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Dedicated to Academician M.G.Voronkov on occasion of his 80th birthday

Stereoisomerism of *N*-(1-Propenyl)thiobenzamide

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Abstract—A prototropic rearrangement of *N*-prop-2-enylbenzocarbothioamide afforded two stereoisomeric *N*-prop-1-enylbenzocarbothioamides (**IIa, b**) isolated as individual compounds. The stereoisomerism is due to hindered rotation around thioamide bond C(S)–N and also to π-diastereoisomerism. The configuration of the isolated isomers was investigated by IR spectroscopy, AM1 and PM3 methods. In the molecules occurs the p,π-conjugation with participation of nitrogen atom and multiple bonds resulting in formation of a united delocalized MO in the planar fragment C(S)–NC=C.

One among the important stereochemical problems is attempt to isolate individual stereoisomers and determination of their configurations that may be the reason of their unlike physical, chemical, and biological properties [1, 2]. Especially significant is the preparation of pure steric isomers used as pharmaceuticals. However this target is often difficult to attain.

In the study of reaction between isothiocyanates and Grignard reagents [3] we obtained *N*-prop-2-enylbenzocarbothioamide (**I**) that in a superbasic system KOH–DMSO–H_2O cleanly rearranged into *N*-prop-1-enylbenzocarbothioamide (**II**) (Scheme 1) existing as two isomers with different melting points. The latter were isolated as individual compounds by means of column chromatography. With the use of ^1H NMR spectroscopy we established that the isomer with mp 42–47°C (**IIa**, 19%) possessed *cis*-configuration of the protons at the double bond, and the isomer with mp 74–76°C (**IIb**, 57%) had *trans*-configuration.

The position of protons with respect to the C=C bond was revealed by the values of the vicinal coupling constants of vinyl protons (7.8 and 14.2 Hz respectively), and also by the observed chemical shifts of CH= protons. Thus the calculations according to an additive scheme show that the δ value of the olefin proton in the gem-position with respect to nitrogen in going from *trans*-isomer **IIb** to *cis*-isomer **IIa** changes insignificantly (the calculated and observed value $\Delta\delta_{NCH=}$ –0.07 ppm) whereas the signal of the olefin proton geminal to the CH_3 group in this case is notably shifted upfield (the calculated value $\Delta\delta_{CH=}$ –0.46 ppm, the observed value –0.35 ppm).

However for the *N*-prop-1-enylbenzocarbothioamide besides the π-diastereoisomerism due to different position of substituents at the C=C bond is also presumable *cis-trans* isomerism caused by hindered rotation around partly sp^2-hybridized thioamide C(S)–N bond. The assignment of signals in the ^1H NMR spectra to this type isomers turned out to be difficult due to overlapping of the NH doublets.

Therefore with the use of IR spectroscopy and quantum-chemical calculations by AM1 and PM3 procedures was investigated the structure of stereoisomers **IIa, b**, was determined the reciprocal orientation of separate structural fragments (thioamide and prop-1-enyl ones), the location of NH and C=S bonds in the thioamide group, and also the intramolecular interactions and the stability of the stereoisomers.

In the IR spectra of compounds **IIa, b** registered from thin films or solutions in CCl_4 are observed the

Scheme 1.

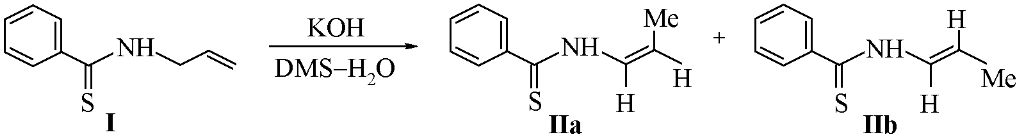


Table 1. Principle frequencies in the IR spectra (cm^{-1}) of geometrical isomers of *N*-prop-1-enylbenzocarbothioamide (**IIa, b**) registered from solution in CCl_4 and from thin film

Compd. no.	ν(N–H)	ν(C=C)	δ(NHCS)	ν(C–N)	ω(CH=)
cis,cis-**IIa**	3420 (3300)[a]	1660 (1660)	1480 (1500)	1330 (1360)	740 (740)
trans,trans-**IIb**	3390 (3260)	1670 (1670)	1500 (1520)	1342 (1370)	970 (970)

[a] The frequencies in spectra recorded from thin film are given in parentheses.

absorption bands corresponding to the vibrations of the main functional groups: benzocarbothioamide, 1480–1500 [NHC(S)], 3260–3400 [ν(N–H)], 1330–1360 [ν(C–N), 1580–1600 cm^{-1} (Ph), and ethene one, bands of stretching and bending vibrations at 1660–1670 and 740–970 cm^{-1} respectively [4–8] (Table 1).

The low frequency of NH stretching vibrations in the spectra taken from thin film show participation of these groups in hydrogen bonds. The significant increase in the ν(NH) values in diluted solutions of compounds **IIa, b** and simultaneous shift of the thioamide band to low frequencies, from 1520–1500 to 1480 cm^{-1} evidence that NH groups take part in intermolecular association and that they provide predominant contribution into the vibration band at 1500 cm^{-1} [8, 9].

Taking into account the ^{1}H NMR spectra (see Experimental) and the spectral laws established by the studies of a great number of vinyl compounds [4] we assigned the band at 1660 cm^{-1} in the spectrum of compound **IIa** to the *cis*-isomer, and the absorption at 1670 cm^{-1} in the spectrum of compound **IIb** to *trans*-isomer. The band ν(C=C) in the spectrum of *cis*-isomer **IIa** is considerably stronger than the corresponding band in the spectrum of the *trans*-isomer **IIb** for it is known that the vibration band of the double bond in the *cis*-isomers of disubstituted alkenes is stronger due to summation of the fragment dipole moments of the substituents [1, 2].

The observed difference in the other vibration frequencies in the IR spectra of isomers **IIa, b** under the same experimental conditions clearly show the presence of considerable dissimilarity in their structures apart the π-diastereoisomerism.

We already mentioned that isomerism originating from the hindered rotation around partially double bond C(X)–N (X = O, S) was investigated on a large series of amides and thioamides with the use of various physical methods, in particular, of IR and NMR spectroscopy [10–12]. This phenomenon still attracts much attention since these moieties function as main blocks of the biologically active compounds and depending on the structure the molecules can possess quite different reactivity and characteristics [12–16]. In thioamides the C–N bond character is notably closer to double bond than in amides due to the larger contribution of a bipolar form, and therefore the barrier separating the *cis* and *trans*-isomers increases by 12.5–21 kJ mol^{-1}. For instance, in the N-substituted thioamides the barrier to rotation along C(S)–N bond according to various sources amounts to 84–105 kJ mol^{-1} [1, 2]. Just this fact provides a possibility to observe the existence of the configurational isomers for thioamide molecules as individual stable compounds.

Proceeding from the data of [9] where the geometrical isomers of N-monalkylthioamides were separated by TLC and subjected to spectroscopic investigation, and also from the data obtained in the stereochemical studies of the other N-substituted thioamides [1, 2, 10] we assigned the high-frequency band ν(N–H) at 3420 cm^{-1} in the IR spectrum of compound **IIa** to the *cis*-isomer with respect to the C(S)–N bond, and the band of lower frequency at 3390 cm^{-1} in the spectrum of compound **IIb** to the *trans*-isomer.

Thus for each of the analyzed stereoisomers **IIa, b** was determined a set of characteristic frequencies of absorption bands in the IR spectra that originated from *cis,cis*- and *trans,trans*-orientation of substituents in the *N*-prop-1-enyl and benzocarbothioamide fragments (Table 1) (the protons orientation with respect to the double bond is given first, then is designated the orientation of the substituents around the amide C–N bond).

cis,cis-Isomer **IIa** is better soluble, and its chain intermolecular associates are less strong. At the solution concentration up to 10^{-3} mol l^{-1} the hydrogen bonds in stereoisomer IIa are completely dissociated, and in the IR spectra appears the only absorption band of vibrations belonging to free N–H group at 3420cm^{-1}. In the spectrum of *trans,trans*-isomer **IIb** under the same conditions the band of the associated NH groups is still conserved. Only at dilution to concentration of 10^{-5} mol l^{-1} we succeeded in destroying the hydrogen bonds and obtained in the spectrum the absorption band of stretching vibrations from the free N–H bonds at 3390 cm^{-1}. This fact is

Table 2. Formation enthalpy and dipole moments of isomers **IIa, b** at possible orientation of the key functional groups (Scheme 2)

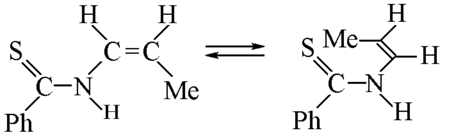
Compd. no.	Configuration	AM1		PM3	
		ΔH_f, kJ mol^{-1}	μ, D	ΔH_f, kJ mol^{-1}	μ, D
IIa	*cis,trans,cis*	265.78	4.26	308.20	5.01
	cis,cis,cis	266.73	4.08	311.56	5.23
IIb	*trans,cis,trans*	268.71	4.31	307.90	5.39
	trans,trans,trans	283.91	4.61	323.88	5.68

due to high thermodynamical stability of cyclic dimers with participation of C=S---H–N groups in solutions of compound **IIb** (caused by higher symmetry) as compared to linear associates containing the same groups [6, 17]. In the capability to hydrogen bonds formation distinguished by their strength is revealed the significant difference in the stereoisomers structure. The contribution of the bipolar structure in the thioamide fragment is more pronounced in the cyclic dimer resulting in stronger association observed in **IIb** isomer as compared to **IIa** [10, 18].

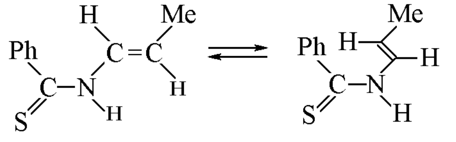
However the reciprocal orientation of *N*-prop-1-enyl and thioamide fragments still remained uncertain. Therefore in order to definitely assign the structures **IIa, b** to certain configurational types we carried out quantum-chemical calculations of geometrical and thermodynamic parameters of two possible combinations of the reciprocal spatial location of the above functional groups for each stereoisomer (Scheme 2). The results obtained are presented in Tables 2 and 3.

It was necessary to obtain an evidence of the existence of intramolecular electronic interactions, in particular, of $p\pi$-conjugation, an important intramolecular interaction in the unsaturated heteroaromatic systems that significantly affects thermodynamic and structural parameters and to considerable degree defines the electron-donor properties of compounds and their reactivity [11, 19–21].

Scheme 2.



cis, trans, cis-**IIa** *cis, cis, cis*-**IIa**



trans, cis, trans-**IIb** *trans, trans, trans*-**IIb**

As seen from Table 2 as energetically feasible structures turned out to be *cis,trans,cis* for compound **IIa** and *trans,cis,trans* for compound **IIb**.

Geometrical characteristics of compounds **IIa, b** are listed in Table 3. Small angles between the plane of C=C and N–C (φ 1.69°) and the plane N–C$_\alpha$ and C=S (φ 3.06°) do not prevent formation of delocalized MO from localized occupied and unoccupied fragment orbitals and favor formation of a conjugation system in isomers **IIa, b**. The nitrogen atom is sp^2-hybridized (bond angle CNC$_\alpha$ ~123° according to calculations) that also provides its efficient p,π-conjugation. The bond system C–N–C=C is virtually planar (φ 1–1.5°) in both types of stereoisomers.

The calculations for molecules **IIa, b** showed that a unified delocalized MO formed including a set of five atomic centers S, C, N, C=C with different contribution from the individual AOs. For instance, with isomer **IIa** these contributions equal to: N 78.69, C 15.43, S 1.93, C$_\alpha$ 2.25%, C$_\beta$ 1.42% (RHF PM3) and N 82.41, C 11.46, S 1.82, C$_\alpha$ 2.57, C$_\beta$ 1.50% (UHF AM1) indicating the presence of a system of p,π-conjugation with maximum electron density on nitrogen.

With **IIb** isomer the contributions of the individual AOs are as follows: N 78.0, C 16.14, S 1.9, C$_\alpha$ 2.23, C$_\beta$ 1.54% (RHF PM3) and N 82.25, C 11.44, S 1.86, C$_\alpha$ 2.67, C$_\beta$ 1.61% (UHF AM1).

The estimation of the contribution of p_z-orbitals into the unshared electron pair of nitrogen (along procedure [19]) accounting also for the value of the bond angle CNC$_\alpha$ allows a conclusion that the *p*-state for the nitrogen atom in the isomers **IIb** and **IIa** amounts to 99.3 and 99.2% respectively.

The p,π-conjugation affects not only the bond angles and conformation of the molecules but also bond lengths. For instance, the length of an N–C bond in unconjugated structures, e.g., in CH_3NH_2 [19], is 1.474 Å whereas the calculated length of N–C bonds in compounds **IIa, b** is considerably less: up to 1.37 Å (Table 3). The aromatic ring is not coplanar with the thioamide fragment: the torsion angle is 51–57° (**IIa**), 68 and –74° (**IIb**) that means no conjugation exists between the thioamide group and the aromatic system.

Thus the results of our quantum-chemical calculations are in agreement with the experimental data.

The stability of isomers **IIa, b** was studied by measuring their IR spectra in octane in the 20–100°C range. At increasing temperature appear additional absorption bands: in the spectrum of isomer **IIa** besides the bands at 3420 and 1660 cm^{-1} is observed an absorption band at 3400 and 1670 cm^{-1}, and in the spectrum of compound **IIb** on the contrary besides the bands at 3390 and 1670 cm^{-1} arise the bands at 3420 and 1660 cm^{-1}. Apparently although the *cis*- and *trans*-isomers are separated by significant energy barriers (both alkenes and thioamides) occurs their interconversion. As a matter of fact in the molecule of *N*-prop-1-enylbenzocarbothioamide the double bond is surrounded with functional groups and heteroatoms that causes its polarization and involve it into a conjugation system. The arising united delocalized electronic system in the isomers of *N*-prop-1-enylbenzocarbothioamide apparently leads to decreasing and levelling of the barriers to internal rotation. As a result the configurational interconversions become possible at heating to 100°C.

The ready configurational transformations were observed, e.g., with compounds of ABC=CX type where A and B were electron-donor groups, and X and Y were electron-acceptor groups (for instance, CN, COOH) [1, 2, 11]. The barriers to rotation around thus polarized bonds are considerably decreased (up to 13–15 kcal mol^{-1}). Interconversion of *Z*- and *E*-isomers was also observed for 2-chlorovinylmercury chloride, tetrasilylated ethylene, nitroenamines, enaminoketones etc. [2]. Therewith in some cases was not even required a significant heating.

The changes observed in the IR spectra of stereoisomers **IIa, b** at heating are due to decrease in barriers to rotation around the thioamide and the double bonds as a result of arising united delocalized MO in the conjugation system. This is just the cause of relatively easy configurational transformations.

Table 3. Bond lengths (Å), values of bond (ω) and torsion (φ) angles (deg) in molecules IIa, b, calculated by AM1 and PM3 methods

Parameter	IIa		IIb	
	AM1	PM3	AM1	PM3
Bond				
C=S	1.58	1.63	1.58	1.63
C_{Ph}–C	1.48	1.48	1.48	1.48
C–N	1.37	1.38	1.37	1.38
N–C_α	1.39	1.43	1.39	1.43
C_α–C_β	1.35	1.34	1.35	1.34
Angle ω				
SCN	125.71	125.67	121.74	121.13
$C_{Ph}CS$	119.83	121.92	119.99	122.05
CNH	118.55	119.72	116.42	116.86
HNC_α	118.13	116.24	117.93	117.76
CNC_α	123.31	123.55	126.65	125.36
$NC_\alpha C_\beta$	125.53	122.34	123.88	121.25
$C_\alpha C_\beta H$	117.35	118.61	122.23	122.08
$C_\alpha C_\beta C_{Me}$	127.76	125.43	122.08	122.04
$NC_\alpha H$	113.25	114.52	114.74	116.04
$HC_\beta C_{Me}$	114.88	115.96	115.69	115.88
Angle φ				
$C_{Ph}CNC_\alpha$	–179.55	–176.68	–3.55	1.012
$CNC_\alpha C_\beta$	–179.05	173.485	–178.33	178.318
$SCNC_\alpha$	–0.43	–4.32	–177.10	179.12
SCNH	179.25	–175.91	0.48	0.56
PhCN	50.97	57.303	67.61	–74.55

EXPERIMENTAL

IR spectra of isomers IIa, b were measured on a double-beam spectrophotometer Specord 75IR from thin film or solution in CCl_4 (c up to 5×10^{-5} mol l^{-1}, cell up to 50 mm thick) and in octane (c up to 8×10^{-3} mol l^{-1}, cell up to 0.254 mm thick). The variable-temperature measurements were carried out in a cell from Karl Zeiss Company equipped with a graduated thermocouple. The resolution in the regions 1700–1600 and 3400–3000 cm^{-1} was equal to 1 and 2 cm^{-1} respectively. ^1H NMR spectra were recorded on spectrometer Bruker DPX-400 in $CDCl_3$ at 18–20°C, internal reference HMDS. Mass spectra were registered on GC-MS instrument LKB-2091, ionization by electron impact (60 eV), direct admission of sample into the ion source (vaporizer temperature 270°C).

Quantum-chemical calculations were performed in RHF and UHF approximations by semiempirical

AM1 and PM3 methods with complete optimization of molecular geometry [22].

***N*-Prop-1-enylbenzocarbothioamide (II).** A mixture of 3.39 g (0.019 mol) of *N*-prop-2-enylbenzocarbothioamide (**I**), 3 g (0.054 mol) of potassium hydroxide, 12 ml of water, and 30 ml of DMSO was stirred at 90°C for 4 h, cooled to 18–20°C, poured into water, and extracted with ether. The organic solution was repeatedly washed with water, dried with potassium carbonate, the ether was distilled off. Yield 2.1 g (62%). The reaction product was subjected to column chromatography (column 1.5 × 20 cm) on silica gel (Silicagel 60, 0.063–0.200 μ, eluent benzene–hexane, 1 : 1). From the early fraction (R_f 0.54, chloroform) on removing the solvent we obtained 0.4 g (19%) of *cis*-isomer **IIa**, light-yellow crystals, mp 42–47°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76 (3H, Me), 5.27 (1H, CH=, $^3J_{\mathrm{MeCH=}}$ 6.3, $^4J_{\mathrm{MeC=CH}}$ 1.6), 7.42 (1H, NCH=, $^3J_{cis\text{-}\mathrm{CH=CH}}$ 7.8), 7.79–8.42 (5H arom), 8.82 br.s (1H, NH). M^+ 177. Found, %: C 67.69; H 6.44; N 7.71; S 18.16. $C_{10}H_{11}NS$. Calculated, %: C 67.75; H 6.25; N 7.91; S 18.09.

From the late fraction (R_f 0.38, chloroform) we obtained 1.2 g (57%) of *trans*-isomera **IIb**, light-yellow crystals, mp 74–76°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.78 (3H, Me), 5.62 (1H, CH=, $^3J_{\mathrm{MeCH=}}$ 6.8, $^4J_{\mathrm{MeC=CH}}$ 1.7), 7.49 (1H, NCH=, $^3J_{trans\text{-}\mathrm{CH=CH}}$ 14.2), 7.75 (5H arom), 8.89 br.s (1H, NH). M^+ 177. Found, %: C 67.76; H 6.33; N 7.78; S 18.13. $C_{10}H_{11}NS$. Calculated, %: C 67.75; H 6.25; N 7.91; S 18.09.

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