ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 11, pp. 2142–2146. © Pleiades Publishing, Ltd., 2014.
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Structure and Intramolecular Flexibility of *N*-(Thio)phosphoryl(thio)amides: XVIII.[1] Structure of *N*-Phenyl,*N*'-(diisopropoxythiophosphoryl)thiourea

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Received May 29, 2014

Abstract—Structure and intramolecular transformations of *N*-phenyl,*N*'-(diisopropoxythiophosphoryl)thiourea has been studied by NMR spectroscopy and the AM1 quantum-chemical simulation. It has been shown that several forms, including two amide forms (*EZ* and *ZE*) and two prototropic forms, coexist in a dynamic equilibrium.

Keywords: *N*-(thio)phosphoryl(thio)urea, intramolecular transformation, tautomerism, phosphorylotropy, *E/Z*-isomerism, NMR spectroscopy

DOI: 10.1134/S1070363214110176

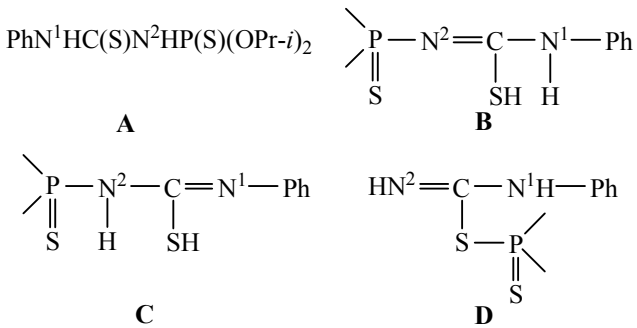
1,3-Disubstituted thioureas $R^1NH–C(S)–NHR^2$ can form four rotational isomers (*ZZ*, *ZE*, *EZ*, and *EE*) depending on the nature and the size of substituents R^1 and R^2 [1, 2]. The room-temperature NMR spectroscopy data are indicative of fast interconversion of the isomers *ZZ*, *ZE*, and *EZ* caused by rotation about the C–N bonds. At lower temperatures, NMR spectra of individual isomers can be observed [2]. The barriers of rotation around the C–N bond in thioureas are of 40–55 kJ/mol [1, 2]. Taking into account partially double character of the C–N bond, the formed structures can be interpreted as *cis*,*trans*-isomers.

Extending the studied on structure and intramolecular transformations of various *N*-thiophosphorylated ureas [3–8], in this contribution we analyze the temperature-dependent ^1H, ^{13}C, and ^{31}P NMR spectra of *N*-phenyl-*N*'-(diisopropoxythiophosphoryl)thiourea (**I**) in CD_2Cl_2 solution.

Earlier reported studies have shown that the most informative part of the ^1H NMR spectra of *N*-(thio) phosphoryl(thio)ureas is the resonance region of the amide protons (δ of 7–10 ppm) [3–7]. Appearance of a singlet (N^1H) and doublet (N^2H) in this region indicates existence of the amide form **A** of the studied compound. Analysis variations of position and shape of the NH signals with temperature as well as appearance of additional signals in the ^{13}C and ^{31}P NMR spectra allows investigation of different intramolecular processes, such as rotation around the C–N bonds, conformational transformations of the molecules, tautomerism giving forms **B** and **C**, and phosphorylotropic rearrangement yielding form **D** [3–6] (Scheme 1).

The signals of amide protons N^1H and N^2H appeared as well separated broadened singlet and doublet at δ_{N^1H} 9.7 ppm and δ_{N^2H} 7.53 ppm ($^2J_{PNH}$ = 8.0 Hz), respectively (see figure) in the ^1H NMR spectrum of compound **I** in CD_2Cl_2 solution at 298 K; that was indicative of existence of amide form **A** of compound **I**. The so different chemical shifts of the amide protons will be discussed below.

Scheme 1.



[1] For communication XVII, see [1].

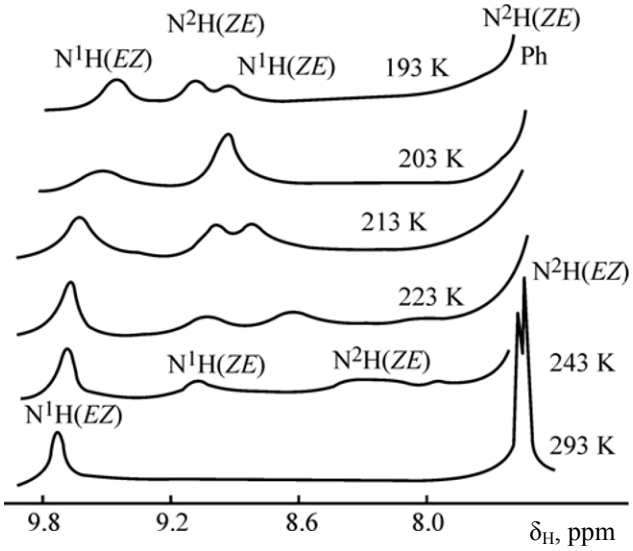
Variation of the position and the shape of the NH signals at 298–193 K is shown in the Figure and in the Table. In particular, the shape of N^1H signal did not change over the studied temperature range, but the peak was shifted upfield by 0.32 ppm. The doublet of N^2H proton was broadened and practically did not change its position ($\Delta\delta$ = 0.07 ppm).

At 243 K, broad and weaker signals of NH protons of the second amide form appeared at $\delta \approx 9.07$ and 8.3 ppm, their integral intensity increased with cooling (see figure and table).

Appearance of the second amide form was also confirmed by temperature-induced variations of the ^{13}C NMR spectra: at 243 K, signals of the main form [δ(Ph) ≈128.0 ppm, δ(C=S) ≈ 181.0 ppm, and δ(OCH) ≈ 76.0 ppm] were found as well as the second set of weaker signals at $\delta \approx 117.0$, 182.0, and 77.0 ppm, respectively. Since it was impossible to assign the NH signals to the *ZE* or *EZ* forms from the NMR spectroscopy data, we performed semiempirical quantum-chemical simulation of the two amide forms **A** (*ZE* and *EZ*), two tautomeric forms **B**, **C**, and phosphorylotropic form **D** using the AM1 method.

In the case of amide form **A,** two energy minima were revealed with close ΔH values, corresponding to the *EZ* and *ZE* structures (Scheme 2).

In the *EZ* form, the N^1–Ph and C=S groups were in *E*-orientation with respect to the C–N^1 bond, and the C=S and N^2–P bonds were in *Z*-orientation with respect to the C–N^2 bond. In the *ZE* form, vice versa, the N^1–Ph and C=S groups were in *Z*-orientation with respect to the C–N^1 bond, and the C=S and N^2–P bonds were in *E*-orientation with respect to the C–N^2 bond Of the two amide forms, the *EZ* one was energetically preferable (ΔH = –0.4 kcal/mol).



Temperature-dependent ^1H NMR spectra of *N*-phenyl-*N*'-(diisopropoxythiophosphoryl)thiourea (**I**) in the range of the NH protons resonance (5 wt % solution in CD_2Cl_2).

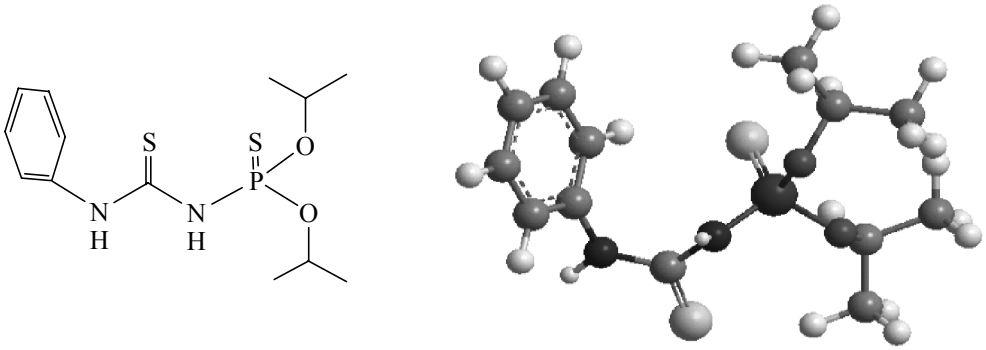
Structural analysis of the two forms explained the observed large difference in the chemical shifts of the N^1H and N^2H protons ($\Delta\delta$ = 2.17 ppm) in the *EZ* form (see table). Indeed, in the *EZ* form the N^1H proton was located inside the deshielding cone of the benzene ring and hence experienced strong downfield shift. Rotation about the C–N bonds (form *ZE*) resulted in weakening of that effect and shifted the N^1H signal upfield.

The analysis of the temperature-dependent ^1H NMR spectra of compound **I** revealed the following features:

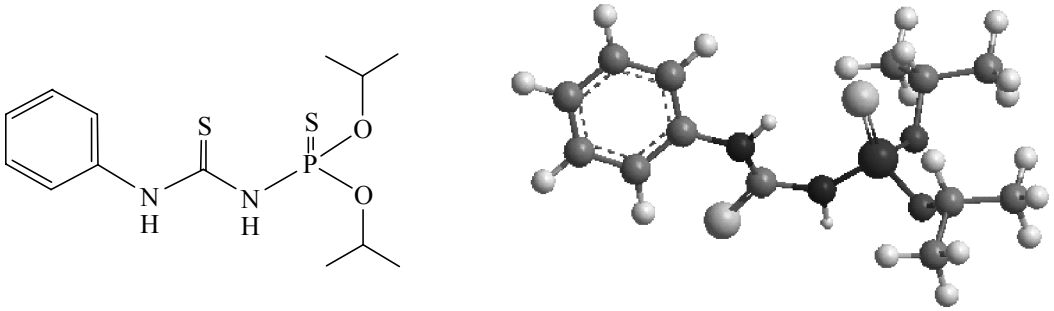
NMR spectra of *N*-phenyl-*N*'-(diisopropoxythiophosphoryl)thiourea (**I**) in CD_2Cl_2 solution δ, ppm, (*J*, Hz)

T, K	N^1H (*EZ*)	N^2H (*EZ*)	N^1H (*ZE*)	N^2H (*ZE*)	OCH	$(CH_3)_2$
298	9.7 br.s	7.53 br.d (–8.0)	–	–	4.87 (6.2)	1.38 (6.2)
243	9.66 br.s	7.48 br.d (–8.0)	9.07 br.s	8.3 br.s	4.85 (6.2)	1.36 (5.0)
233	9.64 br.s	7.47 (–8.0)	9.03 br.s	8.45 br.s	4.84 (6.0)	1.35
223	9.62 br.s	7.45 (–8.0)	8.99 br.s	8.60 br.s	4.84	1.35
213	9.57 br.s	7.43 (–8.0)	8.95 br.s	8.76 br.s	4.84	1.34
203	9.47 br.s	7.42 (–8.0)	8.90 br.s	8.9 br.s	4.83	1.34
193	9.38 br.s	7.46 (–8.0)	8.89 br.s	9.07 br.s	4.82 (5.0)	1.34

Scheme 2.



EZ, Δ*H* –88.97 kcal/mol



ZE, Δ*H* –88.57 kcal/mol

– N^1H signal in the both forms retained its width over the whole studied temperature range, showing an upfield shift of 0.32 ppm (*EZ* form) and of 0.18 ppm (*ZE* form). Taking into account the structures of the two forms, participation of the N^1H proton in the intramolecular exchange of the N^1H(*EZ*) ⇆ SH(B) ⇆ N^1H(*ZE*) type could be assumed. Indeed, the ^1H NMR spectra contained a weak signal of the SH proton that was shifted downfield by 1.3 ppm upon cooling from 298 to 193 K.

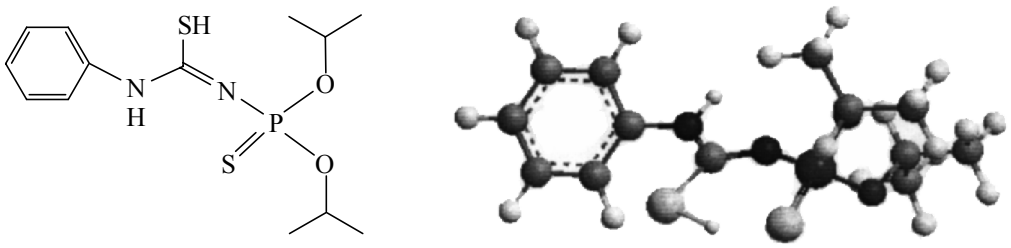
– N^2H signal of the *EZ* form appeared as a doublet practically at the same position over the whole studied temperature range (see table and figure). Taking into account the structure of the *EZ* form, that pointed at fast intramolecular exchange of the N^2H(*EZ*) ⇆ SH(**B**) ⇆ N^2H(*ZE*) type, preserving the spin-spin coupling of that proton with phosphorus atom. In the *EZ* form, N^2H signal was significantly broadened and shifted downfield by 0.77 ppm upon cooling from 298 to 193 K.

Therefore, ^1H NMR signals of the amide protons were shifted accordingly with temperature variation in the case of the predominant *EZ* form, whereas in the case of the *ZE* form the signals were shifted in the opposite directions.

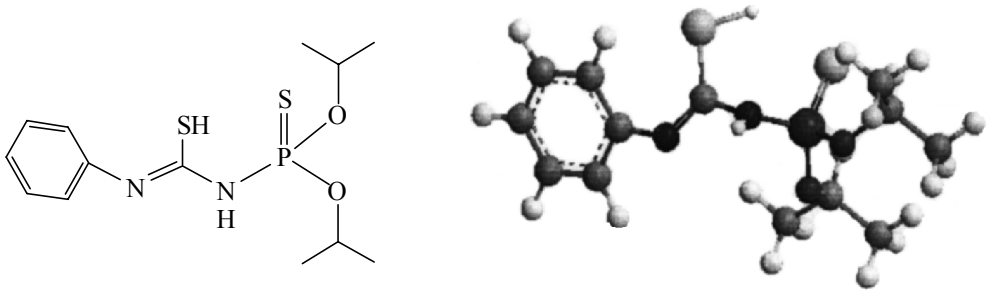
That fact could be rationalized considering steric interactions between the N^1H and N^2H protons in the optimized structures of the amide forms. In the *EZ* form, each proton was *cis*-positioned with the C=S group with respect to the C–N^1 and C–N^2 bonds, respectively; hence, the N^1H and N^2H protons were *cis*-oriented to each other. The established prototropic equilibrium leading to formation of forms **B** and **C** resulted in appearance of a weak averaged SH signal in the ^1H NMR spectrum over the whole studied temperature range. At the same time, the ^{13}C NMR spectrum contained the imine carbon C=N signal at δ 138.88 ppm at 273–193 K. In the *ZE* form, the N^1H proton was *trans*-positioned to the C=S group with respect to the C–N^1 bond, and the N^2H proton was *cis*-positioned to the C=S group with respect to the C–N^2 bond; hence, the N^1H and N^2H protons were *trans*-orientated to each other.

The **B** form should have been preferable over form **C** due to higher acidity of the N^2H proton in **B**; that was confirmed by the simulation (Scheme 3).

Scheme 3.



B, Δ*H* –96.46 kcal/mol



C, Δ*H* –85.26 kcal/mol

Form **B** favored formation of an intramolecular hydrogen bond of the N^2H proton with sulfur atom of the thiophosphoryl group ($N^2H\cdots S{=}P$) to close the five-membered ring; the same was not evident in the case of form **C**. Hence, the downfield shift of the N^2H proton in the amide *ZE* form was due to its simultaneous participation in the two intramolecular processes: prototropic equilibrium with form **B** and formation of the intramolecular hydrogen bond. Noteworthily, the N^2H proton in *EZ* form was involved only in the prototropic equilibrium, and position of its signal practically did not change. The N^1H proton in the both forms participated exclusively in the prototropic equilibrium.

The ^{31}P NMR spectra registered at 293–193 K provided further information on the intramolecular transformations of compound **I** in CD_2Cl_2 solution. At 293 K, broadening of the amide form signal at δ ≈54.0 ppm was observed, being due to the *EZ* ⇆ *ZE* exchange. At 273 K, an additional weak signal appeared at δ ≈ 59.0 ppm; it was transformed into two singlets of the prototropic forms **B** and **C** (δ 58.4 and 58.7 ppm, with the 80 : 20 ratio of the integral intensities corresponding to the ratio of *EZ* and *ZE* isomers) upon cooling to 193 K.

No signs of presence of the phosphorylotropic form **D** were observed in the ^1H, ^{13}C, and ^{31}P NMR spectra.

To conclude, several forms of compound **I** exist in a complex dynamic equilibrium in CD_2Cl_2 solution. On top of the *EZ* ⇆ *ZE* equilibrium, two intramolecular processes occur: prototropic isomerization and formation of the hydrogen bond.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were recorded using a Varian UNITY-300 spectrometer at 300, 75.43, and 121.42 MHz, respectively, at different temperatures and the solution concentrations; the field fluctuations were stabilized by an internal ^2H lock. ^{31}P NMR spectra were recorded with 10°–15° pulses and 1–2 s delay *RD*. The spectrum width *SW* was of 100 ppm; the acquisitions number *NT* was of 10 to 100, without digital filtering. ^{13}C NMR spectra were recorded with 20°–30° pulses and wide-band decoupling of protons *RD* 0, *SW* 200 ppm, *NT* from 400 to 1000, with digital exponential filtering with *LB* 2–4 Hz.

Solutions of 3–5 wt % were used to record the ^1H NMR spectra, 10–15 wt % solutions were used in the cases of ^{13}C and ^{31}P NMR spectra. Chemical shifts were calculated from the resonance lines of standard liquids dissolved in the samples (internal references, TMS and HMDS).

Conformational energy (heat of formation) was calculated via the AM1 method using MOPAC 7 [9]

software. Geometry parameters of the molecules were determined by successive input of internal atomic coordinates using the HYPERCHEM 4 program suite [10].

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