Russian Journal of General Chemistry, Vol. 75, No. 6, 2005, pp. 856–859. Translated from Zhurnal Obshchei Khimii, Vol. 75, No. 6, 2005, pp. 908–911.

Structure and Intramolecular Lability of *N*-(Thio)phosphoryl(thio)amides: XIII.[1] Structure of *N*-Phenyl-*N*'-(diisopropoxythiophosphoryl)thiourea

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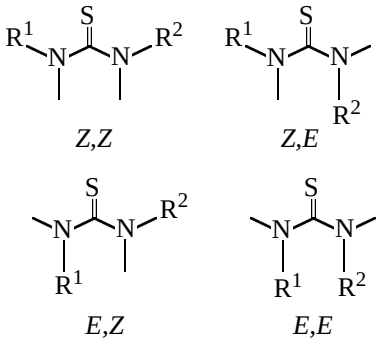
Received January 8, 2004

Abstract—The structure and intramolecular transformations of *N*-phenyl-*N*'-(diisopropoxythiophosphoryl)-thiourea in $(CD_3)_2CO$ solution were studied by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. Combined analysis of NMR data and model calculations gave evidence in favor of high conformational and tautomeric flexibility of the thioureas in solution. The *Z,E* conformation of the amide form with the two N–H bonds *cis* and *trans* to the C=S bond was found to be preferred.

Isomeric (thio)ureas are characteristically prone to various conformational transformations which have repeatedly investigated by means of NMR spectroscopy [2–7]. For example, 1,3-disubstituted thioureas can form 4 rotational isomers.



The *E,E* isomer, as much less probable for structural reasons, is usually omitted from consideration. The NMR spectra at room temperature point to a sufficiently fast *Z,Z* ⇄ *Z,E* ⇄ *E,E* transformation due to rotation about the C–N bond. The barriers to rotation about the C–N bond in thioureas are usually equal to 40–55 kJ mol^{-1} [4, 6]. At low temperatures, one can observe the NMR spectra of the isomers separately and thus assess their stability [4]. With bulky R^1 and R^2 substituents, the *Z,Z* conformation may become preferred.

Monosubstituted ureas, such as 3-isopropyl-1,1-dimethylurea, prefer a planar conformation with the barrier to rotation about the C–N bond of ~41 kJ mol^{-1} [8]. The planar conformation of ureas arises from the mesomerism of dipolar forms with a C=N bond, similar to the dipolar forms of amides.

N-(Thio)phosphorylated (tio)ureas are more complex analogs of (thio)ureas, since, compared to the latter, they contain one more reactive center, viz. the thiophosphoryl group that can exert both steric and electronic assistance to intramolecular transformations of these molecules in solutions. Let us consider this phenomenon using the example of *N*-phenyl-*N*'-(diisopropoxythiophosphoryl)thiourea PhN^{1}H–C(S)–N^{2}H–P(S)(O–Pr-*i*)$_2$.

The ^1H NMR spectrum of this compound in $(CD_3)_2CO$ at 298 K contains N^{1}H and N^{2}H signals as well-resolved broadened singlet and doublet, respectively [δ_{N^1H} 10.05 and δ_{N^2H} 8.67 ppm ($^2J_{PNH}$ 10.1 Hz)]. The evolution of the positions and shapes of the N^{1}H and N^{2}H signals in the 294–183 K range is shown in the Fig. 1 and in the table. Hence, the N^{1}H signal preserves its shape over the entire temperature range but shifts upfield by 0.13 ppm. The N^{2}H signal shifts downfield by 0.6 ppm in the 294–228 K range and strongly broadens to convert into a broadened doublet that collapses into a broadened singlet in the 213–183 K range (see table). At 183 K, two additional weak doublets appear at δ 8.8 ($^2J_{PNH}$ 10.0 Hz) and 10.5 ppm (*J* 5.0 Hz). The first signal can be attributed to the second rotamer about the C–N^2 bond (see table and Fig. 1). The appearance of the second doublet definitely has no relation to rotation about the C–N^1 bond, because in this case a singlet should be "frozen out" of the spectrum. The ^1H NMR spectrum in the entire temperature range contains one more additional SH proton signal (δ 3.9–4.55 ppm) that belongs to

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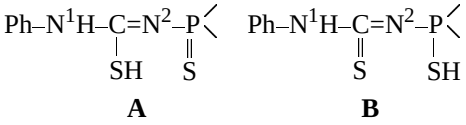
one of prototropic forms **A** and **B** or to both forms [9–11].



A **B**

Note here that prototropism is observed just in the C(S)N^2H–P(S)< pentad, like in *N*-thiophosphorylthioamides [9, 11] where form **A** is preferred over form **B**. The lack of strong broadening and shifting of the N^1H signal over the entire temperature range (Fig. 1) suggests not only lack of hindered rotation about the C–N^1 bond, but also nonparticipation of the N^1H proton in intramolecular prototropic transformations.

The ^{13}C NMR spectra contain signals of the preferred form only, which is connected with the low concentration of the substance and the low content of the other forms. Analysis of the ^{31}P NMR spectra showed that the resonance range of the amide form at 294 K contains two signals at δ_P 60.42 and 60.62 ppm with the intensity ratio of 87.7 : 12.3 (Fig. 2), which agrees with the intensity ratio of the signals of the amide and prototropic forms (SH signal) in the ^{1}H NMR spectra. As the temperature is lowered to 213 K, a weak signal appears in the ^{31}P NMR spectrum at δ_P 63.8 ppm. In the 193–183 K range, it transforms into two signals (δ_P 64.1 and 63.9 ppm0 whose integral intensity corresponds to that of two additional doublets in the ^{1}H NMR spectra in the same temperature range (Fig. 1). However, the concurrent appearance of additional ^{1}H and ^{31}P signals associated with rotation about the C–N^2 bond and migration of the N^2H proton provides no answer to the question of what of the amide forms is preferred, i.e. what is the orientation of the N^1–H, N^2–H, C=S, and P=S bonds with respect to C–N^1 and C–N^2.

To reveal possible conformers of the thiourea under study, we performed quantum-chemical calculations of its geometic structure by the semiempirical AM1 method. To this end, in the input geometric parameters we fixed the φ_1 and φ_2 dihedral angles between the planes accommodating the N^2–H and C=S, as well as N^1–H and C=S bonds, in relation to the C–N bonds. After that geometry optimization was carried out. As a result, heats of formation as a function of φ_1 and φ_2 were obtained, which allowed us to construct the potential energy surface with three minima corresponding to three conformations: *Z,E* and two *E,Z*.

These conformations are characterized as follows. The *Z,E* form has the N^1–Ph and C=S bonds *Z* to the C–N^1 bond, whereas the C=S and N^2–P bonds are *E* to the C–N^2 bond. In the *E,Z*-1 and *E,Z*-2 forms, N^1–Ph and C=S are *E* to C–N^1 and C=S and N^2–P are *Z* to C–N^2.

Chemical shifts, δ, ppm, and coupling constants (J_{PNH}) of the N^1H, N^2H, and SH proton signals of *N*-phenyl-*N'*-(diisopropoxythiophosphoryl)thiourea in $(CD_3)_2CO$ solution

T, K	N^1H (*Z,E*)	N^2H (*Z,E*)	Additional signals
294	10.03 s	8.6 (–9.6)	~3.9 br.s (SH, **A**)
258	10.05 s	8.8 br.s	4.0 br.s (SH, **A**)
243	10.01 s	9.1 br.s	4.16 br.s (SH, **A**)
228	10.00 s	9.2br.d (–10.5)	4.3 br.s (SH)
213	9.95 s	9.3 br.d (–10.06)	4.35 br.s (SH, **A**), 8.3 br.d (N^2H, *E,Z*-1), 10.22 (N^2H, *E,Z*-2)
193	9.95 s	9.4 d (~10.0)	4.4 br.s (SH, **A**), 8.55 br.d (N^2H, *E,Z*-1), 10.35 br.s (N^2H, *E,Z*-2)
183	9.90 s	9.5 br.s	4.55 br.s (SH, **A**), 8.8 br.d (N^2H, *E,Z*-1, –10.0), 10.5 br.d (N^2H, *E,Z*-2, –5.0)

The most preferred form is *Z,E* [heat of formation ΔH –89.8 kcal mol^{-1}, φ_1 (dihedral angle between the planes accommodating the N^2–H and C=S bonds) 8.9°, and φ_2 (dihedral angle between the planes accom-

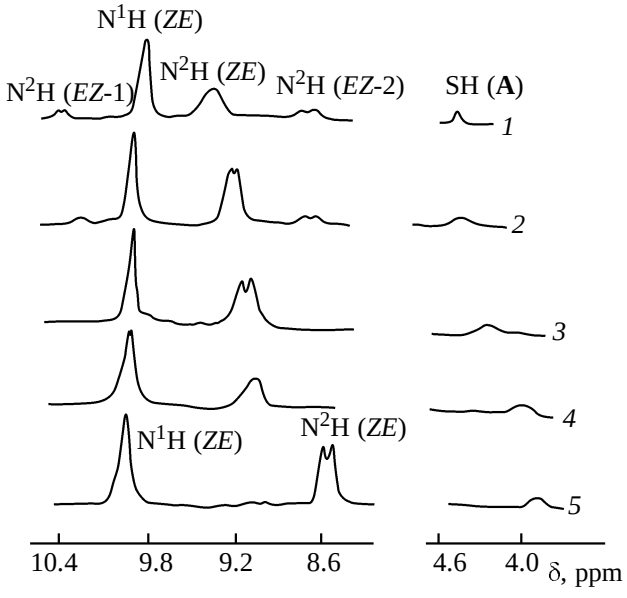
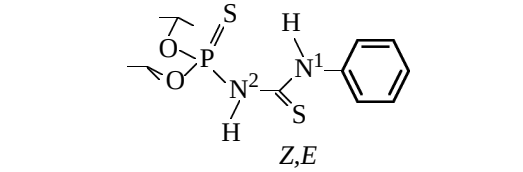
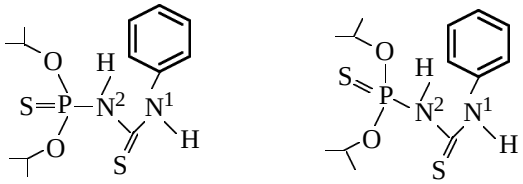


Fig. 1. Temperature dependence of the N^1H and N^2H proton signals of *N*-phenyl-*N'*-(diisopropoxyphosphoryl)-thiourea in $(CD_3)_2CO$ solution. *T*, K: (*1*) 183, (*2*) 193, (*3*) 228, (*4*) 258, and (*5*) 294.

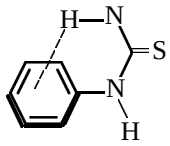


Z,E



E,Z-1 *E,Z*-2

modating the N^1–H and C=S bonds) 175.4°] and the *E,Z*-1 (ΔH –88.5 kcal mol^{-1}, φ_1 –121.5°, φ_2 2.3°) and *E,Z* forms (ΔH –88.7 kcal mol^{-1}, φ_1 –140°, φ_2 19.9°) are less favorable. Comparison of the experimental and calculated data allows the two weak doublets in the ^{1}H NMR spectrum and two additional signals in the ^{31}P NMR spectrum to the two *E,Z* forms with close $-\Delta H$ values and slightly different φ_1 and φ_2. The *trans* orientation of the C=S and N–Ph bonds in these forms agrees with the experimental data for thioureas containing an aryl substituent on the N atom and existing exclusively in the *E* form stabilized by intramolecular hydrogen bonding [8].



To assign signals in the ^{1}H NMR spectra to the two *E,Z* forms, we performed comparative analysis of the geometric characteristics of these forms and δ values. As seen from the table, the difference in the chemical shifts Δδ of the two *E,Z* forms is significant (1.7 ppm). Evidently, the upfield shift of the signal of the N^2H proton (8.8 ppm) in one of these forms is associated with the fact that this proton locates in the shielding band of the "anisotropism cone" of the phenyl ring. Such situation is realized in the *E,Z*-2 conformation.

The mutual *cis* orientation of the N^2–H and C=S bonds in the preferred *Z,E* form seems to be less evident, since *N*-thiophosphorylthioamides most commonly prefer the *trans* orientation [1, 9–11]. However, it is the latter orientation that transfer from the *Z,E* form to prototropic form **A** whose signals are simultaneously observed in the ^{1}H and ^{31}P NMR spectra (Figs. 1 and 2) is the most favored by steric reasons. Moreover, the fact that N^2–H is *trans* to P=S bonds in all the three forms is beyond doubts, since the geminal constants $^2J_{PNH}$ of –5.0 to –10.5 Hz correspond to dihegral angles of 150–180° [12, 13]. Hence, it is safe to state that the experimental and theoretical results nicely fit each other.

To assess the possible scheme of exchange in solutions, we obtained a two-dimensional exchange spectrum (^{1}H NOESY) at 298 K. The spectrum lacks cross peaks, that is signals diagnostic of exchange between two or more forms, which is connected with both low contents of tautomeric forms and low sensitivity of the experiment.

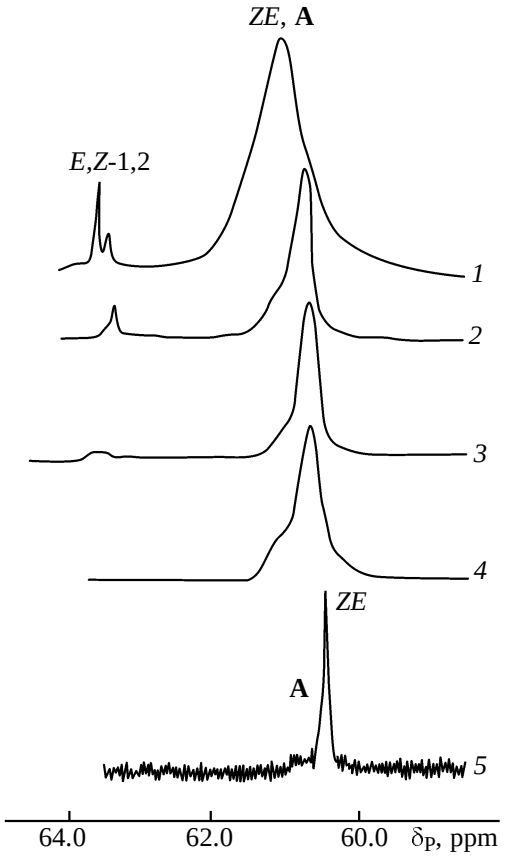


Fig. 2. Temperature dependence of the ^{31}P NMR spectra of *N*-phenyl-*N'*-(diisopropoxythiophosphoryl)thiourea in $(CD_3)_2CO$ solution. *T*, K: (*1*) 183, (*2*) 193, (*3*) 212, (*4*) 243, and (*5*) 294.

EXPERIMENTAL

The objects for study were synthesized as described in [14].

The ^{1}H (300 MHz), ^{13}C (75.43 MHz), and ^{31}P NMR spectra were measured at varied temperatures and solution concentrations on a Varian UNITY-300 NMR spectrometer operated in the ^{2}H stabilization mode and equipped with a temperature-controlled unit. The ^{31}P NMR spectra were recorded using 10–

15° pulses, *RD* 1–2 s, *SW* 100 ppm, *NT* 10–100; no digital filtration was used. The ^{13}C NMR spectra were recorded using 20–30° pulses and broad-band proton decoupling, *RD* 0, *SW* 200 ppm, *NT* 400–1000, and digital exponential filtration with *LB* 2–4 Hz. The samples were 3–5% (^{1}H) and 10–15% solutions (^{13}C, ^{31}P).

The conformational energies (heats of formation) of the compounds in a vacuum were calculated by the PM3 method using the MOPAC 7 program package [Semiempiric package MOPAC 7.0 QCPE no.445 (Public Domain)]. The geometric parameters of the molecules were calculated using the HYPERCHEM 4 program package.

ACKNOWLEDGMENTS

The work was financially supported by the Russian Foundation for Basic Research (project no. 03-03-3312).

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