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Stereochemistry of 1-hydroxyphosphonate–phosphate rearrangement. Retention of configuration at the phosphorus atom

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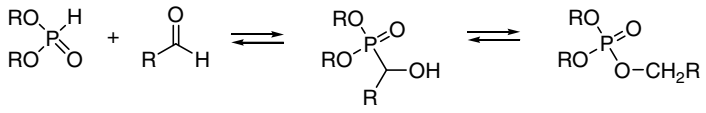
Abstract—1-Hydroxyphosphonate **1** in the presence of triethylamine in acetonitrile solution undergoes irreversible rearrangement to phosphate **2** and reversible *retro*-phospho-aldol (*retro*-Abramov) reaction. The X-ray structures for **1** and **2** revealed that the phosphonate–phosphate rearrangement occurs with retention of configuration at the phosphorus atom.

1-Hydroxyphosphonic acids and their esters exhibit a variety of biological activities as enzyme inhibitors, antiviral, antibacterial, and anticancer drugs.[1] The majority of studies carried out over the last two decades have been dedicated mostly to the asymmetric synthesis of hydroxyphosphonates.[2] 1-Hydroxyphosphonates are easily synthesized from aldehydes and phosphites via the base-catalyzed Pudovik reaction.[3] In the presence of strong bases, 1-hydroxyphosphonates undergo the *retro*-phospho-aldol (*retro*-Abramov)[4] reaction to phosphites and carbonyl compounds and rearrangement to phosphates[5] (Scheme 1). The mechanisms of these reactions were studied by kinetic methods,[6] however, the stereochemical studies were limited to one system. The rearrangement of diethyl 1-hydroxy-1-phenylethylphosphonate to diethyl 1-phenylethylphosphate and the reverse reaction were found to proceed with retention of configuration at the stereogenic carbon.[7,8] In the phosphonate–phosphate rearrangement the enantiomeric excess of phosphate was lowered by the accompanying *retro*-Abramov reaction.[8]

To explore the stereochemistry of phosphonate–phosphate rearrangement at the phosphorus atom, 1-hydroxyphosphonate **1** was chosen as a model system. 5,5-Dimethyl-4-phenyl-1,3,2-dioxaphosphorinane derivatives have been applied as resolving agents,[9,14] chiral synthons[10] as well as in conformational[11] and mechanistic[12] studies. The synthesis of 1-hydroxyphosphonate **1** was based on the reported procedure.[13] Treatment of racemic 2*H*-2-oxo-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane **3**[14] with 2-nitrobenzaldehyde **4** in toluene in the presence of triethylamine afforded 1-hydroxyphosphonate **1** as a mixture of diastereoisomers **1a** and **1b**, which were evident as two signals in the ^{31}P NMR spectrum in a 1:1 ratio at δ_P 12.4 and 13.0, respectively.[15] The diastereoisomers were easily separated by fractional crystallization[16] and crystals suitable for X-ray analysis were obtained.[17] The conformation of the 1,3,2-dioxaphosphorinane ring is a regular chair flattened at the P end and with the 4-phenyl and phosphoryl groups in equatorial orientations (Fig. 1A). Both stereoisomers **1a** and **1b** are racemic mixtures with



Scheme 1.

Keywords: Phosphonate–phosphate rearrangement; *retro*-Abramov reaction; Stereochemistry; Nucleophilic substitution; Reaction mechanism.
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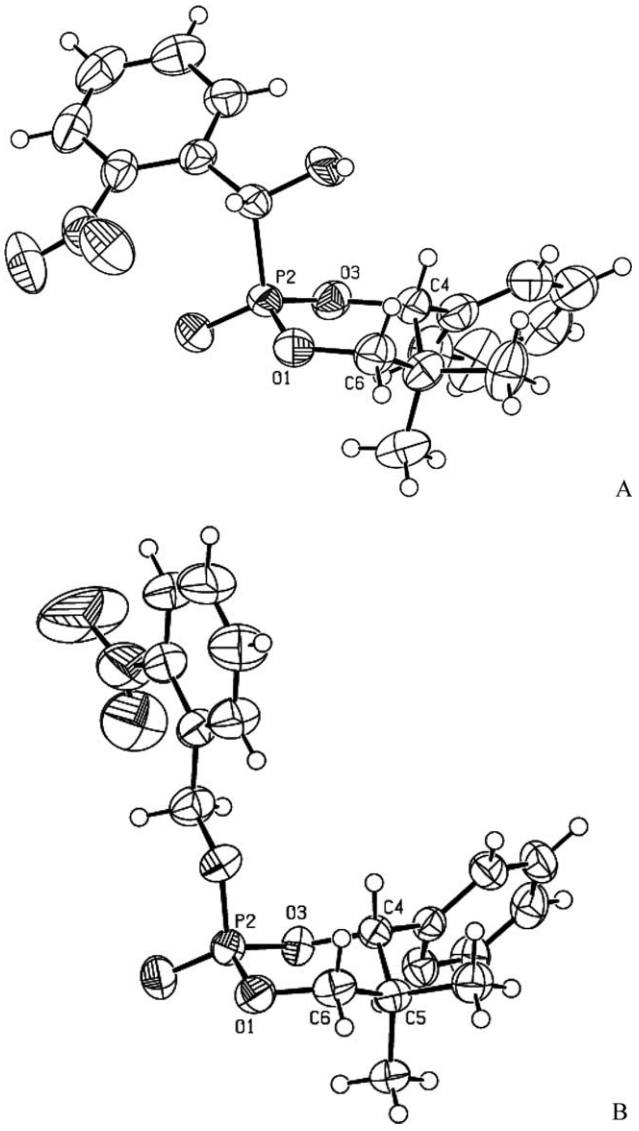


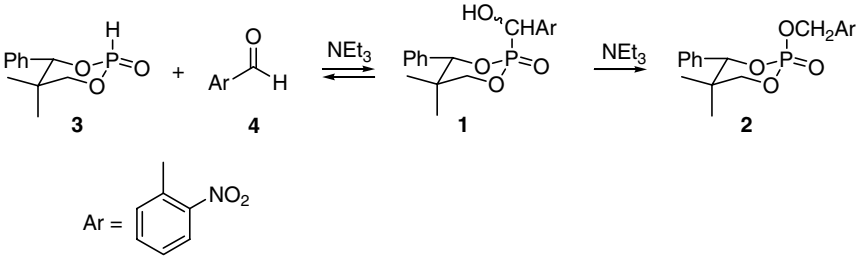
Figure 1. The ORTEP plots of phosphonate **1a** (A) and phosphate **2** (B).

relative configurations R^*, S^*, R^*, and R^*, S^*, S^* at the C-4 and P-2 stereogenic centers of the six-membered heterocycle, and the carbinol atom, respectively.

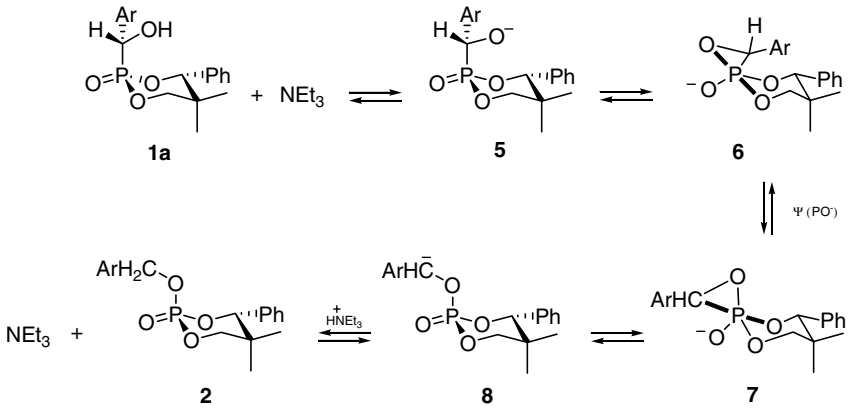
The rearrangement of phosphonate **1a** or **1b** to phosphate **2** was carried out at 65 °C in acetonitrile in the presence of triethylamine as the catalyst and followed by means of ^{31}P NMR. The rate of phosphate formation was the same for both isomers. When isomer **1a** was used as the substrate the formation of the second stereoisomer **1b** was observed simultaneously with the phosphonate–phosphate rearrangement. The appearance of the second stereoisomer proves the presence of the competitive *retro*-Abramov reaction (Scheme 2). The half-life of phosphate formation in acetonitrile at 65 °C was found to be equal to about $20 \times [\text{amine}]^{-1}$ min. The rate of the *retro*-Abramov reaction is comparable to the rate of rearrangement and both reactions were much slower than the Pudovik reaction. The reverse phosphate–phosphonate rearrangement was not observed. Details of kinetic studies will be published elsewhere.

Analysis of the X-ray structure of phosphate **2** (Fig. 1B) revealed the same (R^*) relative configurations at the C-4 and P-2 atoms while they were different in **1** (Fig. 1A). At first the result seemed surprising, because inversion of configuration at the phosphorus atom requires attacking and leaving groups in linear positions, which is unlikely for the intramolecular rearrangement. However, formally the carbon atom in the phosphonate **1** was replaced by the oxygen atom in the phosphate **2** and the positions of the other oxygen atoms were the same. Thus, the change of S_P configuration in **1** to R_P in **2** originates not from a change in the arrangement of atoms surrounding phosphorus, but from the replacement of carbon by oxygen, which possesses higher priority according to Cahn–Ingold–Prelog (CIP) rules.[18]

To explain the retention of configuration at the phosphorus atom we propose the following mechanism (Scheme 3). Overall, the phosphonate–phosphate rearrangement requires P–C bond breakage and formation of the P–O bond. If one of these processes is the rate limiting step, the nucleophilic substitution via trigonal bipyramidal (TBP) intermediates should involve apical addition and apical elimination processes.[19] In the presence of triethylamine, 1-hydroxyphosphonate **1a** exists in equilibrium with an anion **5**. Axial attack of the carbinol oxygen followed by pseudorotation will lead to pentacoordinate intermediate **6** with one of the ring P–O bonds in the axial position. In trigonal bipyramid **6** the axial–equatorial position of the dioxaphosphorinane ring and the equatorial position of the negatively charged oxygen are preferable.[20,21] Subsequent pseudorotation rearrangement is necessary for the placement of the carbon atom into an apical position as in **7** prior to cleavage of the P–C bond.



Scheme 2.



Scheme 3.

In conclusion, this is the first experimental observation of the stereochemistry on the phosphorus atom during the phosphonate–phosphate rearrangement. We are presently working on elucidation of the mechanism of this reaction in detail by kinetic isotope effects.

Acknowledgments

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References and notes

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15. Synthesis of **1a** and **1b**: 0.25 g (2.5 mmol) of triethylamine was added to a solution of 1.13 g (5 mmol) of phosphite **3** and 0.77 g (5.1 mmol) of aldehyde **4** in 50 mL of dry toluene. The solution was stirred at 0 °C (ice bath) and the reaction monitored by ^{31}P NMR. After completion of the reaction (approximately 2 h) the solution was evaporated to dryness. The crude product was subjected to several crystallizations from dichloromethane to give pure **1a** and **1b** with a yield above 90%. Synthesis of phosphate **2**: 1.9 g (5 mmol) of 1-hydroxyphosphonate **1a** and 0.5 g (5 mmol) of triethylamine in dry acetonitrile (40 mL) were heated in a sealed glass ampoule for 15 h at 65 °C. The crude product precipitated at room temperature, then was filtered off and crystallized from dichloromethane/toluene or toluene to give **2** in 96% yield.
16. Data for (5,5-dimethyl-2-oxido-4-(R^*)-phenyl-1,3,2-(2S^*)-dioxaphosphinan-2-yl)(2-nitrophenyl)(R^*)-methanol, **1a**: Colorless solid (CH_2Cl_2), mp 209–212 °C, δ_P (101.3 MHz, $CDCl_3$) 12.4; ν_{max} (KBr) 3192, 1608, 1528, 1472, 1344, 1244, 1088, 1056, 1000 cm^{-1}; δ_H (250.13, $CDCl_3$) 0.79 (3H, s, CH_3), 1.07 (3H, s, CH_3), 3.60 (1H, dd, OH, $^3J = 7.5$ Hz, $^3J_{P-OH} = 17.5$ Hz), 4.05 (1H, AB, CH_2, $^2J = 12.5$ Hz, $^3J_{P-H} = 20.0$ Hz), 4.60 (1H, d, CH_2, $^2J_{AB} = 12.5$ Hz), 5.46 (1H, s, CH–Ph), 6.17 (1H, dd,

C*H*–OH, $^3J = 7.5$ Hz, $^2J_{PH} = 15.5$ Hz), 7.26–7.29 (5H, m, C_6H_5), 7.44 (1H, tt, Ar–C_5H, $^3J = 8.0$, 1.0 Hz); 7.66 (1H, t, Ar–C_4H, $^3J = 8.0$ Hz), 7.95 (1H, t, Ar–C_6H, $^3J = 8.0$ Hz), 7.99 (1H, dt, Ar–C_3H, $^3J = 8.0$, 1.0 Hz); δ_C (62.9 MHz, DMSO) 16.8 (CH_3), 20.4 (CH_3), 35.9 (d, $J = 6.7$ Hz, $C(CH_3)_2$), 66.8 (d, $J = 156.6$ Hz, CH–OH), 79.7 (d, $J = 7.3$ Hz, CH_2), 89.0 (d, $J = 7.9$ Hz, CH–Ph), 124.6 (d, $J = 2.3$ Hz, Ar–C_3), 127.2 (Ph–$C_{2,6}$), 127.8 (Ph–$C_{3,5}$), 128.3 (Ph–C_4), 128.6 (d, $J = 7.1$ Hz, Ar–C_6), 126.62 (Ar–C_5), 132.9 (Ar–C_1), 133.3 (d, $J = 3$ Hz, Ar–C_4), 136.3 (d, $J = 6.9$ Hz, Ph–C_1), 147.4 (d, $J = 5.7$ Hz, Ar–C_2); *m*/*z* (FAB/NBA) 378 (100, MH^+), 307 (10), 234 (18), 145 (80), 137 (45); HRMS (FAB/NBA): MH^+, found 378.1099. $C_{18}H_{21}NPO_6$ requires 378.1107; data for (5,5-dimethyl-2-oxido-4-(*R**)-phenyl-1,3,2-(2*S**)-dioxaphosphinan-2-yl)(2-nitrophenyl)-(*S**)-methanol **1b**: Colorless solid (CH_2Cl_2), mp 214–216 °C, δ_P (101.3 MHz, $CDCl_3$) 13.0; ν_{max} (KBr) 3208, 1608, 1528, 1480, 1352, 1212, 1064, 1048 cm^{-1}; δ_H (250.13, $CDCl_3$) 0.82 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 3.47 (1H, br s, OH), 3.99 (1H, ABX, CH_2, $^2J = 10.6$ Hz, $^3J_{P-H} = 19.2$ Hz), 4.47 (1H, d, CH_2, $^2J_{AB} = 10.6$ Hz), 5.60 (1H, d, $J = 1.3$ Hz, C*H*–Ph), 6.16 (1H, d, C*H*–OH, $^2J_{PH} = 15.0$ Hz), 7.33–7.38 (5H, m, C_6H_5), 7.48 (1H, tt, Ar–C_5H, $^3J = 7.8$, 1.4 Hz); 7.65 (1H, t, Ar–C_4H, $^3J = 7.5$ Hz), 7.96 (1H, dt, Ar–C_6H, $^3J = 7.9$, 1.7 Hz), 8.02 (1H, dt, Ar–C_3H, $^3J = 8.2$, 1.4 Hz); δ_C (62.9 MHz, DMSO) 15.5 (CH_3), 19.1 (CH_3), 34.5 (d, $J = 6.6$ Hz, $C(CH_3)_2$), 65.2 (d, $J = 158.5$ Hz, CH–OH), 78.2 (d, $J = 7.5$ Hz, CH_2), 87.4 (d, $J = 7.9$ Hz, CH–Ph), 123.2 (Ar–C_3), 125.8 (Ph–$C_{2,6}$), 126.4 (Ph–$C_{3,5}$), 126.9 (Ph–C_4), 127.0 (d, $J = 5.0$ Hz, Ar–C_6), 127.3 (Ar–C_5), 131.6 (Ar–C_1), 131.9 (Ar–C_4), 134.9 (d, $J = 6.9$ Hz, Ph–C_1), 146.0 (d, $J = 5.7$ Hz, Ar–C_2); *m*/*z* (FAB/NBA) 378 (100, MH^+), 307 (10), 137 (72), 107 (28); HRMS (FAB/NBA): MH^+, found 378.1100. $C_{18}H_{21}NPO_6$ requires 378.1107; data for 5,5-dimethyl-2[(2-nitrophenyl)oxy]-4-(*R**)-phenyl-1,3,2-(2*R**)-dioxaphosphinane 2-oxide **2**: colorless solid (toluene), mp 171–173 °C, δ_P (101.3 MHz, $CDCl_3$) −7.3; ν_{max} (KBr) 3448, 1528, 1464, 1340, 1288, 1052, 1040, 1016, 1008, 996; δ_H (250.13, $CDCl_3$) 0.80 (3H, s, CH_3), 1.07 (3H, s, CH_3), 3.98 (1H, ABX, CH_2, $^2J_{AB} = 11.1$ Hz; $^3J_{P-H} = 25.0$ Hz); 4.27 (1H, AB, CH_2; $^2J = 11.1$ Hz), 5.20 (1H, s, C*H*–Ph); 5.53 (2H, d, CH_2–O; $^3J_{PH} = 7.0$ Hz), 7.32–7.38 (5H, m, C_6H_5) 7.37 (1H, t, Ar–C_5H,$^3J = 7.50$ Hz), 7.60 (1H, t, Ar–C_4H, $^3J = 7.50$ Hz), 7.72 (1H, d, Ar–C_6H, $^3J = 8.5$ Hz), 8.06 (1H, d, Ar–C_3H; $^3J = 8.50$ Hz); δ_C (62.9 MHz, $CDCl_3$) 16.9 (CH_3), 20.7 (CH_3), 36.0 (d, $J = 3.8$ Hz, $C(CH_3)_2$), 65.4 (d, $J = 3.8$ Hz, CH_2–Ar), 78.9 (d, $J = 6.3$ Hz, P–O–CH_2), 88.3 (d, $J = 6.3$ Hz, CH–Ph), 124.8 (Ar–C_3), 127.2 (Ph–C_2,C_6), 127.8 (Ph–C_3,C_5), 128.5 (Ph–C_4), 129.2 (Ar–C_5), 129.3 (Ar–C_6), 131.7 (d, $J = 7.5$ Hz, Ar–C_1), 133.3 (Ar–C_4), 135.2 (d, $J = 10$ Hz, Ph–C_1), 147.2 (Ar–C_2); *m*/*z* (FAB/NBA) 378 (16, MH^+), 242 (20), 145 (100), 136 (100); HRMS (FAB/NBA): MH^+, found 378.1089. $C_{18}H_{21}NPO_6$ requires 378.1107.

17. Crystal structures of **1a**, **1b**, and **2** were solved by SHELXS[21] and refined by full-matrix least-squares method (SHELXS-97[22]) based on F^2 to *R* factors of 0.054%, 0.045%, and 0.038%, respectively. Crystal data are as follows: compound (**1a**)—CCDC 293580, crystallized from methylene chloride and hexane, $a = 11.142(1)$, $b = 12.486(1)$, $c = 14.494(1)$ Å, $\alpha = 93.60(1)°$, $\beta = 107.12(1)°$, $\gamma = 110.375(1)°$, $V = 1775.5$ Å^3, space group *P*-1, $Z = 4$, $\lambda = 0.71073$ Å, $wR_2 = 0.116$ ($S = 0.936$), 6753 unique data, 3250 with $F_o > 4\sigma$, collected on KM4-CCD at 300 K. Compound (**1b**)—CCDC 293579, crystallized from methylene chloride and hexane, $a = 11.773(1)$, $b = 15.142(1)$, $c = 11.443(1)$ Å, $\beta = 93.435(10)°$, $V = 2036.3$ Å^3, space group $P2_1/c$, $Z = 4$, $\lambda = 1.54178$ Å, $wR_2 = 0.130$ ($S = 1.054$), 3825 unique data, 3069 with $F_o > 4\sigma$, collected on Smart APEX (Bruker) at 300 K. Compound (**2**)—CCDC 293578, crystallized from toluene, $a = 6.247(1)$, $b = 30.993(6)$, $c = 9.334(2)$ Å, $\beta = 96.47(3)°$, $V = 1795.9$ Å^3, space group $P2_1/c$, $Z = 4$, $\lambda = 1.54178$ Å, $wR_2 = 0.102$ ($S = 1.074$), 3366 unique data, 3151 with $F_o > 4\sigma$, collected on Smart APEX (Bruker) at 300 K. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, Cambridge, UK. Copies of the data can be obtained, free of charge, on application to CCDC, 12 union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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