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Study of Intra- and Intermolecular Interactions with Participation of α-Phosphorylated Amines and Alcohols in Different Solvents

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Abstract—Specific interactions of α-hydroxy- and α-aminophosphonates in chloroform and pyridine solutions were studied by theoretical (molecular mechanics) and experimental methods (calorimetry and IR spectroscopy). A competition between intra- and intermolecular interactions and effect of steric factor in molecules of organophosphorus compounds were revealed.

Calorimetric study of series of structurally related organic and heteroelement-containing compounds provides useful information on various fine effects and makes it possible (in combination with other methods) to reveal and characterize various kinds of intra- and intermolecular interactions [1]. The obtained results may be quite important for estimation of structure–reactivity relations holding in various compounds, in particular α-functionalized methylphosphonates [2, 3].

In continuation of our studies on the thermochemistry of α-substituted methylphosphonic acid derivatives [4], in the present work we examined by calorimetry processes of dissolution of α-amino- and α-hydroxyphosphonates in hexane, carbon tetrachloride, chloroform, and pyridine at 298 K. The two latter solvents were taken to estimate the ability of α-substituted phosphonates to participate in hydrogen bonding as proton acceptor or proton donor. The experimental data are collected in Tables 1 and 2.

It is seen (Table 2) that hydroxy derivatives **VIII**–**XII** are characterized by a very weak proton affinity (ΔH_{sp} = –4.2 to –2.2 kJ/mol) and by complete absence of H-donor power. Unlike α-hydroxyphosphonates, fairly high (in absolute value) energies of specific interaction were found for their amino analogs **I**–**VII** not only with chloroform (ΔH_{sp} = –23.8 to –34.8 kJ/mol), but also with pyridine (ΔH_{sp} = –8.6 to –22.6 kJ/mol). Although the enthalpy of specific interaction of aminophosphonates **V**–**VII** with chloroform varies over a fairly wide range (from –29.6 to –34.8 kJ/mol), it exceeds on the average by 8 kJ/mol (in absolute value) the corresponding parameters found for phosphonates **I**–**III** (–23.8 to –26.7 kJ/mol).

The enthalpy of specific interactions of compounds **I**–**XII** with excess chloroform includes pair donor–acceptor interactions with participation of several proton-acceptor fragments of the organophosphorus substrate [1], namely the phosphinoyl group which contributes most to the specific interaction with $CHCl_3$ (–10 to –14 kJ/mol), amino (about –10 kJ/mol) or hydroxy group (–4 to –5 kJ/mol), alkoxy group (–3 to –4 kJ/mol), and phenyl group (–1 to –2 kJ/mol). On the basis of these data, we can roughly estimate the enthalpy of specific interactions of the compounds under study with chloroform using the additivity scheme. In such a way, the energy of specific interaction with chloroform of aminophosphonates **I**–**VII** was estimated at –26 to –34 kJ/mol. These values are quite consistent with the experimental data obtained for derivatives **V**–**VII**, but they exceed those found for their homologs **I**–**III**. Analogous calculations for hydroxyphosphonates **VIII**–**XII** gave enthalpies of specific interaction with chloroform of about –22 to –29 kJ/mol, which exceed by almost an order of magnitude the results of calorimetric measurements.

The observed discrepancies between the calculated and experimental thermochemical parameters of some α-substituted methylphosphonates in the series **I**–**XII**

Table 1. Enthalpies of dissolution (ΔH_{dis}) and solvation ($-\Delta H_{solv}$) in hexane and carbon tetrachloride, enthalpies of vaporization (ΔH^0_{vap}) (kJ/mol, 298 K), molecular refractions (MR_D), and dihedral angles PCXH (deg; X = O, N) of α-aminophosphonates **I**–**VII** and α-hydroxyphosphonates **VIII**–**XII** $(R^1O)_2P(O)CR^2R^3XH$

Comp. no.	R^1	R^2	R^3	X	C_6H_{14}		CCl_4			MR_D	ΔH^0_{vap}	∠PCXH
					ΔH_{dis}	$-\Delta H_{solv}$	ΔH_{dis}	$-\Delta H_{solv}$				
								found	calculated[a]			
I	Et	H	Ph	NMe	14.8	74.6	8.8	80.6	81.2	68.5	89.4	58.81
II	Pr	H	Ph	NMe	15.0	84.3	9.1	90.2	90.6	77.7	99.3	59.76
III	*i*-Pr	H	Ph	NMe	13.3	80.9	7.4	86.8	87.4	77.7	94.2	60.11
IV	Am	$(CH_2)_5$		NCH_2Ph	[b]	117.5[c]	15.9	–	122.9	112.5	138.7	–
V	Am	$(CH_2)_6$		NCH_2Ph	[b]	122.2[c]	16.0	–	127.4	117.0	143.4	–45.33
VI	Et	Me	Me	NCH_2Ph	[b]	80.9[c]	15.8	–	87.4	77.7	103.2	–52.22
VII	Et	Me	Me	NPr-*i*	16.4	63.6	9.5	70.5	70.5	62.8	80.0	–59.88
VIII	Et	H	H	O	4.3	44.0	–3.0	51.3	51.5	37.7	48.3	61.35
IX	Pr	H	H	O	4.6	53.6	–2.4	60.6	60.8	46.9	58.2	–
X	*i*-Pr	H	H	O	2.6	50.3	–4.5	57.3	57.6	46.9	52.8	–
XI	Et	H	Me	O	3.7	47.1	–3.0	53.8	54.5	42.3	50.8	60.32
XII	Et	H	Et	O	3.9	52.0	–2.8	58.6	59.2	46.9	55.8	–

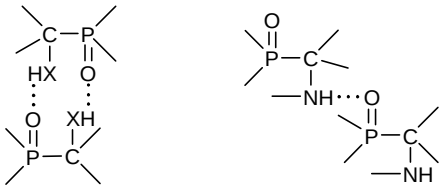
[a] Calculated by the equation $-\Delta H_{solv}(CCl_4) = 13.0 + 1.02 \times MR_D$ [5].
[b] Sparingly soluble in hexane.
[c] Calculated by the equation $-\Delta H_{solv}(C_6H_{14}) = 4.39 + 1.05 \times MR_D$ [1].

Table 2. Enthalpies of dissolution (ΔH_{dis}), solvation ($-\Delta H_{solv}$), and specific interaction (ΔH_{sp}) with chloroform and pyridine (kJ/mol, 298 K) of α-aminophosphonates **I**–**VII** and α-hydroxyphosphonates **VIII**–**XII**

Comp. no.	Chloroform			Pyridine			
	$-\Delta H_{dis}$	$-\Delta H_{solv}$	$-\Delta H_{sp}$	$-\Delta H_{dis}$	$-\Delta H_{solv}$		ΔH_{sp}
					found	calculated[a]	
I	15.0	104.4	23.8	4.3	93.7	84.6	–9.1
II	17.6	116.9	26.7	5.0	104.3	93.9	–10.4
III	18.0	112.2	25.4	5.5	99.7	90.6	–9.1
IV	–	–	–	9.1	147.8	125.8	–22.0
V	18.8	162.2	34.8	9.5	152.9	130.3	–22.6
VI	18.4	121.6	34.2	8.4	111.6	90.6	–21.0
VII	20.1	100.1	29.6	2.6	82.6	74.0	–8.6
VIII	5.2	53.5	2.2	2.1	50.4	55.1	4.7
IX	5.6	63.8	3.2	3.3	61.5	64.4	2.9
X	7.1	59.9	2.6	2.7	55.5	61.1	5.6
XI	6.5	57.3	3.5	4.0	54.8	58.1	3.3
XII	7.0	62.8	4.2	4.2	60.0	62.8	2.8

[a] Calculated by the equation $-\Delta H_{solv}(C_5H_5N) = 17.0 + 1.01 \times MR_D$ [5].

suggest that purely solvation processes, involving hydrogen bonding with the solvent, are accompanied by some other processes. Obviously, we must take into account the possibility for intra- and intermolecular association–dissociation. As shown previously [6–10], α-phosphorylated alcohols and amines in a condensed phase are capable of forming associates like **A** via intermolecular H-bonding. In this case, all X–H fragments (where X = O, N) involved in the associate give rise to spectral patterns typical of the corresponding moieties participating in formation of H-complexes.



A **B**

The IR spectrum (film) of aminophosphonate **I** (as a representative of compounds **I**–**III** having similar substituents at the α-carbon atom and characterized by similar calorimetric parameters) contained a single band from N–H stretching vibrations in associated amino group at about 3300 cm^{-1} [9]. This band disappeared in going to dilute solutions in carbon tetrachloride and chloroform, and in each case one ν(N–H) absorption band appeared at a higher frequency, 3410–3440 cm^{-1}, which is typical of free amino group. A similar pattern was observed previously for diethyl α-(phenylamino)benzylphosphonate (**XIII**) [9], which is structurally related to α-aminophosphonates **I**–**III**. The IR study of phosphonate **XIII** indicated initial formation of dimer **A**, followed by displacement of the equilibrium toward monomeric phosphonate by the action of solvent.

Our spectral data led us to presume that hydrogen bonding of α-aminophosphonates **I**–**III** with chloroform is preceded by complete dissociation of dimers **A**, the energy of dissociation being estimated at –17 to –23 kJ/mol (taking into account rupture of two hydrogen bonds in the dimer) [9]. The contribution of that positive energy component reduces the overall negative effect of specific interaction between compounds **I**–**III** and chloroform. Thus, provided that intermolecular interaction between molecules **I**–**III** is absent, their negative enthalpy of specific interaction with chloroform should be no less than 41 kJ/mol in absolute value.

The spectral properties of compounds **V**–**VII** strongly differ from those of α-aminobenzylphosphonates **I** and **XIII**. Aminophosphonates **V**–**VII** (film) showed in the IR spectra N–H stretching vibration bands belonging to both associated (3300 cm^{-1}) and free amino groups (3400 cm^{-1} and higher). Likewise, in the IR spectra of structurally related diethyl 1-methyl-1-isopropylaminoethylphosphonate (**XIV**) and diethyl 1-benzylamino-1-methylethylphosphonate (**XV**), absorption of the amino group was observed in the region 3300–3500 cm^{-1} [11]. These data contradict formation of type **A** dimers from α-aminophosphonates **V**–**VII**, **XIV**, and **XV** in the condensed phase. On the other hand, the spectral patterns indicating participation of the amino groups in hydrogen bonding suggest association to dimers having a different structure, namely structure **B**.

The IR spectra of dilute solutions of phosphonates **V** and **VI** in chloroform contained only one ν(N–H) band at 3352 and 3384 cm^{-1}, respectively. Their position indicates complete absence of self-association via H-bonding with the amino group. Very similar patterns were observed for solutions in carbon tetrachloride [ν(N–H) 3336 and 3328 cm^{-1}, respectively]. This means that dimers **B** derived from phosphonates **V** and **VI** decompose completely upon dissolution in chloroform and carbon tetrachloride.

The reasons for the observed differences in both thermochemical and spectral parameters of two groups of α-substituted methylphosphonates, **I**–**III,** on the one hand, and **V** and **VI**, on the other, should be sought for in their specific steric structure. For this purpose we performed theoretical molecular mechanics calculations of their structure. The results showed that compounds with reduced (**I**–**III**) and enhanced (**V**, **VI**) proton-acceptor power differ by the sign of the dihedral angle PCNH, the other geometric parameters being essentially similar (Table 1). Aminophosphonates **V** and **VI** with a quaternary (i.e., sterically loaded) α-carbon atom are characterized by a negative PCNH dihedral angle (the P=O and N–H bonds are oriented in the opposite directions with respect to the plane formed by the P, C, and N atoms). In this case, intramolecular hydrogen bonding is impossible, while intermolecular association could occur only via formation of a single hydrogen bond to give dimers like **B**. In particular, the formation of such hydrogen bond follows from the presence of both associated and free amino groups in molecules **V** and **VI** in the condensed phase (according to the IR data).

As with α-aminophosphonates **I**–**III**, hydrogen bonding of compounds **V** and **VI** with chloroform should be preceded by dissociation of dimers **B**. Unlike type **A** dimers, dissociation of dimers **B** involves rupture of one rather than two intermolecular hydrogen bonds. Therefore, the contribution of the corresponding energy component should be estimated at –8 to –11 kJ/mol, and the negative enthalpy of specific interaction of compounds **V** and **VI** with chloroform (provided that no complex **B** is formed), at 42 kJ/mol or greater (in absolute value). This value is in excellent agreement with the corresponding parameter obtained for compounds **I**–**III** (see above).

It should be emphasized that molecules of aminophosphonates **I**–**III** possess a less sterically loaded tertiary α-carbon atom. The P=O and N–H fragments therein are oriented at the same side of the PCN plane, and the dihedral angle PCNH is positive (Table 1). Therefore, derivatives **I**–**III** can give rise to dimers **A** via formation of two intermolecular hydrogen bonds, as was presumed in the early studies [9]. An indirect support to the formation of such dimers is the presence of only one N–H stretching vibration band (associated) in the IR spectra of **I**–**III** in the condensed phase.

Interestingly, the spectral properties of compound **VII** differ from those of the other aminophosphonates examined in this work. The IR spectral patterns of **VII** both in the condensed phase and in solution in chloroform and tetrachloromethane are almost similar: in each case the spectrum contains two ν(N–H) absorption bands from associated and free amino groups at 3345–3350 and 3428–3444 cm^{-1}, respectively. The dihedral angle PCNH is negative (Table 1); therefore, as with compounds **V** and **VI**, associates like **B** should be formed in the condensed phase while formation of dimers like **A** is hampered. However, according to spectral data, associates **B** formed from phosphonate **VII** do not decompose in solution like their analogs **V** and **VI**. The experimental value of ΔH_{sp} for **VII** and chloroform occupies an intermediate place between those found for aminophosphonates **I**–**III**, on the one hand, and **V** and **VI**, on the other (Table 2).

Presumably, the isopropyl group on the α-carbon atom in **VII** shields the phosphinoyl group in dimer **B**, hampering both specific resolvation of the H-bonded (in the dimer) phosphinoyl fragment with chloroform and H-bonding with chloroform of the nitrogen atom involved in the NH···O=P hydrogen bridge. As a result, dimer **B** does not undergo decomposition in solution, and the apparent enthalpy of specific interaction decreases in absolute value by about 10–12 kJ/mol relative to that expected in the absence of complex B. Taking into account the above data on the contributions of particular fragments in phosphonate molecules to specific interaction with chloroform, the lack of binding of one phosphinoyl group with chloroform produces loss in the absolute value of ΔH_{sp} by 10–14 kJ/mol, calculated on two phosphonate molecules in the dimer; the corresponding value for the lack of binding of one amino group is about 10 kJ/mol. Therefore, the enthalpy of specific interaction of compound **VII** with chloroform (provided that complex like **B** is not formed) should be estimated at –40 to –42 kJ/mol. We can conclude that this parameter remains almost the same for all aminophosphonates **I**–**VII** and that the observed differences in the results of calorimetric measurements originate from differences in the association–dissociation processes occurring in solution. The character of these processes is determined by steric factor.

The revealed specific structural features of α-aminophosphonates and their behavior in the condensed phase and in solution, e.g., in chloroform, allowed us to estimate the "true" enthalpies of their specific interaction not only with chloroform but also with pyridine (with no account taken of energy contributions of the other processes). According to the data of [12], specific interaction of functionalized phosphonates with pyridine involves formation of only hydrogen bonds like H···NC_5H_5. As with chloroform, estimation of specific interaction of compounds **I**–**III** with pyridine without formation of dimers **A** requires that the energy contribution for rupture of two hydrogen bonds in the dimer (–17 to –23 kJ/mol) be taken into account. Summation with the experimental value of ΔH_{sp} (Table 2) gives –26 to –33 kJ/mol. Likewise, taking into consideration the energy contribution for rupture of one hydrogen bond in dimer **B** for compounds **V** and **VI** (–8 to –11 kJ/mol) gives a true enthalpy of specific interaction of **V** and **VI** with pyridine of –29 to –34 kJ/mol. It is seen that the estimated enthalpies of purely specific solvation with pyridine are similar for the whole series of the examined aminophosphonates provided that their dimerization does not occur.

Using compounds **VIII** and **XI** as examples, we found that the dihedral angle PCOH in α-hydroxyphosphonates is positive; i.e., the P=O and O–H fragments are oriented at the same side of the PCO plane. Therefore, as in aminophosphonates **I**–**III**, steric structure of α-hydroxyphosphonates should also favor intermolecular hydrogen bonding to give type **A**

dimers. In fact, this was noted in [7] for compounds **VIII** and **XI**. The IR study showed that such dimers decompose in solution. According to published data [1, 7], the energy contribution corresponding to rupture of two P=O···H hydrogen bonds in the dimer upon dissolution should be estimated at about –20 kJ/mol. Therefore, the energy of specific interaction of compounds **VIII**–**XII** with solvents (no dimers **A** are formed), with account taken of the experimental ΔH_{sp} values (Table 2) is equal to –22 to –24 kJ/mol for chloroform and –14 to –17 kJ/mol for pyridine. Thus the effect of specific solvation of α-hydroxyphosphonates is completely eliminated by the energy of dissociation of the phosphonate–phosphonate intermolecular hydrogen bonds in pyridine, whereas in chloroform this effect considerably reduces the absolute value of the energy of specific interaction with the solvent. On the whole, the enthalpies of specific interaction of α-hydroxyphosphonates with chloroform and pyridine are considerably lower (in absolute value) than the corresponding enthalpies obtained for the amino derivatives: –40 to –42 and –26 to –34 kJ/mol, respectively.

The apparent enthalpies of specific interaction of functionalized phosphonates with chloroform and pyridine, determined by calorimetric measurements, indicate that α-aminophosphonates, unlike α-hydroxy analogs, exhibit specific amphoteric properties. They are capable of participating in specific interaction with both proton-donor (chloroform) and proton-acceptor reagents (pyridine). The strength of such interactions varies over a wide range and is determined to a considerable extent by steric structure of the phosphonate. Analogous biphilicity of α-aminophosphonates was demonstrated previously while studying the mechanism of their addition to phenyl isocyanate: variation of substituents at the carbon and nitrogen atoms in the aminomethylphosphinoyl moiety leads to change of the mechanism of addition from nucleophilic to electrophilic [13]. No such behavior was observed for hydroxyphosphonates: in all cases, nucleophilic addition predominates [14]. It should also be noted that consideration of intramolecular hydrogen bonding ensures proper estimation of the relations between the structure and acid–base properties of a wide series of α-aminophosphonates [15].

EXPERIMENTAL

Compounds **I**–**XII** were synthesized and purified according to the procedures reported in [12, 14, 16]. Their purity was checked by GLC using a Chrom-5D chromatograph [1.5-m column packed with 3% OV-17 on Chromaton N Super (0.160–0.200 mm); carrier gas helium, inlet pressure 0.4 atm] and ^{31}P NMR spectroscopy using a Varian Unity-300 instrument (121 MHz).

The enthalpies of dissolution were measured at 298 K using an Arnett–Rogers adiabatic differential calorimeter [17, 18]. The solute concentration was $(1–3)\times10^{-3}$ M; the error was within 0.3–0.5 kJ/mol. No concentration and temperature (293–300 K) dependences of the enthalpies of dissolution were observed in the given ranges. The solvents were prepared by standard procedures [19].

The enthalpies of vaporization of phosphonates **I**–**III** and **VII**–**XII** were calculated by the Solomonov equation [20, 21] from the experimental enthalpies of dissolution in hexane and molecular refractions. For aminophosphonates **IV**–**VI** which are insoluble in hexane, the calculations were performed using an analogous equation [5, 20] from the corresponding enthalpies of dissolution in CCl_4. The overall enthalpies of solvation were calculated from the enthalpies of dissolution and vaporization (Tables 1, 2).

The enthalpies of specific interactions of phosphonates with chloroform were calculated from the difference in the enthalpies of solvation in chloroform and carbon tetrachloride, following the procedure described in [1] which proved to be well suitable for studying organophosphorus compounds. The enthalpies of specific interaction with pyridine were calculated from the difference in the experimental overall enthalpies of solvation and enthalpies of nonspecific solvation determined from the molecular refraction data [5] (Table 2).

The IR spectra were recorded on a Specord M-80 spectrometer. The molecular mechanics calculations were performed using MMX program built in PC MODEL 1.0.

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