Synthesis of stereoisomeric P—H-spirophosphoranes based on hydrobenzoin

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Stereoisomers of P—H-spirophosphorane were synthesized by the reaction of racemic (*d,l*)- and scalemic *d*- and *l*-hydrobenzoins with $(MeO)_3P$ or $(Me_2N)_3P$. A reversible interconversion of two possible diastereomeric forms of racemic spirophosphorane was observed.

Key words: hydrobenzoin, hydrospirophosphorane, stereoisomerism, enantiomerism.

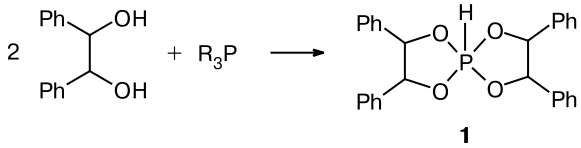
Current interest in the development of procedures for the synthesis of enantiopure compounds is due to ever-increasing demands of pharmaceutical industry placed on the technology of production of pharmaceuticals.[1] In this connection, organophosphorus compounds have attracted considerable attention as potential physiologically active compounds possessing various activities. Among them are antibacterial,[2] antiviral,[3,4] neurotropic,[5] and antitumor[6] activities. In many cases, the synthesized products are chiral and it is necessary to resolve them into optical antipodes. Therefore, the search for starting compounds that contain chirality inducers and can serve as precursors of homochiral physiologically active organophosphorus compounds is an important problem. Hydrophosphoryl compounds containing a phosphorus atom in an appropriate environment, which afford chiral α-heterosubstituted alkylphosphonates, are most often used for these purposes.[7] However, examples of the asymmetric synthesis of organophosphorus compounds that makes use of high reactivity of the P—H bond of hydrospirophosphoranes in reactions with compounds containing multiple bonds are scarce.[8]

Numerous hydrospirophosphoranes containing the phosphorus atom in different environment have been synthesized.[9] However, as a rule, either this environment is symmetrical or phosphoranes were prepared as racemates. The following enantiopure compounds served as precursors for hydrospirophosphoranes: esters of tartaric, α-phenypropionic, mandelic,[10] and α-amino carboxylic acids,[11] ephedrine and its derivatives,[12] and diamino diols.[13] Unfortunately, addition reactions to unsaturated centers were studied for only a limited number of the hydrospirophosphoranes obtained.

With the aim of extending the range of hydrospirophosphoranes containing the phosphorus atom in a chiral environment, we examined the possibility of preparing these compounds from stereoisomers of *d,l*-1,2-diphenylethane-1,2-diol (*d,l*-hydrobenzoin). A symmetrical hydrospirophosphorane prepared by the reaction of *meso*-hydrobenzoin with $(Me_2N)_3P$ was documented.[14]

5-Hydro-2,3,7,8-tetraphenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4,4]nonane ((*dl*)-hydrospirophosphorane (**1**)) was synthesized by the reaction of (*dl*)-hydrobenzoin with $(Me_2N)_3P$[14] or with $(MeO)_3P$ (Scheme 1).

Scheme 1



1

R = MeO, Me_2N

In both cases, the reaction was performed at the 2 : 1 ratio of the diol to the organophosphorus compound. According to the results of ^{31}P NMR spectroscopy, both reactions afforded phosphorane **1** in quantitative yield. The NMR spectra contained two singlets at $\delta_P^{maj} = -29.41$ and $\delta_P^{min} = -28.96$ due to the formation of two possible diastereomers in a ratio of 2.87 : 1. The major diastereomer is the *l*P*l*- and *d*P*d*-enantiomeric pair, and the second diastereomer is the *d*P*l* isomer (Scheme 2). Both singlets are transformed with time into broadened doublets with the coupling constants $^2J_{P,H}^{maj} = 834$ H and

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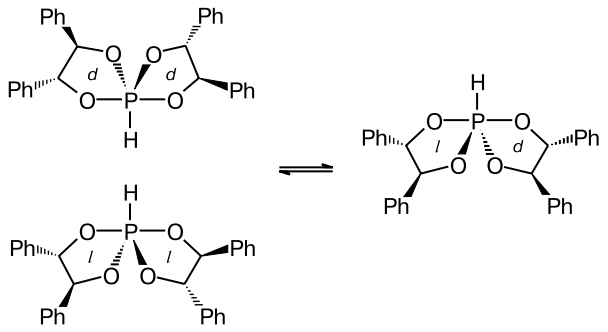
$^2J_{P,H}{}^{min}$ = 829 Hz (the accuracy of measurements was ±8 Hz) characteristic of the P—H bond. It should be noted that no signals at δ 140 are present, which is evidence for the absence of noticeable amounts of the tautomeric form of phosphorane **1** containing the trivalent phosphorus atom in the reaction mixture.[9b]

Scheme 2



X-ray diffraction study showed that crystals of phosphorane **1** contained only one of the diastereomers as the *l*P*l*- and *d*P*d*-enantiomeric pair. The structure of **1** is shown in Fig. 1.

Both enantiomers crystallize as a racemate in the centrosymmetric space group $P2_1/n$. In the crystal, the molecule has the noncrystallographic symmetry C_2 (the twofold axis passes along the P—H axis). As expected, the coordination environment of the phosphorus atom in the molecule can be described as a trigonal bipyramid containing the P—O bonds in diaxial and diequatorial positions and the P—H bond in the equatorial position. The heterocycle of the dioxaphospholane fragment P(1)O(1)C(1)C(2)O(2) adopts an O-envelope conformation, and the heterocycle of the P(1)O(3)C(3)C(4)O(4) fragment has a half-chair conformation. The O(1)—P(1)—O(3) bond angle is 173.8(1)°. The axial P—O bonds (aver., 1.664(3) Å within experimental error) are somewhat longer than the equatorial P—O bonds (aver., 1.602(3) Å within experimental error). The angles between the equatorial O—P and H—P bonds, on the one hand, and the axial O—P bonds, on the other hand, are close to 90°. The phenyl substituents at the C(1) and C(3) atoms are in equatorial positions, and the substituents at the C(2) and C(4) atoms are in axial positions. The angle between the planes of the benzene rings bound to the C(2) and C(4) atoms is 70.74°, and the distance between the centers of these rings is 5.213 Å.

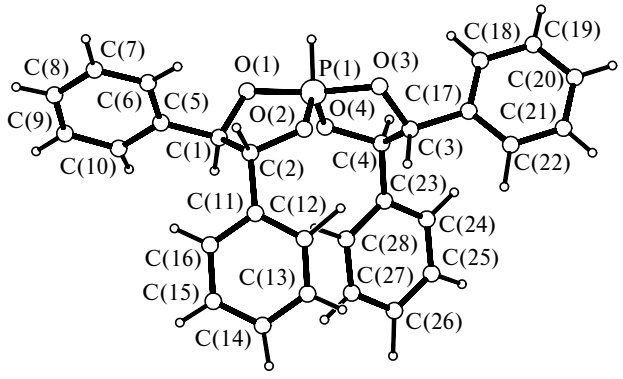


Fig. 1. Molecular structure of racemic 5-hydro-2,3,7,8-tetraphenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4,4]nonane. The *d*P*d* enantiomer is shown.

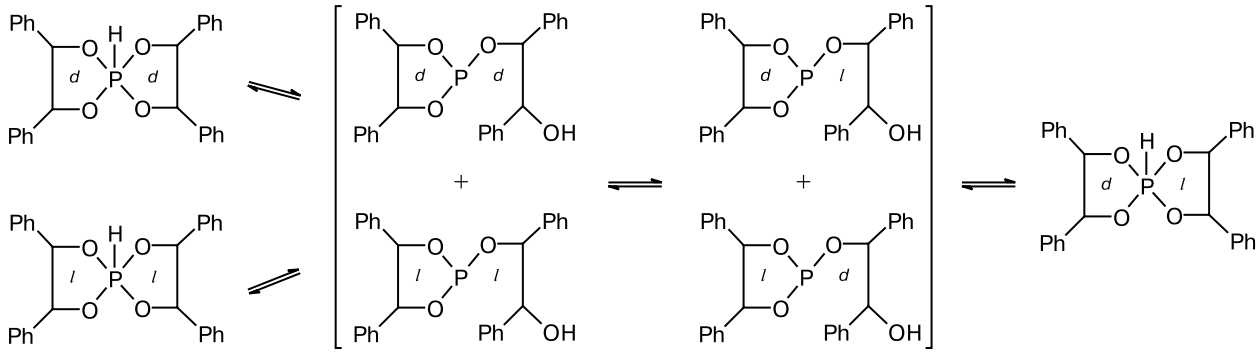
Immediately after dissolution of the crystals in benzene or toluene, the $^{31}P\{^1H\}$ NMR spectrum of the solution shows only one singlet at $\delta_P = -29.41$ assigned to the *d*P*d*,*l*P*l* diastereomer. However, another signal at $\delta_P = -28.96$ appears with time. This signal is apparently associated with the formation of the second *d*P*l* diastereomer, the intensity of the signal increasing with time or on heating (at 75 °C for 5 h). Finally, the integrated intensity ratio of the signals of the diastereomers at $\delta_P{}^{maj}$ and $\delta_P{}^{min}$ becomes equal to 2.87 : 1, *i.e.*, equal to that observed in the reaction mixture (apparently, due to establishment of equilibrium, see Scheme 2).

The ^1H NMR spectrum of the diastereomer of racemic (*d*P*d*,*l*P*l*) phosphorane **1** recorded immediately after dissolution of the sample contains a doublet of doublets for the methine proton H_A at δ 4.95 with $^3J_{H,H}$ = 8.6 Hz and $^3J_{H,P}$ = 2.7 Hz and a doublet for the methine proton H_B at δ 5.07. Both these protons belong to the five-membered phospholane ring. The proton at the phosphorus atom appears as a doublet at δ 7.88 with $J_{H,P}$ = 836 Hz. Signals for the protons of the second diastereomer appear in the spectrum with time or on heating: the signal for $H_A{}'$ at δ 4.94, which partially overlaps with the signal for the proton H_A, and the signal for $H_B{}'$ at δ 5.00 with $^3J_{H,H}$ = 8.2 Hz. The proton at the P atom appears as a doublet at δ 7.98 with $J_{H,P}$ = 827 Hz. The aromatic protons give a multiplet at δ 7.07—7.40.

Analogous reactions of $(MeO)_3P$ or $(Me_2N)_2P$ with the individual *d*-(*R*,*R*) or *l*-(*S*,*S*) enantiomers of hydrobenzoin, which were prepared from racemic hydrobenzoin according to a procedure described earlier,[15] produced homochiral *d*P*d* and *l*P*l* enantiomers of phosphorane **1**. As expected, neither storage nor heating of a solution of this phosphorane gives rise to signals of the second isomer in the ^1H and ^{31}P NMR spectra. Homochiral spirophosphoranes were also prepared as crystalline compounds.

The parameters of the NMR spectra of racemic samples of phosphorane **1** are similar to those of homochiral samples. It should be noted that the coupling constant $^4J_{H,H}$ = 0.7 Hz was observed for the high-field signal for H_A at δ 4.82 in the ^1H NMR spectrum of enantiopure phosphorane **1**. Presumably, this long-range coupling constant is due to coupling of the protons at the C(2) and C(4) atoms, located on the same side of the dioxa-

Scheme 3



phospholane rings, with the PH proton. According to the X-ray diffraction data, it is these protons that are in a nearly W-like conformation, which is most favorable for spin-spin coupling.

The following hypothesis as to the mechanism of interconversion of the diastereomers can be proposed. On the one hand, it is known that ring-chain tautomerism involving the form with the tricoordinate phosphorus atom is characteristic of hydrospirophosphoranes.[9b] On the other hand, unsymmetrical full esters of phosphorous acid can exchange the alkoxy substituents at the phosphorus atom,[16] which occurs particularly rapidly in the presence of acid catalysts.[17] A combination of these two processes in one reaction scheme would be expected to give rise to the observed equilibrium between the diastereomers. The ring opening in the *d*P*d* and *l*P*l* enantiomers of hydrospirophosphorane will result in the formation of the corresponding open-chain forms with the tricoordinate phosphorus atom. An exchange of the linear *d* and *l* dihydrobenzoin substituents followed by the five-membered ring closure will give rise to the second *d*P*l* diastereomer (Scheme 3).

To summarize, hydrospirophosphorane based on racemic and homochiral hydrobenzoins was synthesized for the first time.

Experimental

The $^{31}P\{^1H\}$ NMR spectra were recorded on a CXP 100 spectrometer in $CDCl_3$ (85% H_3PO_4 as the external standard). The ^1H and ^{13}C NMR spectra were measured on a Bruker MSL-400 instrument in $CDCl_3$. The IR spectra were recorded on a Vector 22 Fourier-transform IR spectrometer (Bruker). The optical rotation was measured on a Perkin—Elmer 341 polarimeter.

The crystallographic data for 5-hydro-2,3,7,8-tetraphenyl-1,4,6,9-tetraoxa-5-phosphaspiro[4,4]nonane at 20 °C: crystals of $C_{28}H_{25}O_4P$ are monoclinic, $a = 10.744(4)$ Å, $b = 16.270(7)$ Å, $c = 13.736(6)$ Å, $\beta = 106.91(4)°$, $V = 2297(2)$ Å^3, $Z = 4$, $M = 456.48$, $d_{calc} = 1.32$ g cm^{-3}, $F(000) = 960$, space group $P2_1/n$. The intensities of 2982 reflections were measured on an Enraf Nonius CAD-4 diffractometer at 20 °C (λ(Mo-Kα), $\omega/2\theta$ scanning technique, $2\theta_{max} < 53.8°$), of which 1756 reflections were with $I > 3\sigma$. The intensities of three check reflections showed no decrease in the course of X-ray data collection. The absorption correction was ignored because of the small absorption coefficient (μ(Mo) = 1.47 cm^{-1}). The structure was solved by direct methods first isotropically and then anisotropically using the SIR program.[18] The hydrogen atoms were located from difference electron density maps and their contributions to the structure amplitudes were taken into account in the final step of the refinement with fixed positional and isotropic displacement parameters. The final reliability factors were $R = 0.052$ and $R_w = 0.062$ using 1779 independent reflections with $F^2 \geq 3\sigma$. All calculations were carried out using the MOLEN complex program[19] on an AlphaStation 200 computer.

The atomic coordinates were deposited with the Cambridge Structural Database (CCDC 273247).

Synthesis of spirophosphorane 1 (general procedure). Hydrobenzoins *d*-(*R*,*R*) and *l*-(*S*,*S*) were synthesized according to a modified procedure.[15] The enantiomers were crystallized from 70% aqueous ethanol. For *d*-hydrobenzoin, m.p. 148 °C, $[\alpha]_D^{20}$ +120 (*c* 0.5, benzene). For *l*-hydrobenzoin, m.p. 148 °C, $[\alpha]_D^{20}$ −119 (*c* 0.5, benzene). Lit data:[20] for *d*-hydrobenzoin m.p. 148—150 °C, $[\alpha]_D^{20}$ +122 (*c* 0.5, benzene), for *l*-hydrobenzoin m.p. 148—150 °C, $[\alpha]_D^{20}$ −122 (*c* 0.5, benzene).

A. A mixture of *d*-, *l*-, or *d,l*-hydrobenzoin and $(MeO)_3P$ (2 : 1) was heated in a fivefold volume of toluene at 100—110 °C for 12—15 h using a Dean—Stark trap. The course of the reaction was followed by monitoring the amount of MeOH eliminated and the residual signal of $(MeO)_3P$ in the ^{31}P NMR spectrum of the reaction mixture. After completion of the reaction, the solvent was either completely removed *in vacuo* (a white powdered product) or partially removed with subsequent slow crystallization of phosphorane **1** in the cold.

B. A mixture of *d*-, *l*-, or *d,l*-hydrobenzoin and $(Me_2N)_3P$ (2 : 1) was refluxed in a fivefold volume of benzene for 5 h. After completion of the reaction, the solvent was either completely removed *in vacuo* or partially removed with subsequent slow crystallization of the product in the cold.

***d,l*-Hydrospirophosphorane (mixture of diastereomers upon rapid removal of the solvent).** The yield was 97.6%, white powder, m.p. 135 °C. Found (%): C, 73.11; H, 5.32; P, 6.40. $C_{28}H_{25}O_4P$. Calculated (%): C, 73.68; H, 5.52; P, 6.79. ^{31}P NMR (C_6D_6), δ: −29.41 (br.d, J = 834 Hz); −28.96 (br.d, J = 829 Hz). The integrated intensity ratio was 2.87 : 1.

***d,l*-Hydrospirophosphorane (*dPd,lPl* diastereomer).** The yield was 92.8%, white crystals, m.p. 149.5—151 °C. IR (KBr pellets), ν/cm^{-1}: 999—1060 (P—O—C); 1455, 1496 (Ph); 2430 (P—H); 3032, 3062, 3088 (CH_{arom}).

(*dPd*)-Hydrospirophosphorane. The yield was 81.0%, colorless crystals, m.p. 135—136 °C, $[\alpha]_D^{20}$ +24 (*c* 0.67, benzene). ^{31}P NMR (C_6D_6), δ: −29.41 (br.d, J = 834 Hz). ^{13}C NMR (C_6D_6), δ: 78.81 and 81.04 (both s, CHO); 124.94—136.16 (C_{arom}).

(*lPl*)-Hydrospirophosphorane. The yield was 83.2%, colorless crystals, m.p. 134—135 °C, $[\alpha]_D^{20}$ −20 (*c* 0.5, benzene). ^{31}P NMR (C_6D_6), δ: −29.41 (d, J = 834 Hz).

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