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Acid-Catalyzed Cleavage of Some Chromone, Coumarin and Pyrone Derivatives of Aminomethylphosphonic Acid. Products and Kinetics of the Reaction

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Treatment of chromone-2, coumarin-4 and pyrone-2 derivatives of *N*-benzylaminomethylphosphonic acid with strong mineral acids leads to formation of the corresponding heterocyclic amines and phosphoric acid. Kinetic studies of this cleavage reaction demonstrate that protonation has a remarkable influence on a cleavage of C–P bonds. In aq. H_2SO_4, cleavage of the acids **1**–**3** exhibits a kinetic dependence on $[H^+]$. The measured solvent isotope effect (k_H/k_D) was about 1.5 for the **1** and **2** and only 1.1 for the **3**. The existence of the isotope effect shows that protons are involved on the rate-determining step. The data obtained suggest that the protonated phosphonate molecule is split by a dissociative mechanism with A-S_E2 character and this is combined with an elimination of the phosphonate group as a positive-charged phosphorus moiety.

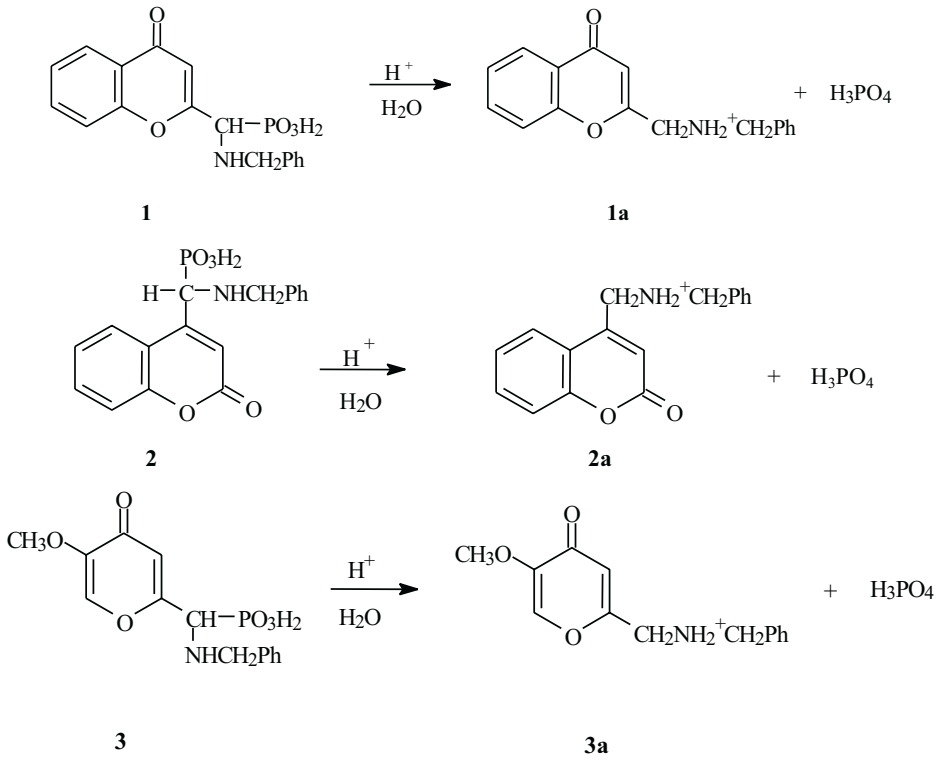
Key words: cleavage, protonation, chromone, coumarin and pyrone derivatives of aminomethylphoshonic acid, kinetics, isotope effect, activation parameters

Working on some heterocyclic derivatives of aminomethylphosphonic acid we found that the 2-pyridyl and 4-pyridyl derivatives of that acid undergo a cleavage in strong acidic media, forming the corresponding amines and phosphoric acid [3]. This interesting reaction became a subject of intensive studies in our group. Later, some kinetic measurements of that cleavage [3] were done and the results obtained were published [4]. We found recently, that some oxygen heterocyclic derivatives of aminomethylphosphonic acid also undergo a similar cleavage in a strong acidic medium; thus, the chromone-2-yl, coumarin-4-yl and pyrone-2-yl derivatives of *N*-benzylaminomethylphosphonic acid [1,2] were cleaved by aqueous hydrochloric or sulfuric acid to form the corresponding heterocyclic amine and phosphoric acid, as shown in Scheme 1.

In order to establish an acceptable mechanism for the cleavage reaction of these oxygen heterocyclic derivatives of aminomethylphosphonic acid, we looked upon a chemistry of a cleavage of the chosen compounds **1**, **2** and **3** (to establish the products of the reaction) and also carried out some kinetic measurements, which would provide a better understanding of this reaction.

RESULTS AND DISCUSSION

When aminophosphonic acids **1**, **2** or **3** are refluxed with aqueous mineral acids (*i.e.* HCl, H_2SO_4) for several hours, a cleavage reaction takes place and the corresponding heterocyclic amines **1a**, **2a** or **3a** and phosphoric acid (H_3PO_4) are formed in an almost quantitative yield. This reaction can be easily monitored by ^{31}P NMR spectroscopy. No other products except the heterocyclic amines and phosphoric acid were detected in this process. A course of this cleavage reaction is depicted in Scheme 1.



Scheme 1. Cleavage of chromone-2-, coumarin-4- and pyrone-2- derivatives of aminomethylphosphonic acid in strong mineral acids. Formation of amines and phosphoric acid.

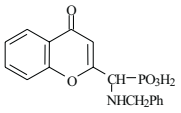
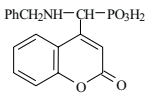
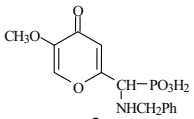
The heterocyclic amines formed were easily isolated from the reaction mixture by alkalization with aqueous sodium bicarbonate and subsequent extraction of the formed products with methylene chloride. Because of observed instability of free amines (**1a**–**3a**), the amine products were identified and characterized as the oxalate salts, which in turn were easily obtained by treatment of the crude **1a**, **2a** or **3a** with oxalic acid in acetone solution.

It is worthy to mention, that the related chromone-3-yl derivatives of aminomethylphosphonic acid are stable in strong acidic conditions and do not undergo such a cleavage [1]. The observed susceptibility of the chromone-2, pyrone-2 and coumarin-4 derivatives for such a cleavage, contrary to the stable 3-substituted derivatives,

shows a resemblance of this reaction to the cleavage of 2-pyridyl or 4-pyridyl derivatives of aminomethylphosphonic acid in acidic conditions [3]. Based on our previous results [3], there is no doubt that the electronic phenomena (*i.e.* resonance effects), occurring in these definite structures, are responsible for this cleavage.

In order to take a mechanistic insight into this reaction, we examined the cleavage by some kinetics. Due to the fact, that the cleavage can be easy monitored by ^{31}P NMR, we measured the pseudo-first-order cleavage constant (k_{obs}) and found a dependence of k_{obs} on concentration of H^+ for the used representative compounds **1**, **2** and **3**. Kinetic measurements were made by the following way: A solution of the aminophosphonic acid **1**, **2** or **3** (~ 0.05 mol·L^{-1}) in a DMSO-H_2O mixture (1:1), containing a fixed concentration of sulfuric acid, were heated in NMR tubes at 95°C for specified period of time and (after cooling) ^{31}P NMR spectra were recorded. Kinetic data were obtained from the spectra on the basis of observed decrease with time in the concentration of the aminophosphonic acid (**1**, **2**, **3**) and the simultaneous increase in the concentration of H_3PO_4 formed. The concentrations were calculated from the integration values of individual phosphorus compounds. The pseudo-first-order rate constants (k_{obs}) can be accurately determined from ^{31}P NMR spectra by plotting dependence of log*(a-x)* on time (where the *„a-x"* represents an actual concentration of the unreacted phosphonic acid). The data obtained are summarized in Table 1.

Table 1. Kinetics for acid-catalyzed cleavage of chromone, coumarin and pyrone derivatives of aminomethylphosphonic acid in DMSO-H_2O (D_2O) (1:1) solutions, at 95°C.

Compound	Conc. of compd. mol·L^{-1}	Acid	Conc. of acid mol·L^{-1}	$10^5 \cdot k_{obs}$ [a] s^{-1}	k_H/k_D
 **1**	0.050	H_2SO_4	0.5	14.30±0.11	
	0.069	H_2SO_4	1.0	17.30±0.13	
	0.050	H_2SO_4	2.0	20.30±0.18	1.49
	0.069	D_2SO_4	1.0	11.60±0.09	
 **2**	0.073	H_2SO_4	0.5	0.69±0.04	
	0.056	H_2SO_4	1.0	0.81±0.03	
	0.073	H_2SO_4	2.0	0.96±0.07	1.59
	0.056	D_2SO_4	1.0	0.51±0.02	
 **3**	0.077	H_2SO_4	0.5	5.80±0.09	
	0.083	H_2SO_4	1.0	8.06±0.11	
	0.077	H_2SO_4	2.0	13.60±0.12	1.11
	0.083	D_2SO_4	1.0	7.26±0.11	

[a] Rates reproducible to ± 5%

Table 1 shows that k_{obs} depends on the acid concentration. For D_2SO_4 solutions the rates are decreased markedly in comparison with H_2SO_4 at the same concentrations. The calculated kinetic isotope effects (k_H/k_D) are rather small if compared with typical values of the k_H/k_D reported for acid-catalyzed reactions. However, the obtained values of k_H/k_D are comparable with the values given for hydration of olefins in acidic

conditions [5] or desulfonation of aromatic sulfonic acids [5]. Comparison of the rates for the cleavage of chromone-2 derivative (**1**) with the rates determined for coumarin-4 one (**2**) shows a substantial difference. The chromone-2 derivative undergoes cleavage about twenty times faster than the coumarin-4 compound. The pyrone-2 derivative (**3**) cleaves about twice slower than the **1**, but about ten times faster than the **2**. In order to find the activation parameters for these reactions, we measured the cleavage rates for the two most representative compounds (**1** and **2**) at different temperatures. The results are summarized in Table 2.

Table 2. Effect of temperature: rates and activation parameters for acidic cleavage of aminophosphonic acids **1** and **2** in 1.0 mol·L^{-1} H_2SO_4 solutions (DMSO-H_2O, 1:1).

Temp.	$10^5 \cdot k_{obs}$, s^{-1}	
K	**1**[a]	**2**[b]
348	2.14 ± 0.08	0.38 ± 0.02
368	17.30 ± 0.13	0.81 ± 0.03
388	105.0 ± 0.6	2.74 ± 0.08
	E_a = 108.9 ± 6.1 kJ·mol^{-1}	E_a = 55.4 ± 3.0 kJ·mol^{-1}
	$\Delta H^{\neq}$ = 105.8 ± 5.4 kJ·mol^{-1}	$\Delta H^{\neq}$ = 52.3 ± 2.6 kJ·mol^{-1}
	$\Delta S^{\neq}$ = –31.2 ± 1.7 J·mol^{-1}·K^{-1}	$\Delta S^{\neq}$ = –201.8 ± 11.0 J·mol^{-1}·K^{-1}

[a] Conc. of **1**: 0.069 mol·L^{-1}
[b] Conc. of **2**: 0.056 mol·L^{-1}

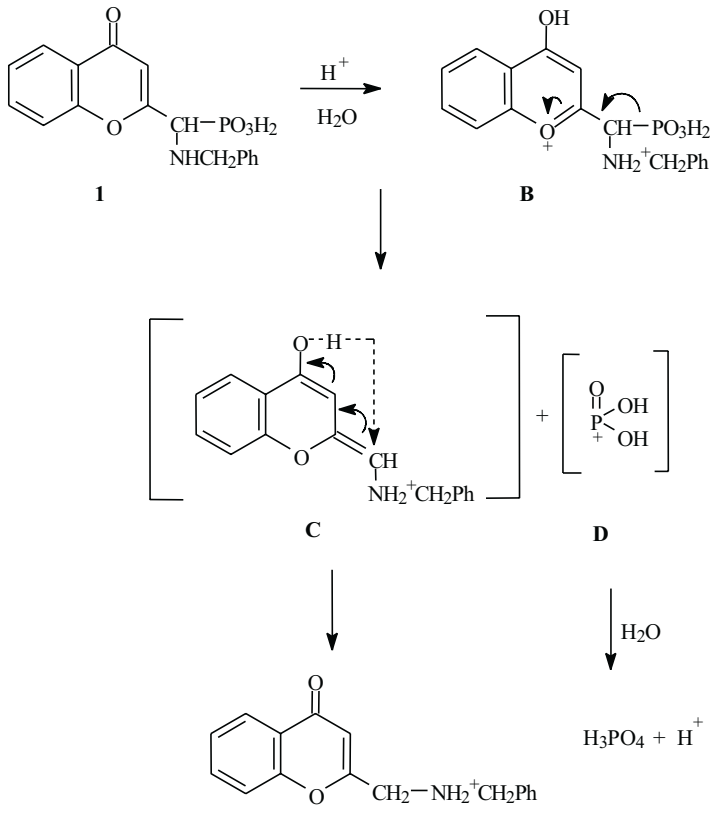
According to the data obtained (Table 2), the entropy of activation for cleavage of the **1** has a exceptionally small value. For the unimolecular reaction the $\Delta S^{\neq}$ should be near zero and for bimolecular one the $\Delta S^{\neq}$ is > –83 J·mol^{-1}·K^{-1} (> –20 e.u.) [11]. The observed $\Delta S^{\neq}$ (in this case) actually consists of $\Delta S^{\neq}$ (protonation) plus $\Delta S^{\neq}$ (cleavage). Entropies of protonation for weak oxygen bases (*i.e.* chromones and coumarins) are negative [12], and usually are ≅ –80 J·mol^{-1}·K^{-1} [13]. Therefore, the obtained small $\Delta S^{\neq}$ (–31.2 J·mol^{-1}·K^{-1}) for the cleavage of **1** could support the proposed unimolecular mechanism of the cleavage of chromone-2-ylmethyl(*N*-benzylamino)phosphonic acid (**1**) in a strong acidic medium.

The high negative $\Delta S^{\neq}$ for coumarin aminophosphonic acid **2** (Table 2) can be rationally explained by exceptionally high negative entropy for protonation of the oxygen atom in **2**, due to a very low basicity of heterocyclic oxygen in coumarin derivatives.

The data obtained suggest that the phosphonate fragment can be torn off from the aminophosphonic acid molecule as a metaphosphate moiety, likewise as it was found for the cleavage of 2- and 4-pyridyl derivatives of aminomethylphosphonic acid [3,4]. Formation of the metaphosphate species in cleavage reactions of some organophosphorus compounds is well documented [6,7]. Hence, all of these data suggest that the cleavage presented here would be a next example of an electrophilic substitution of a phosphonate group by an electrophile. The proton would be such a electrophilic agent here, likewise as it was found in a previous case [3].

The evidence for a metaphosphate formation in this cleavage was found by carrying out a special experiment. Thus, when the chromone-2-yl-(*N*-benzyl-amino)methylphosphonic acid (**1**) and sulfuric acid were heated with an excess of anisole in nitromethane, the *p*-methoxyphenylphosphonic acid was isolated from the reaction mixture (among other products). Formation of this compound, which is by no doubt a result of an electrophilic substitution of the aromatic ring of anisole by the protonated metaphosphate (which can be considered as a phosphacylium type cation [10]) may be a direct proof for the existence of the metaphosphate species in this cleavage.

From these results we can sketch a general mechanistic picture of the overall process, which is shown in Scheme 2, on an example of the cleavage of chromone-2-yl-(*N*-benzyl-amino)methylphosphonic acid (**1**). The electronic demand of the protonated heterocyclic oxygen in the molecule causes a departure of a metaphosphate moiety **D** (from the protonated molecule **B)** and incorporates an electrophilic attack of electrophilic species, presumably H^+ on the α-carbon (the transition state **C**), to form the final product (amine **1a**). The formed metaphosphate species **D** can be then quenched by water to form phosphoric acid with a simultaneous regeneration of the H^+.



Scheme 2. Proposed mechanism for the cleavage of chromone-2-yl(*N*-benzylamino)methylphosphonic acid (**1**).

CONCLUSIONS

The chromone-2, coumarin-4 and pyrone-2 derivatives of aminomethylphosphonic acid undergo a C–P bond cleavage during heating with aqueous strong mineral acids. The observed cleavage bears a resemblance to a cleavage of the 2-pyridyl and 4-pyridyl derivatives of aminomethylphosphonic acid [3]. Likewise, as it was found for the pyridyl derivatives, this reaction is straight and leads to two products only; *i.e.* the corresponding heterocyclic amines and phosphoric acid. The kinetics reveals that the cleavage is an acid-catalyzed reaction. Because of the observed kinetic isotope effects, the protons are involved on the rate-determining step of the cleavage. This indicates that the reaction bears an electrophilic character and would be an example of the S_E2 type reaction. The calculated entropy of activation for the cleavage of **1** suggests, that the cleavage has a unimolecular character and proceeds with formation of a metaphosphate moiety. A direct proof for the formation of a metaphosphate in this cleavage was found by carrying out of a phosphonylation of anisole by a mixture of the aminophosphonic acid **1** and H_2SO_4, in an aprotic medium.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in DMSO-d_6, using 300.13 MHz for ^{1}H NMR, and 121.51 MHz for ^{31}P NMR spectra. G.C.-M.S. analyses were carried out with a Hewlett Packard HP 5971A apparatus, at an ionization potential of 70 eV, equipped with HP-1 capillary column. Elemental analyses were done in the Institute Laboratory of Instrumental Analysis. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200 and were uncorrected. ^{31}P NMR spectra for kinetics were recorded on a Bruker Avance TM DRX 300 MHz spectrometer (121.51 MHz), in DMSO- D_2O solutions. In the case of ^{31}P NMR spectra in non-deuterated DMSO-H_2O solutions, an external reference standard (DMSO-d_6) was used. The oxygen heterocyclic aminophosphonic acids **1**, **2**, and **3** were synthesized as described earlier [1,2].

Kinetics: The stock solutions of H_2SO_4 or D_2SO_4 in DMSO-H_2O or in DMSO-d_6-D_2O (1:1) (volume by volume) (with concentration of the acid; c = 0.5, 1.0 and 2.0 mol·L^{-1}, respectively) were prepared. The exactly weighed samples of the aminophosphonic acid **1**, **2** or **3** (usually in the range: 10–15 ±0.1 mg) and a 0.5 mL aliquot of the desired concentration of sulfuric acid were mixed in NMR tubes and thermostated at 95°C for a specified period of time (0.5, 1.0, 1.5h for the **1,** 10, 20, 30, 40 h for the **2**, and 1.0, 2.0, 3.0, 4.0 h for the **3**, respectively), then the NMR tubes were cooled and the ^{31}P NMR spectra were recorded. The rates for **1** and **2** at different temperatures (75°C and 115°C) were determined similarly. Kinetic runs were repeated three times. In all cases a pseudo-first-order dependence was obeyed very well. The obtained k_{obs} were means of each three kinetic runs and were reproducible within ± 5%.

Cleavage of the acids 1, 2 and 3 in aqueous hydrochloric acid solution. Isolation of the amines 1a, 2a and 3a.: A sample of aminophosphonic acid (**1**, **2** or **3**) (1.0 mmol) was dissolved in 20% aq. HCl (50 mL) and the solution was refluxed for 2 h in the case of **1**, for 40 h in the case of **2** and for 4 h in the case of **3**, respectively. Then, the mixture was evaporated to dryness and obtained the semi-solid residue was treated with an excees of 5% aq. sodium bicarbonate solution (20 mL). The separated oil was extracted twice with methylene chloride (25 mL), the extract was dried (anh. Na_2SO_4), filtered and evaporated to give crude amines **1a**, **2a** or **3a**, as thick oils, partially solidifying during standing. Yield; crude **1a**: 92%, crude **2a**: 74%, crude **3a**: 72%. The obtained heterocyclic amines were characterized as oxalate salts; thus, a sample of the free amine (100 mg) was dissolved in acetone (2.0 mL) and then a solution of oxalic acid (150 mg) in acetone (2.0 mL) was added. A separated white solid of the oxalate was collected by filtration and dried. The oxalates were additionally recrystallized from water (1.5–2 mL).

Oxalate of **1a**: Yield: 85 mg., m.p. 212–213°C. Lit. m.p. [1] 209–211°C. ^{1}H NMR (DMSO): 8.02 (d, 1H, J = 7.75 Hz), 7.80 (t, 1H, J = 7.15 Hz), 7.61 (d, 1H, J = 8.3 Hz), 7.51–7.28 (m, 6H, arom.), 6.47

(s, 1H, H-3), 4.03 (s, 2H, CH_2N), 3.98 (s, 2H, NCH_2). Anal. calc. for **1a**·$(COOH)_2$; $C_{19}H_{17}NO_6$ (355.333): Calc. C, 64.22; H, 4.82; N, 3.94; found: C, 63.98; H, 5.05; N, 3.81.

Oxalate of **2a**: Yield: 95 mg., mp. 208–209°C (dec.). ^{1}H NMR (DMSO): 7.79 (d, 1H, J = 7.77 Hz), 7.64 (t, 1H, J = 7.26 Hz), 7.49–7.31 (m, 7H, arom.), 6.63 (s, 1H, H-3), 4.29 (s, 2H, CH_2N), 4.12 (s, 2H, NCH_2). Anal. for **2a**·$(COOH)_2$; $C_{19}H_{17}NO_6$ (355.333): Calc. C, 64.22; H, 4.82; N, 3.94; found: C, 64.03; H, 5.01; N, 3.82.

Oxalate of **3a**: Yield 80 mg., m.p. 206–208°C (dec.). ^{1}H NMR (DMSO): 8.10 (s, 1H, H-6), 7.44–7.34 (m, 5H, arom.), 6.47 (s, 1H, H-3), 4.04 (s, 2H, CH_2N), 3.94 (s, 2H, NCH_2), 3.66 (s, 3H, OCH_3). Anal. for **3a**·$(COOH)_2$; $C_{16}H_{17}NO_7$ (335.303): Calc. C, 57.31; H, 5.11; N, 4.18; found: C, 57.18; H, 5.23; N, 4.07.

Cleavage of 1 by sulfuric acid in the presence of anisole. Isolation of 4-methoxyphenylphosphonic acid: A mixture of chromone-2-yl(*N*-benzylamino)methylphosphonic acid (**1**) (0.35 g, 1.0 mmol), anisole (1.08 g, 10 mmol) and sulfuric acid (1.0 g, 10 mmol) in nitromethane (15 mL) were refluxed for 7 h and cooled. The solid separated was filtered off, washed with 1–2 ml nitromethane and diethyl ether and dried. A white-gray product was obtained, which resulted to be a mixture of 4-methoxyphenylphosphonic acid and 4-methoxybenzenesulfonic acid, combined as a salt with the amine **1a**. Some other sulfonic derivatives of anisole were also detected. After repeated recrystallization from methanol-diethyl ether solution, a small amount of a pure 4-methoxyphenylphosphonic acid [8,9] (0.04 g) was obtained. M.p. 157–158°C. Lit. [8] m.p. 158°C. ^{1}H NMR (D_2O): 7.62 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.6 Hz), 3.72 (s, 3H, OCH_3). ^{31}P NMR (D_2O): 6.965(s).

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