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Structure and Intramolecular Lability of *N*-(Thio)Phosphoryl(Thio)Amides: XII.[1] NMR Study and Computational Modeling of the Tautomeric Forms of *N*-[Dimethoxy(Thio)Phosphoryl]benzamides

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Abstract — The structure and intramolecular processes in solutions of *N*-(thio)phosphorylbenzamides were studied by means of ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. Combined analysis of the NMR data and computational modeling gave evidence for the high lability of the compounds under study, that are capable of forming various tautomeric forms in solutions. The amide form with the NH proton arranged *trans* with respect to the C=O group was found to be preferred.

Systematic investigations of the structure and intramolecular transformations of *N*-(thio)phosphoryl(thio)-amides in solutions by means of ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy have shown that the general scheme of the exchange includes rotation about the C–N and P–N bonds, prototropism [1-6], phosphorylotropism [4], acylotropism [6], and *N*-benzoyl(acetyl)-amidothiophosphate → *N*-thiobenzoyl(acetyl)amidophosphate rearrangement (P=S → P=O rearrangement) [1, 7, 8]. The medium (solvent and temperature) significantly affects the dynamics of the processes [1–9].

We previously showed [2] that *N*-[diisopropoxy-(thio)phosphoryl](thio)benzamides in solutions exist mainly in the *trans*-amide form. Continuing research into the structure and molecular dynamics of benzamides, we turned to *N*-[dimethoxy(thio)phosphoryl]-benzamides PhC(O)–NH–P(X)(OCH_3) [X = S (**I**), X=O (**II**)].

In view of the tendency of these molecules for forming intermolecular associates of different type (cyclic dimers, infinite chains) [10], we have studied the concentration dependence of the chemical shift of the amide NH proton in an inert solvent (CCl_4). In the ^{1}H NMR spectrum of a 30% solution of compound **I**, the NH proton signal is a strongly broadened singlet at δ ~10.0 ppm. As the solutions is diluted to 3–5%, the signal shifts upfield by 0.2 ppm and transforms into a doublet with $^{2}J_{PNH}$ –10.0 Hz (see Table 1). Analogous concentration-dependent changes are observed with the NH proton signal of compound **II**. The weak effect of the concentration on the chemical shift points to the presence of weak, readily cleaved intermolecular hydrogen bonds, and at concentrations below 5% these compounds exist in the monomeric form.

Studying such dilute CCl_4, CD_2Cl_2, and CD_3CN solutions at various temperatures allowed different types of intramolecular processes to be revealed. The results of a combined study of the ^{1}H, ^{13}C, and ^{31}P NMR spectra measured at various temperatures are listed in Tables 1–3.

In ^{1}H NMR spectra of compound **I**, the NH proton signal transforms from the strongly broadened singlet to a doublet in the range 313–203 K (Table 1). Analogous tendency in the behavior of the NH proton signal at varied temperature is also observed with compound **II** (Table 1). The large temperature-induced shift $\Delta\delta_{NH}$ for compounds **I** and **II** (0.3–1.2 ppm, Table 1) as compared to that characteristic of *N*-[diisopropoxy(thio)phosphoryl](thio)benzamides (0.09–0.26 ppm) [2] does not exclude involvement of the NH proton in intermolecular hydrogen bonding, which agrees with the IR spectra of compound **I** in CCl_4, where the intensity of the associated NH band ν(NH) in the at 3310 cm^{-1} increases and that of the free NH band at 3440 cm^{-1} decreases as the temperature is lowered to 263 K. The latter band at temperatures below 263 K gets strongly broadened and enhances. Yarkova *et al.* [10] explain these changes

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

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Table 1. Parameters of the ^{1}H NMR spectra of *N*-[dimethoxy(thio)phosphoryl]benzamides **I** and **II**

Comp. no.	Solvent	*T*, K	δ, ppm (*J*, Hz)			
			Ph	OCH_3 ($^3J_{POCH}$)	NH ($^2J_{PNH}$)	additional signals
I	CCl_4[a]	298	7.6 m	3.7 (14.0)	~10.0 br.s	2.8 br.s, 6.15 br.s (=NH, **D**)
	CCl_4[b]	298	7.6	3.8 (14.0)	9.8 br.d (–10.0)	2.1 br.s
	CD_3CN	313	7.6 m	3.8 (14.0)	8.3 br.d (–12.0)	2.2 br.s
		298	7.6	3.9 (14.3)	8.2 br.d (–12.0)	2.1 br.s, 2.3 d (~8.0) (SH, **B**)
		233	7.7	3.8 (14.0)	8.6 d (–12.0)	2.8 br.s
	CD_2Cl_2	313	7.7 m	3.8 (14.5)	~7.8	1.2 d (~7.0) (SH, **B**), 2.0 br.s
		203	7.7	3.8 (14.0)	8.2 d (–13.8)	3.1 br.s
II	CCl_4[a]	298	7.7	3.8 (12.0)	–	–
	CCl_4[b]	298	7.8	3.8 (12.0)	9.8 br.d (–9.0)	–
	CD_3CN	303	7.6	3.7 (12.0)	~7.8	2.36 br.s
		243	7.8	3.8 (12.0)	9.0 br.d (–10.0)	2.64 br.s, 3.64 br.s, 3.8–4.2
	CD_2Cl_2	313	7.7	3.8 (12.0)	9.3 br.s	–
		193	7.7	3.1 (12.0)	10.1 (–9.0)	–

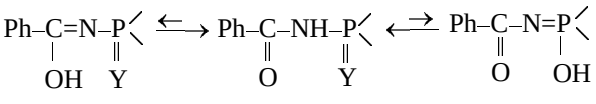
[a] Concentration 10%. [b] Concentration 3%.

Table 2. Parameters of the ^{13}C NMR spectra of *N*-[dimethoxy(thio)phosphoryl]benzamides **I** and **II**

Comp. no.	Solvent	*T*, K	δ, ppm (*J*, Hz)			
			C=O	C_6H_5	OCH_3	additional signals
I	CCl_4	293	165.4	128.5, 129.0, 132.8, 133.4 (8.1)	54.6 (4.4)	128.7, 129.3 (*o*, *m*), 131.9 (*p*), 131.1 (C^1), 167.5 (P=S → P=O), 169.0 (C=O, **B**), 147.0 (C=N, **C**), 54.8 (5.3) (OCH_3)
	CCl_4 + CD_3CN	293	165.6	127.4, 127.9, 131.9, 132.1	53.4 (4.4)	126.9, 127.0, 127.6, 128.2, 128.3, 139.0 (Ph), 168.8 (P=S → P), 168.1 (C=O, **B**), 174.2 (**D**), 143.0 (C=N, **C**), 236.4, 56.0 (OCH_3), 138.3, 132.9 (Ph)
II	CD_3CN	233	168.0 (1.7)	128.1, 128.6, 132.6, 132.8	53.9 (5.1)	–
	$CDCl_3$	298	168.1	128.1, 128.5, 132.8	53.8 (5.1)	–

with migration of the NH proton and formation of an N–H···O=C bond.

The presence of additional signals in the ^{1}H NMR spectra of compounds **I** and **II** in the selected temperature range is indicative of fast prototropic transformations like **B** ⇄ **A** ⇄ **C**:



C **A** **B**

The signals at δ 2.1–4.2 ppm relate to prototropic forms **B** and **C** (Table 1). The appearance of weak doublets in the ^{1}H NMR spectra of solutions of compound **I** in CCl_4 and CD_2Cl_2 at δ 2.3 and 1.2 ppm ($^2J_{PSH}$ –8.0 and –7.0 Hz, respectively) (Table 1), assignable to the SH proton in form **B** is unusual, because derivatives of *N*-(thio)phosphoryl(thio)amides are seldom present in this form. In particular, such

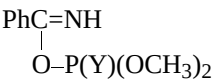
Table 3. Temperature dependence of the proton-coupled and proton-decoupled ^{31}P NMR spectra of *N*-(dimethoxythiophosphoryl)benzamide (**I**) in solutions

T, K	$\delta(^{31}P-\{^1H\})$, ppm (%)	Proton-coupled spectrum		
		form of the multiplet	$^3J_{POCH}$ ($^2J_{PNH}$), Hz	form
293	66.9 (70.21)	Dublet of septets	~14.0 (–14.0)	**IA**
	58 (3.38)	"	11.4 (~–11.0)	**IB**
	0.9 (26.41)	"	10.6 (–11.4)	P=O[a]
	67.2 (84.89)	"	13.7 (–13.7)	**IA**
348	58.9 (0.87)	[b]	[b]	
	1.1 (13.0)	Dublet of septets	[b]	P=O[a]
	3.5 (1.24)	[b]	[b]	

[a] P=S → P=O rearrangement. [b] Hardly identified because of the weak intensity of the signal.

form was identified for *N*-(diisopropoxythiophosphoryl)thioacetamide in CD_2Cl_2 solution [5]. Usually this resonance region contains a broadened signal associated with the equilibrium **B** ⇄ **C** [1–6] what is more probable in view of the fast prototropism in such compounds. It is also known that *N*-benz(acyl)phosphazenes (form **B**) are quite unstable and easily convert into corresponding amides [11–13], which complicates their spectral registration. At the same time, compounds containing multiple carbon–nitrogen bonds (forms **C** and **D**) are more stable [13] and readily identified by the ^1H NMR spectra. From that it follows that among the two prototropic forms structure **B** should be preferred. However, the ^{13}C NMR spectrum of compound **I** in CCl_4 displays at δ_C 169.0 ppm (Table 2) an additional weak C=O signal that can be assigned exclusively to form **B**, since form **C** lacks the C=O group. The ^{31}P NMR spectrum contains, along with the signal of the amide form at δ_P 66.9 ppm, a weak signal at δ_P 58 ppm, that in the proton-coupled spectrum looks like a doublet of septets and relates to coupling of phosphorus with protons of the two methyl groups and the SH proton (Table 3); there observables provide unambiguous evidence in favor of form **B**. Notable also is the difference in the $^2J_{PSH}$ values obtained from the ^1H (–8.0 and –7.0 Hz, Table 1) and ^{31}P (–11.0 Hz, Table 3) NMR spectra. This is probably connected with solvent effects, the more so as the magnitudes of the $^2J_{PNH}$ constant that relates to the amide form, too, are rather scattered (10.0–13.8 Hz, Table 1). Indirect evidence for the presence of form **B** is provided by the large difference in δ_P between forms **A** and **B** (8.3 and 8.9 ppm, Table 3) compared to the respective value for *N*-(diisopropoxythiophosphoryl)benzamide (0.3–2.2 ppm) in which the **B** ⇄ **C** equilibrium has been detected [3].

The ^{13}C NMR spectra of compound **I** in CCl_4 and CCl_4 + CD_3CN solutions display, along with the signals of amide form **A**, additional weaker signals. They relate to the imine carbon atom of forms **C** (δ_C 147 and 143.0 ppm) and **D** (δ_C 174.2 ppm) (Table 2), that arise from migration of the thiophosphoryl group to the C=O oxygen.



D

Signals of form **D** are also present in the ^{31}P NMR spectra in toluene-*d* at δ_P ~73.0 (**I** and 13.8 ppm (**II**) (see Table 3). Additional signals are observed also in the ^{13}C NMR spectra in regions characteristic of Ph, OCH_3, and C=O groups (Table 2). Hence the spectrum of compound **I** in CCl_4 + CD_3CN at 298 K shows three signals of different intensity at δ_C 165.6 (60.3%), 168.8 (28.9%), and 168.1 ppm (10.8%). The first of them we assigned to the C=O group of amide form **A** and the latter signal, to form **B**, taking into account that this signal has the same intensity as the signal of the SH group in the ^1H NMR spectrum. The second downfield signal is difficult to assign unambiguously to any tautomeric form. The case in point is that the complication of the spectrum in the δ(C=O) range of the amide form is usually explained by rotation about the C–N bond [5, 6]. Therefore, the appearance of additional signals in regions characteristic of Ph, OCH_3 and C=O groups might be explained just in terms of this process, the more so as the integral intensities of the additional C=O and OCH_3 carbon signals coincide. However, were this the case, one would observe in ^1H NMR spectrum two doublets of the amide protons *cis* and *trans* to the C=O bond [5, 6]. However, in our case we observe in the range 313-203 K the only NH signal from the

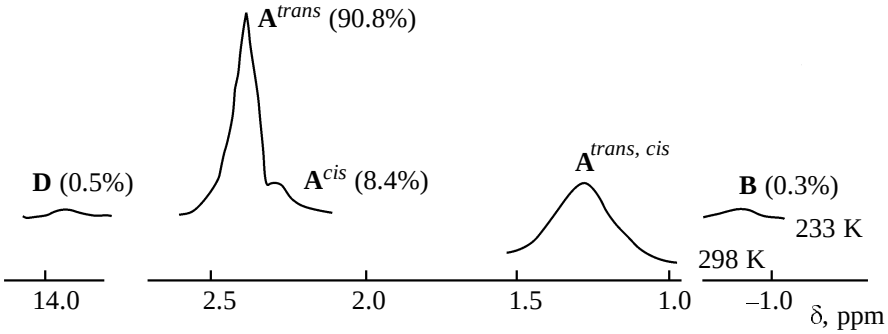
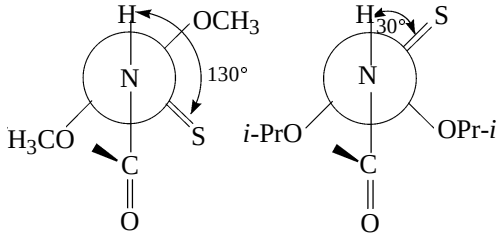


Fig. 1. Temperature dependence of the ^{31}P NMR spectra of compound **II**.

trans rotamer (Table 1), and the ^{31}P NMR spectrum contains only one signal in the range of the amide form (Table 3). But there exists one more explanation that does away with the inconsistence of the ^{1}H, ^{13}C, and ^{31}P NMR characteristics, but is lies in the frames of another process. Hence, let us correlate the geminal coupling constants $^{2}J_{PNH}$ and the dihedral angles Θ between the planes accommodating the N–H and P=S bonds [14,15] for compound **I** (–12 to –13.8 Hz, Table 1) and *N*-(diisopropoxythiophosphoryl)benzamide (**III**) (–13 to –14 Hz) [3]. The above-mentioned $^{2}J_{PNH}$ values correspond to pairs of dihedral angles of ~30° or 130°.



I **III**

The appropriate angles can be chosen from an analysis of steric relationships in molecules **I** and **III** on the assumption that each molecule has the N–H bond *trans* to C=O. Hence, in the case of the bulkier substituent R = OPr-*i* (**III**), the angle of ~30° is preferred in view of the steric hindrances that arise from rotation of two isopropyl groups about the P–N bond. In compound **I**, these steric hindrances are excluded, the angle Θ increases to 130°, and, since the C–N–P fragment is planar (126.325°, calculations and data in [16]), the O and S atoms get as proximate to each other as possible (anticlinal orientation of the C=O and P=S bonds). In its turn, the latter circumstance renders the P=S → P=O exchange more active compared to the analogous process in product **III**. Just this heteroatom exchange explains the appearance of additional C=O, P=O (0.9 ppm, Table 3), OCH_3, and Ph signals in the NMR spectra of compound **I**. The detailed interpretation by means of NMR spectroscopy of the rearrangement of N-benzoyl(acetyl)amidothiophosphate into *N*-thiobenzoyl(acetyl)amidophosphate in CCl_4 and toluene-d_8 solutions is presented in [1].

Replacement of sulfur at the phosphorus atom by the less bulky oxygen in compound **II** evidently decreases the rotation barrier about the C–N bond, and the C=O (Table 2) and P=O signals of the *trans* and *cis* forms an integral intensity ratio of ~90 : 10 are frozen out in ^{13}C and ^{31}P spectra in CD_3CN at 233 K. The evolution of the ^{31}P NMR spectra is shown in Fig. 1. As seen, the spectrum at 233 K contains, along with the signals of the *trans*- and *cis*-amide forms (2.369 and 2.276 ppm, respectively), weak signals of forms **C** (–1.1 ppm) and **D** (13.8 ppm). The signals were assigned with account for the ^{1}H and ^{13}C NMR data (Tables 1 and 2).

It is known [17] that in P(V) compounds the effect of substituents on δ_P is in most cases opposite to that expected by their electronegativities, and more important here are other factors related to the nature of the chemical bond (in particular, with the degree of double bonding) between phosphorus and neighboring nuclei (in our case, the P–N bond). Actually, comparison of the experimental δ_P values with the calculated charges on the phosphorus nucleus P^+ for the tautomeric forms of *N*-[dimethoxy(thio)phosphoryl]-(thio)benzamides (Fig. 2) revealed no unambiguous correlation between these values. Specifically, the small difference in δ_P between the *trans* and *cis* forms (0.093 ppm) of compound **II** is consistent with their ΔP^+, whereas the P^+ and δ_P values for prototropic forms **B** and **C** vary in opposite directions (Table 3, Figs. 1 and 2). Nevertheless, the close values of P^+ for the two amide and two prototropic forms are experimentally confirmed by the close values of δ_P for these forms. This tendency is preserved in *N*-[dimethoxy(thio)phosphoryl](thio)benzamides with the SS and SO combinations of hetero-

atoms on the carbon and phosphorus atoms (Fig. 2). The considerable alteration in the shielding of phosphorus in form **D** leads to a significant downfield signal shift (Table 3, Fig. 1), which is connected with increased P^+, that is decreased electron density on phosphorus in products **I** and **II**. With derivatives with the SS and SO combinations of heteroatoms, the picture is reversed (Fig. 2).

Computational modeling of the tautomeric forms of compounds **I** and **II** showed that, according to the heats of formation ΔH of different tautomeric forms, the most energetically favorable for compound **I** is *trans*-amide form **A** (ΔH –100.07 kcal mol^{-1}), and of the two prototropic forms, form **C** is preferred.

	$\mathbf{A}^{trans}$	$\mathbf{A}^{cis}$	**B**	**C**	**D**
I	–100.07	–98.032	–93.45	–98.51	–87.18
II	–151.5	–152.09	–162.79	–149.26	–139.23

Note the close ΔH values of these forms in both compounds. It is prototropic forms **B** and **C**, that the largest departure of the experimental values from calculation, in terms of preference of one the forms, would be expected, in view of the fact that in the calculations forms **B** and **C** were regarded as blocked, even though they both are formed by an intramolecular hydrogen bond. Actually, among the two forms of compound **I**, form **C** is energetically more favorable than form **B** (ΔH 5.05 kcal mol^{-1}). In compound **II**, form **B** is 13.51 kcal mol^{-1} energetically more favorable than form **C**, and it is 11.29 kcal mol^{-1} more stable than the *trans*-amide form which was experimentally determined as the preferred one (Table 4). Thus, form **B** can be isolated as an individual isomer. However, the ^{13}C NMR spectra of product **I** display signals of both prototropic forms (Table 2), and in the ^{31}P NMR spectrum no signal of form **C** was found (Table 3). The spectra of compound **II** lack signal of form **B**. The least preferred form of compounds **I** and **II** is form **D**, which agrees with experiment.

As follows from the calculation of the principle angles in the *trans*- and *cis*-amide forms of molecules **I**–**III** by means of the HYPER CHEM 4.0 program package, the C–N–P angle (126.326°–134.26°, Table 4) is close to the angle of a flattened nitrogen atom [16]. A satisfactory fit to experiment is also observed with other angles. For example, in the most stable *trans*-amide form of *N*-dimethoxythiophosphorylbenzamide (**I**), the H–N–P=S dihedral angle is 127.98°, and the P=S and C=O bonds (angle φ) have an anticlinal orientation (58.3°) that is sterically favorable for the P=S → P=O rearrangenent. At the same time, the φ angle in the *trans* form of **III** is

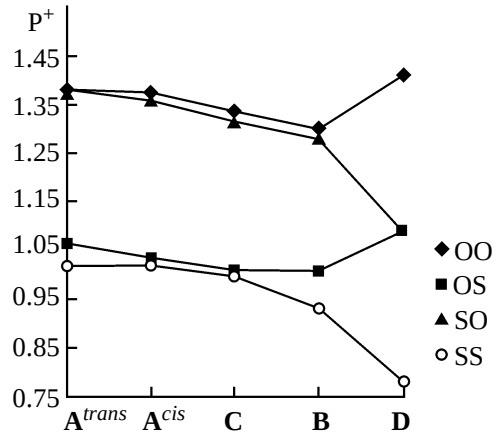


Fig. 2. Charges on the phosphorus atom in the tautomeric forms of *N*-(thio)phosphoryl(thio)benzamides.

173.95° (Table 4), which agrees with the experimental values obtained by means of the $^2J_{PNH}$ constants.

EXPERIMENTAL

The target compounds were synthesized as described in [16].

The ^{1}H NMR spectra were measured on a Varian HA-100D spectrometer. The ^{13}C NMR spectra were obtained on a Bruker WH-90 MNR spectrometer. The ^{1}H (300 MHz), ^{13}C (75.43 MHz) and ^{31}P NMR spectra (121.42 MHz) spectra at varies temperatures and solution concentrations were also recorded on a Varian Unity-300 spectrometer in the ^{2}H stabilization mode. The spectroeter was equipped with a temperature-controlled unit. The ^{31}P NMR spectra were recorder 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

Table 4. Principal angles in the *cis* and *trans* rotamers of benzamides **I**–**III**

Comp. no.	CNP	HNC=O	HNP=X	φ[a]
$\mathbf{I}^{trans}$	126.326	165.55	127.98	58.35
$\mathbf{I}^{cis}$	134.26	2.8	7.22	15.8
$\mathbf{II}^{trans}$	129.43	159.512	14.734	174.98
$\mathbf{II}^{cis}$	133.37	1.8	6.16	12.89
$\mathbf{III}^{trans}$	130.89	172.4	2.5	173.95
$\mathbf{III}^{cis}$	130.173	4.4	169.42	171.77

[a] Angle between the projections of the C=O and P=X bonds on the same plane.

LB 2–4 Hz. The samples were 3–5% (^{1}H) and 10–15% solutions (^{13}C, ^{31}P).

The heats of formation in a vacuum were calculated by the PM3 method using the MOPAC 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.

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