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Aminophosphine oxides in a pyridine series. Studies on the cleavage of pyridine-2- and pyridine-4-yl-(*N*-benzylamino)-methyldiphenylphosphine oxides in acidic solutions

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Abstract—The synthesis and reactions of 1-(*N*-benzylamino)-1-(2-pyridyl)- and 1-(*N*-benzylamino)-1-(4-pyridyl)-methyldiphenylphosphine oxides are described. It was found that these compounds were exceptionally easy to cleave in aqueous sulfuric acid solutions to form diphenylphosphinic acid and the corresponding *N*-(pyridylmethyl)-benzylamines. The structure of a single diastereoisomer, that is, the (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-(*S*)-methyldiphenylphosphine oxide was determined by X-ray crystallography. The acidic alcoholysis of the selected model chiral pyridine aminophosphine oxides was investigated by means of ^{31}P NMR spectroscopy. The cleavage kinetics were also studied. On the basis of the obtained results, a mechanism of the cleavage was formulated.

1. Introduction

Organophosphorus compounds, aminophosphonic acids in particular, are believed to be stable, durable compounds, resistant to decomposition in both basic and acidic solutions. However, there were a few reports describing the C–P bond cleavage in some functionalized phosphonate compounds in acidic conditions.[1–8] For example, the acid-catalyzed fragmentation of aromatic α-oxyiminophosphonates was reported in the late 1980s.[1–3] Recently, an example of the oxidative cleavage of a C–P bond in 1-amino-1-(3,4-dihydroxyphenyl)-methylphosphonic acid in low pH was described.[4] First of all, we reported[5–7] that certain heterocyclic aminophosphonates were amenable to definite cleavage in acidic solutions at elevated temperatures. It mainly concerned the pyridine derivatives of aminomethylphosphonic acid, namely the pyridine-2-yl or pyridine-4-yl-(*N*-alkylamino)-methylphosphonic acids[5,6] and their esters,[5] which are easily cleaved when heated for a few hours in aqueous sulfuric, or hydrochloric acid at 95 °C. As a result, the formation of secondary *N*-(pyridylmethyl)-alkylamines and phosphoric acid (H_3PO_4) was observed. Similarly, some oxygen heterocyclic phosphonic acids, that is, the pyrone-2, chromone-2 and coumarin-4 derivatives of the aminomethylphosphonic acid were reportedly cleaved in the same manner.[7] Interestingly, we also observed[8] that the pyridine aminophosphinic acids were likewise cleaved by aqueous sulfuric acid to form the corresponding secondary pyridylamines and arylphosphonic acids. The latter cleavage proceeded quickly, even at room temperature.[8] All of these cleavages, which occurred on pyridine aminophosphonic acids and related phosphorus compounds, are illustrated in Scheme 1.

The chemical nature of these cleavage reactions still remains unclear, despite some attempts to explain it.[5–7] Therefore, these reactions became the subject of a more detailed study in our laboratory.

Particular importance was placed on pyridine aminophosphine oxides, which are suitable compounds for studying the cleavage in acidic conditions due to the exceptional ease of the C–P bond cleavage. Likewise, the actual possibility of the synthesis of certain optically active pyridine aminophosphine oxides with a definite configuration at α-carbon and (or) at phosphorus atom is of great importance in clarifying the basic questions connected with the plausible mechanism of these cleavage reactions.

Keywords: Aminophosphine oxides; Pyridine; Acidic solutions.
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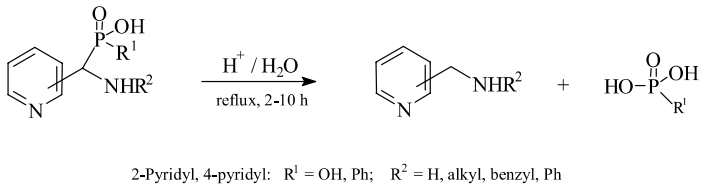


Scheme 1. Cleavage of the pyridine aminophosphonic acids in acidic solutions.

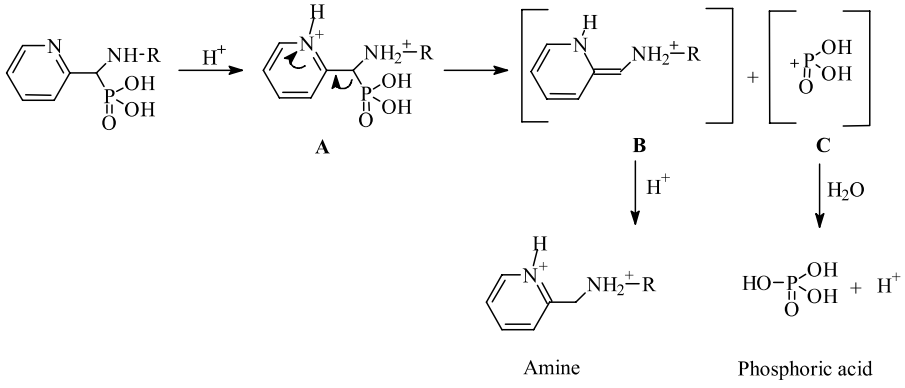
There are two main alternative mechanisms for a C–P bond breaking in the functionalized phosphonates in acidic conditions presented in the chemical literature.[2]

The first mechanism is a dissociative-type mechanism [$S_N1(P)$], which assumes the formation of a monomeric metaphosphate moiety after the rupture of a C–P bond. The metaphosphate, as a reactive intermediate, is then trapped by the solvent to form products in a nucleophilic process. The second mechanism is an associative-type mechanism [$S_N2(P)$], which involves a direct nucleophilic attack of a solvent molecule at phosphorus in the phosphonate prior to the breaking of a C–P bond. The aforementioned alternative mechanisms would be taken in consideration for the cleavage of the pyridine aminophosphonic acids on the condition that in the considered dissociative mechanism, the formed species is really 'protonated' metaphosphate moiety **C** due to the strong acidic conditions. These mechanisms are shown in Schemes 2 and 3, respectively.

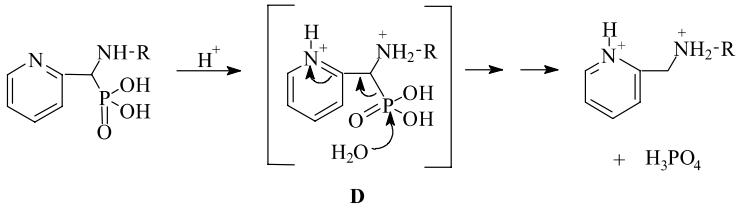
The proposed dissociative mechanism,[5,6] shown in Scheme 2, relies upon the breaking of a C–P bond in aminophosphonate **A** and the formation of two fragmentary products (**B**, **C**). One of the intermediates is an enamine-like moiety **B** and the second one is a metaphosphate-like moiety **C**. The **C** is actually the 'protonated' metaphosphate (a phosphinylium,[12,13] or phosphacylium cation[14,15]) and therefore, as a reactive intermediate, can react with solvent (water) to form a final product. The **B** fragment transforms into the amine (Scheme 2), by incorporating the proton. A driving force to trigger the cleavage is the presence of a positive charge of protonated nitrogen in the aminophosphonate **A**.

An alternative associative mechanism[6] assumes that after the preceding protonation of an oxygen atom in a phosphoryl group coincides with an attack of a solvent molecule at a positively charged phosphorus atom in the aminophosphonate **D** (Scheme 3). Further reorganization of the **D** gives the final fragmentary products as a result of the breaking of the C–P bond.

In this paper, we describe in detail the results of our studies regarding the cleavage of racemic and optically active pyridine aminophosphine oxides **4a–i** in aqueous acidic solutions. Additionally, the cleavage of aminophosphine oxides in the presence of some alcohols was explored. Also, the use of certain optically active aminophosphine oxides with defined configurations at phosphorus and α-carbon



Scheme 2. Dissociative mechanism of the cleavage of pyridine aminophosphonic acids.



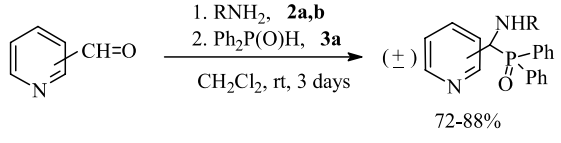
Scheme 3. Associative mechanism of the cleavage of pyridine aminophosphonic acids.

atoms was studied in order to find the final conclusions about the proposed mechanism.

2. Results and discussion

2.1. Synthesis of pyridine aminophosphine oxides

The new pyridine aminophosphine oxides were prepared from pyridinecarboxaldehydes, primary amines and phosphine oxides, according to a method described earlier.[8] Thus, treatment of the pyridinecarboxaldehydes **1a**,**b** with benzylamine **2a**, or butylamine **2b**, followed by the addition of diphenylphosphine oxide **3a**, led to the formation of racemic 1-(*N*-alkylamino)-1-(2-pyridyl)- and 1-(*N*-alkylamino)-1-(4-pyridyl)-methyldiphenylphosphine oxides **4a–d** in high yields (Scheme 4).



1a: 2-pyridyl
1b: 4-pyridyl

2a: R = $PhCH_2$
2b: R = *n*-Bu

4a: 2-pyridyl, R = $PhCH_2$
4b: 4-pyridyl, R = $PhCH_2$
4c: 2-pyridyl, R = *n*-Bu
4d: 4-pyridyl, R = *n*-Bu

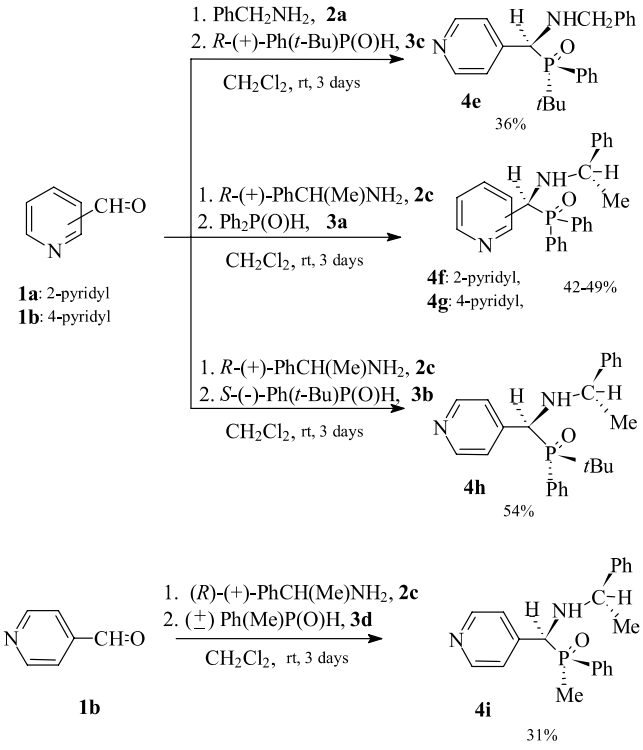
Scheme 4. Synthesis of the racemic pyridine aminophosphine oxides.

The most obvious route for the synthesis of optically active aminophosphine oxides is the addition of enantiomerically pure *P*-chiral phosphine oxides to chiral imines, or imines bearing a chiral auxiliary.[9] Thus, diastereomerically pure pyridine aminophosphine oxides **4e–h** were obtained in a sequence of reactions starting from the corresponding pyridinecarboxaldehyde **1** and enantiomerically pure (*R*)-(+)-α-methylbenzylamine (**2c**) and (*S*)-(−)-*tert*-butylphenylphosphine oxide (**3b**),[11b] or (*R*)-(+)-*tert*-butylphenylphosphine (**3c**),[11b] respectively (Scheme 5).

These reactions proceeded with significant stereoselectivity and gave a non-equal mixture of two diastereoisomers. The ratios of the stereoisomers were determined by ^{31}P NMR spectroscopy and were equal to 60:40 for **4e**, 75:25 for **4f**, 84:16 for **4g**, and 82:18 for **4h**. The separation of the major diastereoisomers was achieved by a simple crystallization from acetone to give, in each case, the prevailing diastereoisomer (Scheme 5).

Major diastereoisomers (**4e–h**) possessed with a *S* configuration on the tertiary α-carbon atom (in the methine group), according to the ^{1}H and ^{31}P NMR spectra of the aminophosphine oxides and by comparison with X-ray analysis for the diastereoisomer **4g** (Fig. 1). The predominance in the formation of the diastereoisomers with a *S* configuration at the α-carbon is in agreement with the literature data.[9]

Optically active phosphine oxides **3b** and **3c** (*S* and *R* enantiomers), used for the synthesis of aminophosphine oxides **4h** and **4e**, were obtained from racemic *tert*-butylphenylphosphine oxide[10] by resolution of the racemate with the use of (*S*)-(+)-mandelic acid, according to a method described by Drabowicz, et al.[11a]



Scheme 5. Synthesis of the optically active pyridine aminophosphine oxides.

For further cleavage studies, one more example of an optically active aminophosphine oxide, that is, the (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenylmethylphosphine oxide (**4i**), was synthesized (Scheme 5). The aminophosphine oxide was obtained from pyridine-4-carboxaldehyde (**1b**), (*R*)-(+)-α-methylbenzylamine (**2c**) and racemic phenylmethylphosphine oxide **3d**.[37,39]

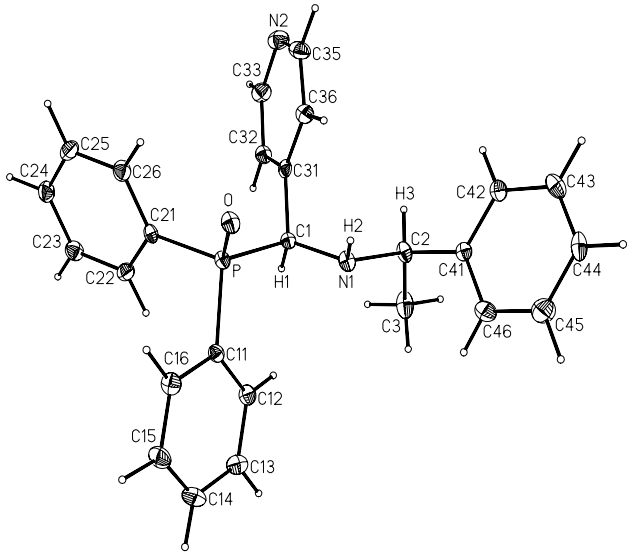


Figure 1. Structure of pyridine-4-yl-(*N*-α-methylbenzylamino)-methyldiphenylphosphine oxide **4g**.

The single diastereoisomer **4i** was isolated from the product by recrystallization from acetone.

By analogy to the preceding results, the **4i** was assigned as the stereoisomer with a *S* configuration at the α-carbon. The configuration at phosphorus was the same as in the case of **4e** (see the Sections 2.7 and 4.8.6).

In summary, all of the syntheses were carried out in dichloromethane solutions at room temperature, in a simple way, to give the diastereomerically pure pyridine aminophosphine oxides **4a–h** as crystalline solids in moderate yields.

2.2. Cleavage of pyridine aminophosphine oxides 4a–h

The cleavage of pyridine aminophosphine oxides **4a–h** occurred when the solution of these aminophosphine oxides in aqueous 10% sulfuric acid was heated at 95 °C for 2–10 h. As a result, there was the formation of the *N*-(pyridylmethyl)-alkylamines **5a–c**, **6a–c** and diphenylphosphinic acid **7**, or *tert*-butylphenylphosphinic acid **8**, respectively. Because of a low solubility of the formed phosphinic acids in the aqueous medium, the acids **7** and **8** separated from the reaction solution. In turn, amines **5a–c**, **6a–c** were isolated by extraction from alkaline reaction mixture. The overall cleavage of the **4a–h** is shown in Scheme 6.

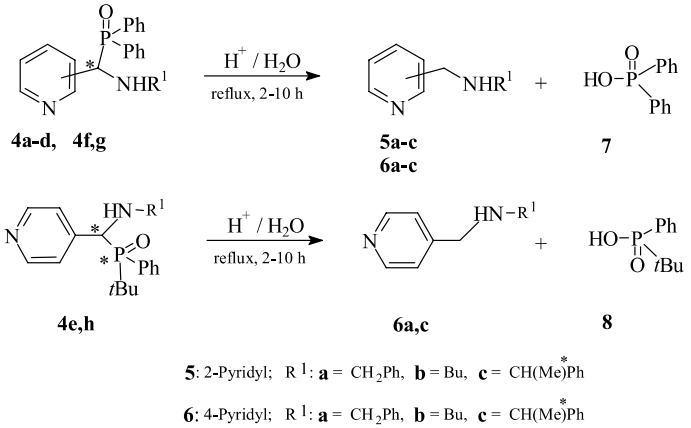
The cleavage of **4a–h** also proceeded at room temperature; however, much slower, requiring a considerable longer period of time to complete the reaction. It was found, according to the ^{31}P NMR data, that the pyridine-2 aminophosphine oxides were cleaved 3–4 times faster than corresponding pyridine-4 compounds.

2.3. Kinetic measurements

For kinetic purposes, the cleavage of the selected aminophosphine oxides (**4a**,**b**,**f**,**g**,**h**) were run in 50% (v/v) aqueous methanol solutions, containing a definite quantity of sulfuric acid. The use of aqueous methanol was to evade the precipitation of the formed phosphinic acid **7** (or **8**), during kinetic measurements. The reactions were run and measured in NMR tubes by ^{31}P NMR spectroscopy and the relative quantities of the phosphorus-containing products and starting materials were estimated from the corresponding integrated ^{31}P NMR signals. In this case, the appearance of a signal due to phosphinic acid **7** (or **8**), together with the subsequent decay of a signal corresponding to the **4** was observed. On the basis of ^{31}P NMR data, the rate constants were calculated. The measured cleavages followed pseudo-first-order kinetics. It was found that the rate constants were strongly dependent on the concentration of the sulfuric acid (entry; 1 and 2, Table 1).

The measured cleavages followed pseudo-first-order kinetics. It was found that the rate constants were strongly dependent on the concentration of the sulfuric acid (entry; 1 and 2, Table 1). It was also illustrative that the 2-pyridyl derivative **4a** underwent cleavage 3–4 times faster than the corresponding 4-pyridyl one (**4b**). The runs, which were performed in deuterated solvents and with the use of deuterated reagents, proved that the cleavages were considerably faster in solutions of common, non-deuterated acids. It was also possible to calculate the kinetic isotope effects in some cases (entry; 4, 6, 8, data for **4f**, **4g** and **4h**, Table 1). All kinetic results demonstrate that the protonation of pyridine aminophosphine oxides has a profound effect on the cleavage of C–P bonds. The kinetic isotope effects pointed out that the protons were involved on the rate-determining step of the cleavage. Such values of the kinetic isotope effects ($k_H/k_D > 2$, Table 1) rather exclude an alleged nucleophilic attack of the solvent molecule on the phosphorus atom in the aminophosphine oxide, because in such a case $k_H/k_D < 1$ should be expected (due to a higher concentration of deuterated phosphorus species in D_2O, in comparison with the concentration of the corresponding protonated ones in H_2O). The obtained rate constants are summarized in Table 1.

It is noteworthy that the rate constants were calculated from estimated ^{31}P NMR integrated signals, and therefore, these results should not be considered as exact data for mere kinetic studies. More persuasive arguments for the proposed mechanism were found during further studies on the cleavage of optically active pyridine aminophosphine oxides in methanolic solutions.



Scheme 6. Cleavage of the pyridine aminophosphine oxides in acidic solutions.

Table 1. Rate constants for cleavage of the aminophosphine oxides (**4a**,**b** and **4f**,**g**,**h**) at 20 °C

Entry	Compound	Solvent	Concn of compound mol L^{-1}	Concn of acid mol L^{-1}	Kinetic parameters	
					10^2 k_{obsd} h^{-1}	$t_{1/2}$, k_H/k_D
1	**4a**	50% Aqueous methanol	0.10	0.5 (H_2SO_4)	0.83	$t_{1/2}$[a] = 11.2 h
			0.10	1.0 (H_2SO_4)	6.17	
			0.10	2.0 (H_2SO_4)	15.08	
2	**4b**	50% Aqueous methanol	0.10	0.5 (H_2SO_4)	1.17	$t_{1/2}$[a] = 38.9 h
			0.10	1.0 (H_2SO_4)	1.78	
			0.10	2.0 (H_2SO_4)	2.78	
3	**4f**	50% Aqueous methanol	0.10	1.0 (H_2SO_4)	1.08	$t_{1/2}$ = 64.2 h
4	**4f**	50% CH_3OD in D_2O	0.10	1.0 (D_2SO_4)	0.43	$t_{1/2}$ = 161 h, k_H/k_D = 2.53
5	**4g**	50% Aqueous methanol	0.10	1.0 (H_2SO_4)	0.95	$t_{1/2}$ = 73.0 h
6	**4g**	50% CH_3OD in D_2O	0.10	1.0 (D_2SO_4)	0.30	$t_{1/2}$ = 231 h, k_H/k_D = 3.17
7	**4h**	50% Aqueous methanol	0.20	1.0 (H_2SO_4)	0.81	$t_{1/2}$ = 85.3 h
8	**4h**	50% CH_3OD in D_2O	0.20	1.0 (D_2SO_4)	0.34	$t_{1/2}$ = 202 h, k_H/k_D = 2.36

[a] $t^{1/2}$ was measured for 1 M H_2SO_4 solution.

2.4. Cleavage of (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(2-pyridyl)-(*S*)-methyldiphenylphosphine oxide (4f) and (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-(*S*)-methyldiphenylphosphine oxide (4g) in D_2O

The basic question connected with a mechanism of the considered cleavage is the formation of a highly reactive intermediate, that is, the metaphosphate, or its equivalent. The dissociative mechanism assumes the formation of such species by a rupture of a C–P bond and the elimination of a 'protonated' metaphosphate (a phosphinylium cation[12,13]) in the first stage of a reaction. In order to find out that the phosphinylium cation is formed, a trapping agent for it should be used. Usually, in aqueous solutions, the corresponding phosphinic acids were formed. If alcohol is used as a solvent, the corresponding phosphoester should be obtained. In turn, the final amine may be formed by the incorporation of a proton to an enamine-like heterocyclic fragment, or by a bimolecular process, in which, the attachment of the proton coincides with the departure of the phosphinylium cation. In this case, the amine would be formed directly, as a result of the electrophilic substitution of the phosphorus moiety.

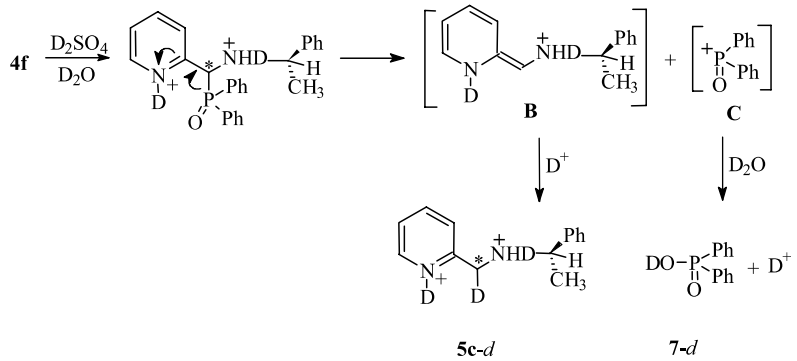
On the other hand, the cleavage might be caused by a direct nucleophilic attack of the solvent on a phosphorus atom with a positive charge in the aminophosphine oxide molecule. Such displacement might be considered a nucleophilic substitution occurring at phosphorus in the aminophosphine oxide.

It was described[14–16] that the heterolytic cleavage of a bond between phosphorus and a leaving group, occurring on a chiral center, should lead to the formation of racemic products, in the case of a dissociative mechanism. Likewise, the inversion of the configuration at phosphorus should be observed in the case of a bimolecular, associative mechanism, that is, the nucleophilic substitution of a phosphorus atom.[15,16]

The questions that arise with the mechanism of the present cleavage could be answered by the use of appropriate optically active aminophosphine oxides. Therefore, we took the aminophosphine oxides (**4f**, **4g**) into account for further studies. The cleavage of **4f** and **4g** was invoked by D_2SO_4 in D_2O solutions. The use of D_2SO_4 should generate an additional stereogenic center at the α-carbon of the formed amine due to formation of the CHD group. One might expect that the cleavage of aminophosphine oxide by the elimination of phosphorus moiety should lead to racemization at the α-carbon in the amine due to the formation of a planar, imine-like intermediate. Such a course of reaction is illustrated in Scheme 7 for the cleavage of **4f** and the formation of the deuterated amine **5c–d**, via the intermediate **B**.

The experiments have demonstrated that the cleavages of **4f** and **4g** led to the racemization at the α-carbon (as shown by ^1H NMR spectra of the formed amines).

Signals attributed to the CHD groups in the amines **5c–d**, **6c–d**, with deuterium incorporated can be easily



Scheme 7. Mechanism of the cleavage of aminophosphine oxide **4f** in D_2SO_4 solution.

rationalized by analyzing the corresponding ^{1}H NMR spectra. The ratios of the formed diastereoisomers were determined from ^{1}H NMR signals of the CHD groups. A similar question was exploited by Japanese researchers[17] and others[18] for some titanium, and chromium complexes of deuterated benzylamine derivatives, where the proper ratio of the diastereoisomers with the incorporated deuterium were calculated from integrated ^{1}H NMR signals.

These results support a dissociative mechanism, at least in the case of **4f** and **4g**, which is connected with the formation of a phosphinylium species (**C**, Scheme 7).

The four-coordinate phosphinylium cation **C** that is assumed to be formed in the first stage of the fragmentation of the **4f** and **4g** is closely associated with the monomeric metaphosphate ($HOPO_2$), which is well-known. The metaphosphate and its chemistry is also the subject of two reviews.[19,20] First of all, the metaphosphate, as transient species, is postulated as the putative intermediate in biological phosphoryl-transfer reactions[20] and in many fragmentations of organophosphorus compounds.[19,20]

2.5. Cleavage of 1-(*N*-benzylamino)-1-(2-pyridyl)-methyldiphenylphosphine oxide (4a) in aqueous solutions of different alcohols

One of the commonly accepted diagnostic tests for an involvement of metaphosphate, is phosphorylation of alcohols, especially hindered alcohols,[19–21] or amines.[22] The metaphosphate ($ROPO_2$) is considered a strong electrophile,[19] and therefore, it takes place in an aromatic substitution, coinciding with an activated aromatic ring.[23] This criterion was examined in the present work by the cleavage of the representative aminophosphine oxide **4a**, in aqueous solutions of different alcohols. The formation of phosphoesters (i.e., the corresponding alkyl esters of diphenylphosphinic acid, in this case) was expected if the 'protonated' metaphosphate (a phosphinylium cation) was involved in the cleavage.

The cleavages of **4a** were carried out in 50% aqueous solutions of various alcohols. The solutions containing methanol, ethanol, isopropanol, or *tert*-butanol and a definite amount of sulfuric acid were used. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. The solutions were kept for 2 weeks at room temperature to complete the reaction and then worked-up to isolate the products. The products were phosphinic alkyl esters **9a–d**, *N*-(2-pyridylmethyl)-benzylamine (**5a**) and diphenyl-phosphinic acid (**7**). The structures of the phosphoesters **9a–d** were established on the basis of their literature data.[27–32] A course of the reaction is shown in Scheme 8.

Due to the steric effects linked with a particular alcohol, the yield of the phosphoesters should fall in this order: MeOH > EtOH > *i*-PrOH > *t*-BuOH. This is seen in the present case.

The formation of the phosphoesters confirms the assumed dissociative mechanism of the cleavage of the aminophosphine oxide **4a**. The formation of the **9a–d** and diphenylphosphinic acid **7**, with the amounts corresponding to the molar ratio of alcohol and water, additionally verifies this assumption. These results exclude an alternative associative mechanism, at least in the case of the aminophosphine oxide **4a**.

More convincing proof for the proposed mechanism of the cleavage should come from the cleavage of the *P*-chiral aminophosphine oxide **4e**.

2.6. Methanolysis of (+)-1-(*N*-benzylamino)-1-(4-pyridyl)-(*S*)-methyl-*t*-butylphenyl-(S_P)-phosphine oxide (4e)

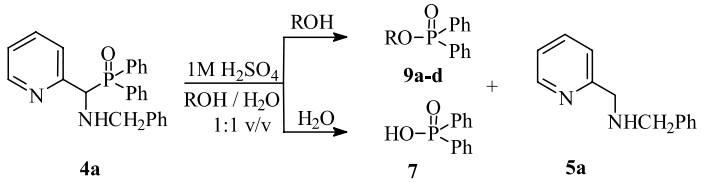
The phosphinylium species, which is allegedly formed in the case of the cleavage of a *P*-chiral aminophosphine oxide, should lead to the formation of racemic products, that is, the formation of the racemic methyl phosphoester when the cleavage is carried out in methanol. On the contrary, if the product is formed by a bimolecular process (a nucleophilic substitution at phosphorus), the formed phosphoester should exhibit optical activity (an inversion of configuration is expected in this case).

In order to verify such a hypothesis, the *P*-chiral, aminophosphine oxide **4e** was cleaved by 1 M sulfuric acid in methanol.

The projected cleavages were carried out at room temperature. The reactants were kept for a month to accomplish the reaction. Surprisingly, the major products found and isolated from the reaction mixtures were starting reagents; that is, the phosphine oxide **3c** and the imine **11** (see the Scheme 9). The expected phosphoester **10** was formed in a minimal amount.

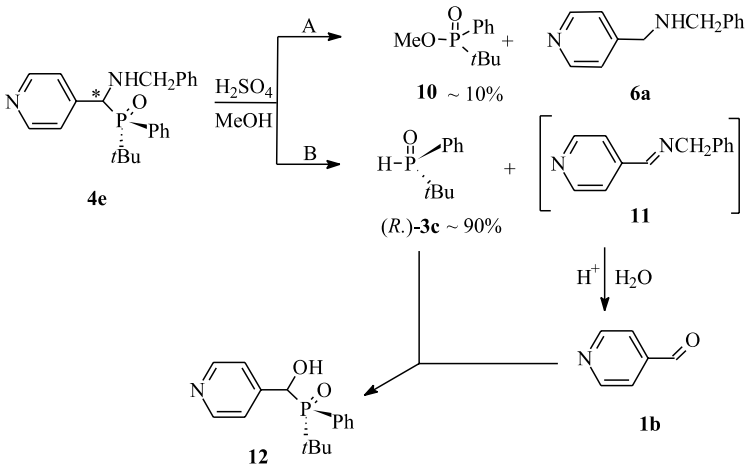
The cleavage was in fact a reverse reaction of the formation of pyridine aminophosphine oxide **4e**. Such a reaction was observed only in pure methanol, in the presence of sulfuric acid.

During work-up, the formed products underwent further transformations. The imine **11** decomposed to aldehyde **1b**,



9a: R = Me, **9b**: R = Et, **9c**: R = *i*Pr, **9d**: *t*Bu

Scheme 8. Cleavage of the pyridine aminophosphine oxide **4a** in 50% aqueous alcohols.



Scheme 9. Cleavage of the pyridine aminophosphine oxide **4e** in pure methanol.

which partially reacted with phosphine oxide **3c** to give the pyridine hydroxyphosphine oxide **12**, as a final, stable product (see the Scheme 9).

In this case, there are two competitive reactions, shown in the Scheme 9, relying upon the site of an attack of an electrophile in the aminophosphine oxide **4e**. If a proton attacks the α-carbon, it should lead to methyl ester **10** (pathway A, Scheme 9) via the elimination of metaphosphate-like moiety. In the second case, while the proton attacks the phosphorus atom (pathway B, Scheme 9), such a process should give the phosphine oxide **3c** by the elimination of the imine **11** (see the Scheme 10).

It was assumed[15,16] that the heterolytic bond cleavage between phosphorus and carbon would lead to the formation of the products with a retained configuration. It happened in the considered case, where the substitution at phosphorus caused the formation of *t*-butylphenylphosphine oxide **3c**, with the retained configuration. Such a pathway seems to be preferable for the pyridine aminophosphine oxides with a bulky group at phosphorus, demonstrating a large steric effect, as for example, the *tert*-butyl group.

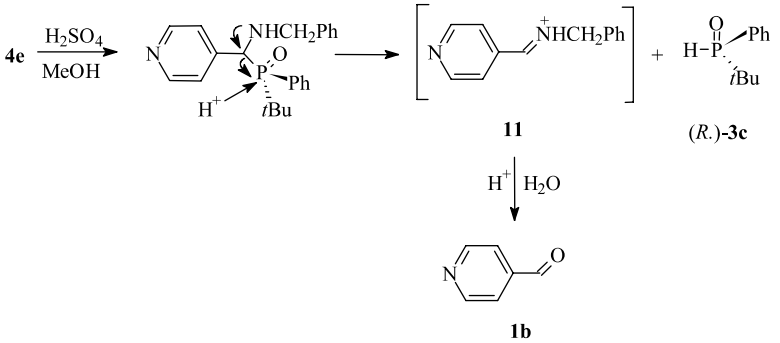
The expected methyl *t*-butylphenylphosphinate (**10**)[11a,33–36] was also formed, but the quantity was very low. Due to the small amount of ester, isolation and the measurement of the optical activity of **10** was hard to realize. In order to avoid such difficulties, we turned to another optically active aminophosphine oxide **4i**, which ended up being more suitable for the isolation of the corresponding phosphoester. The aminophosphine oxide **4i** comprised the methyl and phenyl groups at phosphorus, which should not offer such steric obstacles responsible for the pathway B.

2.7. Methanolysis of the (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenylmethylphosphine oxide (4i)

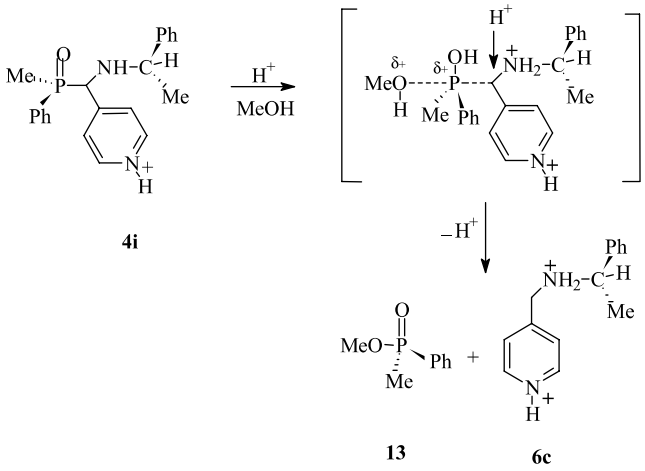
The optically active aminophosphine oxide **4i**, $\{[\alpha]^{20}_D$ +33.0 (*c* 1.0, $CHCl_3$)} was cleaved in the methanolic solution of sulfuric acid. Likewise, as in the previous case, the phosphine oxide **3d**[37,39] and methyl phosphoester **13**,[40,41] together with the corresponding amine **6c** and aldehyde **1b**, were isolated from the reaction mixture (see the Scheme 11).

The ester **13** and phosphine oxide **3d** were formed roughly in a molar ratio equal to 1:1.

After the separation of the ester **13** and phosphine oxide **3d**, the corresponding optical rotations of the **3d** and **13** were measured. Phosphine oxide **3d** showed the optical activity $\{[\alpha]^{20}_D$ +26.0 (*c* 0.4, $CHCl_3$)}, likewise as did the ester **13**, which has the optical activity $\{[\alpha]^{20}_D$ +20.0 (*c* 0.4, $CHCl_3$)}. The formation of the optically active ester **13** indicates that the cleavage of **4i** is a complex process, having among other things a bimolecular character (Scheme 11).



Scheme 10. Substitution at phosphorus in **4e** (pathway B).



Scheme 11. Cleavage of the pyridine aminophosphine oxide **4i** in pure methanol.

In the transition state (Scheme 11), methanol is displacing the enamine-like moiety in the **4i**, which is attached to a phosphorus atom, in the bimolecular process. However, the decrease of the optical activity of the ester indicates that a partial racemization of the product also occurred during the cleavage. The enantiomerically pure (+)-(R_P)-methyl phenylmethylphosphinate[40,41] (**13**) has the specific rotation: $[\alpha]^{20}_D$ +45.2 (*c* 3.7, MeOH).[41]

Aminophosphine oxides possessing aliphatic, or more basic groups at phosphorus (**4e**, **4i**) are more preferential for the bimolecular process, involving an attack of the proton on the α-carbon and the simultaneous formation of the phosphoester by an interaction of methanol with a positively charged phosphine oxide moiety. In turn, the corresponding phosphine oxide (**3c** or **3d**) is formed in a parallel process, involving an attack of the proton at phosphorus.

Examining the cleavage of amino-diphenylphosphine oxides **4a**, **4f** and **4g**, possessing electron-withdrawing groups at phosphorus, it looks that the monomolecular, dissociative mechanism is preferable there.

3. Conclusions

A series of racemic and optically active pyridine aminophosphine oxides were prepared by the addition of the phosphine oxides to chiral and achiral pyridine aldimines. The obtained pyridine aminophosphine oxides were easily cleaved in acidic solutions to form the corresponding *N*-(pyridylmethyl)-benzylamines and aryl(alkyl)phosphinic acids. The cleavage of pyridine aminophosphine oxides was studied in different solutions, containing water, deuterium oxide and various alcohols, respectively. The obtained results demonstrated that the cleavage was a dissociative process and proceeded via a phosphinylium cation stage, in the case of the pyridine aminodiphenylphosphine oxides **4a** and **4b**. In the case of aminophosphine oxides **4e** and **4i**, possessing bulky groups at phosphorus, the cleavage in methanol underwent by two parallel, different ways. It was found that the main products were initial *t*-butyl- and methylphenylphosphine oxides, with the retention of the configuration at phosphorus. In the case of **4i**, the corresponding phosphoester **13** was also formed, with the inversion of the configuration.

The *t*-butylphosphine oxide (**3c**) was formed in an action of the proton on the phosphorus atom in the hindered aminophosphine oxide **4e**, accompanied by the elimination of the corresponding aldimine.

The formation of methyl phosphoester **13** with the inversion of the configuration at phosphorus indicates that, in the case of **4i**, the cleavage had a bimolecular character, and a prospective formation of the metaphosphate-like moiety was doubtful. However, a partial loss of the optical activity of the formed ester suggested that the dissociative mechanism was possible to some extent.

The results showed that the presented cleavages of the pyridine aminophosphine oxides have had diversified mechanisms depending on the chemical nature of the groups attached to phosphorus.

4. Experimental

4.1. General

^{1}H and ^{31}P NMR spectra were measured on a Bruker Avance 300 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. GC/MS analyses were determined on a Hewlett Packard 5890 II gas chromatograph (HP-5, 25 m capillary column) with a Hewlett Packard mass spectrometer 5971 A (EI, 70 eV) and on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI+ Q1MS). Optical rotations were measured at 589 nm using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Melting points were determined using an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and were uncorrected. Elemental analyses were done in the Laboratory of Instrumental Analysis in the Institute. Thin-layer chromatography analyses were performed on silica gel 60 precoated plates (Merck). Reagents used were obtained from the Sigma–Aldrich Company (Poznań, Poland). Solvents were of commercial quality and purchased from a local supplier (POCh Gliwice, Poland).

Racemic methylphenylphosphine oxide **3d**[37] was prepared from ethyl methylphosphinate[38] according to the procedure described in.[39]

Resolution of the racemic *t*-butylphosphine oxide was done by the method described by Drabowicz et al.[11a]

4.2. Procedure for preparation of racemic pyridine aminophosphine oxides 4a–d

To a solution of pyridine aldehyde (**1a** or **1b**; 1.07 g, 10 mmol) in dichloromethane (25 mL) benzylamine (**2a**; 1.07 g, 10 mmol), or butylamine (**2b**; 0.73 g, 10 mmol) was added, respectively, and a mixture was left for 24 h at room temperature. After this, anhydrous sodium sulfate (5 g) was added, followed by addition of diphenylphosphine oxide

(**3a**; 2.02 g, 10 mmol). The whole mixture was left for 24 h and filtered. Filtrate was evaporated to dryness and an oily residue was kept at 60 °C for 2 h to finish up the reaction. Solidified products were crystallized from acetone (25 mL); (4-pyridyl derivatives), or from a mixture of toluene and hexane (1:1 v/v, 25 mL); (2-pyridyl derivatives). After cooling separated crystals were filtered off, washed with hexane and dried to give the racemic pyridine aminophosphine oxides **4a**–**d**.

4.2.1. Compound 4a. White solid, 3.50 g, yield 88%, mp 120–122 °C, lit.[8] 102–104 °C. Spectroscopic data consistent with that reported.[8]

4.2.2. Compound 4b. White solid, 2.87 g, yield 72%, mp 158–160 °C, lit.[8] 148–149 °C. Spectroscopic data consistent with that reported.[8]

4.2.3. Compound 4c. White solid, 2.95 g, yield 81%, mp 100–102 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.37 (1H, d, J=4.8 Hz, 6-Py*H*); 7.84–7.08 (13H, m, Py*H*, Ar*H*); 4.72 (1H, d, J=13.3 Hz, C*H*–P); 2.59–2.43 (2H, m, NCH_2); 1.41 (2H, m, CH_2); 1.23 (2H, m, CH_2); 0.81 (3H, t, J=7.3 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 29.62 (s). IR, ν_{max} (KBr): 3387 (NH); 3039; 2916; 2806; 1578; 1471; 1428; 1146 (P=O); 1108; 1037; 990; 831; 744; 733 (P–C); 690; 634; 611; 549; 511 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_2OP$, requires C, 72.51; H, 6.92; N, 7.69; P, 8.45. Found: C, 72.21; H, 6.98; N, 7.54; P, 8.43%.

4.2.4. Compound 4d. White solid, 3.13 g, yield 86%, mp 145–147 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.43 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.85 (2H, m, 3,5-Py*H*); 7.62–7.21 (10H, m, Ar*H*); 4.56 (1H, d, J=12.7 Hz, C*H*–P); 2.53–2.41 (2H, m, NCH_2); 1.40 (2H, m, CH_2); 1.23 (2H, m, CH_2); 0.83 (3H, t, J=7.3 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 30.52 (s). IR, ν_{max} (KBr): 3297 (NH); 3046; 3006; 2973; 2808; 1582; 1493; 1455; 1326; 1154 (P=O); 1112; 987; 835; 772; 732 (P–C); 681; 641; 558; 512; 491 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_2OP$, requires C, 72.51; H, 6.92; N, 7.69; P, 8.45. Found: C, 72.31; H, 7.08; N, 7.55; P, 8.52%.

4.3. Procedure for preparation of optically active pyridine aminophosphine oxides 4e–h

To a solution of pyridine aldehyde (**1a** or **1b**; 1.07 g, 10 mmol) in dichloromethane (25 mL) benzylamine (**2a**; 1.07 g, 10 mmol), or (*R*)-(+)-α-methylbenzylamine (**2c**; 1.21 g, 10 mmol) was added, respectively, and a mixture was left for 48 h at room temperature. Then, the solution was dried (anh. Na_2SO_4), filtered, and diphenylphosphine oxide (**3a**; 2.02 g, 10 mmol), or (*S*)-(−)-*tert*-butylphenylphosphine oxide[11] **3b**, 1.82 g, 10 mmol, $[\alpha]^{20}_D$ −24.8 (*c* 1.0, $CHCl_3$), or (*R*)-(+)-*tert*-butylphenylphosphine[11] **3c**, 1.82 g, 10 mmol, $[\alpha]^{20}_D$ +24.6 (*c* 1.0, $CHCl_3$) was added, respectively. The formed solution was left for 24 h and evaporated to dryness to give an oily residue, which was kept for 2 h at 60 °C. After this, the oil turned to a whitish solid. The solid was dissolved in warm acetone (25 mL) and the solution was kept at room temperature for several hours. The product crystallized out from the solution. The product was collected by filtration and dried. If necessary, the crystallization from acetone was repeated. In the case of 4-pyridyl derivative, the product **4g** was crystallized from a mixture of methylene chloride and hexane (1:1, v/v), while in the case of 2-pyridyl derivative **4f**, the crude product was treated first with warm acetone (5 mL) in order to remove an unsoluble by-product (the 1-hydroxy-1-(2-pyridyl)-methyl-diphenyl-phosphine oxide). The filtrate was evaporated to dryness and the residue was recrystallized from methylene chloride and hexane (1:1, v/v).

The remaining mother solution was evaporated to give a product, composed with two stereoisomers, in which the *R*,*R* stereoisomer was predominant over of the *S*,*R* one.

4.3.1. Compound 4e. White solid, 1.36 g, yield 36%, mp 162–165 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.55 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.60 (2H, m, 3,5-Py*H*); 7.50–6.86 (10H, m, Ar*H*); 4.05 (1H, d, J=7.6 Hz, C*H*–P); 3.62 (1H, d, J=13.4 Hz, NCH_2); 3.22 (1H, d, J=13.4 Hz, NCH_2); 2.22 (1H, br s, N*H*), 0.79 (9H, d, J=14.6 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 50.15 (s). IR, ν_{max} (KBr): 3350; 3259 (NH); 3028; 2961; 2868; 1593; 1495; 1437; 1165 (P=O); 1105; 818; 743 (P–C); 699; 640; 554; 490 cm^{-1}. $[\alpha]^{20}_D$ +2.1 (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{23}H_{27}N_2OP$, requires C, 72.99; H, 7.19; N, 7.40; P, 8.18. Found: C, 72.81; H, 7.28; N, 7.25; P, 8.22%.

4.3.2. Compound 4f. White solid, 1.73 g, yield 42%, mp 135–137 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.34 (1H, d, J=4.8 Hz, 6-Py*H*); 7.95–7.87 (4H, m, Py*H*, Ar*H*); 7.55–7.40 (9H, m, Ar*H*); 7.20–7.15 (2H, m, Ar*H*); 7.13–7.05 (3H, m, Ar*H*); 4.76 (1H, d, J=13.5 Hz, C*H*–P); 3.51 (1H, q, J=6.5 Hz, C*H*); 3.23 (1H, br s, N*H*); 1.30 (3H, d, J=6.5 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 31.37 (s). IR, ν_{max} (KBr): 3439 (NH); 3053; 3005; 2926; 2875; 2808; 1601; 1584; 1566; 1470; 1447; 1437; 1431; 1375; 1309; 1262; 1186 (P=O); 1119; 1101; 1067; 1048; 1038; 1030; 993; 912; 831; 747; 738 (P–C); 722 (P–C); 693; 639; 606; 555; 515; 487 cm^{-1}. $[\alpha]^{20}_D$ +29 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_2OP$, requires N, 6.79; P, 7.51. Found: N, 6.49; P, 7.28%.

4.3.3. Compound 4g. White solid, 2.02 g, yield 49%, mp 174–176 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.39 (2H, d, J=4.7 Hz, 2,6-Py*H*); 7.96 (2H, dd, J=4.7, 3.1 Hz, 3,5-Py*H*); 7.64–7.02 (15H, m, Ar*H*); 4.61 (1H, d, J=11.2 Hz, C*H*–P); 3.62 (1H, q, J=6.4 Hz, C*H*); 2.59 (1H, br s, N*H*); 1.29 (3H, d, J=6.4 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 32.22 (s). IR, ν_{max} (KBr): 3337 (NH); 3057; 3026; 2973; 2848; 2808; 1590; 1560; 1494; 1469; 1451; 1436; 1378; 1326; 1176 (P=O); 1121; 1102; 1070; 1025; 991; 833; 795; 773; 742 (P–C); 723 (P–C); 691; 639; 603; 559; 531; 514; 495 cm^{-1}. $[\alpha]^{20}_D$ +79 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_2OP$, requires N, 6.79; P, 7.51. Found: N, 6.60; P, 7.77%.

4.3.4. Compound 4h. White solid, 2.12 g, yield 54%, mp 210–212 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.21 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.44 (2H, d, J=5.9 Hz, 1.7 Hz, 3,5-Py*H*); 7.20–7.05 (10H, m, Ar*H*); 4.51 (1H, d, J=8.3 Hz, C*H*–P); 3.43 (1H, q, J=6.4 Hz, C*H*); 2.65 (1H, br s, N*H*); 1.31 (9H, d, J=15.0 Hz, *t*-Bu); 1.24 (3H, d, J=6.4 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 48.97 (s). IR, ν_{max} (KBr): 3351 (NH); 3064; 2967; 2868; 1592; 1557; 1459;

1437; 1162 (P=O); 1105; 822; 752 (P–C); 698; 642; 557; 492 cm^{-1}. $[\alpha]^{20}_D$ +121.8 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{24}H_{29}N_2OP$, requires N, 7.14; P, 7.89. Found: N, 7.01; P, 7.87%.

4.4. Procedure for preparation of optically active pyridine aminophosphine oxide 4i

To a solution of pyridine-4-carboxaldehyde (**1b**; 250 mg, 2.34 mmol) in dichloromethane (25 mL) (*R*)-(+)-α-methylbenzylamine **2c** (280 mg, 2.34 mmol) was added and a mixture was left for 48 h at room temperature. Then, the mixture was dried (anh. Na_2SO_4), filtered, and the racemic methylphenylphosphine oxide **3d** (330 mg, 2.35 mmol) was added. The solution was refluxed for 4 h and left for 24 h. After evaporation of the solvent, an oily product was obtained (840 mg). The product was dissolved in warm acetone (10 mL) and refrigerated. After several hours, white crystals separated out, which were then collected by filtration and dried on air. The obtained product was a pure stereoisomer **4i**, according to the NMR data.

4.4.1. Compound 4i. White solid, 252 mg, yield 31%, mp 138–140 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.41 (2H, d, *J*=4.3 Hz, 2,6-Py*H*); 7.53–7.53–7.40 (5H, m, Py*H*, Ar*H*); 7.19–6.95 (8H, m, Ar*H*); 4.06 (1H, d, *J*=13.5 Hz, C*H*–P); 3.48 (1H, q, *J*=6.45 Hz, C*H*); 1.86 (1H, br s, N*H*); 1.59 (3H, d, *J*=15.3 Hz, P–CH_3); 1.17 (3H, d, *J*=6.45 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 39.11 (s). IR, ν_{max} (KBr): 3265 (NH); 3051; 2955; 2810; 1588; 1437; 1160 (P=O); 1105; 820; 751 (P–C); 695; 641; 552 cm^{-1}. $[\alpha]^{20}_D$ +33.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2OP$, requires C, 71.98; H, 6.62; N, 8.00; P, 8.84. Found: C, 71.81; H, 6.75; N, 7.88; P, 8.72%.

4.5. Cleavage of pyridine aminophosphine oxides 4a–h and isolation of the products

A sample of pyridine aminophosphine oxide **4a**–**h** (1.0 mmol) was dissolved in 10% aqueous H_2SO_4 solution (10 mL) and heated at 95–100 °C for 2 h for 2-pyridyl derivatives, or 10 h for 4-pyridyl derivatives. The reaction mixture was allowed to stand at room temperature for 24 h in order to separate the phosphinic acids (**7** or **8**). Crystals of the phosphinic acids were collected by filtration and dried on air. Yield of the **7**: 67–90% diphenylphosphinic acid **7** is a known, commercial compound and its data are given elsewhere.

4.5.1. *t*-Butylphenylphosphinic acid 8. Crystalline solid, yield 131–143 mg, 66–72% (depending from the experiment), mp 157–158 °C, lit.[24] 154–156 °C, lit.[26] 155–157 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.75–7.69 (2H, m, Ar*H*); 7.49–7.43 (1H, m, Ar*H*); 7.39–7.33 (2H, m, Ar*H*); 5.67 (br s, 1H, PO*H*); 1.03 (9H, d, *J*=15.7 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 54.178 (s). ^{31}P NMR; δ_P (DMSO; 121.5 MHz): 49.883 (s).

Spectroscopical and physico-chemical data of the *t*-butylphenylphosphinic acid **8** were in agreement with the literature data.[24–26]

4.5.2. Amines 5a–c, 6a–c. The remained filtrate was alkalized with an excess of aqueous sodium bicarbonate solution and extracted with methylene chloride (25 mL). Evaporation of the extract gave the crude amines **5a–c** and **6a–c**, which were characterized as oxalate salts. The oxalates were obtained by a following way; the crude amine dissolved in acetone (5 mL) and oxalic acid [$(COOH)_2 \cdot 2H_2O$ (0.25 g, 2 mmol)] in acetone (5 mL) was added and the mixture refrigerated. The separated precipitate was filtered, washed with acetone and dried on air.

The spectroscopic data for *N*-(pyridylmethyl)-benzyl(butyl)amines **5a**,**b** and **6a**,**b** are consistent with those reported.[5,8] The amines **5c** and **6c** are new compounds and their spectroscopic data are given below.

4.5.2.1. *N*-(2-Pyridyl-methyl)-(*R*)-(+)-α-methylbenzyl amine 5c. Compound **5c** oxalate; white solid, 229 mg, yield 76%, mp 135–137 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 8.46 (1H, d, *J*=4.5 Hz, 6-Py*H*); 7.79 (1H, dt, *J*=1.65, 7.8 Hz, 4-Py*H*); 7.44–7.28 (7H, m, Py*H*, Ar*H*); 4.43 (1H, q, *J*=6.9 Hz, C*H*CH_3); 4.20 (1H, d, *J*=14.3 Hz, NCH_2); 4.05 (1H, d, *J*=14.3 Hz, NCH_2); 1.64 (3H, d, *J*=6.9 Hz, CH_3). $[\alpha]^{20}_D$ +9.0 (*c* 1.0, H_2O).

For GC/MS analysis, a sample of oxalate (50 mg) was treated with 10% aqueous solution of Na_2CO_3 (3 mL), extracted with 5 mL CH_2Cl_2, the extract dried (anh. Na_2SO_4) and evaporated to give the free amine **5c**, as an oil (31 mg). GC/MS (HP-5 column, 25 m, temperature program; 100/6/290): t_R (retention time)=10.41 min; *m*/*z* (EI, 70 eV): 212 (0.1, M^+), 211 (1, M−1), 197 (18), 180 (3), 135 (5), 120 (76), 105 (19), 93 (100), 92 (28), 79 (8), 77 (10), 65 (10), 51 (5%).

4.5.2.2. *N*-(4-Pyridyl-methyl)-(*R*)-(+)-α-methylbenzyl amine 6c. Compound **6c** oxalate; white solid, 208 mg, yield 69%, mp 178–181 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.80 (2H, d, *J*=6.7 Hz, 2,6-Py*H*); 7.62 (2H, d, *J*=6.7 Hz, 3,5-Py*H*); 7.36 (5H, br s, Ar*H*); 4.44 (1H, q, *J*=6.9 Hz, C*H*CH_3); 4.37 (1H, d, *J*=14.8 Hz, NCH_2); 4.15 (1H, d, *J*=14.8 Hz, NCH_2); 1.62 (3H, d, *J*=6.9 Hz, CH_3). $[\alpha]^{20}_D$ +4.0 (*c* 1.0, H_2O).

For GC/MS analysis, a sample of oxalate (50 mg) was treated with 10% aqueous solution of Na_2CO_3 (3 mL), extracted with 5 mL CH_2Cl_2, the extract dried (anh. Na_2SO_4) and evaporated to give the free amine **6c**, as an oil (28 mg). GC/MS (HP-5 column, 25 m, temperature program; 100/25/290): t_R (retention time)=7.49 min; *m*/*z* (EI, 70 eV): 212 (1, M^+), 211 (1, M−1), 197 (100), 135 (13), 105 (33), 92 (64), 79 (14), 77 (18), 65 (23), 51 (9%).

4.6. Kinetic measurements

Solutions of samples of the corresponding pyridine aminophosphine oxides (*c* 0.1 mL^{-1}) in aqueous 50% methanol, containing an appropriate quantity of H_2SO_4 (the 0.5, 1.0 and 2.0 m L^{-1} H_2SO_4 solutions) in NMR tubes were prepared and thermostated at 20 °C for a desired period of time (1, 2, 4, 8, 16 h, respectively). The ^{31}P NMR spectra were consecutively recorded. The kinetic runs in D_2O/MeOD with use of D_2SO_4 were done similarly. The use of

different concentrations of H_2SO_4, (or D_2SO_4) was allowed to calculate the pseudo-first-order rate constants (k_{obsd}). The rate constants were determined by plotting the dependence of $\log(a-x)$ on time (where the 'a' is a relative quantity of the starting aminophosphine oxide and the '$a-x$' represents a relative quantity of unreacted aminophosphine oxide).

4.7. Cleavage of optically active pyridine aminophosphine oxides 4f and 4g in D_2O/D_2SO_4 solution

A sample of optically active pyridine aminophosphine oxide (**4f** or **4g**, 0.412 g, 1.0 mmol) was dissolved in 10% D_2SO_4/D_2O solution (10 mL) and heated at 95–100 °C for 3 h. The reaction mixture was allowed to stand at room temperature for 24 h in order to separate the phosphinic acid **7**. Crystals of the phosphinic acid **7** were collected by filtration and dried on air. Yield of the **7** was 93% in the case of **4f**, and 82% in the case of **4g**.

The remaining filtrate was alkalized with an excess of aqueous sodium bicarbonate solution and extracted with methylene chloride (25 mL). Evaporation of the extract gave the deuterated amines **5c–d** (181 mg) and **6c–d** (170 mg), as thick oils, which were transformed to the corresponding oxalate salts, likewise as described in the preceding case. The oxalates were equimolar mixtures of *S*,*R* and *R*,*R* stereoisomers of the corresponding amines (according to the NMR data).

4.7.1. Mixture of *S*,*R* and *R*,*R* stereoisomers of deuterated *N*-(2-pyridylmethyl)-(*R*)-(+)-α-methylbenzylamine 5c–d. Oxalate; white solid, yield 233 mg, (77%). ^{1}H NMR; δ_H (D_2O; 300 MHz): 8.46 (1H, d, J= 4.8 Hz, 6-Py*H*); 7.79 (1H, dt, J=1.5, 7.8 Hz, 4-Py*H*); 7.40–7.28 (7H, m, Py*H*, Ar*H*); 4.43 (1H, q, J=6.9 Hz, C*H*CH_3); 4.17 (0.5H, br t, J=not determined, NC*H*D); 4.05 (0.5H, br t, J=not determined, NC*H*D); 1.64 (3H, d, J=6.9 Hz, CH_3).

Free amine; GC/MS (HP-5 column, 25 m, temperature program; 100/6/290): t_R=10.38 min; m/z (EI, 70 eV): 213 (0.1, M^+), 212 (0.4, M−1), 198 (16), 136 (5), 120 (81), 105 (18), 94 (100), 93 (37), 79 (8), 77 (10), 66 (10), 51 (5%).

4.7.2. Mixture of *S*,*R* and *R*,*R* stereoisomers of deuterated *N*-(4-pyridylmethyl)-(*R*)-(+)-α-methylbenzylamine 6c–d. Oxalate: white solid, yield 215 mg, (71%). ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.84 (2H, d, J= 6.0 Hz, 2,6-Py*H*); 7.64 (2H, d, J=6.0 Hz, 3,5-Py*H*); 7.36 (5H, br s, Ar*H*); 4.45 (1H, q, J=6.8 Hz, C*H*CH_3); 4.38 (0.5H, br t, J=not determined, NC*H*D); 4.17 (0.5H, br t, J=not determined, NC*H*D); 1.63 (3H, d, J=6.8 Hz, CH_3).

Free amine; GC/MS (HP-5 column, 25 m, temperature program; 100/25/290): t_R=7.49 min; m/z (EI, 70 eV): 213 (1, M^+), 212 (1, M−1), 199 (29), 198 (100), 197 (20), 136 (9), 105 (19), 93 (32), 79 (7), 77 (10), 66 (9), 51 (4%).

4.8. Cleavage of 4a in the presence of 50% aqueous alcohols

Samples of the pyridine-2-methyl-(*N*-benzylamino)-diphenylphosphine oxide (**4a**) (0.40 g, 1.0 mmol), were dissolved in 10 mL aqueous-alcoholic solutions (1:1, v/v), containing 0.98 g (10 mmol) H_2SO_4. The particular solutions contained methanol, ethanol, *iso*-propanol and *tert*-butanol, respectively. The solutions were kept for 2 weeks at room temperature. Progress of the reaction was monitored by ^{31}P NMR spectroscopy. The formed diphenylphosphinic acid (**7**) crystallized partially in the reaction mixtures. The mixtures were filtered to remove the acid **7** and treated with an excess of aqueous 5% $NaHCO_3$ solution. An oily product separated, which was extracted with dichloromethane (25 mL). The extract was dried (anhydrous Na_2SO_4), filtered and evaporated to give an oil (0.22–0.28 g), which was a mixture of *N*-(2-pyridylmethyl)-benzylamine **5a** and corresponding alkyl phosphoester **9a–d**. Separation of the esters and amines was done as follows; the whole mixture was treated with 1 M aqueous HCl (10 mL) and extracted with dichloromethane (25 mL). After drying (anh. Na_2SO_4), the extract was evaporated to give the ester (**9a–d**), as an oily product, solidified after several hours.

The formed amine **5a** was isolated from the remaining acidic solutions by subsequent alkalization with aqueous $NaHCO_3$ and extraction with methylene chloride as described in Section 4.5.2. Yield of the **5a** exceeded 90%.

4.8.1. Methyl ester 9a. A whitish solid, yield 75 mg (27%), mp 52–55 °C, lit.[30] 55–57 °C, lit.[31] 50 °C, lit.[32] 56–58 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.43–7.37 (6H, m, Ar*H*); 3.71–3.67 (3H, d, J=10.1 Hz, OCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 34.908 (s).

4.8.2. Ethyl ester 9b. A colorless oil, yield: 35 mg (14%), lit.[29] oil. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.41–7.35 (6H, m, Ar*H*); 4.08–3.98 (2H, m, OCH_2), 1.29 (3H, t, J=7.1 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 33.058 (s).

4.8.3. *iso*-Propyl ester 9c. White solid, yield: 18 mg (7%), mp 99–101 °C, lit.[27] 97–99 °C, lit.[29] 100.6–101.5 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.40–7.35 (6H, m, Ar*H*); 4.66–4.55 (1H, m, OC*H*), 1.27 (6H, d, J=6.2 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 31.397 (s).

4.8.4. *tert*-Butyl ester 9d. White solid, yield: 14 mg (5%), mp 108–110 °C, lit.[28] 111.5–112 °C. lit.[29] 108.6–109.6 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.75–7.68 (4H, m, Ar*H*); 7.39–7.30 (6H, m, Ar*H*); 1.26 (9H, d, J=2.0 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 32.582 (s).

4.8.5. Cleavage of 4e in the presence of methanol. A sample of optically active the pyridine-4-methyl-(*N*-benzylamino)-*tert*-butylphenyl-phosphine oxide (**4e**) (0.38 g, 1.0 mmol), was dissolved in methanol (10 mL), containing 0.98 g (10 mmol) H_2SO_4. The solution was refluxed for 5 h, cooled and left for 2 weeks. After this, the solvent (methanol) was evaporated, the resulting oil was dissolved in water (10 mL) and heated at 60 °C for 5 h, cooled and extracted with methylene chloride (50 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil, which solidified after several hours. The obtained product was mainly the (*R*)-(+)-*tert*-butylphenyl-phosphine oxide **3c**, mixed with a small quantity of the

methyl ester of *tert*-butylphenylphosphinic acid (**10**). Additional purification of the obtained product by crystallization from hexane–diethyl ether gave the pure (*R*)-(+)-*tert*-butylphenylphosphine oxide (**3c**)[11a,b]. White solid, yield 54 mg (29%), mp 69–72 °C, lit.[11b] 72–74 °C. $[\alpha]^{20}_D$ +23.5 (*c* 1.0, $CHCl_3$), lit.[11a] $[\alpha]^{20}_D$ +14.6 (*c* 1.68, MeOH). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 7.62–6.11 (1H, d, J=453.2 Hz, P–*H*); 7.55–7.32 (5H, m, Ar*H*); 1.01–0.95 (9H, d, J=16.6 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 51.764 (s). Evaporation of mother liquid gave an oily product, partially solidified (18 mg), which was composed with the phosphine oxide **3c** and methyl ester **10**, in a ratio 2:1, approximately. The NMR spectrum ($CDCl_3$) of the crude product showed the dublet of the OMe group at 3.69–3.65 ppm (J=10.45 Hz), which was consistent with the literature data[11a,33–36].

The remaining aqueous layer was made alkaline by adding of an excess of aqueous sodium bicarbonate solution and extraction with chloroform (50 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil, solidified after short time (0.21 g). Recrystallization of the product from acetone gave a white crystalline solid, which was the pyridine hydroxyphosphine oxide **12**, as a diastereomeric mixture. **12**; white solid, yield 120 mg (42%), mp=172–175 °C. ^1H NMR; δ_H (DMSO; 300 MHz): 8.25 (2H, d, J=4.9 Hz, 2,6-Py*H*); 7.71 (2H, m, 3,5-Py*H*); 7.39–7.19 (5H, m, Ar*H*); 6.70–6.45 (1H, m, CHO*H*); 5.52–5.41 (1H, m, C*H*–P); 1.14–0.92 (9H, m, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 44.848 (s), 44.565 (s) in a ratio 1:1.25. IR, ν_{max} (KBr): 3409; 3207; 3081; 2973; 2868; 1597; 1475; 1436; 1415;1149 (P=O); 1107; 833; 747; 715; 697; 610; 572; 551; 517 cm^{-1}. MS; (ESI+Q1MS): 291.0 (43, M^++1), 313.1 (100, M^++1+Na). Anal. Calcd for $C_{16}H_{20}NO_2P$, requires N, 4.84; P, 10.71. Found: N, 4.67; P, 10.59.

4.8.6. Cleavage of 4i in the presence of methanol. A sample of optically active (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenyl-methylphosphine oxide (**4i**) (108 mg, 0.31 mmol), was dissolved in methanol (5 mL), containing 0.49 g (5 mmol) H_2SO_4. The solution was refluxed for 3 h, cooled, left for 24 h and the solvent (methanol) was evaporated. The resulting oil was dissolved in water (5 mL) and extracted twice with methylene chloride (2×25 mL). The combined extracts were dried (anh. Na_2SO_4), filtered and evaporated to give an oil (47 mg). According to NMR data, the product was a mixture composed with methylphenylphosphine oxide (**3d**) and methyl phenylmethylphosphinate (**13**), in a ratio ~1:1. Separation of the mixture for individual products was done by column chromatography (silica gel, eluent; pure acetone) to afford the products: (+)-(R)$_P$ methyl phenylmethylphosphinate (**13**), as a colorless oil.[40] R_f 0.88, yield 22 mg (0.13 mmol), $[\alpha]^{20}_D$ +20.0 (*c* 0.4, $CHCl_3$), lit.[41] $[\alpha]^{20}_D$ +45.2 (*c* 3.7, MeOH). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 7.79–7.72 (2H, m, Ar*H*); 7.53–7.45 (3H, m, Ar*H*); 3.60–3.56 (3H, d, J=11.3 Hz, POCH_3); 1.66–1.61 (3H, d, J=14.6 Hz, PCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 45.734 (s); methylphenylphosphine oxide (**3d**), as a colorless oil[37–39] R_f 0.32, yield 20 mg (0.14 mmol), $[\alpha]^{20}_D$ +26.0 (*c* 0.4, $CHCl_3$). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 8.28–6.71 (1H, dq, J=471.5, 3.8 Hz, P–*H*); 7.61–7.53 (2H, m, Ar*H*); 7.42–7.36 (3H, m, Ar*H*); 1.67–1.61 (3H, dd, J=13.9, 3.8 Hz, PCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 21.747 (s).

The remaining aqueous layer was made alkaline by adding an excess of aqueous sodium bicarbonate solution and extracted twice with chloroform (2×25 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil (45 mg), which was a mixture of amine **6c** and aldehyde **1b** and traces of other not identified products, according to NMR data.

Supplementary data are deposited with the Cambridge Crystallographic Data Centre as a supplementary publication numbers CCDC 283498 (CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail; deposit@ccdc.cam.ac.uk).

The X-ray diffraction measurements were performed in Department of Chemistry, University of Wroclaw, on a Kuma KM4 CCD four circle diffractometer, equipped with an Oxford Cryosystem Cooler, using graphite monochromated Mo K_α radiation.

The structure of **4g** was solved by direct methods using SHELXS-97[42] and refined on S^2 by full-matrix least-squares methods using SHELXL-97.[43] Non-hydrogen atoms were refined with anisotropic thermal parameters. During the refinement, an extinction and absorption correction was applied. The correction for the absorption was done using the empirical method included in the SHELXA program from the SHELXL-97[43] package. The XP package[44] was used to generate the molecular drawings.

The absolute configuration of the molecule **4g** was assigned as (*S*,*R*) with reference to the known *R* configuration of the (+)-α-methylbenzylamino moiety.

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