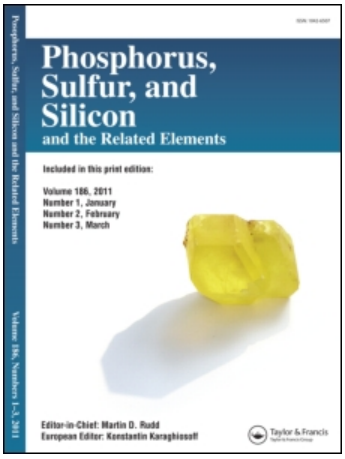

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Reactivity of Functionalized Phosphonates 1. Acid-Base Properties and Reactivity of Methyl Esters of Alpha-Aminophosphonic Acids

Roustem D. Saiakhov[ab]; Artem R. Cherkasov[a]; Alphia A. Shajmardanova[c]; Vladimir I. Galkin[a]; Rafael A. Cherkasov[a]; Paolo Finocchiaro[d]; Salvatore Failla[c]
[a] Department of Chemistry, Kazan State University, Kazan, Russia [b] Department of Chemistry, Case Western Reserve University, Cleveland, Ohio [c] Arbusov's Institute of Organic and Physical Chemistry, Kazan, Russia [d] Instituto di Chimico, University of Catania, Viale, Catania, Italy

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REACTIVITY OF FUNCTIONALIZED PHOSPHONATES 1. ACID-BASE PROPERTIES AND REACTIVITY OF METHYL ESTERS OF ALPHA-AMINOPHOSPHONIC ACIDS

Roustem D. Saiakhov,[a,b] *Artem R. Cherkasov,*[a] *Alphia A. Shajmardanova,*[c] *Vladimir I. Galkin,*[a] *Rafael A. Cherkasov,*[a] *Paolo Finocchiaro,*[d] *and Salvatore Failla*[c]
Department of Chemistry, Kazan State University, Kazan, Russia;[a] *Department of Chemistry, Case Western Reserve University, Cleveland, Ohio;*[b] *Arbusov's Institute of Organic and Physical Chemistry, Kazan, Russia;*[c] *and Instituto di Chimico, University of Catania, Viale, Catania, Italy*[d]

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Acid-base properties and reactivity of series of alpha-aminophosphonates has been investigated. The reaction of addition of the aminophosphonates to phenylisocyanate was used as a model reaction. The influence of steric and electronic effects of substituents at alpha-carbon or nitrogen in amino group on the mechanism inversion from AdN to AdE is discussed.

Keywords: Aminophosphonates; basicity; mechanism; phenylisocyanate; reactivity; substituent effect

INTRODUCTION

Alpha-functionalized organophosphorous compounds $R^1R^2P(O)CH_2X$ (where X → a functional group), especially alpha-aminophosphonates are widely used and are convenient molecules for quantitative studies on the influence of an organophosphorous group on the mechanism of side-chain reactions and on the activity of the reaction centers. It was shown that such influence could be very significant and complex

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Address correspondence to R. D. Saiakhov, Department of Chemistry, Case Western Reserve University, 10900 Euclide Avenue, Cleveland, OH 44106, USA. E-mail: rds2@po.ewru.edu

including electronic and steric effects.[1–3] However, a systematic investigation of the problem through quantitative analysis of all possible effects connected with the organophosphorous substituent has not been performed as yet. Recently we began to study the electronic and steric effects of complex organophosphorous substituted molecules in the addition reactions of alpha-hydroxy and alpha-amino-phosphonates to phenylisocyanate.[4,5]

Previous Findings

Using accurate kinetic techniques for the reaction of phenylisocyanate with phosphorylated and nonphosphorylated alcohols and amines, we have discovered a significant influence of organophosphorous fragment located near the reaction center, not only on kinetics, but also on the mechanism of the addition itself. We have observed a change of the mechanism from concerted Ad_N-mechanism with dominance of the nucleophilic component (which is a common feature for nonphosphorylated alcohols, amines and aminophosphonates) (see Figure 1a) to electrophilic concerted Ad_E-mechanism for alpha-hydroxyphosphonates with a predominance of the electrophilic component over the nucleophilic one in the transition state (see Figure 1b).

Compared to hydroxyphosphonates, aminophosphonates have a stronger nucleophilic reaction center,—that is, the nitrogen in N—H

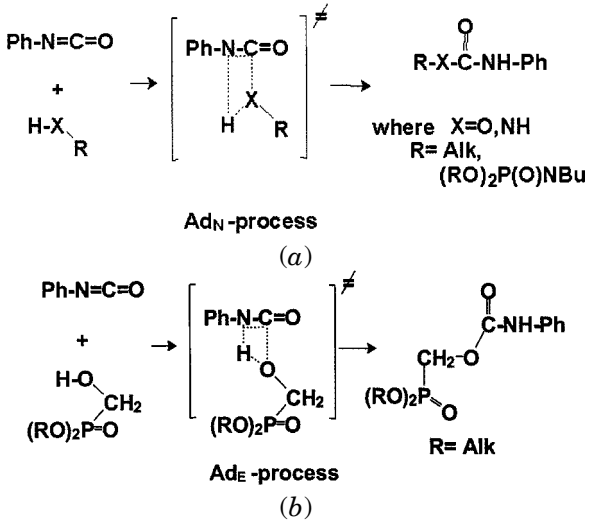


FIGURE 1 Proposed mechanisms for nucleophilic (a) and electrophilic (b) addition reaction.

fragment. That feature prevents the electrophilic possibility of the addition even in acetonitrile media. However, the activity of aminophosphonates in acetonitrile decreases significantly compared to aliphatic amines.

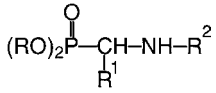
Therefore, due to the above mentioned factors and flexible structures for the following series of compounds

$$R_2NH > (AlkO)_2P(O)CH_2NHAlk > ROH > (AlkO)_2P(O)CH_2OH$$

continuous transformation of the transition state structure has been observed in acetonitrile. The structure is transformed from an asymmetric one with shorter C—X bond (result of dominating Ad_N-interaction) to the structure with shorter N—H bond as a result of dominating electrophilic interaction Ad_E.

Hypothesis, Goals, and Objects of the Investigation

We supposed that an analogous change in mechanism would be possible not only for hydroxyphosphonates, but also for aminophosphonates. However, according to the above-mentioned factors, the electronic and steric influence of only the organophosphorous substituents are not strong enough to support such a process. We believe that an additional influence of bulky and electron-withdrawing substituents located near the reaction center—nitrogen (substituent R^2) and neighboring alpha-carbon (substituent R^1)



will significantly decrease the basicity of the nitrogen and, hence, will change the mechanism from Ad_N to Ad_E.

To check our hypothesis we have studied the main properties and reactivity in the addition reaction of substituted phosphonates with phenylisocyanate. These phosphonates contain an electron withdrawing substituent R^1 at the alpha-carbon atom and the bulky cyclohexyl substituent R^2 at the nitrogen. We have also studied the same reaction with a series of aliphatic aminophosphonates, synthesized by using the Kabachnik-Fields method.[4]

The model reaction proceeds rapidly and quantitatively according to equation

$$(RO)_2P(O)CHR^1NHR^2 + PhNCO \rightarrow (RO)_2P(O)CHR^1N(R^2)C(O)NHPh$$

MATERIALS AND METHODS

Spectroscopy Experiments

IR experiment have been performed using spectrometer UR-20 in a layer, suspension in vaseline and crystals from evaporation of CCl_4 solution on KBr and CaF_2 surfaces. NMR P^{31} spectra have been recorded using spectrometer RIA-2305(24.3 MHz), external standard—85% H_3PO_4. NMR H^1 spectra were recorded on spectrometer Tesla T-60 (60 MHz).

Synthetic Experiments

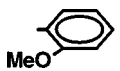
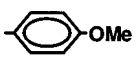
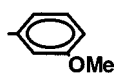
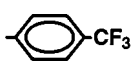
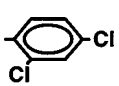
Aliphatic aminophosphonates have been synthesized by previously described method,[4] aromatic aminophosphonates were synthesized according to.[6]

N-(dimethoxyphosphorylarylmethyl)-N-cyclohexyl-N′-phenyl-ureas (I–VII). A solution of 0.01 mol of dimethyl n-cyclohexylamino arylmethylphosphonate in 5 ml dry acetonitrile was added slowly to 0.01 mol phenylisocyanate. The reaction was slightly exothermic. After 16 h the solvent was evaporated and the adduct was recrystallized from hexane. Adducts are colorless cubic crystals. The main physical and spectroscopic data for all adducts are presented in Table I.

Kinetic Experiments

Kinetic experiments were performed using the spectrophotometer SF-46 with a built-in thermostat (±0.1°C). All measurements were made in acetonitrile media at 25°C, 280 nm. During the reaction an increase of optical density was observed due to conversion of the isocyanate chromophore to the urea chromophore. For the whole series, a global second order reaction has been found, to be first order in each reagent. Kinetic experiments were performed in pseudofirst order conditions with a large excess concentration of phosphonates, which was varied from 0.001 to 0.005M. Kinetic results have been treated using standard statistical analysis packages with minimization methods for calculating the first-order constants. Second order constants were calculated by dividing first-order constants by the concentration of the reagent in excess. Solvents were purified by standard methods.

TABLE I Main Characteristics of Ureas $(MeO)_2P(O)CHRNcyclo\text{-}HexC(O)NHPh$

N	R	Yield (%)	t_{melt} (°C)	MW	Formula	Elementary analysis C:H:N:O:P % calc.(found.)	δP^{31} ppm	δH^1 ppm
I		92	84	430.46	$C_{23}H_{29}NO_5P$	64.18:6.79:3.25:18.58:7.20 (64.05:6.70:3.32:18.61:7.32)	18	CHR[a] 4.78 NHPh[b] 8.53 O=P(OCH_3)[c] 3.50, 3.80
II		90	88	430.46	$C_{23}H_{29}NO_5P$	64.18:6.79:3.25:18.58:7.20 (64.08:6.72:3.29:18.60:7.31)	18	CHR[a] 4.24 NHPh[b] 8.78 O=P(OCH_3)[c] 3.54, 3.75
III		91	73	430.46	$C_{23}H_{29}NO_5P$	64.18:6.79:3.25:18.58:7.20 (64.13:6.73:3.29:18.59:7.26)	19	CHR[a] 4.23 NHPh[b] 8.67 O=P(OCH_3)[c] 3.52, 3.76
IV		88	oil	468.43	$C_{23}H_{26}F_3NO_4P$	58.97:5.59:2.99:13.66:6.61 (58.93:5.63:2.95:13.70:6.65)	21	CHR[a] 4.38 NHPh[b] 8.63 O=P(OCH_3)[c] 3.59, 3.76
V		93	oil	434.87	$C_{22}H_{26}ClNO_4P$	60.76:6.03:3.22:14.72:7.12 (60.72:6.07:3.24:14.71:7.15)	20	CHR[a] 4.90 NHPh[b] 8.65 O=P(OCH_3)[c] 3.48, 3.84
VI		95	77	469.32	$C_{22}H_{25}Cl_2NO_4P$	56.30:5.37:2.98:13.64:6.60 (56.28:5.40:2.96:13.66:6.62)	18	CHR[a] 4.88 NHPh[b] 8.74 O=P(OCH_3)[c] 3.55, 3.83
VII		92	oil	469.32	$C_{22}H_{25}Cl_2NO_4P$	56.30:5.37:2.98:13.64:6.60 (56.31:5.35:2.30:13.63:6.64)	19	CHR[a] 4.99 NHPh[b] 8.79 O=P(OCH_3)[c] 3.53, 3.88

[a] Doublet (J_{HP} = 22–23 Hz).
[b] Broad singlet.
[c] Doublets (J_{HP} = 10–12 Hz).

Potentiometric Experiments

The potentiometric titrations of aminophosphonates conjugated acids with 75% water-isopropanol solution of 0.0811M NaOH have been carried out using LOMO (Russia) potentiometer pH-121 with two parallel glass electrodes. The glass electrodes used were LOMO combination electrode with an Ag/AgCl, $KCl_{(sat.)}$ reference. The pH readings ($\pm$0.001 pH unit) were carried out after a sufficient stabilization period by digital meter LOMO F-283. The titration vessel was thermostated at $25 \pm 0.1^{\circ}C$. The concentration of aminophosphonates, taken for titration, was 0.1M. Aminophosphonates were neutralized before the titration by 0.1M HCl in 75% water-isopropanol media. Ionic strength equal to 0.25 (NaCl) was maintained for all solutions.

The potentiometer settings were calibrated every 70 hours with 0.0811M NaOH in 75% water-isopropanol media with ionic strength equal to 0.25 (NaCl). The degree of aminophosphonates protonization was calculated from monitored pH by Wingefors method[7] by the least square statistical procedure.

RESULTS AND DISCUSSION

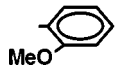
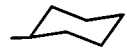
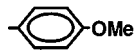
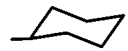
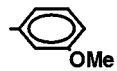
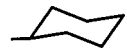
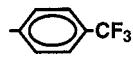
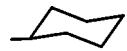
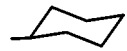
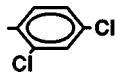
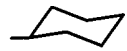
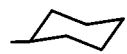
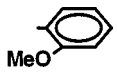
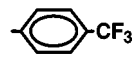
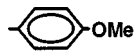
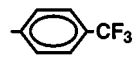
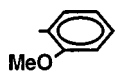
All adducts were isolated as colorless crystalline compounds. Elementary analysis, NMR P^{31} and H^1 confirmed their structure and purity. Ionization constants for the whole series have been estimated in 75% isopropanol media by a modified method of potentiometric titration.[7]

The values of pK_a for aromatic and aliphatic aminophosphonates and kinetic data for their reaction to phenylisocyanate are presented in Table II.

It easily to see from Table II that basicity of the aromatic aminophosphonates compared to the aliphatic ones is significantly decreased (10–1000$\times$). Moreover, we have observed the same significant decrease of the reactivity in the reaction with phenylisocyanate. For not very strong basic aliphatic aminophosphonates, the reaction rate increases with increasing basicity (see points 1–6, Figure 2), but for sterically hindered and less basic aromatic phosphonates the reaction rate decreases with increasing basicity (see points 7–9 and 10–13, Figure 2). That clearly indicates a change in the mechanism from the one in which the nucleophilic component is dominant of to the one in which the electrophilic component in the transition state is dominant.

It is interesting to note, that arylaminophosphonates with electron-donating (like methoxy group, see point 7–9) and electron-withdrawing (halogens, CF_3-group, see points 10–13) substituents in the aromatic ring seem to belong to different reaction series (see Figure 2). That may

TABLE II Experimental Parameters of Basicity and Reactivity of Aminophosphonates $(RO)_2P(O)CHR^1NHR^2$ and Calculated Parameters of Inductive (σ^*) and Steric (R_s) Effects[8,9]

	R	R^1	R^2	pK_a conj. acids	lgk	$-\sigma^*$	$-R_s$
1	Me	H	n-Bu	5.71	0.80	4.20	6.80
2	Et	H	n-Bu	5.55	0.65	4.03	7.05
3	n-Pr	H	n-Bu	5.42	0.60	3.84	7.12
4	i-Pr	H	n-Bu	5.3	0.53	4.15	7.80
5	i-Bu	H	n-Bu	5.21	0.43	4.05	7.63
6	i-Am	H	n-Bu	5.31	0.46	4.28	7.60
7	Me			4.31	−0.48	3.79	11.07
8	Me			4.25	−0.17	3.87	10.25
9	Me			3.95	0.19	3.73	10.33
10	Me			3.38	−1.15	3.68	10.28
11	Me			3.15	−0.93	3.28	11.02
12	Me			2.86	−0.24	3.20	11.13
13	Me			2.80	−0.49	3.16	11.20
14	Me			—	—	2.63	11.01
15	Me			—	—	2.62	11.20
16	Me			—	—	2.84	10.57

be related to different levels of deformation in the transition state structure, producing shortest N—H initial distance (see Figure 1). Introducing substituted aromatic moieties at nitrogen instead of the cyclohexyl fragment completely deactivates the aminophosphonates in the addition reaction. Thus, it was impossible to measure the kinetic and the acid-base parameters for such compounds.

To investigate these factors, and to predict the acid-base properties and the reactivity of aminophosphonates, we have calculated inductive and steric parameters of the substituents at nitrogen, using previously designed models of steric and inductive effects.[8,9] These models are

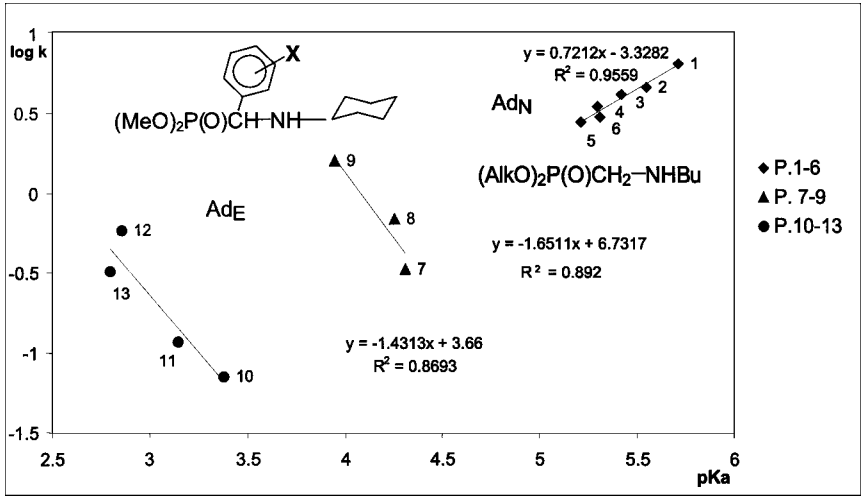


FIGURE 2 Correlation between log k of addition of the aminophosphonates and pKa of their conjugated acids.

capable of theoretical estimation of inductive and steric parameters for any substituents at any reaction center, using only simple structure and conformation parameters (see Table II). Substituent parameters have been calculated for the four most probable conformations of the aminophosphonates. Comparison of these four sets of parameters with experimental pK_a values produced some interesting results.

For example, we have found that the best way to describe the basicity of the whole series is to assume the different conformation for sterically hindered and non-hindered phosphonates. For simple aliphatic phosphonates the configuration with trans-location of P═O and C─N bonds is preferable, but for sterically hindered arylaminophosphonates gauche-located C─N and C─R relative to the P═O fragment conformation seems to be more preferable. We believe that this is reasonable, because the molecule in this conformation possesses minimum steric interactions. Besides, this conformation in arylaminophosphonates may be additionally stabilized by hydrogen-bonds between the phosphoryl group and the acid N─H proton, as was confirmed by IR spectroscopy and x-ray data.[6]

We were able to describe the basicity of whole set by one equation

$$\begin{gathered} \mathrm{pKa} = 1.93 - 1.41\sigma^* + 0.32\mathrm{R_s} \\ \mathrm{N} = 13, \mathrm{R} = 0.9736, \mathrm{S_0} = 0.272 \end{gathered} \tag{1}$$

It is easily to see from Eq. 1, that increasing the electron-donor ability of the substituents increases the basicity, but increasing their size

decreases the basicity. The presence of the last (steric) parameter in the Eq. 1 looks reasonable, because it is known that large substituents are a serious obstacle for a solvation of ammonia cations by polar solvent.[10]

CONCLUSION

Therefore, large and electron withdrawing dialkoxyphosphoryl groups along with electron-withdrawing substituents at the alpha-carbon and nitrogen atoms have significant influence on the rate and on the mechanism of the reaction. The reducing of the nucleophilic component in a four-center transition state until full change of the mechanism from the concerted Ad_N to concerted Ad_E with predominance of the electrophilic component is observed also in arylaminophosphonates exactly as was the case for hydroxyphosphonates.

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