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STEREOSPECIFICITY OF SHIELDING CONSTANTS OF CARBON-13 NUCLEI IN ^{13}C NMR SPECTRA OF OXIMES OF HETARENECARBALDEHYDES AND ALKYL HETERYL KETONES

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It has been discovered that the chemical shifts of carbon atoms in ^{13}C NMR spectra of oximes having pyrrolyl, furyl, benzofuryl, thienyl, and pyridyl rings as substituents are changed systematically on going from the E- to the Z-isomer. This makes it possible to use the indicated chemical shifts for establishing the configuration of oximes with heterocyclic substituents and studying the special features of their electronic structure.

Keywords: oximes with heterocyclic substituents, ^{13}C NMR spectra, stereospecificity of shielding constants.

The stereospecificity of NMR spectral parameters of aldoximes and ketoximes has been studied for several decades [1-22]. In particular it is necessary to select investigations of ^{1}H, ^{13}C, and ^{15}N spectra of oximes having a heterocyclic substituent. The ^{1}H NMR spectra of furfural oximes were investigated in the earlier studies [4, 5]. The most interesting data were obtained for oximes enriched with ^{15}N isotope, in which a dependence was discovered of the geminal ^{15}N–^{1}H coupling constant on the steric orientation of the unshared pair of the nitrogen atom [5]. Ideas on the stereospecificity of parameters of ^{15}N NMR spectra in ^{15}N-labeled furfural oximes were developed in [9, 12], in which the stereospecificity of the ^{15}N nuclear shielding constants, the geminal ^{15}N–^{13}C coupling constants, and the vicinal ^{15}N–^{1}H coupling constants was shown. The aim of the present work was to study the stereospecificity of the shielding constants of the carbon-13 nuclei in ^{13}C NMR spectra of the series of oximes **1-6** having various heterocyclic substituents.

The chemical shifts of ^{13}C atoms of oximes **1-6**, and also of model oximes **7a,b**, are given in Table 1. Two-dimensional ^{1}H–^{13}C correlation procedures HSQC and HMBC were used to assign the signals in the ^{13}C NMR spectra. Configurational assignment of aldoximes **1** and **2** was made on the basis of the differences of the chemical shift values of the "oxime" proton for the *E*- and *Z*-isomers, taking into account that in the *E*-isomer

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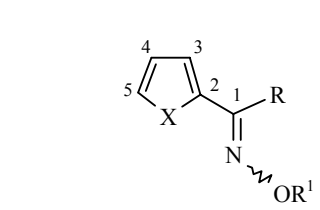
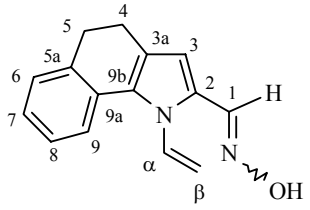
this proton resonates at 0.6-0.7 ppm towards low field in comparison with the *Z*-isomer [12]. In the *E*-isomers of aldoximes **1** and **2** the value of the chemical shift of the "oxime" proton is 8.10 and 8.17 ppm respectively, while for the *Z*-isomer it is equal to 7.49 and 7.55 ppm respectively. To establish the configuration of ketoximes **3a-c**, **4**, **5a-c**, and **6** the fact that the carbon of the methyl or methylene group in the position neighboring the C=N bond in *E*-isomers resonates at 4-8 ppm towards higher field than in *Z*-isomers was used [3, 6, 8, 13, 16]. In the case of phenyl 2-pyridyl ketone O-vinyloxime (**6**) the chemical shift of the *ipso* carbon atom of the phenyl ring served as the criterion for configurational assignment. In *E*-isomers this shift is also reduced by 2-3 ppm relative to the *Z*-isomers [7]. The appropriate values of $\Delta\delta$ ^{13}C (*E*-*Z*) are given in Table 1.



1, 3a–c, 5a–c



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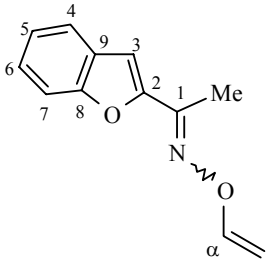

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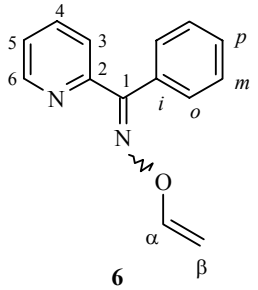

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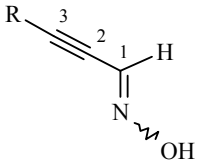

7a,b

1 X = N–C_αH=$C_\beta H_2$, R = R^1 = H; **3 a** X = O, R = Me, R^1 = CH=CH_2, **b** X = O, R = Me, R^1 = H, **c** X = O, R = Et, R^1 = H; **5 a** X = S, R = Me, R^1 = CH=CH_2, **b** X = S, R = Me, R^1 = H, **c** X = S, R = *n*-Pr, R^1 = H; **7 a** R = CMe_3, **b** R = $SiMe_3$

It follows from the data given in Table 1 that the chemical shifts of certain carbon atoms in oximes **1-6** undergo systematic changes on going from the *E*- to the *Z*-isomer. Thus in the *E*-isomer of oximes **1-6** the chemical ahift of the C(2) carbon atom is always greater than in the *Z*-isomer (from 2.1 to 8.1 ppm), but the chemical shift of the C(3) atom is always less than in the *Z*-isomer (from 1.9 to 8.3 ppm, Table 1). This effect is displayed for various heterocycles differing in nature, *viz.* pyrrolyl, furyl, benzofuryl, thienyl, and pyridyl. Furthermore, in the *E*-isomer of oximes **1-6** the chemical shift of the C(1) atom of the C=N azomethine bond is always greater than in the **Z-**isomer (from 0.6 to 7.6 ppm, Table 1). The low field shift of the C(2) atom signal in the *E*-isomer of furfural oximes relative to the *Z*-isomer was noted previously and was assigned to the steric effect of the oxygen atom [12]. However it is doubtful whether this may explain the simultaneous changes of the chemical shifts of atoms C(1), C(2), and C(3) on going from the *E*- to the *Z*-isomer of oximes **1-6**, and even more so the extremely significant changes undergone by the chemical shift of the C(1) carbon atom located in the geminal position to the oxygen atom.

Analogous changes of the chemical shifts of C(1), C(2), and C(3) atoms in the *E*-isomer relative to the *Z*-isomer were detected previously for a series of oximes of substituted propynals [22]. The ^{13}C NMR data of two examples of this class, oximes **7a,b**, are also given in Table 1 as an example. The chemical shifts of the C(2) and

TABLE 1. Values of the Chemical Shifts in the ^{13}C NMR Spectra of Oximes **1, 2, 3a-c, 4, 5a-c, 6, 7a,b**

Com-pound	Chemical shifts, δ, ppm								
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	R	R^1	$\Delta\delta^{13}C$ (*E*–*Z*)
1	2	3	4	5	6	7	8	9	10
E-**1***	142.96 (+7.6)*[2]	124.80 (+2.3)	115.77 (-4.1)	110.74 (-0.4)	121.70 (+0.5)	—			
Z-**1***	135.36	122.45	119.63	111.12	121.18	—			
E-**2***	142.66 (+5.1)	126.40 (+2.9)	110.60 (-6.6)	124.50 (+0.4) (C-3a)	131.46 (+0.8) (C-9b)	—			
Z-**2***	137.54	123.53	117.18	124.05 (C-3a)	130.67 (C-9b)	—			
E-**3a**	149.09 (+3.5)	149.09 (+3.8)	111.02 (-7.3)	111.28 (-0.7)	143.88 (+1.0)		12.10 (CH_3)	152.60 (C(α)); 88.31 (C(β))	-4.9
Z-**3a**	145.57	145.27	118.35	112.02	142.90		16.97 (CH_3)	152.48 (C(α)); 88.08 (C(β))	
E-**3b**	147.70 (+3.5)	150.22 (+4.2)	110.05 (-7.9)	111.31 (-0.8)	143.59 (+1.0){		11.23 (CH_3)		-6.2
Z-**3b**	144.43	146.03	117.95	112.15	142.61		17.39 (CH_3)		
E-**3c**	152.47 (+3.9)	149.70 (+4.1)	109.96 (-8.3)	111.25 (-0.8)	143.69 (+1.3)		19.27 (CH_2); 11.14 (CH_3)		-5.8
Z-**3c**	148.55	145.65	118.24	112.05	142.40		25.08 (CH_2); 12.00 (CH_3)		
E-**4***	150.95 (+4.5)	149.51 (+3.5)	107.99 (-6.6)	127.77 (-0.5) (C-9)	155.34 (+1.7) (C-8)		12.57 (CH_3)	152.90 (C(α)); 89.09 (C(β))	-5.1
Z-**4***	146.49	146.05	114.61	128.23 (C-9)	153.65 (C-8)		17.66 (CH_3)	152.73 (C(α)); 88.89 (C(β))	
E-**5a**	153.13 (+4.4)	139.25 (+7.1)	127.55 (-3.2)	127.18 (+1.2)	127.83 (-3.7)		13.42 (CH_3)	152.59 (C(α)); 88.39 (C(β))	-6.2
Z-**5a**	148.73	132.20	130.72	125.95	131.52		19.58 (CH_3)	152.03 (C(α)); 88.85 (C(β))	
E-**5b**	151.84 (+4.7)	140.20 (+8.0)	126.55 (-3.4)	127.20 (+1.5)	126.86 (-4.2)		12.46 (CH_3)		-7.4
Z-**5b**	147.12	132.19	129.93	125.68	131.05		19.81 (CH_3)		
E-**5c**	155.59 (+5.3)	139.91 (+8.1)	126.36 (-3.2)	127.17 (+1.5)	126.78 (-3.9)		28.74 (α-CH2); 20.22 (β-CH2); 14.33 (CH3)		

TABLE 1. (continued)

1	2	3	4	5	6	7	8	9	10
Z-**5c**	150.30	131.81	129.59	125.69	130.65		35.81 (α-CH_2); 21.27 (β-CH_2); 13.94 (CH_3)		
E-**6**	158.56 (+0.6)	153.85 (+2.1)	123.09 (-1.9)	136.25 (+0.3)	123.90 (+0.4)	149.34 (-0.2)	131.58 (+2.1) (C(*i*)); 129.29 (-1.9) (C(*o*)); 127.84 (-0.4) (C(*m*)); 129.21 (-0.7) (C(*p*))	152.58 (C(α)); 89.03 (C(β))	-2.6
Z-**6**	157.92	151.72	125.00	135.95	123.51	149.59	134.13 (C(*i*)); 127.79 (C(o)); 128.23 (C(*m*)); 129.93 (C(*p*))	152.37 (C(α)); 88.76 (C(β))	
E-**7a***[3]	135.49 (+4.3)	71.84 (+3.1)	104.57 (-6.9)				28.18 (C); 26.29 (CH_3)		
Z-**7a**	131.16	68.73	111.45				28.48 (C); 26.22 (CH_3)		
E-**7b***[3]	134.40 (+4.1)	96.30 (+3.4)	101.55 (-6.9)				-0.50 (CH_3)		
Z-**7b**	130.34	92.87	108.49				-0.48 (CH_3)		

* Chemical shifts, δ, ppm: 132.65 (C(α)), 100.56 (C(β)) (*E*-**1**); 130.20 (C(α)), 104.04 (C(β)) (*Z*-**1**); 132.59 (C(α)), 113.72 (C(β)), 22.15 (C(4)), 30.65 (C(5)), 126.34 (C(6)), 128.51 (C(7)), 125.82 (C(8)), 122.29 (C(9)), 128.99 (C(9a)) (*E*-**2**); 132.39 (C(α)), 115.57 (C(β)), 22.15 (C(4)), 29.77 (C(5)), 126.40 (C(6)), 128.62 (C(7)), 126.22 (C(8)), 122.54 (C(9)), 128.89 (C(9a)) (*Z*-**2**); 121.56 (C(4)), 123.34 (C(5)), 126.03 (C(6)), 111.78 (C(7)) (*E*-**4**); 121.52 (C(4)), 122.51 (C(5)), 126.59 (C(6)), 111.59 (C(7)) (*Z*-**4**).

*[2] The differences of the chemical shifts of carbon atoms for *E*- and *Z*-isomers of oximes **1, 2, 3a-c, 4, 5a-c, 6, 7a,b** are given in parentheses.

*[3] Data of [22].

C(3) atoms of the triple bond of oximes **7a,b** are also changed in value and in the same direction as the chemical shifts of the C(2) and C(3) atoms in the heterocycles of oximes **1-6** (see Table 1). This indicates the generality of the reasons causing the changes of chemical shift of the carbon atoms in the indicated classes of oximes.

The significant differences in the shielding constants of the C(2) and C(3) atoms in the *E*- and *Z*-isomers of oximes **7a,b** are caused by the different extent of polarization of the triple bond in the configurational isomers, which is caused by the different extent of a *p*-π interaction of the oxygen atom and the π-system of the oximes at *cis* and *trans* disposition of the oxygen atom relative to the triple bond [22]. At a *trans* disposition of the oxygen atom and the triple bond, the π-system of the triple bond is polarized to a greater extent in comparison with a *cis* disposition which is expressed as an increase in the shielding of the C(3) atom and a reduction of shielding of the C(2) atom in the *E*-form of oximes **7a,b** in comparison with the *Z*-form. An analogous effect is also observed for oximes **1-6,** with the only difference being that the C(2)–C(3) bond of the heterocyclic fragment is subjected to a different degree of polarization. The chemical shifts of atoms C(4) and C(5), with the exception of oximes **5a-c** with a thienyl substituent, undergo only insignificant changes on going from the *E*- to *Z*-form (Table 1). This indicates that the interaction of π-systems of the heterocycle and the –C=N–O fragment occurs predominantly with the participation of the C(2)–C(3) π-bond.

In addition, while having the same directions of changes, the absolute values of the changes of chemical shift of the C(1), C(2), and C(3) atoms in the *E*-isomers of oximes **1-6** relative to the *Z*-isomers differ significantly as a function of the nature of the heterocycle. In oximes **1-4**, having pyrrolyl, furyl, or a benzofuryl ring as substituent, the chemical shift of the C(3) atom displays the greatest sensitivity towards the type of isomer (Table 1). In the indicated oximes the heterocycles possess high π-donating ability, consequently here must be expected the greatest extent of π,π interaction of the heterocycle and the –C=N–O fragment and as a result their close to coplanar disposition [17]. The π-donor ability of the thienyl ring is significantly less and therefore the extent of π,π interaction in oximes **5a-c** is also significantly less. Consequently in the sterically conjugated *Z*-form of oximes **5a-c** the coplanarity of the disposition of the heterocycle and the –C=N–O fragment is disturbed [17]. This explains the far lower sensitivity of the chemical shift of the C(4) atom to the type of isomer in the case of oximes **5a-c** with a thienyl substituent. The noticeable displacement to low field of the resonance of the C(5) atom, and also the anomalously large high field displacement of the C(2) atom resonance in the *Z*-isomer of oximes **5a-c** in comparison with those in the *E*-isomer (from -3.7 to -4.2 and from +7.1 to +8.1 respectively) is probably linked with the charge redistribution in the π system of the thienyl ring on disturbing its coplanar disposition relative to the –C=N–O fragment.

In 1-vinyl-4,5-dihydrobenz[*g*]indole-2-carbaldoxime **2** going from the *E*- to the *Z*-form is accompanied by significantly larger changes of chemical shift of the C(2) and C(3) atoms than in aldoxime **1** (+2.9, -6.6, and +2.3, -4.1 ppm respectively), indicating the more intense π,π-interaction of the pyrrole ring and the –C=N–O fragment in the first case compared to the second. In the isomers of aldoxime **2** the signal of the C(β) atom of the vinyl group is displaced towards low field compared with that for the isomers of 1-vinylpyrrole-2-carbaldoxime **1** (113.72 in the *E*- and 115.57 ppm in the *Z*-form of compound **2** compared with 100.56 in the *E*- and 104.04 ppm in the *Z*-form of compound **1**). This means that in aldoxime **2** the vinyl group is brought out of the plane of the pyrrole ring due to the steric effects of the substituents neighboring the vinyl group, and the *p*-π conjugation with it is disturbed [23, 24]. As a result of this, the π-donating ability of the pyrrole ring in aldoxime **2** is increased compared with aldoxime **1**, and as mentioned above the intensity of its π,π-interaction with the –C=N–O fragment increases.

In phenyl 2-pyridyl ketone O-vinyloxime (**6**) the observed changes of chemical shift of the C(1), C(2), and C(3) atoms on going from the *E*- to the *Z*-form were, as a rule, significantly less than for the other oximes **1-5** having heterocyclic substituents. The pyridine ring is a π-acceptor and, as follows from the tendency mentioned above, is conjugated to the least extent with the π-system of the –C=N–O fragment. At the same time it is possible to detect the opposite character of the change of chemical shifts of C(2) and C(3) of the pyridine ring and of the chemical shifts of C(*i*) and C(*o*) of the phenyl ring in oxime **6** (+2.1 and -1.9 compared with -2.6 and

+1.5 ppm, respectively). Consequently the C(2)–C(3) bonds in the pyridine ring and C(*i*)–C(*o*) in the phenyl ring in the case under discussion are polarized in opposite directions. In the *E*-isomer of oxime **6** the pyridine ring is in a *trans* position relative to the oxygen atom, consequently the C(2)–C(3) bond is polarized more than in the *Z*-isomer, where the pyridine ring has the *cis* position relative to the oxygen atom. In contrast the phenyl ring in the *E*-isomer of oxime **6** is in the *cis* position relative to the oxygen atom, consequently the C(*i*)–C(*o*) bond is polarized less than in the *Z*-isomer, where the phenyl ring has the *trans* disposition relative to the oxygen atom.

Systematic differences in the chemical shifts of the C(1), C(2), and C(3) atoms in the *E*- and *Z*-isomers of oximes having heterocyclic substituents, may be used both for determining their configurations and for the study of their electronic structure.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on Bruker DPX-250 and Bruker AVANCE 400 spectrometers (63 and 100 MHz respectively) in $CDCl_3$, internal standard was HMDS, concentration of samples was 5-10 wt %. Parameters of the impulse sequence when recording ^{1}H and ^{13}C NMR spectra are described in [17]. Standard programs, optimized for values of coupling constants $^{1}J_{CH}$ = 160 and $^{n}J_{CH}$ = 8 Hz, with which the Bruker DPX-250 and AVANCE 400 spectrometers were fitted, were used for carrying out HSQC and HMBC experiments.

Aldoximes **1** and **2** were obtained by the condensation of the appropriate aldehydes [25] with hydroxylamine hydrochloride in pyridine by the procedure of [26]. Synthesis of furylketoximes **3a-c** was described in [27], thienyl ketoximes **5a-c** in [28], benzofurylketoxime **4** in [29], and phenyl 2-pyridyl ketone O-vinyloxime (**6**) in [30].

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