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Stereochemistry of 1,2-Oxaphospholanes, III Evidence for the Retro-*Abramov* Pathway in Methoxide-Catalysed Equilibration of Substituted 2-Methoxy-2-oxo-1,2-oxaphospholan-3-ols

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Diastereomeric 3,4-dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ols (**2a–d**) were obtained by the cyclisation of the phosphite **3** and their relative configurations were established by ^{13}C-NMR spectra. Equilibrations of pure **2a** and **2b** as well as a 3:2 mixture of **2b** and **2d** with sodium methoxide in methanol afforded a mixture of **2a–d**. The mechanism of the equilibration involves the P—C_3 bond cleavage (retro-*Abramov* reaction), and the epimerization of the chiral P-anion **5** and/or the P—O_1 bond scission. The ratios of diastereomers **2a–d** obtained in equilibration and from the cyclisation of **3** were interpreted in terms of the thermodynamic and kinetic preferences.

(Keywords: Configuration by ^{13}C-NMR; 1,2-Oxaphospholan-3-ols, synthesis, equilibration; Retro-Abramov reaction)

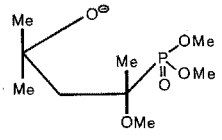
Stereochemie der 1,2-Oxaphospholane, III. Bestätigung des Retro-Abramov-Reaktionsweges der mit Methoxid katalysierten Äquilibrierung von substituierten 2-Methoxy-1,2-oxaphospholan-3-ol-2-oxiden

Diastereomere 3,4-dimethyl-2-methoxy-1,2-oxaphospholan-3-ol-2-oxide wurden über die Cyclisierungsreaktion von Phosphit **3** erhalten und ihre relativen Konfigurationen mit ^{13}C-NMR-Spektren bestätigt. **2a** und **2b** sowie eine 3:2-Mischung von **2b** und **2d** geben unter Gleichgewichtsbedingungen mit Natriummethoxid in Methanol eine Mischung von **2a—d**. Der Mechanismus dieser Äquilibrierung schließt die Spaltung der P—C_3-Bindung (Retro-*Abramov*-Reaktion) und die Epimerisierung des chiralen P-Anions **5** und/oder die Spaltung der P—O_1-Bindung ein. Die Verhältnisse der Diastereomeren **2a—d**, berechnet im Gleichgewichtszustand sowie aus der Cyclisationsreaktion von **3**, wurden mittels thermodynamischer und kinetischer Bevorzugung interpretiert.

Introduction

Addition of dialkyl phosphites to aldehydes or ketones—known as the *Abramov* reaction[1]—is a particularly useful way for the formation of the P—C bond[2–4]. The retro-*Abramov* reaction plays an important role as a method for the removal of a phosphorus residue from the corresponding α-hydroxyphosphonates[5].

In the previous paper from this laboratory it was shown that diastereomerically pure 2-methoxy-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ols as well as their methyl ethers undergo methoxide-catalysed equilibration[6]. The latter reaction involves breaking of the P—O_1 bond with the ring-opened species **1** as the intermediate while in the former also the P—C_3 bond cleavage (retro-*Abramov* reaction) can be expected[6]. In connection with the recently reported synthesis of polyhydroxy 1,2-oxaphospholanes[7] we became interested in the behaviour of the C_3 and P chiral centers of the 1,2-oxaphospholan-3-ol system under equilibration conditions. We reasoned that the strategy of the studies on this problem would consist of the following steps: (i) synthesis of substituted 1,2-oxaphospholan-3-ols containing chiral centre at C_4 or C_5, (ii) separation of at least one pure from the four possible diastereomers, and (iii) methoxide-catalysed equilibration of this diastereomer. Here, we wish to show an evidence for the retro-*Abramov* pathway in the methoxide-catalysed equilibration of diastereomeric 3,4-dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ols (**2a–d**).



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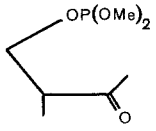
Results and Discussion

Dimethyl-(2-methyl-3-oxobutyl) phosphite (**3**) was prepared under standard conditions[8] from 4-hydroxy-3-methylbutanon-2 and dimethyl phosphorochloridite. The cyclisation of **3** with the equivalent of water[6] gave a 58 : 24 : 16 : 3 mixture of **2a**, **2b**, **2c** and **2d** respectively, together with less than 10% of the ring-opened phosphonates **4** and some unidentified impurities. From the reaction mixture **2a** and **2b** were isolated and identified based on the ^{13}C-NMR data. The relative configuration of the OH and P=O groups was deduced from the upfield shifts of the CH_3—C_3 and CH_3O in **2a** in comparison to those in **2b**. This



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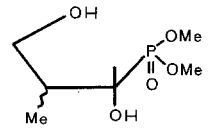

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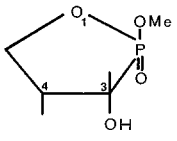
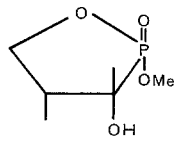
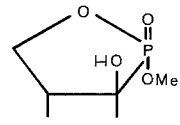


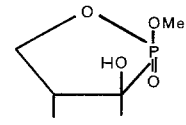
2a



2b



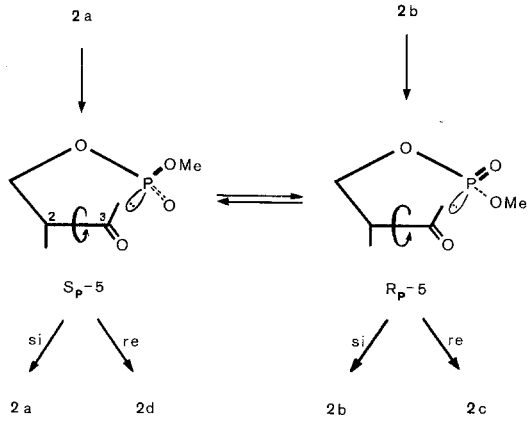
2c



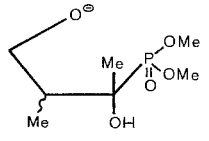
2d

corresponds to our previous observations[6]. In **2a** and **2b** CH_3-C_4 had very close chemical shifts and both were substantially shielded. This effect is expected for CH_3-C_4 *cis* to the OH group and it was earlier observed for the substituted cyclopentanols[9,10]. Furthermore, in the spectrum of a 3 : 2 mixture of **2b** and **2d** CH_3-C_4 in **2d** appeared in lower field than that in **2b**, and CH_3-C_3 in **2d** was shifted upfield in comparison to those in **2a** and **2b** in agreement with the expected increase of crowding around CH_3-C_3 in **2d** as compared to **2a** and **2b**. The assignment of configuration at P in **2d** is based on its upfield shift in ^{31}P-nmr relative to that in **2c**[11].

Scheme 1



Equilibration experiments involved isomerisations of pure diastereomers **2a** and **2b** as well as the 3 : 2 mixture of **2b** and **2d**. To ca. 2 *M* methanolic solutions of **2** 10 mol% of sodium methoxide was injected and the progress of the reaction was monitored by ^{31}P-NMR at room temperature. Regardless on which diastereomer was used as the starting material always a mixture of **2a**, **2b**, **2c** and **2d** was formed instantaneously together with some contaminations. This result strongly suggests the P—C_3 bond cleavage in **2a–d** in the retro-*Abramov* mode and the intermediacy of the species **5** (Scheme 1). For example, the result of equilibration of **2a** could be rationalized in the following manner. The carbonyl group in S_P-**5** can be attacked from the *si* face affording **2a** or alternatively after rotation around the C_2—C_3 bond from the *re* face giving **2d**. For the formation of diastereomers with opposite configurations at phosphorus, such as **2b** and **2c**, two pathways should be considered. First, racemization of the chiral dialkyl phosphite anion in **5** seems to be quite easy. However, to our knowledge there is no evidence in the literature for the configurational instability of P-anions derived from chiral dialkyl phosphites. Although anions prepared in the absence of methanol from O-alkyl phenylphosphinates[12,13] are configurationally stable, traces of sodium methoxide caused slow racemization of benzylphenylphosphine oxide[14] and instantaneous one of O-iso-propyl methylphosphinate[15]. Taking into account these observations it is highly likely that P-chiral anion in S_P-**5** as well as in R_P-**5** would be also readily epimerized under conditions of equilibration. From the R_P-**5** anion **2b** or **2c** will be produced after an attack on the *si* or *re* faces, respectively. The other pathway would involve direct transformation of **2a** into **2b**, and **2d** into **2c** *via* the P—O_1 bond scission mechanism[6]. In this mechanism the *pro*-R or *pro*-S methoxy group is eliminated from the intermediate **6** through the trigonal bipyramid transition states.



6

Although all equilibrations have been performed under similar conditions the ratios of **2a** : **2b** : **2c** : **2d** slightly varied from 42 : 28 : 6 : 24 while starting from **2a**, to 40 : 41 : 6 : 13 when **2b** was equilibrated, and to 35 : 44 : 6 : 13 when the 3 : 2 mixture of **2b** and **2d** was treated with methanolic sodium methoxide. The discrepancies arise most likely from

the consumption of the catalyst in side reactions. However, the significant excess of **2a** and **2b** over **2c** and **2d** is noticed in every experiment. The observed ratios of diastereomeric **2** reflect nonbonded repulsive interactions expected in **2a–d** between substituents around the C_3-C_4 and $P-C_3$ bonds. The interactions of the *cis*-oriented **Me**$-C_4$ and **Me**$-C_3$ in **2c** and **2d** are greater[16] than those of **Me**$-C_4$ and **HO**$-C_3$ in **2a** and **2b**. Equilibrations produce almost equal amounts of **2a** and **2b** and this corresponds to comparable repulsions of **MeO** and **Me**$-C_3$ in **2a**, and **MeO** and **HO**$-C_3$ in **2b**. On the other hand, the significant excess of **2d** over **2c** (3 : 1) is found. In **2c** the three largest substituents occupy the same side of the 1,2-oxaphospholane ring and their interactions diminish the stability of this isomer to such a degree that traces of it were detected in all experiments. In this pair of diastereomers the **Me**$-C_4$ and **Me**$-C_3$ groups are in *cis* configuration and for this reason interactions of P=**O** and **Me**$-C_3$ in **2d** are smaller those of **MeO** and **Me**$-C_3$ in **2c**.

A comparison of the ratios of diastereomeric **2a–d** obtained from equilibrations and from cyclisation of **3** suggests that the latter is most likely kinetically-controlled. Unindependently of the mode of control **2a** and **2b** are produced in excess over **2c** and **2d**. Within diastereomeric pairs **2a** and **2b**, and **2c** and **2d** the isomers in which the intramolecular $P=O\cdots H-O-C_3$ hydrogen bond exists are significantly favoured. This is especially well documented for **2c** which is formed from **3** in ca. five-fold excess over **2d**.

We expect that the observations presented in this paper could be fruitfully applied to the transformations of enantiomeric polyhydroxy 1,2-oxaphospholanes[7] into their epimers.

Acknowledgements

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Experimental

^{13}C and ^{31}P-NMR spectra were taken on Bruker HX 72 at 22.63 and 36.43 MHz, respectively by operating in the *FT* mode. The conditions for the ^{13}C-NMR measurements were as follows: SW = 2000 Hz and data points 8 K/4 K. Chemical shifts were referenced to the central signal of $CDCl_3$ (77.1 ppm) and recalculated relative to *TMS*. For ^{31}P-NMR spectra the chemical shifts are expressed with positive sign when downfield from internal 85% H_3PO_4. ^1H-NMR spectral data were obtained on a Tesla BS 487 C (80 MHz) for the $CDCl_3$ solutions with *TMS* as the internal standard. Other instrumentation and general techniques were as described in Ref.[6].

4-Hydroxy-3-methylbutanon-2 was prepared in 32% yield according to the literature procedure[17].

Dimethyl-(2-methyl-3-oxobutyl) Phosphite (**3**)

To a mixture of 4-hydroxy-3-methylbutanon-2 (2.04 g, 0.02 mol) and triethylamine (2.8 ml, 0.02 mol) in 20 ml of benzene cooled to 10° a solution of dimethyl phosphorochloridite[18] (2.8 g, 0.022 mol) in 5 ml of benzene was added dropwise below 10° under argon atmosphere. Stirring was continued for 1 h at this temperature and the reaction mixture was filtrated, thoroughly washed with benzene and evaporated under reduced pressure (0.05 mm Hg) to give crude **3** (3.80 g, 98%) as colorless unstable oil.

^{1}H-NMR: $\delta = 1.11$ (d, $J = 7.0$, 3 H, CH_3CH), 2.18 (s, 3 H, CH_3CO), 2.85 (sextet, $J = 7.0$, 1 H, CH_3CH), 3.49 [d, $J = 11.0$, 6 H, $(CH_3O)_2$], 3.7–4.4 (m, 2 H, CH_2O).

^{31}P-NMR ($CDCl_3$): $\delta = 139.9$.

Reaction of **3** *with Water*

To magnetically stirred **3** (3.80 g, 0.019 mol) water (0.35 ml, 0.019 mol) was added *drop by drop* with external cooling. After 2 h the crude product was examined by ^{31}P-NMR and subjected to column chromatography on 60 g of silica gel (Merck, catalog number 7734). Separation was effected with chloroform/methanol 100/1.

(2S,3S*,4R*)-3,4-Dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ol* (**2a**)

$R_F = 0.31$ (chloroform/methanol 20 : 1). — Yield 0.75 g (21%). M. p. 122.5–123° (chloroform-hexane).

^{1}H-NMR: $\delta = 1.00$ (d, $J = 6.7$, 3 H, CH_3-C_4), 1.44 (d, $J = 15.7$, 3 H, CH_3-C_3), 2.1–2.4 (m, 1 H, H—C_4), 3.81 (d, $J = 10.6$, 3 H, CH_3-OP), 3.9–4.2 (m, 2 H, CH_2).

^{13}C-NMR: $\delta = 7.46$ (d, $J = 10.3$, CH_3-C_4), 18.67 (d, $J = 9.8$, CH_3-C_3), 41.28 (d, $J = 16.1$, C_4), 53.15 (d, $J = 7.3$, CH_3-OP), 67.55 (d, $J = 141.1$, C_3), 70.67 (d, $J = 8.3$, C_5).

^{31}P-NMR ($CDCl_3$): $\delta = 45.8$.

IR (KBr): 3250 (OH), 1250 (P=O), 1060 cm^{-1} (P—O—C).

$C_6H_{13}O_4P$ (180.13). Found. C 39.67 H 7.31 P 17.05.
Calc. C 40.01 H 7.27 P 17.19.

(2R,3S*,4R*)-3,4-Dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ol* (**2b**)

$R_F = 0.20$ (chloroform/methanol 20 : 1). — Yield 0.134 g (3.7%). — M. p. 89–90° (chloroform-hexane).

^{1}H-NMR: $\delta = 1.01$ (d, $J = 6.7$, 3 H, CH_3-C_4), 1.50 (d, $J = 15.8$, 3 H, CH_3-C_3), 2.2–2.6 (m, 1 H, H—C_4), 3.89 (d, $J = 10.6$, CH_3-OP), 3.7–4.4 (m, 5 H, CH_2).

^{13}C-NMR: $\delta = 7.52$ (d, $J = 10.3$, CH_3-C_4), 20.16 (d, $J = 7.8$, CH_3-C_3), 41.91 (d, $J = 18.1$, C_4), 54.94 (d, $J = 7.3$, CH_3-OP), 69.35 (d, $J = 140.6$, C_3), 70.88 (d, $J = 8.8$, C_5).

^{31}P-NMR ($CDCl_3$): $\delta = 44.5$.

IR (KBr): 3250 (OH), 1240 (P=O), 1050 cm^{-1} (P—O—C).

(2R,3R*,4R*)-3,4-Dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ol* (**2c**)

^{31}P-NMR ($CDCl_3$): $\delta = 43.9$.

(2S,3R*,4R*)-3,4-Dimethyl-2-methoxy-2-oxo-1,2-oxaphospholan-3-ol* (**2 d**)

^{13}C-NMR: $\delta = 10.13$ (d, $J = 8{,}8$, $\mathbf{C}H_3-C_4$), 16.52 (d. $J = 6.8$, $\mathbf{C}H_3-C_3$), 41.50 (d, $J = 18.1$, $\mathbf{C}_4$), 53.84 (d, $J = 7.3$, $\mathbf{C}H_3-OP$), 69.83 (d, $J = 6.8$, $\mathbf{C}_5$), 70.33 (d, $J = 144.0$, $\mathbf{C}_3$).

^{31}P-NMR ($CDCl_3$): $\delta = 41.6$.

Equilibration of **2 a**

To a solution of **2 a** (2.75 g, 15.3 mmol) in 7.5 ml of methanol 1.5 ml of 1 *M* sodium methoxide in methanol was added at room temperature. After 20 min methanol was evaporated (bath 30°) and the residue was chromatographed on 26 g of silica gel with chloroform/methanol 100/1 (300 ml) and 20/1 (50 ml) to give 1.38 g (50.0%) of **2 a** and 1.12 g (40.6%) of a mixture of **2 b**, **2 c** and **2 d**. Repeated chromatography of this mixture allowed separation of 0.304 g of **2 b** and 0.60 g of a 3 : 2 mixture of **2 b** and **2 d**.

References

[1] *Abramov V. S.*, Doklady Akad. Nauk S.S.S.R. **73**, 487 (1950).
[2] *Texier-Boullet F., Foucaud A.*, Synthesis **1982**, 165, and references therein.
[3] *Yamashita M., Long P. T., Shibata M., Inokawa S.*, Carbohydr. Res. **84**, 35 (1980).
[4] *Paulsen H., Kuhne H.*, Chem. Ber. **108**, 1239 (1975), and former papers from this series.
[5] *Hata T., Hashizume A., Nakajima M., Sekine M.*, Tetrahedron Lett. **1978**, 363.
[6] *Wróblewski A. E.*, Tetrahedron **39**, 1809 (1983).
[7] *Wróblewski A. E.*, Carbohydr. Res. **125**, C 1 (1984).
[8] *Kosolapoff G. M., Maier L.*, Organic Phosphorus Compounds, Vol. 5, p. 32. New York: Wiley-Interscience. 1973.
[9] *Christl M., Reid H. J., Roberts J. D.*, J. Amer. Chem. Soc. **93**, 3463 (1971).
[10] *Plantema O. G., de Koning H., Huisman H. O.*, Rec. Trav. Chim. Pays-Bas **96**, 129 (1977).
[11] *Wróblewski A. E.*, unpublished results.
[12] *Farnham W. B., Murray jr., R. K., Mislow K.*, J. Amer. Chem. Soc. **92**, 5809 (1970).
[13] *Van den Berg G. R., Platenburg D. H. J. M., Benshop H. P.*, J. Chem. Soc. D **1971**, 606.
[14] *Emmick T. L., Letsinger R. L.*, J. Amer. Chem. Soc. **90**, 3459 (1968).
[15] *Reiff L. P., Aaron H. S.*, J. Amer. Soc. **92**, 5275 (1970).
[16] *Eliel E. L., Allinger N. L., Angyal S. J., Morrison G. A.*, Conformational Analysis, pp. 42—47. New York: Interscience. 1967.
[17] *Pinder A. R., Saunders W. D.*, J. Org. Chem. **39**, 3061 (1974).
[18] *Ramirez F., Chaw Y. F., Marecek J. F., Ugi I.*, J. Amer. Chem. Soc. **92**, 2429 (1974).