

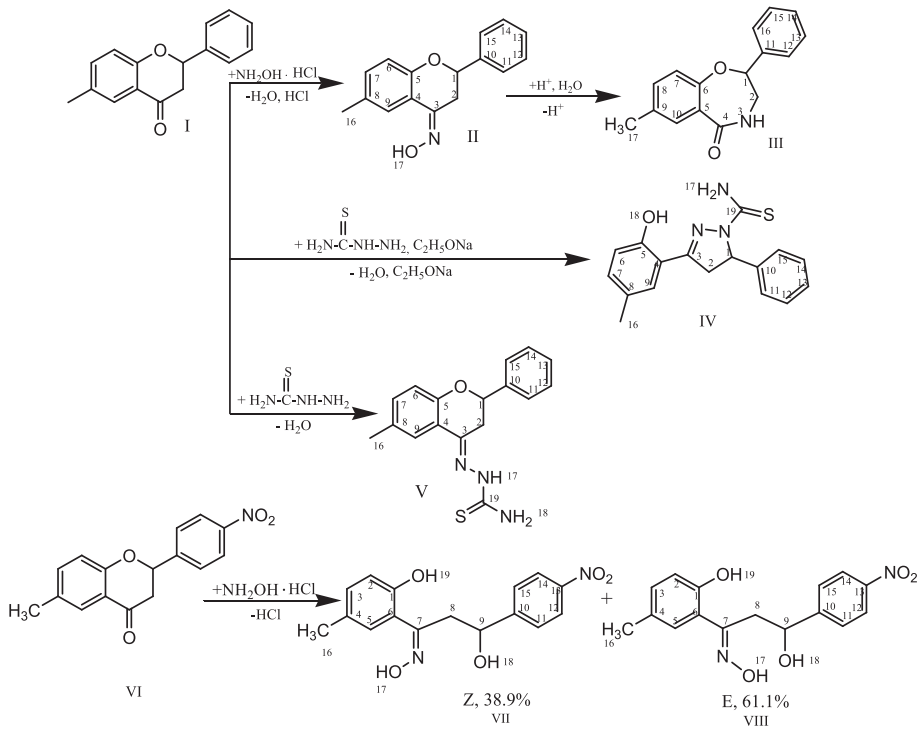
Subsequently, the 7-methyl-2-phenyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**III**) being the product of the Beckman rearrangement of (4*Z*)-6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one oxime (**II**) has been investigated. The preferred twist-boat conformation for seven-membered ring of 7-methyl-2-phenyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**III**) (Fig. 1) was confirmed by dynamic NMR (DNMR) investigation at the temperature interval of −90 to +50 °C in 5% acetone-d_6 solution, NOESY experiment, and literature data.[39,40] DNMR spectra do not show any changes in the signals from the investigated compound. That means the time average conformation is present in the solution.

The ^{1}H NMR spectrum at −50 to −90 °C showed that hygroscopic H_2O from compound (**III**) in acetone-d_6 gave two signals instead of one at 3.20 and 3.32 ppm. These results can be explained by the formation of stable intermolecular hydrogen bond (in the low exchange at −50 to −90 °C) between the compound (**III**) and hygroscopic water.

In continuation of the researches, we have investigated the product of the reaction between 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one (**I**) and thiosemicarbazide at the presence of sodium ethoxide in ethanol. The 1D and 2D NMR investigations confirmed the opening of the six-membered pyrone ring in the 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one (**I**) and the reformation of the new five-membered pyrazole ring in the (**IV**).

In earlier studies, research groups showed the presence of two conformers for the molecule thiosemicarbazones (Scheme 2) as the result of the rotation around the N^2–C^3 bond and theoretically calculated the existence of a partial double bond between N^2 and C^3.[12,41]

For the molecule 3-(2-hydroxy-5-methylphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**IV**), DNMR investigations have been carried out in 5% DMSO-d_6 and 0.5–5% CCl_4 solutions by ^{1}H and ^{13}C NMR spectroscopy at the temperature interval of 20–90 °C. In the ^{13}C spectrum of 5% DMSO-d_6 solution, we observed one signal for all carbons (from the compound **IV**) as a result of fast exchange between the conformers at the 20–90 °C.



Scheme 1. Synthesis of the oximes (**II**, **VII**, and **VIII**), benzoxazepin (**III**), pyrazole (**IV**), and thiosemicarbazone (**V**) derivatives of flavanones (**I** and **VI**).

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Table 1. ^{1}H and ^{13}C NMR data of compounds **II–V**, **VII**, and **VIII** (δ in ppm and J in Hz)

Compound	Position									
	1	2	3	4	5	6	7	8	9	10
II (CCl4)	5.12 (d-d, $^{3}J_{H-H}=11.9$ and $^{3}J_{H-H}=3.2$); 77.4	2.69 and 3.55 (d-d, $^{2}J_{H-H}=-17.1$, $^{3}J_{H-H}=11.9$ and $^{3}J_{H-H}=3.2$); 31.6	147.3	119.5	154.6	6.95–7.75 (m, arom.); 118.3	131.2	129.5	123.8	141.6
III (acetone-d_6)	5.78 (d-d, $^{3}J_{H-H}=10.9$ and $^{3}J_{H-H}=2.3$); 81.4	3.55 and 4.15 (d-d, $^{2}J_{H-H}=-17.3$, $^{3}J_{H-H}=10.9$ and $^{3}J_{H-H}=2.3$); 44.6	7.21 (s, NH)	157.6	121.5	156.3	6.95–7.55 (m, arom.); 116.3	132.3	127.7	128.3
IV (DMSO-d_6)	5.9 (d-d, $^{3}J_{H-H}=8.6$ and $^{3}J_{H-H}=1.8$); 63.4	3.25 and 3.95 (d-d, $^{2}J_{H-H}=-16.5$, $^{3}J_{H-H}=8.6$ and $^{3}J_{H-H}=1.8$); 44.7	157.7	126.7	156.4	6.85–7.55 (m, arom.); 116.3	130.1	128.7	134.3	143.7
V (acetone-d_6)	5.21 (d-d, $^{3}J_{H-H}=12.0$ and $^{3}J_{H-H}=3.0$); 77.6	2.85 and 3.65 (d-d, $^{2}J_{H-H}=-17.1$, $^{3}J_{H-H}=12.0$ and $^{3}J_{H-H}=3.0$); 33.7	142.4	120.2	156.7	6.87–8.13 (m, arom.); 117.5	133.2	131.1	128.9	141.2
VII (acetone-d_6)	156.9	7.35 (d, $^{3}J_{H-H}=8.4$); 117.0	7.75 (d, $^{3}J_{H-H}=8.4$); 133.7	138.1	7.85 (s); 129.4	128.8	157.6	3.45 (d, $^{3}J_{H-H}=9.9$); 36.7	5.55 (t, $^{3}J_{H-H}=9.9$); 71.3	148.5
VIII (acetone-d_6)	156.0	6.73 (d, $^{3}J_{H-H}=8.4$); 116.5	7.02 (d, $^{3}J_{H-H}=8.4$); 131.7	137.3	7.35 (s); 128.9	127.7	159.3	3.35 (d, $^{3}J_{H-H}=9.8$); 35.0	5.43 (t, $^{3}J_{H-H}=9.8$); 70.8	147.1

Compound	Position								
	11	12	13	14	15	16	17	18	19
II	126.3	128.1	127.6	128.1	126.3	2.36 (s); 21.6	10.85 (s, OH)		
III	141.7	128.5	126.2	128.7	126.2	128.5	2.25 (s); 21.7		
IV	125.6	129.5	127.2	129.5	125.6	2.22 (s); 20.3	8.15 (d, NH_2)	9.53 (s, OH)	177.6
V	127.5	129.4	126.4	129.4	127.5	2.29 (s); 20.8	10.25 (s, NH)	8.01 (s, NH_2)	179.6
VII	8.55 (d, $^{3}J_{H-H}=8.9$); 128.3	8.75 (d, $^{3}J_{H-H}=8.9$); 124.2	154.7	124.2	128.3	2.42 (s); 20.5	12.01 (s, N–OH)	4.73 (s, OH)	12.51 (s, OH)
VIII	7.72 (d, $^{3}J_{H-H}=8.9$); 127.6	8.21 (d, $^{3}J_{H-H}=8.9$); 123.5	153.2	8.21 (d, 8.9); 123.5	7.72 (d, $^{3}J_{H-H}=8.9$); 127.6	2.21 (s); 19.9	10.80 (s, N–OH)	4.83 (s, OH)	11.10 (s, OH)

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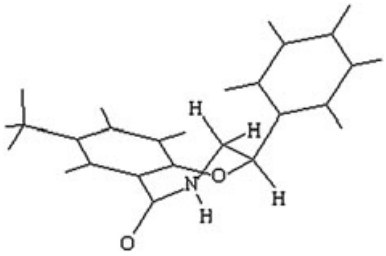
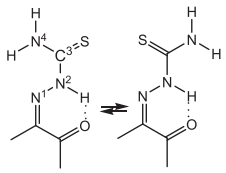


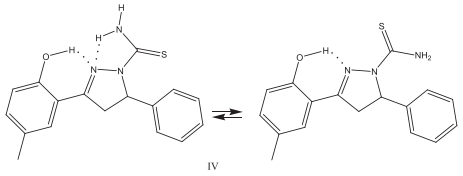
Figure 1. Twist-boat conformation for seven-membered ring of 7-methyl-2-phenyl-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**III**).



Scheme 2. The presence of two conformers for the molecule thiosemicarbazones resulting from rotation around the N^2–C^3 bond.

But in the ^{1}H NMR spectrum of 5% DMSO-d_6 solution at 20 °C, two singlet signals appear instead of one for the $-NH_2$ protons resulting from rotations around the N^2–C^3 bond (Scheme 3).

Concentrations and temperature changes have only a weak influence on the OH and NH_2 chemical shifts at 9.53 and 8.07 ppm (Table 2).



Scheme 3. Two conformers of the molecule 3-(2-hydroxy-5-methylphenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**IV**).

Our studies confirmed the formation of two intramolecular hydrogen bonds (O–H···N and N···H–N type) for the one conformer and O–H···N type for the other one (intermolecular hydrogen bond strongly depends on concentration and temperature). The energy of O–H···N-type intramolecular hydrogen bonds at 20 °C in the 0.5% CCl_4 solution is equal to 5.41 ± 0.2 kcal/mol (or 22.7 kJ/mol). Intramolecular hydrogen bond energies for the molecule (**IV**) have been calculated with Schaefer's formula.[35]

The rotational barrier around the N^2–C^3 bond for the molecule (**IV**) has been calculated from the ^{1}H NMR spectra in 5% DMSO-d_6. The NMR spectrum of the two exchange sites have been calculated by formula $k_c = 2.22\delta\nu$ resulting in the rate constants ($k_c = 57.48\ s^{-1}$ at $T_c = 297$ K) in DMSO-d_6 solution. The free energy of activation has been calculated by the formula[2]

$$\Delta G_c = 2.3RT_c[10.32 + \log(T_c/k_c)] \approx 14.95\ \text{kcal/mol}$$

Table 2. Chemical shifts of OH (δ_{OH}) and NH_2 (δ_{NH}) protons of **IV** and **VIII**, in different solvents at various concentrations and temperatures

IV				**VIII**			
Solvent	Concentration, %	Temperature, °C	δ_{OH} and δ_{NH2}, ppm	Solvent	Concentration, %	Temperature, °C	δ_{OH} and δ_{N-OH}, ppm
DMSO-d_6	5	20	9.53 (OH) and 8.07 (NH_2)	DMSO-d_6	5	20	11.10 (N–OH) and 11.50 (OH)
	5	24	9.51 (OH) and 7.96 (NH_2)				
	5	40	9.49 (OH) and 7.85 (NH_2)				
	5	60	9.43 (OH) and 7.82 (NH_2)				
	5	90	9.35 (OH) and 7.62 (NH_2)				
CCl_4	5	20	9.50 (OH) and 7.98 (NH_2)	DMSO-d_6	1	20	10.99 (N–OH) and 11.49 (OH)
	3	20	9.40 (OH) and 7.95 (NH_2)				
	0.5	20	9.30 (OH) and 7.87 (NH_2)				
				CCl_4	5	20	10.43 (N–OH) and 10.92 (OH)
					1	20	10.40 (N–OH) and 10.88 (OH)
					0.5	20	10.40 (N–OH) and 10.87 (OH)
				Acetone-d_6	5	20	10.80 (N–OH) and 11.10 (OH)
				Acetone-d_6	1	20	10.57 (N–OH) and 11.00 (OH)

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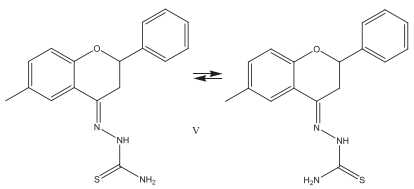
Subsequently, we have investigated the (4*E*)-[(4-aminocarbonothioyl)hydrazono]-3,4-dihydro-6-methyl-2-phenyl-2*H*-1-benzopyran (**V**) (or 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one thiosemicarbazone). Detailed NMR investigations confirmed that pyrone ring in the 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one (**I**) has not opened and the compound (**V**) has been obtained.

For the molecule (**V**), DNMR investigations have been carried out in 5% DMSO-d_6 solution by ^{1}H and ^{13}C NMR spectroscopy in the temperature interval of 22–70 °C. In the ^{13}C spectrum of 5% DMSO-d_6 solution, we observed one signal for all carbons as a result of fast exchange between the conformers at the 20–70 °C. But in the ^{1}H NMR spectrum at 22 °C, two singlet signals (at 8.05 and 8.33 ppm) are observed instead of a singlet for the $-NH_2$ protons (the singlet signal at 8.1 ppm belongs to aromatic CH, which probably presents interaction between CH N). Our NMR investigations confirm the possible existence of two conformers in 5% DMSO-d_6 solution in the temperature interval of 22–70 °C for the molecule 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one thiosemicarbazone (**V**) (N^2-C^3 rotational conformers; Scheme 4). Obtained data explain the temperature dependence of the ^{1}H NMR spectra (the free energy of activation is equal to 16.25 kcal/mol, then $k_c = 139.19\ s^{-1}$ at $T_c = 333$ K).

In continuation of our investigations, we have researched the new products of the reaction being between 6-methyl-2-(4-nitrophenyl)-2,3-dihydro-4*H*-chromen-4-one (**VI**) and hydroxylamine hydrochloride in ethanol. Our studies confirmed that comparing the (I), in the 6-methyl-2-(4-nitrophenyl)-2,3-dihydro-4H-chromen-4-one (VI) opening the pyrone ring and formation of 8.9% (Z)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (VII) and 61.1% (E)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (VIII). The isomers have been separated by CCl_4 (*E*-isomer by cold CCl_4 solution).



Scheme 4. Two conformers of the molecule 6-methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one thiosemicarbazone (**V**).

In the ^{1}H NMR spectra for the molecule (**VII**) obtained in CCl_4 solutions, a doublet for the CH_2 group at 3.45 ppm and a triplet for the CH group at 5.55 ppm have been observed (also in ^{1}H NMR spectra in DMSO-d_6 and acetone-d_6, the same multiplicity between CH and CH_2 groups have been observed).

In the ^{1}H NMR spectra for the molecule (**VIII**) obtained in acetone-d_6 solution at 22 °C, we have observed a doublet for the CH_2 group at 3.35 ppm and a triplet for the CH group at 5.41 ppm. The ^{13}C NMR spectrum in acetone-d_6 solution at −90 °C (Fig. 2) has showed two signals instead of one for some carbons. But in the ^{1}H NMR spectra obtained in DMSO-d_6 and CCl_4 solutions at 22 °C, a doublet of doublets for the CH_2 and a multiplet for the CH groups at 3.2 (or 3.21) and 5.1 (or 5.28) ppm have been observed. Concentration changes for CCl_4 solutions have only a weak influence on the oxime and phenol OH chemical shifts at 10.4 and 10.9 ppm (Table 2). Our studies confirmed the formation of two intramolecular hydrogen bonds (O–H···N and OH···O type) for the molecule (**VIII**) in CCl_4 and DMSO-d_6. The energy of O–H···Ntype intramolecular hydrogen bonds at 22 °C in the 0.5% CCl_4 solution is equal to 7.1 ± 0.2 kcal/mol (or 29.7 kJ/mol).

The splitting of the proton and carbon signals at −90°C, a doublet from the CH_2 and a triplet from the CH groups in acetone-d_6 solution at 22°C show possible existence of conformers (a, b) due to the predomination rotation around the CH_2-CH bond, a doublet of doublet from the CH_2 and a multiplet from

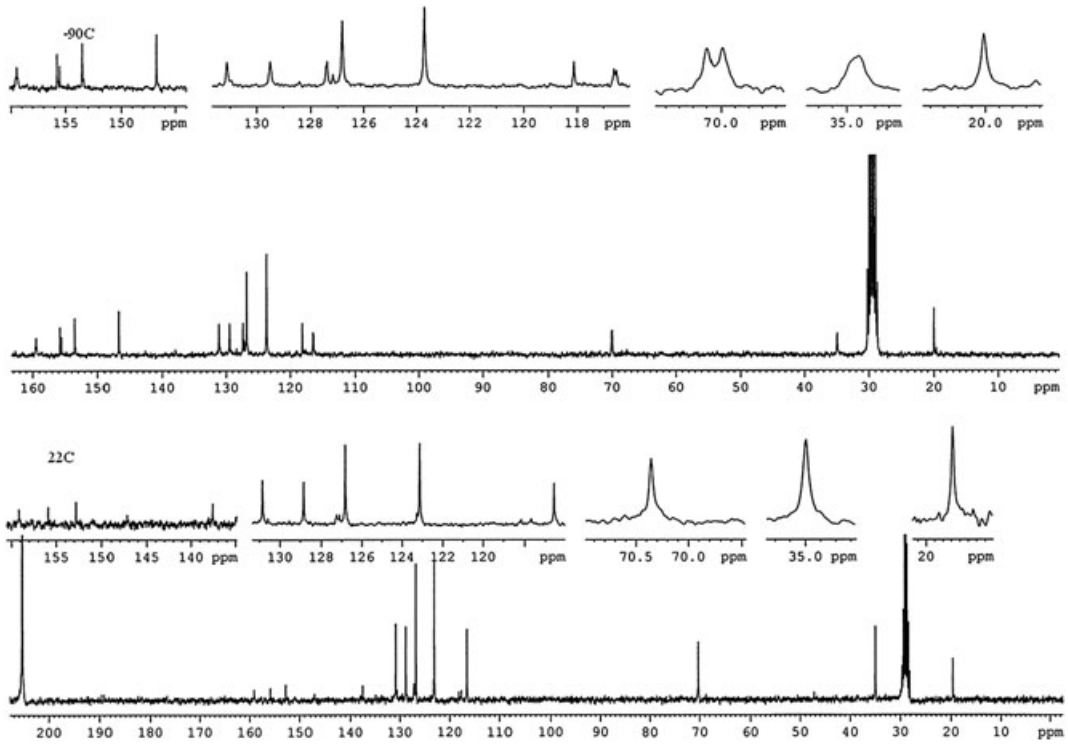


Figure 2. ^{13}C NMR spectral sections of **VIII** in acetone-d_6 at the temperature interval −90 and +22 °C.

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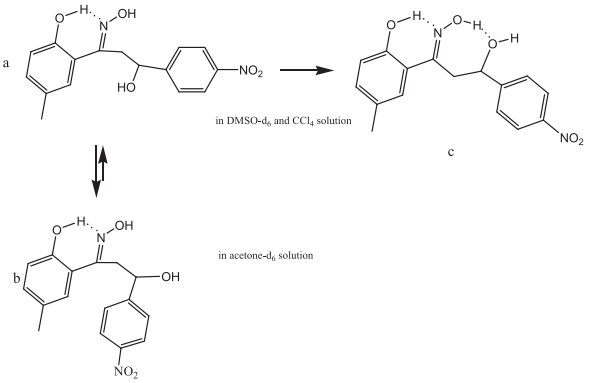

Scheme 5. Conformers of the molecule (*E*)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (**VIII**) in acetone-d_6, DMSO-d_6, and CCl_4 solutions.

the CH groups in DMSO-d_6, CCl_4 solution show possible existence of conformer (c) as a result of the formation of two intramolecular hydrogen bonds and complication of rotation around the CH_2–CH bond (Scheme 5).

Conclusions

Our detailed NMR investigations confirmed the formation of only (*Z*)-oxime for the compound (**II**). The preferred twist-boat conformation for seven-membered ring of the molecule (**III**) is confirmed by the DNMR investigation at different temperature, NOESY experiment, and literature data. The 1D and 2D NMR experiments showed the opening of the six-membered pyrone ring in the (**I**) and the formation of the new five-membered pyrazole ring in the (**IV**). Detailed NMR explorations confirmed the presence of two conformers for the molecules (**IV**) and (**V**) as a result of the rotation around the N^2–C^3 bond.

Our studies showed that comparison of (**II**) and (**VI**), where in contradistinction to (**II**) in the (**VI**) the pyrone ring have opened and 38.9% (Z)- (**VII**) and 61.1% (E)-oxime (**VIII**) have obtained. The results can be explained by the existence of conformers (as a result of the rotation around the CH_2–CH bond) for the molecule (*E*)-3-hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one oxime (**VIII**).

For the molecules (**IV**) and (**VIII**), the O–H···N- and O–H···O type intramolecular hydrogen bond energies and, for the (**IV**) and (**V**), rotational barrier energies (≈14.95 and 16.25 kcal/mol) have been calculated.

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