Cyclic phosphorochloridites (chloridates) based on chiral butane-2,3-diol and dihydrobenzoin as reagents for the analysis of enantiomeric compositions of alcohols by ^{31}P NMR spectroscopy

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The use of cyclic phosphorochloridites which were prepared based on PCl_3 and chiral butane-2,3-diol or hydrobenzoin as possible reagents for the analysis of the enantiomeric composition of chiral alcohols by ^{31}P NMR spectroscopy is considered. The diastereomeric dispersion of chemical shifts of the resulting phosphites as well as of derived phosphates and thiophosphates is compared with that of structurally similar reagents.

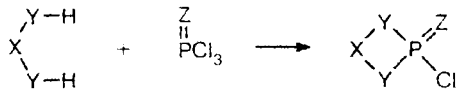
Key words: C_2-symmetrical chiral diols, chiral alcohols; enantiomeric composition; ^{31}P NMR spectra.

Phosphorus derivatives are widely used as reagents in the ^{31}P NMR analysis of enantiomeric compositions of organic compounds.[1] Presently, two different approaches to the design of these reagents are known. The first approach is based on the "principle of doubling" proposed by Horeau.[2] The realization of this principle requires that two fragments of the chiral substrate under study be located about the indicator phosphorus atom.[3,4] The advantage of this approach is the achirality of the reagent used and the drawbacks are the quadratic dependence of the determined value (enantiomeric excess, *ee*) on the experimentally observed intensities of signals and the complication of the ^{31}P NMR spectra due to the manifestation of isomerism of the pseudochiral phosphorus atom in *meso* adducts.[1]

The second approach is based on the use of cyclic organophosphorus reagents for enantioselective analysis (OPRESA). In these reagents, the organic fragment of the ring is chiral but has an axial twofold symmetry, which leads to the achirality of the phosphorus center and eliminates the problem of its static and dynamic stereochemistry. Phosphorus acid chlorides[5–9] and amides[10] have been used as such reagents. In some cases, an apparent advantage of the latter (primarily, their higher stability compared to acid chlorides) becomes a drawback because "linking" with the substrate under study either requires higher temperatures or is time consuming. Subsequently, the authors who have designed OPRESA based on amides of phosphorus acids recommended use of the corresponding acid chlorides.[9]

The standard procedure for the preparation of OPRESA with an axially symmetrical unit involves the reaction of an appropriate organic ligand containing two active H-functions with phosphorus acid trichlorides.

Scheme 1



X — C_2-symmetrical chiral fragment
Y = O, NR
Z = lone electron pair, O.

Reagents based on nitrogen heterocycles (Y = NR), which have been prepared previously,[9,10] show good characteristics of diastereomeric dispersion of chemical shifts ($\Delta\delta$, DDCS*) for derivatives of alcohols, thiols, *etc.* However, the DDCS value is an important but not the only factor which should be taken into account in the design and which is particularly essential in actually choosing OPRESA. Commercial nonracemic C_2-symmetrical *N,N'*-disubstituted diamines are few in number and these reagents are rather expensive. Commercial nonracemic C_2-symmetrical diols are substantially more abundant. Besides, derivatives of natural tartaric acid are among the cheapest nonracemic reagents. A general procedure for their preparation with high enantiomeric purity from the initial achiral com-

* The term DDCS has been used previously[1] and denotes the difference between the chemical shifts observed in the NMR spectra of the diastereomeric derivatives that formed in the reaction of the reagent and the substrate under study.

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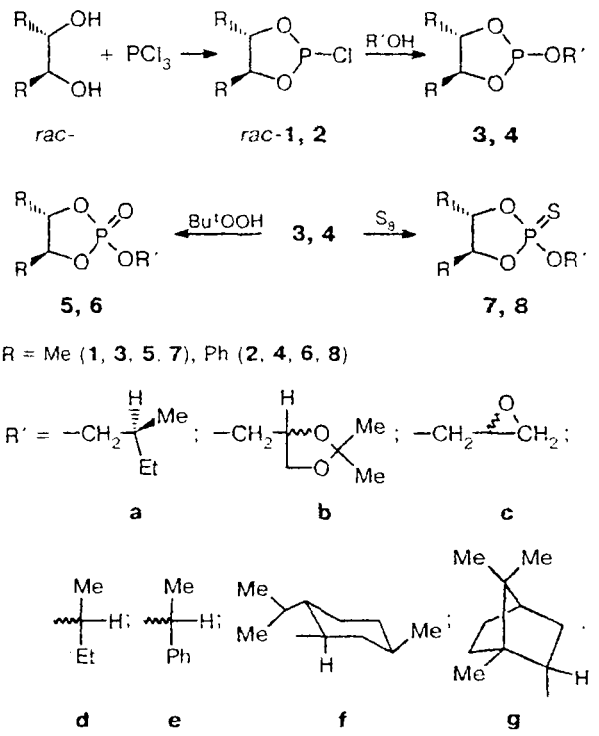
pounds by catalytic asymmetrical dihydroxylation according to Sharpless[11] is an additional argument in favor of a search for matrices for OPRESA in the series of C_2-symmetrical vicinal diols.

We examined the possibility of the use of 2-chloro-*trans*-4,5-dimethyl- (**1**) and 2-chloro-*trans*-4,5-diphenyl-1,3,2-dioxaphospholanes (**2**), which were prepared from the *threo* isomers of butane-2,3-diol and hydrobenzoin, respectively, as OPRESA. Both initial alcohols are commercial enantiomerically pure reagents and can also be prepared by asymmetrical dihydroxylation of *trans*-but-2-ene and *trans*-stilbene.[11,12] We used racemic *threo* isomers **1** and **2** because the racemic form made it possible to perform studies with the use of both racemic and nonracemic chiral substrates. The ^{31}P NMR spectra of adducts of both types of substrates have two signals with close integral intensities. This character of the spectral patterns makes it possible to readily identify these signals even in complicated spectra. Moreover, in the case of enantiomerically pure alcohols as substrates (such as **a**, **f**, and **g** in Scheme 2), the racemic reagent allows one to suffice with the only spectrum in the stage of determination of the diastereomeric dispersion of chemical shifts, whereas the use of enantiomerically pure reagents in this stage either does not allow one to determine DDCS (because in this case, only one signal of the derivative should be observed) or requires that two spectra of the derivatives, which are prepared with the use of enantiomerically pure reagents with the opposite configurations, be recorded. The latter situation is not always possible. In addition, the DDCS value in this case is determined indirectly and less accurately. Finally, the possible undesirable kinetic diastereoselectivity in the case of racemic reagents is manifested as a deviation of the signal ratio of the derivatives from the known value of 1 : 1, which makes it possible to reliably reveal this important characteristic.

Previously, 2,3-butanediol phosphorochloridate, *viz.*, 2-chloro-(4*R*,5*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane, has already been used as OPRESA.[5] The DDCS values of

Scheme 2



the phosphates (analogous to compounds **5** in Scheme 2) under investigation appeared to be insignificant, which is (as is presently obvious) customary for P^{IV} derivatives. The development of new procedures for the analysis of the enantiomeric composition of chiral substrates which do not require isolation of derivatizing reagents in individual form[6–9] made it possible to use more efficient P^{III} derivatives for enantioselective analysis. Within the framework of the general problem of the rational design of derivatizing reagents for NMR analysis of the enantiomeric composition, the lack of data on the DDCS values of 1,3,2-dioxaphospholane derivatives containing the simplest sub-

Table 1. Chemical shifts (δ_P) and the diastereomeric dispersion of chemical shifts ($\Delta\delta_P$) in compounds **3—8**

R'OH	3		4		5		6		7		8	
	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ
a	137.75, 137.33	0.42	141.19	<0.01	12.42, 12.37	0.05	12.11	<0.01	79.36, 79.30	0.06	79.51, 79.50	0.01
b	138.87, 138.72	0.15	141.66, 141.23	0.43	12.55	<0.01	12.05, 12.03	0.02	80.21	<0.01	79.31, 79.27	0.04
c	138.01, 137.53	0.48	141.91, 141.81	0.10	12.83, 12.81	0.02	12.07, 12.01	0.05	80.24, 79.96	0.28	79.42, 79.37	0.05
d	140.25, 139.48	0.77	141.44, 141.15	0.29	11.95	<0.01	11.39, 11.36	0.03	78.75, 78.72	0.02	78.31, 78.29	0.02
e	139.80, 139.18	0.62	141.34, 141.16	0.19	11.72, 11.62	0.10	11.06, 11.04	0.02	78.66, 78.53	0.14	77.97, 77.95	0.02
f	141.62, 140.33	1.29	142.73, 142.06	0.66	12.48, 12.37	0.12	11.65, 11.35	0.31	79.10, 78.89	0.21	78.47, 78.04	0.42
g	140.59, 138.77	1.82	141.90, 141.09	0.80	12.57, 12.46	0.11	12.26, 12.20	0.06	79.25	<0.01	79.32, 79.19	0.13

stituents (—Me) and the substituents which are the most popular chirality inductors (—Ph) is considered a logical gap. In the present work, we obtained data which close this gap.

Operations with both diols were performed according to the common scheme. Reagents **1** and **2** were prepared in THF solutions from the corresponding glycols under the action of an equimolar amount of PCl_3 in the presence of a 3—5-fold excess of Py or Et_3N and were stored in solutions without isolation. The alcohols under study were added to an aliquot of the solution of the reagent taken in a small excess, and the $^{31}P\{^1H\}$ NMR spectra of the resulting mixtures of diastereomeric phosphites **3** and **4** were analyzed. The chemical shifts of the signals for the individual diastereomers and the differences between these values ($\Delta\delta$) are given in Table 1. After the spectra of the phosphites were recorded, one portion of the reaction mixture was oxidized with Bu^{t}OOH and the second portion was treated with elemental sulfur, thus completely converting the phosphites into phosphates (**5** and **6**) or thiophosphates (**7** and **8**).

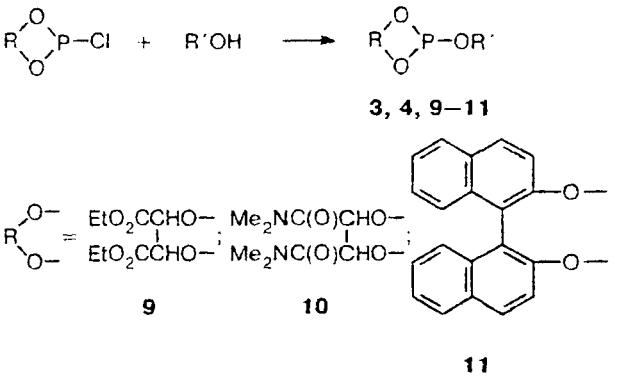
The DDCS values for these P^{IV} derivatives are given in Table 1. The chiral alcohols R′OH under investigation included three primary and four secondary alcohols. Their structures are shown in Scheme 2.

The data for both ligands given in Table 1 support the regularity of the advantage of P^{III} derivatives over P^{IV} derivatives from the standpoint of the observed values of the diastereomeric dispersion of ^{31}P chemical shifts. The fact that the $\Delta\delta_{aver}$ values for dimethyl-substituted phosphites **3** (0.791) surpass those for diphenyl derivatives **4** (0.353) is somewhat unexpected. On the whole, the $\Delta\delta$ values for derivatives **3** and **4** are large enough to allow one to use the corresponding reagents **1** and **2** as OPRESA. It should be also noted that these reagents do not exhibit pronounced kinetic diastereoselectivity and, except for **3a** and **3c**, the diastereomeric ratio (*dr*) of **3** and **4** (*dr* for derivatives **5**—**8** in the cases where it can be determined is equal to that for the initial compounds **3** and **4**), which was determined from the integral intensities, is 1±0.05.

Cyclic phosphorochloridites, derivatives of C_2-symmetrical chiral diols, proposed as OPRESA can be quantitatively arranged in the order of increasing efficiency based on the average DDCS values ($\Delta\delta_{aver}$) for phosphites **3**, **4**, and **9**—**11** (Scheme 3), which were estimated for the common set of chiral alcohols R′OH.

The complete series of the alcohols R′OH shown in Scheme 2 cannot be used for this purpose because data for isoamyl alcohol **a** and borneol **g** are lacking in the original studies.[6,7] Because of this, in the case of phosphites, we calculated the average DDCS values for five residues **b**—**f**. The values of $\Delta\delta_{aver}$ calculated based on the data of the present work and previous studies[6—8] are 0.66, 0.31, 0.64, 2.74, and 3.12 ppm for compounds **3**, **4**, **9**, **10**, and **11**, respectively. In this series, phosphites **10** and **11**, which were prepared based on tartaric acid bisdimethylamide and axially chiral 1,1′-binaphthyl-2,2′-diol, respectively, apparently stand out as possessing the highest chiral discrimination of alcohols. Phosphorochloridite based on hydrobenzoin, *viz.*, reagent **2**, is the last in the series and can be recommended for practical use only in special cases, for example, as an auxiliary reagent. The characteristics of reagent **1**, which was prepared from chiral butanediol, competes favorably with those of tartrates recommended previously.[6] Enantiomerically pure 2,3-butanediol is more expensive than esters of natural tartaric acid, but its advantages are the higher chemical inertness of the methyl substituent compared to the ester group and the simplicity of the ^1H and ^{13}C NMR spectra, which may be of importance in the analysis of the DDCS values using other (except for phosphorus) nuclei.

Scheme 3



Experimental

The $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker MSL-400 spectrometer (161.92 MHz) relative to the external standard, H_3PO_4; THF was used as the solvent.

Commercial *threo*-butane-2,3-diol (Ferak, Berlin) was additionally distilled before use. *threo*-Hydrobenzoin was synthesized from *trans*-stilbene according to a known procedure.[13]

2-Chloro-(4*R,5*R**)-dimethyl-1,3,2-dioxaphospholane (*rac*-1)** was synthesized according to known procedures[6,7] from PCl_3 (2.2 mL, 24.2 mmol) and *threo*-butane-2,3-diol (2.17 g, 24.2 mmol). ^{31}P NMR, δ: 170.25. Based on the ^{31}P NMR spectral data, the content of *meso*-**1** (δ 166.59; *cf.* Ref. 14: δ 167.5) in the product obtained was no more than 5% of the total amount of dioxaphospholane.

2-Chloro-(4*R,5*R**)-diphenyl-1,3,2-dioxaphospholane (*rac*-2)** was prepared in THF according to a known procedure.[15] ^{31}P NMR, δ: 172.20.

Diastereomeric phosphites **3** and **4**, phosphates **5** and **6**, and thiophosphates **7** and **8** were prepared as described previously.[7,8]

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