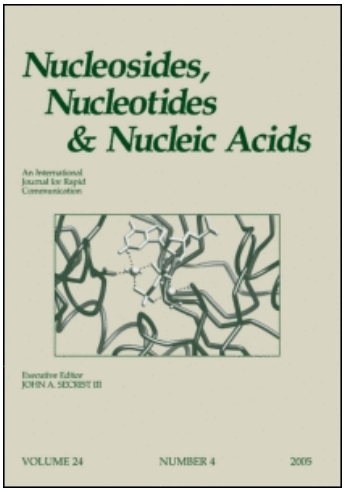

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A Proposal for a New Stereochemical Notation for *P*-Chiral Nucleotide Analogues and Related Compounds

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A PROPOSAL FOR A NEW STEREOCHEMICAL NOTATION FOR *P*-CHIRAL NUCLEOTIDE ANALOGUES AND RELATED COMPOUNDS

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▫ *A new stereochemical notation for P-chiral nucleotide analogues and related compounds is proposed. In this notation, the names of configurations, designated as D_P and L_P, are derived from a geometrical relationship, rather than from priority rules, of substituents at the phosphorus centre. This new stereochemical description offers clear advantages over the CIP R/S nomenclature, particularly when used for comparing the influence of absolute configuration at the phosphorus centre on physicochemical and biological properties of oligonucleotide analogues or in stereochemical correlation analysis of P-chiral nucleotide derivatives.*

Keywords Stereochemical Notation, D_P/L_P, *P* = Chiral, Nucleotide Analogues

INTRODUCTION

The R/S convention of Cahn, Ingold, and Prelog (CIP) for describing an absolute configuration around a chiral carbon atom[1] is commonly used in organic chemistry and is applicable to other stereogenic centers. However, since the notation is based on a priority order of substituents around the chiral center, it may lead to a non-intuitive relationship between R/S configurations and the spatial arrangements of the substituents. The problem is particularly acute for biologically important *P*-nucleotide analogues for which, due to changes in a priority order of

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substituents, the configuration changes while a geometrical relationship of the relevant substituents remains the same. This makes it difficult to find directly a relationship between absolute configuration at the phosphorus center and physicochemical or biological properties of even closely related nucleotide analogues, without detailed comparison of structural features of such compounds. For example, snake venom phosphodiesterase is known to preferentially hydrolyze dinucleoside phosphorothioates with R_P configuration at the phosphorus center, but for methyl 5′-nucleoside phosphorothioates, it is the S_P diastereomer that is a substrate for the enzyme.[2] This change from R_P to S_P in a stereochemical preference of the snake venom enzyme is only apparent and it is solely due to changes in the priority order of substituents upon replacement of the 3′-nucleoside moiety by the methyl group, as the spatial arrangement around phosphorus remains the same in both compounds.

There are many other examples of nucleotides containing tetra-coordinated phosphorus, in which the change of a ligand CIP priority due to a reaction may lead to a non-intuitive R_P/S_P relationship of the substrates and products[3–7] (e.g., methanephosphonates, boranophosphates, phosphoroselenoates, phosphorohalogenates, phosphorotriesters, etc.).[8] This makes the analysis and comparison of stereochemical courses of related reactions troublesome and may easily lead to mistakes.

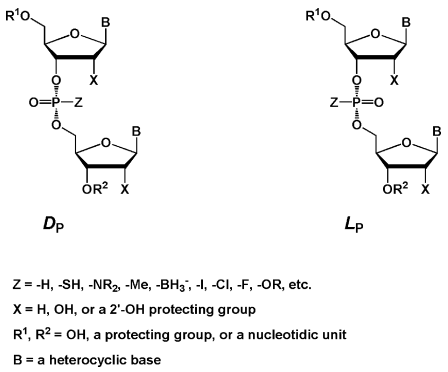
To alleviate this sort of inconvenience of the CIP nomenclature, we propose a new stereochemical notation for *P*-chiral nucleotide analogues and related compounds, which, similarly to D/L notation commonly used in carbohydrate and peptide chemistry, would emphasize a geometrical relationship between closely related compounds and permit direct, intuitive comparison of properties that are due to a spatial arrangement of substituents; e.g., susceptibility to enzymatic digestion, stability of the formed complexes, correlation between configuration at the phosphorus centre and the ^{31}P NMR chemical shifts, etc.

DISCUSSION

Definitions of D_P/L_P Stereochemical Notation

The proposed new naming system is devoted primarily for designation of configuration at the tetra-coordinated phosphorus center of nucleotide analogues and is based on structural relationships between molecules rather than on priority order of ligands at the chiral center.

Taking as a starting point a generally adopted way of presenting dinucleoside phosphates with a nucleosid-3′-yl unit placed up and a nucleosid-5′-yl unit down, we can consider such pictures as Fischer projections (Scheme 1) and define a D_P configuration as one having a single-bonded ligand **Z** (e.g., –H, –SR, –NR_2, –Me, –BH_3^-, –I, –Cl, –F, –OR, etc.) to the right, and the phosphoryl group to left. For L_P configuration, the arrangement of ligands **Z** and the phosphoryl function are opposite; i.e., **Z** group in place to the left, and the P = O group to the right (Scheme 1).



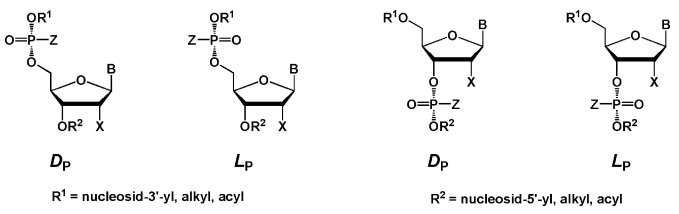
SCHEME 1 Representative structures for D_P and L_P configurations.

This notation seems to be simple and intuitive, as dinucleotide unit is drawn in the typical manner for this type of molecules and the L_P/D_P descriptors were chosen to indicate left (L_P) or right (D_P) position of the **Z** group. The most important feature of this notation is that the name of a configuration is independent of the nature of the ligands and will change to the opposite one only when a stereochemical environment of the ligand **Z** changes. Thus, the inversion of configuration at the phosphorus center will always be accompanied by a change in the notation from D_P to L_P or from L_P to D_P, while for stereoretentive transformations, the names of the configurations remain unchanged.

The D_P/L_P stereochemical notation can be expanded further via replacing a nucleoside-3′-yl or nucleoside-5′-yl moiety in the structures in Scheme 1 with another functionality (Scheme 2) to permit its use, e.g., in a stereochemical correlation analysis of mononucleoside phosphate derivatives (vide infra). These aspects will be discussed in details in the future publications on this subject.

Application of D_P/L_P Stereochemical Notation in Structural Studies

In Table 1, the R_P/S_P versus D_P/L_P notations for several dinucleotide analogues are compared. One should note that R_P/S_P configurations among these derivatives vary depending on the priority order of the ligands at the phosphorus center, while



SCHEME 2 D_P/L_P notation for mononucleoside phosphate analogues.

TABLE 1 Comparison of the R_P/S_P vs. D_P/L_P Notations for Selected Dinucleotide Analogues

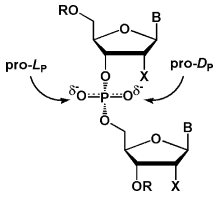
Ligand **Z**	CIP notation for D_P isomers	CIP notation for L_P isomers
–H	S_P	R_P
–SR′	R_P	S_P
$-NR'_2$	S_P	R_P
$-CH_3$	S_P	R_P
$-BH_3^-$	S_P	R_P
–I	R_P	S_P
–Cl	R_P	S_P
–F	R_P	S_P

For abbreviations, see Scheme 1.

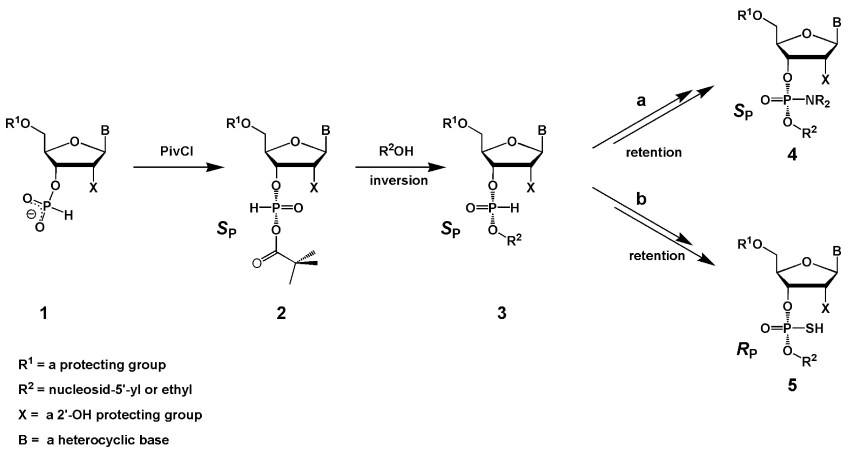
in the new stereochemical notation proposed in this article, all compounds in the left column, irrespective of their chemical identity, will have D_P configurations, while those in the right column, L_P configurations.

This invariance of D_P/L_P notation with changes in a chemical character of a **Z** group is useful for structural comparison of *P*-modified nucleic acid analogues. For example, in the canonical B-form of DNA double helix, the single-bonded ligands **Z** are always directed to the major groove for D_P diastereomers (an inward pointing modification), while for L_P isomers, these are directed outside, to the bulk-solvent (an outward pointing modification). Thus, in the D_P/L_P notation, a geometrical placement of ligands at an internucleotide bond becomes immediately apparent from the name of a configuration and should facilitate a comparative analysis of oligonucleotides bearing various modifications at phosphorus center.

This notation can also be useful when analyzing the influence of an absolute configuration at the phosphorus center of nucleotide analogues on their susceptibility to enzymatic digestion. For example, R_P-dinucleoside phosphorothioate and S_P-methyl nucleoside-5′-yl phosphorothioate (compounds mentioned in the Introduction), despite opposite absolute configurations, are both substrates for snake venom phosphodiesterase, because they have the same geometrical arrangement of ligands at the phosphorus center. This fact is clearly reflected in the D_P/L_P notation, as both compounds have the same D_P configuration, and thus a similar geometrical relationship to the active site of the enzyme.



SCHEME 3 A structure for definition of pro = D_P and pro = L_P configurations.

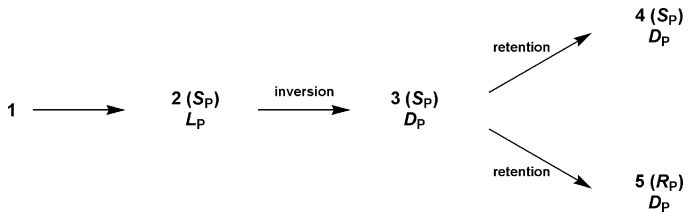


SCHEME 4 Stereochemistry of a sequence of reactions described using the R_P/S_P convention. Note that the descriptors often do not follow the stereochemical course of reactions.

For prochiral phosphate centers, e.g., as those in the native internucleotide bonds, pro-D_P and pro-L_P notation can be used. This can be useful when discussing a geometrical relationship between ligands of the phosphorus centre and a protein, e.g., in the context of enzymatic reactions (Scheme 3).

Application of the D_P/L_P Notation for Describing Stereochemistry of Reactions

Recently, during our studies on stereoselective synthesis of dinucleoside *H*-phosphonate diesters, we experienced severe difficulties in discussing stereochemistry of the involved transformations using the R_P/S_P nomenclature, due to frequent changes in priority order of substituents occurring during the investigated processes. For example, in the esterification of S_P diastereomer of mixed anhydride **2** (Scheme 4) with 5′-OH-nucleoside (or a primary alcohol), the produced diester **3** has the same configuration (S_P) as the substrate, despite the fact that the reaction proceeds with inversion of configuration. This is because the pivalic residue, a substituent of higher CIP priority, is replaced by a primary alkyl residue, which has



SCHEME 5 The same sequence of reactions as in Scheme 4 described using the D_P/L_P convention.

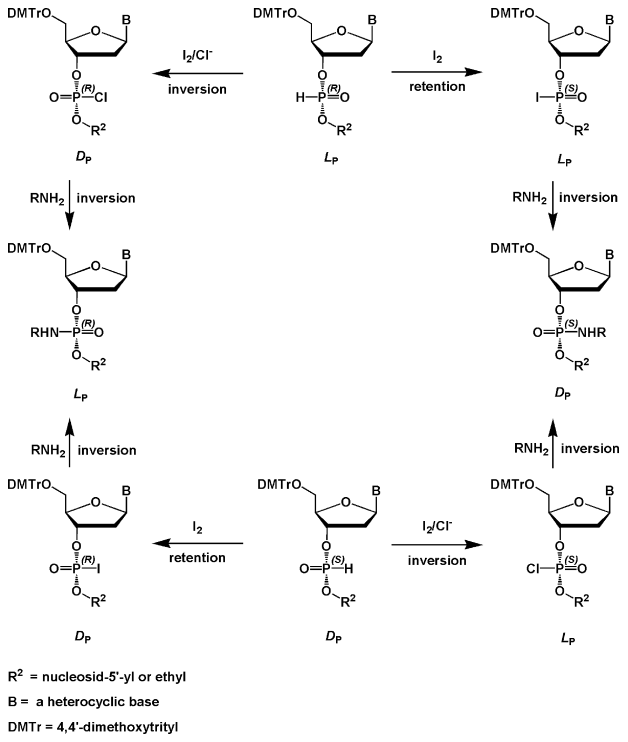
a lower CIP priority order. However, if the introduced alcohol would be a tertiary one (e.g., *tert*-butanol), the resulting diester would have R_P configuration.

The diester **3** produced can be subjected to further transformations, for example, to form phosphoramidate **4** (Scheme 4, path **a**). Such process, if performed with an overall retention of configuration [7] would yield product **4** with the same configuration (S_P) as the substrate. However, if the same S_P-diastereomer of diester **3** is stereoretentively sulfurized, the produced phosphorothioate **5** has opposite absolute configuration (R_P) to that of **3** due to CIP substituents priority rules.

All these inconveniences are alleviated in the D_P/L_P nomenclature. Thus, the transformations presented in Scheme 4 become much more intuitive, when the D_P/L_P notation is used since stereochemical courses of the reactions investigated are reflected in the name of configurations (Scheme 5) and geometrical relationship between substrates and products are immediately apparent.

Another example of application of the new notation in a stereochemical correlation analysis of diastereomeric phosphoramidates is shown in Scheme 6 (adapted from Nilsson and Stawinski).[7]

Also here, in contrast to the *R/S* notation (indicated above the phosphorus atoms), the inversion of configuration during the course of the reaction is always



SCHEME 6 An example of application of the new notation in a stereochemical correlation analysis.

clearly reflected in changing the name of configuration form D_P to L_P (or vice versa), while for the reactions occurring with retention of configuration, the notation remains unchanged.

CONCLUSIONS

We propose a simple, new stereochemical notation for *P*-chiral nucleotide analogues and related compounds that is based on a geometrical relationship, rather than on priority rules, of substituents at the phosphorus centre. D_P/L_P names reflect a spatial arrangement of substituents at the chiral centre and the notation changes to the opposite one only when a geometrical rearrangement of ligands occurs during the course of the reaction. Since the notation emphasizes a structural relationship between closely related compounds, it permits direct and intuitively understandable comparison of properties of related *P*-chiral nucleotide analogues that are due to a spatial arrangement of substituents. The notation also alleviates most inconveniences of the CIP nomenclature and helps to avoid possible mistakes in description of stereochemical courses of reactions in stereochemical correlation analysis, as the configuration of the phosphorus center is immediately apparent.

The work is in progress to elaborate a more general concept of the D_P/L_P nomenclature to encompass a wider range of biomolecules containing phosphorus.

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