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Two step acidic hydrolysis of dialkyl arylphosphonates

Nikoletta Harsági,[a] Zita Rádai,[a] Nóra Zsuzsa Kiss,[a] Áron Szigetvári[b] and György Keglevich*[a]

[a] *Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary. Fax: +361 463 3648; e-mail: gkeglevich@mail.bme.hu*

[b] *Gedeon Richter Plc., 1475 Budapest, Hungary*

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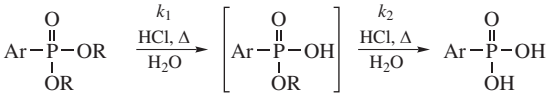
The HCl-catalyzed hydrolysis of dialkyl arylphosphonates monitored by ^{31}P NMR spectroscopy has revealed two consecutive steps characterized by pseudo first order rate constants k_1 and k_2. A reactivity order for the two steps and for the overall two step hydrolysis has been derived depending on the alkoxy and aryl substituents. Besides the $A_{Ac}2$ mechanism, the $A_{Al}1$ route has been substantiated for the Pr^{i}O substituent.



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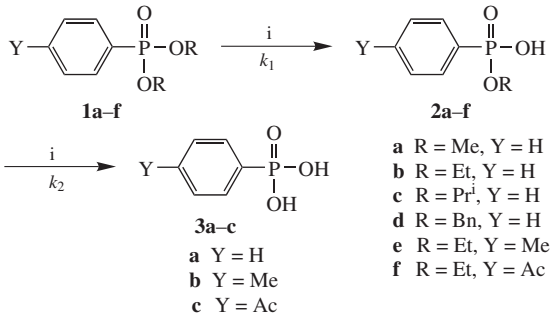
The hydrolysis of phosphinic, phosphonic and phosphoric acid esters (P-esters), being somewhat analogous to that of carboxylates, is of definite synthetic importance.[1,2] Mostly, the acid-catalyzed hydrolysis carried out in aqueous hydrochloric acid at the boiling point is the method of choice. Typically, the hydrolyses have not been optimized in terms of the amount of hydrochloric acid and the reaction time.[3–6] For example, the 'hydrolysis' of diethyl arylphosphonates was performed in six equivalents of conc. HCl at the boiling point for 12 h to afford the corresponding arylphosphonic acids in yields of 71–93%.[7] It is also possible to perform hydrolyses using aqueous NaOH or KOH,[8,9] enzymatic hydrolysis is another option.[10] A special method for the hydrolysis is the fission of the P–O–C with trimethylsilyl bromide.[11,12]

Here, we report a study of the two step hydrolysis of a series of dialkyl arylphosphonates under acidic conditions. The effect of substituents on the rate of the two elemental reaction steps has also been evaluated.

Dialkyl arylphosphonates **1a–f** were hydrolyzed using conc. HCl (3 mmol) and water (0.5 ml) per 1 mmol of the substrate (Scheme 1). The hydrolyses were performed under reflux and monitored by ^{31}P NMR spectroscopy and LC-MS, as has been carried out for phosphinates.[13] After specified periods, aliquots were evaporated and the residues were analyzed by ^{31}P NMR and LC-MS.[†]

The experimental results are summarized in Table 1, while the concentration profiles for the hydrolysis of phosphonates **1a–f** are demonstrated in Figure 1 and Figures S1–S3 (see Online Supplementary Materials). According to expectations, the relative amount of the starting phosphonates **1a–f** decreased, while that of the phosphonic acids **3a–c** gradually increased. The concentration of the intermediate monoesters **2a–f** went through a maximum. The different instances were characterized by the time related to the maximum concentration of intermediate **2**, namely $t_{c_{max2}}$, and the time required for complete hydrolysis t_{compl}, as well as by pseudo first order rate constants k_1 and k_2, related to steps **1** → **2** and **2** → **3**, respectively.

Apparently, in the two step hydrolysis, which proceeds *via* the $A_{Ac}2$ mechanism, the formation of phosphonic acid **3a** from dimethyl ester **1a** is faster than that from diethyl ester **1b** (Table 1, entries 1 and 2). It is a general experience that hydrolysis of methyl esters of P-acids is faster than that of ethyl ones.[13] The acyl substituent in the phenyl ring in diester **1f** had only a slight accelerating effect on the rate of hydrolysis to acid **3c** (t_{compl} of 8.5 h *vs.* 9.5 h for R = Et), while the presence of methyl group in compound **1e** had a significant impact on the course of the reaction. In the latter case, hydrolysis to acid **3b** was complete within 17.5 h (Table 1, entries 6 and 5 *vs.* entry 2). Hydrolysis of diisopropyl ester **1c** was faster, and that of dibenzyl ester **1d** was much faster compared with the similar reaction for the dimethyl analogue **1a** (Table 1, entries 3 and 4 *vs.* entry 1). Fission of somewhat hindered P–O–Pr^i moiety may be enhanced by competing $A_{Al}1$ mechanism. Removal of the benzyl group in benzyl esters is known to be easy. The $t_{c_{max2}}$ values for monoesters **2a–f** mostly coinsided with the gross reactivity, and fell in the range of 5 min to 3 h.



Scheme 1 *Reagents and conditions*: i, HCl, H_2O, Δ.

[†] *General procedure for the hydrolysis of dialkyl arylphosphonates* **1a–f**. A mixture of phosphonate (3.8 mmol, **1a**: 0.75 g, **1b**: 0.80 g, **1c**: 0.90 g, **1d**: 1.3 g, **1e**: 0.90 g, **1f**: 0.95 g), conc. HCl (1.0 ml, 12.0 mmol) and water (2.0 ml) was stirred at reflux for 45 min to 17.5 h. Evaporation of the organic phase *in vacuo* and recrystallization from methanol afforded a solid residue that was analyzed by ^{31}P NMR spectroscopy and LC-MS. To monitor the hydrolyses, aliquots were taken and simply evaporated. The ^{31}P NMR and mass spectral data for phosphonates **1a–f**, phosphonic monoesters **2a–f**, and phosphonic acids **3a–c** are summarized in Table S1 (see Online Supplementary Materials).

Table 1 Experimental data for the acidic hydrolysis of dialkyl arylphosphonates **1a–f**.

Entry	Reactant	k_1/h^{-1}	$t_{c_{max2}}$/min	k_2/h^{-1}	t_{compl}/h	Final product	Yield (%)
1	**1a**	2.67	40	0.70	5.5	**3a**	95
2	**1b**	0.88	120	0.27[a]	9.5	**3a**	90
3	**1c**	2.08	35	1.33	4.5	**3a**	99
4	**1d**	23.8	5	9.36	0.75	**3a**	80
5	**1e**	0.86	180	0.16	17.5	**3b**	87
6	**1f**	0.90	105	0.35	8.5	**3c**	86

[a] Independent experiment PhP(O)(OEt)(OH) → PhP(O)(OH)$_2$ resulted in k_2 = 0.29 h^{-1}.

The gross reactivity of arylphosphonates **1a–f** in the **1** → **3** transformation changes as follows:

R/Y Bn/H ≫ Pr^i/H ≳ Me/H > Et/MeC(O) ≳ Et/H ≫ Et/Me.

The reactivity of phosphonates **1a–f** in the first (**1** → **2**) step of the hydrolysis is the following:

R/Y Bn/H ≫ Me/H > Pr^i/H > Et/MeC(O) ~ Et/H ~ Et/Me.

It is noteworthy that the hydrolysis of the second ethoxy group of phosphonate **1b** could also be performed as a neat **2b**[14] → **3a** transformation under similar conditions (Figure S3). In this case, a k_2 value of 0.29 h^{-1} was obtained, which is in excellent agreement with the value of 0.27 h^{-1} obtained from the two step experiment (see Table 1, entry 2). Considering alkyl phosphonates **1a–c**, the sterically hindered isopropyl ester **1c** was the most reactive. As suggested by the ratio of k_1/k_2 = 2.08/1.33, the reactivities of both Pr^{i}O groups are closer than that of the alkoxy groups of ethyl ester **1b** or methyl derivative **1a**, characterized by the k_1/k_2 ratios of 0.88/0.27 and 2.67/0.70, respectively. These results originate from the predominance of the $A_{Al}1$ mechanism over the $A_{Ac}2$ route for the Pr^{i}O derivative. In comparison with the unsubstituted analogue, the 4-Me group had more significant impact on the hydrolysis rate of the second EtO group than on that of the first EtO substituent (k_1/k_2 = 0.86/0.16 *vs.* k_1/k_2 = 0.88/0.27).

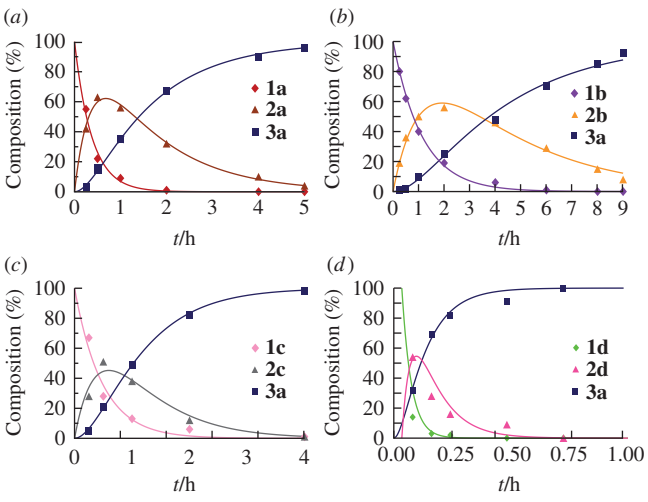


Figure 1 Concentration profiles for the components in the hydrolysis of phenylphosphonates (*a*) **1a**, (*b*) **1b**, (*c*) **1c** and (*d*) **1d** under optimized conditions. The R^2 values of goodness of fits are 0.995, 0.994, 0.979 and 0.934, respectively.

Regarding the second (**2** → **3**) step, the order of reactivity is somewhat different to that of the first (**1** → **2**) step:

R/Y Bn/H ≫ Pr^i/H > Me/H > Et/MeC(O) ~ Et/H > Et/Me.

At the same time, the gross reactivity coinsided with that observed for the hydrolysis of the second P–O–R moiety of the phosphonate. It means that the second step is the rate determining one. Thus, this is the first case when the two step acidic hydrolysis of phosphonates has been evaluated in detail and characterized quantitatively.

In summary, the course and the substituent dependence for the HCl-catalyzed two step hydrolysis of dialkyl arylphosphonates has been evaluated, and the two steps have been characterized by pseudo first order rate constants. It has been substantiated that in the case of hydrolysis of the isopropyl ester, the $A_{Al}1$ mechanism predominates over the $A_{Ac}2$ route, and that the gross reactivity follows the trend observed for the hydrolysis of the second P–O–R moiety of dialkyl arylphosphonates.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.012.

References

1 G. M. Kosolapoff and L. Maier, in *Organic Phosphorus Compounds*, J. Wiley & Sons, Inc., New York, 1973, vol. 4, pp. 264–265.
2 *Methoden der organischen Chemie (Houben-Weyl), Band E2, Phosphor-Verbindungen II*, ed. M. Regitz, Georg Thieme Verlag, Stuttgart, 1982, pp. 142–143, 310–313.
3 J. Desai, Y. Wang, K. Wang, S. R. Malwal and E. Oldfield, *ChemMedChem*, 2016, **11**, 2205.
4 K. V. Tcarkova, O. I. Artyushin and N. A. Bondarenko, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2016, **191**, 1520.
5 N. Gavande, I. Yamamoto, N. K. Salam, T.-H. Ai, P. M. Burden, G. A. R. Johnston, J. R. Hanrahan and M. Chebib, *ACS Med. Chem. Lett.*, 2011, **2**, 11.
6 P. Haake and G. Hurst, *J. Am. Chem. Soc.*, 1966, **88**, 2544.
7 G. Keglevich, A. Grün, A. Bölcskei, L. Drahos, M. Kraszni and G. T. Balogh, *Heteroat. Chem.*, 2012, **23**, 574.
8 J. Rahil and P. Haake, *J. Org. Chem.*, 1981, **46**, 3048.
9 A. E. Wróblewski and J. G. Verkade, *J. Am. Chem. Soc.*, 1996, **118**, 10168.
10 R. Ray, L. J. Boucher, C. A. Broomfield and D. E. Lenz, *Biochim. Biophys. Acta, Gen. Subj.*, 1988, **967**, 373.
11 C. J. Salomon and E. Breuer, *Tetrahedron Lett.*, 1995, **36**, 6759.
12 P. Jansa, O. Hradil, O. Baszczyňski, M. Dračínský, B. Klepetářová, A. Holý, J. Balzarini and Z. Janeba, *Tetrahedron*, 2012, **68**, 865.
13 G. Keglevich, Z. Rádai, N. Harsági, Á. Szigetvári and N. Z. Kiss, *Heteroat. Chem.*, 2017, **28**, e21394.
14 R. Henyecz, A. Kiss, V. Mórocz, N. Z. Kiss and G. Keglevich, *Synth. Commun.*, 2019, **49**, 2642.

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