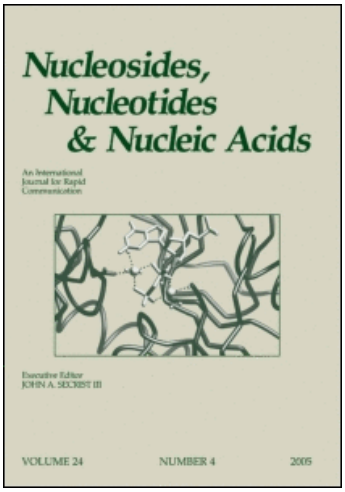

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A proposal for a convenient notation for *P*-chiral nucleotide analogues. Part 3. Compounds with one nucleoside residue and nonnucleosidic derivatives

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A PROPOSAL FOR A CONVENIENT NOTATION FOR *P*-CHIRAL NUCLEOTIDE ANALOGUES. PART 3. COMPOUNDS WITH ONE NUCLEOSIDE RESIDUE AND NONNUCLEOSIDIC DERIVATIVES

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□ *Recently, we have proposed a new D_P/L_P stereochemical notation for P-chiral dinucleoside monophosphate analogues that permits simple correlation between spatial arrangement of the substituents and the configuration at the phosphorus center. As an extension of this work, we present here applications of the D_P/L_P notation to derivatives containing only one nucleoside unit (*e.g.*, alkyl nucleoside phosphodiesters, nucleoside phosphomonoesters, cyclic phosphate derivatives, nucleoside di-, and triphosphates) and to nonnucleosidic phosphorus compounds.*

Keywords Stereochemical notation; D_P/L_P; *P*-chiral; Nucleotide analogues

INTRODUCTION

In the previous parts of this series, we presented a concept of a new notation for configuration of *P*-chiral nucleosidic phosphates and their analogues.[1] According to this proposal, four ligands at the phosphorus center of an nucleotide analogue are designated as $\mathbf{G_1}$, $\mathbf{G_2}$, **X**, and **Z**, and the compound is presented in a Fischer-like projection, in such a way that

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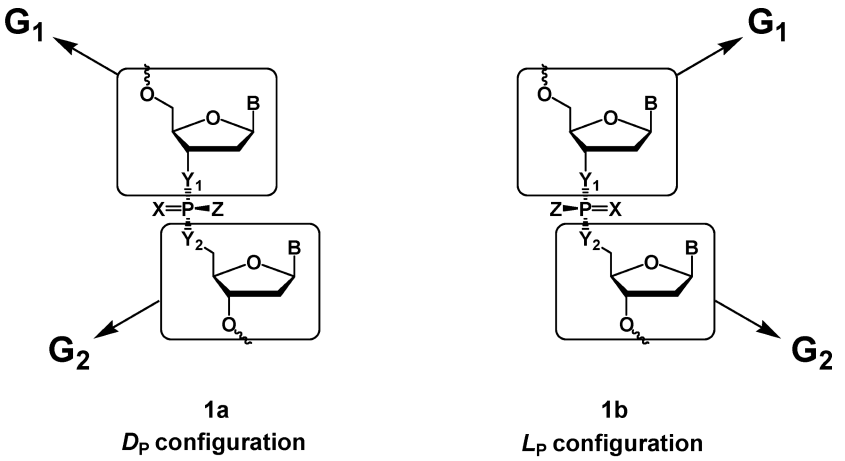


Z: -H, -SR, -NR_2, -Me, -SiR_3, -BH_3^-, -I, -Cl, -F, -OR, *etc.*
Y_1, Y_2 : O, S, NR, CR_2, *etc.*
X : O, S, Se, Te, NR, CR_2, *etc.* or a free electron pair
G_1: nucleoside-3'-yl, nucleoside-2'-yl, alkyl, aryl, acyl, *etc.*
G_2: nucleoside-5'-yl, alkyl, aryl, acyl, *etc.*

FIGURE 1 Structures for definition of the extended D_P/L_P system.

ligands $\mathbf{G_1}$ and $\mathbf{G_2}$ occupy vertical, and **X** and **Z**, horizontal positions, as shown in Figure 1. The positions of ligands $\mathbf{G_1}$ and $\mathbf{G_2}$ are fixed ($\mathbf{G_1}$ is an upper unit and $\mathbf{G_2}$, the lower unit), and the D_P/L_P configuration of a *P*-chiral center is determined by a relative position of ligands **Z** and **X**.

For compounds of type **1** with known absolute configuration at the phosphorus center, the D_P/L_P configuration is derived by designating the phosphorus-bound ligands as $\mathbf{G_1}$, $\mathbf{G_2}$, **X**, and **Z**, according to the following rules (see also Sobkowski et al. [1b]):

Rule 1: For dinucleoside phosphates presented in a form similar to the Fischer projection as shown in Figure 1, that is, with a nucleosid-3′-yl standing for $\mathbf{G_1}$ and a nucleosid-5′-yl standing for $\mathbf{G_2}$ moiety, D_P configuration is defined as the one having a single-bonded ligand **Z** to the right, and the P=X group to left. For compounds with L_P configuration, **Z** is to the left, and the P=X group to the right. **X** is any atom double-bonded to the phosphorus or a free electron pair. $\mathbf{Y_1}$ and $\mathbf{Y_2}$ are atoms, or group of atoms, that are integral parts of $\mathbf{G_1}$ and $\mathbf{G_2}$ units.

Rule 2: For nucleotide analogues having carbohydrate residues other than ribo- or deoxyribofuranose, the assignment of ligands as $\mathbf{G_1}$ and $\mathbf{G_2}$ is done primarily with respect to their resemblance to the natural

nucleosidic residues. If such analogy is not obvious, the following rules should be used:

(a) A carbohydrate residue having a phosphorus center bound to a carbon atom of higher order is assigned as $\mathbf{G_1}$.

(b) If carbon atoms to which the phosphorus center is attached are of the same order in both carbohydrate residues, the residue of higher CIP priority is assigned as $\mathbf{G_1}$.

Rule 3: If both **X** and **Z** can form a double bond with phosphorus, the following order of priority should be used for the assignment of ligand **X** (P=X bond):

(a) P=O > P=S > P=Se > P=Te > P=N.

(b) In other instances, the double bond should be set to an atom of lower CIP priority.

Configurations with **X** and **Z** assigned oppositely to that specified by Rule 3a or 3b, should be referred to as pseudo-D_P or pseudo-L_P.

In this article, 2 additional rules (Rule 4 and 5) were formulated to extend the D_P/L_P notation to compounds with only one nucleoside unit or to nonnucleosidic derivatives.

Rule 4: If $\mathbf{G_1}$ or $\mathbf{G_2}$ group is a nonnucleosidic residue (e.g., alkyl, aryl, acyl, sulfonyl, phosphoryl, etc.), the nucleoside keeps its original position as $\mathbf{G_1}$ or $\mathbf{G_2}$, while the assignment of nonnucleosidic ligands is done as follows:

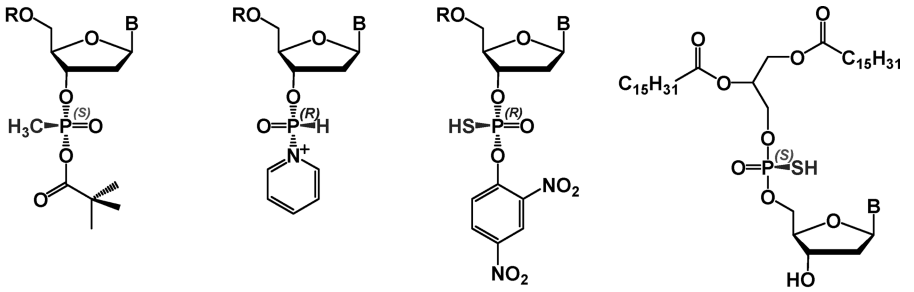
(a) If only one ligand can form double bond with phosphorus, this one should be designated as **X** (P=X bond) while from among the remaining ligands the residue of lower CIP priority should be assigned as **Z**.

(b) If 2 ligands can form double bond with phosphorus, these 2 should be designated as **X** and **Z** according to Rule 3.

(c) If 3 ligands can form double bond with phosphorus, the assignment of **X** (P = X bond) should be done according to Rule 3, and from among the remaining ligands the residue of lower CIP priority should be designated as **Z**.

(d) If a nonnucleosidic residue is a phosphate, polyphosphate, or their analogues, it should be designated as $\mathbf{G_1}$ or $\mathbf{G_2}$ group while **X** and **Z** should be assigned according to Rule 3.

In the cases a–c, the fourth ligand becomes the second **G** group.



L_P-(S_P)-methanephosphonate **2**

D_P-(R_P)-*H*-phosphonate **3**

L_P-(R_P)-phosphorothioate **4**

D_P-(S_P)-phosphorothioate **5**

FIGURE 2 D_P/L_P notation for compounds with one nucleoside residue.

Rule 5: If $\mathbf{G_1}$ and $\mathbf{G_2}$ groups are nonnucleosidic residues, ligands **X** and **Z** should be assigned according to the appropriate Rules 1–4, while the ligand allocation to $\mathbf{G_1}$ and $\mathbf{G_2}$ positions is governed by the CIP convention: the group with higher CIP priority should be designated as $\mathbf{G_1}$, and the one with lower CIP priority, as $\mathbf{G_2}$.

DISCUSSION

An unequivocal assignment of the D_P/L_P descriptors to dinucleoside monophosphate analogues can be done using Rules 1–3, and this was discussed in detail in Part 2 of this series.[1b] To extend the D_P/L_P notation to *P*-chiral phosphate analogues having only one nucleosidic residue and to *P*-chiral nonnucleosidic compounds, 2 additional rules were required (Rules 4 and 5). In this article, we present applications of the D_P/L_P stereochemical notation to these classes of phosphorus compounds.

1. *P*-Chiral Analogues of Mononucleotides

The basic framework of the D_P/L_P notation was developed for nucleotide analogues containing two nucleosidic units attached to a chiral phosphorus center. However, by a formal replacement of one of the ligands **G** in the structure **1a** or **1b** (Figure 1) by an alkyl, aryl, acyl, sulfonyl, etc. group, this notation can be extended to compounds with only one nucleoside moiety. In this way, stereochemistry of reactive nucleotide derivatives, for example, mixed anhydrides of nucleoside methanephosphonates (**2**), *H*-phosphonate intermediates (**3**), or various model compounds (**4**, **5**), could be discussed using the D_P/L_P convention (Figure 2).

To assign D_P/L_P descriptors to such compounds, first, a nucleosidic residue has to be designated as ligand $\mathbf{G_1}$ or $\mathbf{G_2}$, according to basic rules

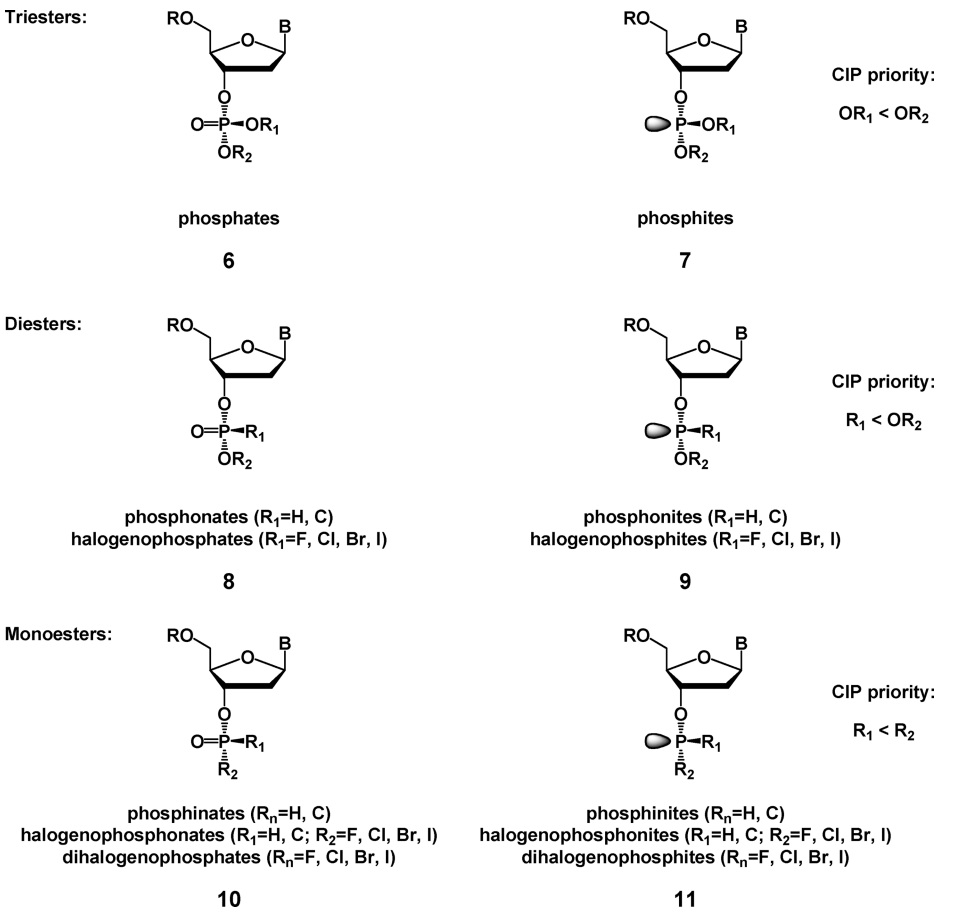


FIGURE 3 General structures of nonionic phosphorus esters with one nucleoside residue.

of the *D*P/*L*P notation. Then, the remaining nonnucleosidic ligands are designated as **X**, **Z**, and $\mathbf{G_1}$ or $\mathbf{G_2}$, according to Rule 4. This class of compounds can be divided into 3 groups, depending on the number of ligands that can form a double bond to phosphorus.

*(a) D*P*/L*P *Notation For Compounds with One Ligand Able to Form a P=X Bond*

Nucleoside monophosphate analogues containing only one phosphorus ligand that can form a double bond encompass a broad spectrum of tri- and tetracoordinated phosphorus compounds. Examples include esters **6–11** (Figure 3) as well as their various analogues in which one or more oxygen atoms in phosphoric center were replaced, for example, by other chalcogens or a nitrogen.

In all cases, after assignment of nucleosidic residue and P=X moiety (or the lone electron pair), the remaining ligands should be compared each

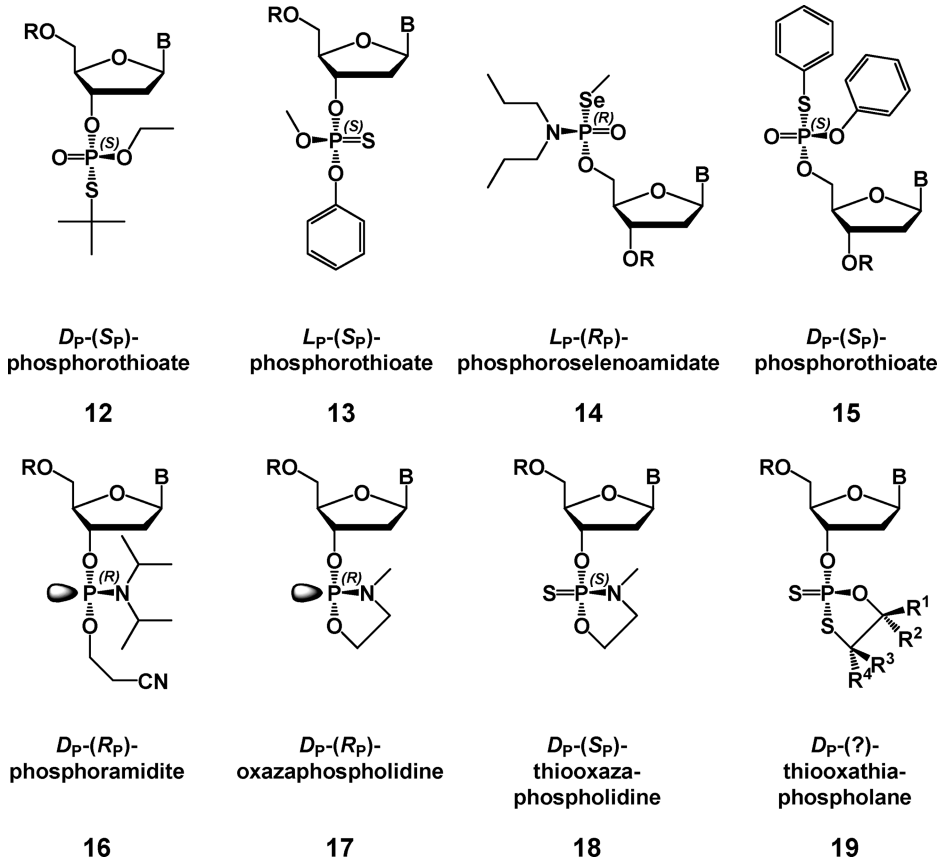


FIGURE 4 D_P/L_P notation for phosphate and phosphite triesters (and their derivatives) with one nucleoside residue.

other regarding their CIP priority. The ligand of lower priority is designated then as **Z** and the one of higher priority, as the second **G** group (Rule 4a).

Examples of application of the D_P/L_P notation to phosphate and phosphite triesters and their thio and amido derivatives are shown in Figure 4. For all compounds the position of a nucleoside unit ($\mathbf{G_1}$ for a nucleosid-3′-yl in **12–13** and **16–17**, and $\mathbf{G_2}$ for a nucleosid-5′-yl in **14–15**) and the choice of **X** is obvious (double-bonded oxygen for **12**, **14**, **15**, sulfur for **13**, **18**, **19**, and an electron pair for **16** and **17**), while ligand **Z** easily is found as the one of lower CIP priority among the 2 remaining residues (e.g, –OEt < –S-*t*Bu in compound **12,** –OR < –Cl in **14**, or $-NR_2$ < –OR in **17** and **18**). For compound **19** the R^n substituents are undefined, which precludes the assignment of R_P/S_P configuration. For the D_P/L_P notation, this is irrelevant as the position of a nucleoside moiety is fixed and CIP priority rules define which group should occupy position $\mathbf{G_2}$ (-SR moiety for phospholane **19**) and which should be designated as ligand **Z** (in this case, -OR moiety).

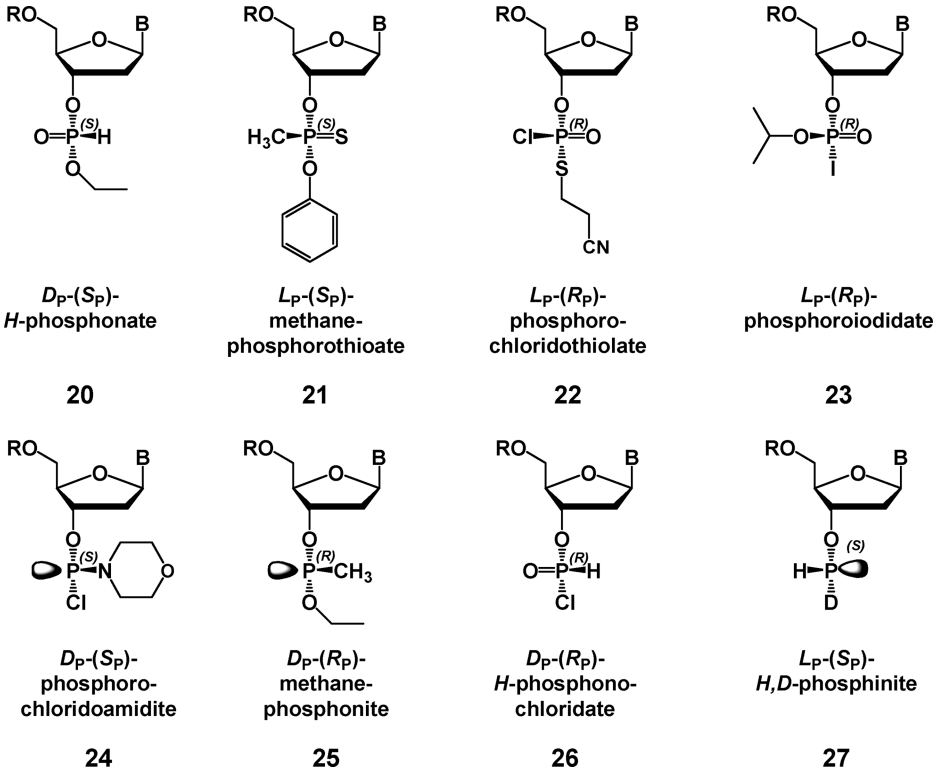


FIGURE 5 D_P/L_P notation for nonionic mononucleotide analogues.

Similarly as for the triesters discussed above, the assignment of **X** for nonionic diester derivatives (e.g., compounds **20–25**, Figure 5) is apparent (the double-bonded atom or the lone electron pair), and from among the remaining ligands the one of lower CIP priority is chosen as **Z** for each compound. The same procedure is applied for neutral monoesters **25** and **27** (Figure 5).

(b) D_P/L_P Notation for Compounds with 2 Ligands Able to Form a P=X bond

Ambident mononucleotidic esters contain more than one ligand capable of forming a double bond to phosphorus. General structures of compounds having 2 such ligands (derivatives of phosphate diesters **28** and phosphonate or halogenophosphate monoesters **29**) are shown in Figure 6. In order to find the D_P/L_P configuration for these compounds, Rule 4b should be applied. Thus, the nucleoside and the second ligand than cannot form a double-bond to phosphorus should be designated as vertical groups $\mathbf{G_1}$ and $\mathbf{G_2}$ while the 2 other ligands as **X** and **Z**. Then, Rule 3 should be used for judgment which of these two ligands should be assigned as **X** and which one as **Z**.

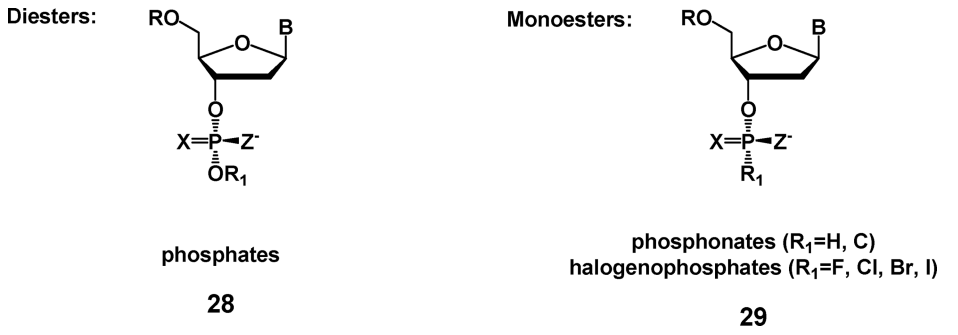


FIGURE 6 General structures of mononucleotidic esters with 2 ligands able to form a double bond to phosphorus.

For example, for *H*-phosphonothioate **30** (Figure 7), vertical positions are reserved for the nucleoside moiety ($\mathbf{G_1}$ group) and the hydrogen atom (not able to form double bond; $\mathbf{G_2}$ group). The atoms that can form double bond with phosphorus are an oxygen and a sulfur. Among them, it is the oxygen that gains the upper hand in the double bond formation (Rule 3), and it becomes the ligand **X** while the sulfur, ligand **Z**.

Similarly, for phosphonates **31** and **32**, halogenophosphate analogue **33,** and phosphorothioate **34**, nucleoside residues are designated as $\mathbf{G_1}$ while ligands forming exclusively single bond to phosphorus, as $\mathbf{G_2}$. Then, Rule 3 governs which chalcogen should be double bonded to phosphorus in the horizontal ambident moiety: P=S > P=Se (**31**), P=^{16}O > P=^{18}O (**32**), P=S > P=N (**33**), and P=O > P=S (**34**).

(c) D_P/L_P Notation for Compounds with 3 Ligands Able to Form a P=X bond

Only one class of phosphorus acid esters falls into this category, namely derivatives of phosphate monoesters of type **36** (Figure 8). The assignment

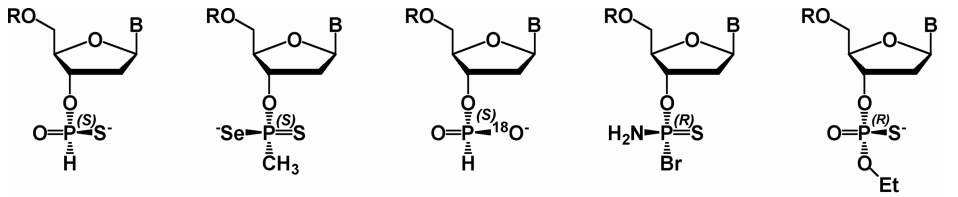


FIGURE 7 Examples of mononucleotidic esters with 2 ligands able to form a double bond to phosphorus.

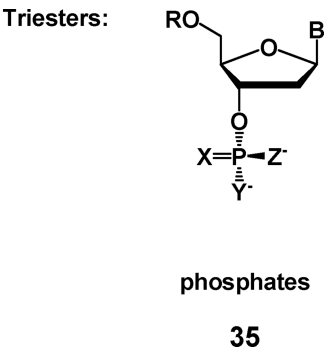


FIGURE 8 General structure of mononucleosidic esters with 3 ligands able to form a double bond to phosphorus.

of configuration for such compounds is controlled by Rule 4c. As all 3 nonnucleosidic ligands can form a double bond to phosphorus, each of them should be considered as potential ligand **X**, which is found according to Rule 3. Then, the remaining two ligands are assigned as **Z** (a ligand of lower CIP priority) and as $\mathbf{G_2}$ (a ligand of higher CIP priority).

Typical structures that fall into this category are shown in Figure 9. For example, for phosphoroselenothioate **36**, comparison of the potential **X** ligands (O, S, Se) returns oxygen as ligand **X** due to the priority order: P=O > P=S > P=Se (Rule 3a). The remaining heteroatoms, sulfur and selenium, are designated as ligands **Z** and $\mathbf{G_2}$, respectively, according to their CIP priority (S < Se). For amidothioate **37**, the nucleoside moiety is assigned as $\mathbf{G_1}$ ligand, the oxygen as ligand **X** (P = O > P=S > P=N, Rule 3a), and the sulfur as ligand $\mathbf{G_2}$ (higher CIP priority: S > N). In the case of selenothioate **38**, the sulfur atom should be chosen as ligand **X** (P=S > P=Se, Rule 3a), while ^{80}Se is set as ligand $\mathbf{G_2}$

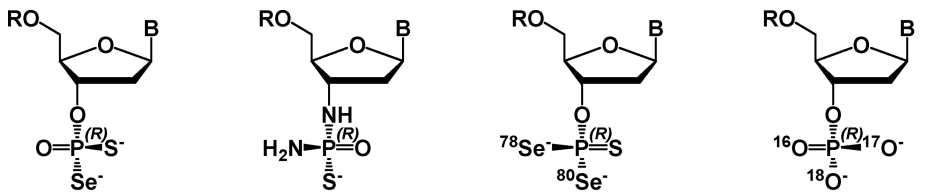


FIGURE 9 *D*P/*L*P notation for nonionic di- and monoesters (and their derivatives) with one nucleoside residue.

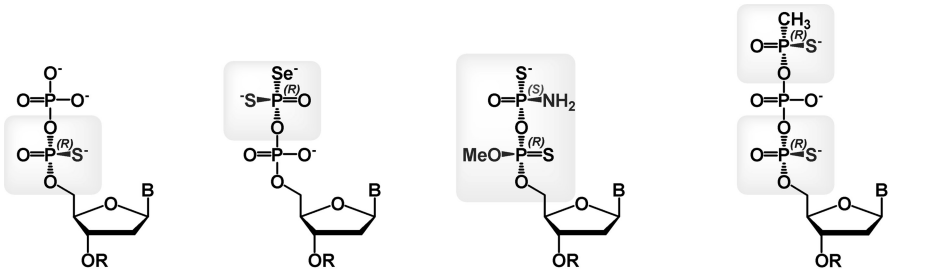


FIGURE 10 D_P/L_P notation for chiral di- and triphosphates.

by CIP order. The assignment of oxygen isotopes as ligands **X**, **Z,** and $\mathbf{G_2}$ in a multilabeled monoester **39** is governed by Rule 3b and 4c, consecutively.

2. *P*-Chiral Analogues of Nucleoside Di- and Triphosphates

The D_P/L_P notation is applicable also for the assignment of configuration of *P*-chiral nucleoside di- and triphosphates. For this purpose, the structures of interest are drawn as in Figure 10 with the di- or triphosphate group in a vertical position. This graphical presentation should be treated as the Fischer projection.

For nonterminal *P*-chiral phosphate moiety (as in compound **40**), the corresponding nucleoside or nucleotide residue and the other phosphate group are assigned as ligands $\mathbf{G_1}$ and $\mathbf{G_2}$ (Rule 4d). A configurational assignment for a terminal *P*-chiral phosphate moiety is carried out as for ambident esters (*cf.* Sections 1b and 1c) with a nucleotide residue set as ligand $\mathbf{G_1}$ or $\mathbf{G_2}$. For di- and triphosphate analogues with multiple *P*-chiral centers, the assignment of D_P/L_P configurations is done separately for each phosphorus atom, using the rules presented above.

For example, diphosphate **42** contains 2 chiral phosphorus centers. For the α-thiophosphate residue, the β-phosphate moiety, and the nucleoside residue are assigned as $\mathbf{G_1}$ and $\mathbf{G_2}$, respectively (Rule 4d), and the sulfur and the methoxy group are set according to Rule 1 as **X** and **Z** ligands, respectively. For the β-phosphoroamidothioate residue, $\mathbf{G_2}$ is designated to the nucleoside α-phosphorothioate residue and the remaining positions are assigned as for phosphate monoesters: $\mathbf{X} = \mathrm{O}$ (Rule 3a) and $\mathbf{Z} = \mathrm{NH_2}$ (Rule 4c). In the case of nucleoside 5′-triphosphate analogue **43**, for the α-phosphorothioate residue, Rule 3a governs the setting O as ligand **X** and S^- as ligand **Z**; for the γ-methanephosphonothioate residue, oxygen is designated as **X** due to Rule 3a, and the methyl group as ligand $\mathbf{G_2}$, according to Rule 4b.

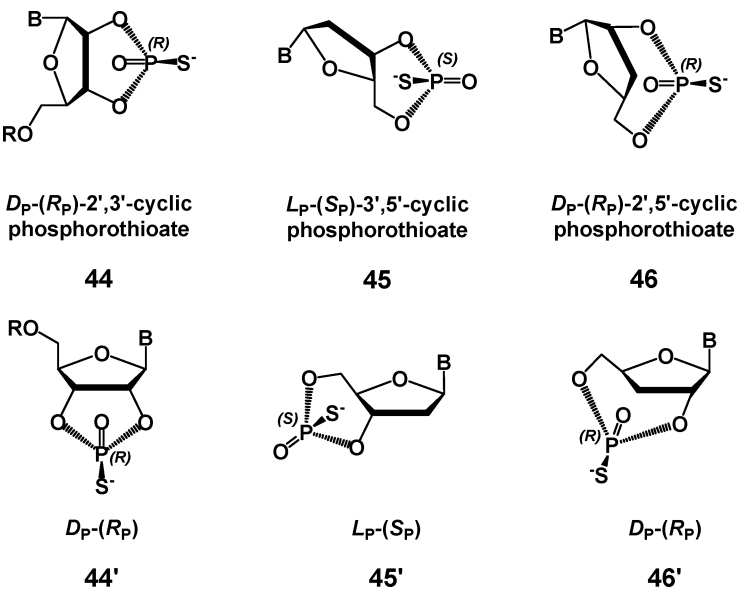


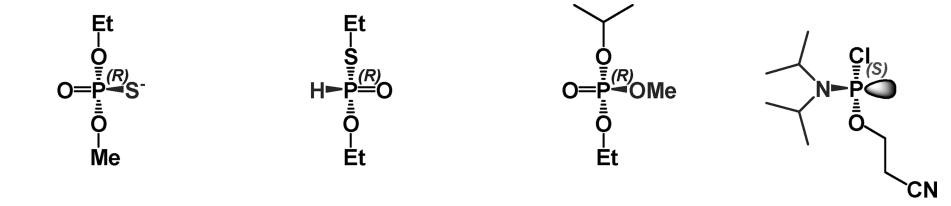
FIGURE 11 D_P/L_P notation for chiral cyclic nucleotide analogues.

3. *P*-Chiral Cyclic Phosphate Analogues

In order to use the D_P/L_P notation for *P*-chiral cyclic nucleotides, these compounds have to be graphically presented as shown in Figure 11. In this way a spatial position of ligands attached to the phosphorus center is congruent with the general requirements of the D_P/L_P convention. The placement of a sugar moiety in these structures is governed by Rule 2.

For example, in the case of R_P-2′,3′-cyclic phosphorothioate **44**, the ribose is attached to a phosphorus center via 2 secondary alcohol groups, thus, the assignment of $\mathbf{G_1}$ and $\mathbf{G_2}$ ligands is done according to their CIP properties: the 2′ position has higher priority than the 3′ one, and thus, 2′ site should be assigned as $\mathbf{G_1}$ (the upper position) (Rule 2b). Then, according to Rule 3a, the sulfur is set as ligand **Z** resulting in D_P configuration for this compound. For phosphorothioates **45** and **46**, the 5′ position is a primary while the 2′ and 3′ ones are secondary residues. On this basis the 5′ part of the ribose is designated as $\mathbf{G_2}$ ligand, and it is put in the lower position.

Although for the sake of D_P/L_P configurational assignment compounds **44**–**46** are presented in rather unusual manner, when the assignment is completed, these structures can be rotated to give a conventional view of cyclic nucleoside phosphates (**44′**–**46′**). A simply rule of thumb allows a correlation between both types of presentation. If a cyclic nucleoside phosphate analogue is drawn in a traditional manner with the endocyclic P-O bonds pointing behind and the exocyclic bonds pointing above the



D_P-(R_P)-phosphorothioate	L_P-(R_P)-*H*-phosphonothioate	D_P-(R_P)-phosphate	L_P-(S_P)-phosphoro-amidochloridite
47	**48**	**49**	**50**

FIGURE 12 D_P/L_P notation for *P*-chiral nonnucleosidic compounds.

plane of paper (e.g., **44′–46′**), then compounds with **Z** atom placed inward the ring have L_P configuration (e.g., **45′**), while those with **Z** atom pointing outward the ring, have D_P configuration (e.g., **44′** and **46′**).

4. *P*-Chiral Nonnucleosidic Compounds

The so far presented structures contained at least one nucleoside (or its analogue) unit that could be designated as $\mathbf{G_1}$ or $\mathbf{G_2}$ ligand and served as an anchor for the assignment of D_P/L_P configuration. However, the D_P/L_P convention can in principle also be used for nonnucleosidic phosphorus compounds. While usually there is no need for invoking the D_P/L_P notation for such compounds, in some cases it might be convenient to treat nonnucleosidic phosphoesters as models for nucleosidic derivatives. Such an extension of the D_P/L_P system could facilitate comparison of the phosphorus centers in nucleosidic and nonnucleosidic compounds or can be used for tracing the stereochemistry during phosphorylation of nucleosides.

The assignment of D_P/L_P configuration for nonnucleosidic phosphoesters can be done in 2 steps as prescribes by Rule 5. In the first step, 2 of the 4 ligands should be designated as **X** and **Z** according to Rules 1, 3, and 4. Then, the upper $\mathbf{G_1}$ position should be assigned to one of the remaining 2 ligands having higher CIP priority, while $\mathbf{G_2}$ position, to the one of lower CIP priority (Figure 12). For example, for ambident phosphorothioate **47**, Rule 4b is used in the first step to assign **X** = O and **Z** = S^-. In the second step, the ethoxy group is compared with the methoxy one according to the CIP rules. This gives higher priority to the ethoxy group, which, thus, adopts $\mathbf{G_1}$ position, while the methoxy group, $\mathbf{G_2}$ position. For nonionic *H*-phosphonothioate **48**, Rule 4a is used for the assignment of oxygen and hydrogen as **X** and **Z** ligands, respectively. Then, as the thioethyl group has higher CIP priority than the ethoxy group, EtS group is assigned as $\mathbf{G_1}$ and EtO, as $\mathbf{G_2}$. In triester **49**, the methoxy group is set as ligand **Z** (lowest CIP

priority, Rule 4a), and in phosphoroamidochloridite **50**, the lone electron par is designated as ligand **X**, and the amino group as **Z** (lowest CIP priority, Rule 4a).

SUMMARY

An extension of the D_P/L_P notation for the assignment of configuration at the phosphorus center of analogues with one nucleoside unit and for nonnucleosidic *P*-chiral compounds, have been elaborated. The assignment of configuration is done using 5 rules, 3 of them already being defined for dinucleoside monophosphate analogues (see the accompanying paper.[1b]) In this way, the D_P/L_P notation covers a wide range of phosphorus compounds met in bioorganic phosphorus chemistry.

Work on application of the D_P/L_P system to analysis of stereochemical courses of chemical transformations of *P*-chiral nucleotide derivatives is in progress.

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