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Conformational Transmission in Nucleotides Containing Trigonal Bipyramidal Phosphorus as the Internucleoside Linkage

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A set of nucleotide analogues containing a stable triagonal bipyramidal phosphorus (P^V TBP) moiety (5-11) has been developed, and their conformational properties were studied by both VPC analysis and 1H NMR. In the solvent acetone-d6, it is found that the conformation of the model compounds is determined by a hydrogen bond between the backbone atom C\(\beta\) and the base proton H\(\alpha\) (imidazole base) or H\(\alpha^\prime\) (purine base), resulting in a preference for the standard gauche- (\(g^-\)) conformation around the C\(\beta\)-C\(\beta\) bond. In the hydrogen bond disrupting solvent DMSO-d6, the P^V TBP nucleotides 5-8 clearly show conformational transmission, i.e., a preference for the unusual gauche+ (\(g^+\)) rotamer around the C\(\beta\)-C\(\beta\) bond is found. This structural distortion opposesstacking of the bases, as is confirmed by the observation that the preference for \(g^+\) is strongest for 7 and 8, in which stacking is eliminated. The present results provide support to our earlier proposition that formation of P^V TBP locations in DNA can lead to a marked change of the secondary structure (Buck, H. M. Recl. Trav. Chim. Pays-Bas 1980, 99, 181).

In the past years we developed and firmly established a concept for conformational transmission in a variety of trigonal bipyramidal phosphorus (P^V TBP) compounds. It was shown that the construction of specific ligands...
Conformational Transmission in Nucleotides

Chart I

directly linked to phosphorus as $P^V=O-C-C-O(R)$ makes it possible to select a different conformational behavior around the C-C linkage for equatorial or axial position in the TBP. Compounds 1 and 2 are typical model compounds used to study the conformational transmission effect in our previous work (Chart I). A pronounced trans orientation of both oxygens is found for the axial sites, whereas the well-known gauche arrangement has an equatorial preference. The introduction of the concept of conformational transmission is based on the observation that in the corresponding $P^V$ tetrahedral compounds ($P^V=O-C-C-O(R)$) the gauche arrangement of both oxygens is unique, whereas after introduction of an extra (similar) ligand the $P^V$ TBP with its (chemically) different sites selects the conformational change from gauche to trans via exchange of axial and equatorial positions respectively. The addition of an extra ligand which is reflected in the intrinsic chemical-bonding properties of a $P^V$ TBP configuration results in an enhanced electron density on the axial oxygens directly linked to phosphorus. In its turn this effect is transmitted in a conformational change around the C-C linkage via an increased Coulombic repulsion between both oxygens leading to a trans orientation. Very recently, de Keijzer et al. investigated the impact of conformational transmission on the rate of intramolecular ligand exchange in $P^V$ TBP model systems (pseudorotation). With variable-temperature $^{13}$C NMR on the monocyclic $P^V$ TBP compounds 3a,b and 4a,b it was established that pseudorotation in 3a and 4a is 2–4 times faster than in 3b and 4b. With the acceptance of the intermediacy of a square pyramid in controlling the pseudorotation, it could be shown that conformational transmission in the basal ligands in the square pyramid is responsible for lowering of the activation barrier for pseudorotation by 2–3 kJ/mol. In previous publications, we have regularly emphasized that the concept of conformational transmission might be of significance in activating phosphorylated biomolecules. A straightforward example has been given by Meulendijks et al. in their studies on conformational transmission in model systems for phospholipids. For monomeric phospholipid models in solution, it was found that going from $P^V$ toward $P^V$ TBP results in a structural change in the glyceryl fragment leading to stronger van der Waals interaction between the two acyl chains. Precise conclusions could be drawn for a set of phospholipid analogues in the solid state, which have been studied with cross polarization MAS $^{13}$C NMR. It was observed that conformational transmission results in a more downfield $^{13}$C chemical shift for the $\omega$-methyl groups and a reduced cross polarization optimal contact time, which show that the chain ends are forced into a more proximate position. Based on these results, the suggestion was put forward that conformational transmission might be of importance for controlling ion transport in phospholipid bilayers.

Now we will offer a detailed study of the impact of $P^V$ TBP locations in the backbone of nucleotides for conformational transmission on the level of single-strand phosphate-methylated DNAs in various solvents. The $P^V$ TBP nucleotides 5–11 (Chart II) were chosen as representative model systems. The selection of phosphate-methylated DNAs is necessary to guarantee stable $P^V$ TBP. The presentation of the results will be discussed with the intermediary of a square pyramid in controlling the pseudorotation, it could be shown that conformational transmission in the basal ligands in the square pyramid is responsible for lowering of the activation barrier for pseudorotation by 2–3 kJ/mol. In previous publications, we have regularly emphasized that the concept of conformational transmission might be of significance in activating phosphorylated biomolecules. A straightforward example has been given by Meulendijks et al. in their studies on conformational transmission in model systems for phospholipids. For monomeric phospholipid models in solution, it was found that going from $P^V$ toward $P^V$ TBP results in a structural change in the glyceryl fragment leading to stronger van der Waals interaction between the two acyl chains. Precise conclusions could be drawn for a set of phospholipid analogues in the solid state, which have been studied with cross polarization MAS $^{13}$C NMR. It was observed that conformational transmission results in a more downfield $^{13}$C chemical shift for the $\omega$-methyl groups and a reduced cross polarization optimal contact time, which show that the chain ends are forced into a more proximate position. Based on these results, the suggestion was put forward that conformational transmission might be of importance for controlling ion transport in phospholipid bilayers.

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different contributions of the bioorganic ligands leading to a relaxed P\textsuperscript{V} TBP structure.

**Methods**

**Synthesis of 5-16.** The model compounds 5-8 (P\textsuperscript{V} TBP) and 12 and 13 (P\textsuperscript{V}V) were synthesized from the corresponding phosphate triester (P\textsuperscript{III}) nucleotides via reaction with butanediol, and ozone/oxygen, respectively. The precursor P\textsuperscript{III} nucleotides were prepared from 5'-protected thymidine 3'-(methylisopropylphosphoramidite) (in the case of 5, 6, and 12), or 5'-protected 1',2'-dideoxyribose 3'-(methylisopropylphosphoramidite) (in the case of 7, 8, and 13), in a tetrazole-catalyzed coupling reaction in dry pyridine. Standard column chromatography using Woelm silica gel as the stationary phase and dry butanone as eluent afforded these compounds in protected thymidine 3'-(methyldiisopropylphosphoramidite) (in the case of P\textsuperscript{V}V, and P\textsuperscript{V}V, respectively). (In the case of 5-8, the 31P NMR spectrum consists of a single line. This proves that stereomers. For 5-8, it was observed that the 31P NMR spectrum consists of a single line. This proves that steremutation around the Pv TBP is rapid on the NMR time scale.\textsuperscript{6} The model compounds 9-11 and 14-16 were prepared by phospholation of the corresponding 3-O-acetylated nucleosides with dimethoxy-(N,N-dimethylamino)phosphine, leading to the 5'-P\textsuperscript{III} precursors. Purification of these compounds was also accomplished with chromatography on a silica gel column with dry butanone as eluent.

**Conformational Analysis.** The structural aspects of 5-16 were investigated with 300- and 500-MHz 1H NMR. Conformational analysis was focused on the C\textsubscript{4'C\textsubscript{5}} bonds, as well as on the sugar moieties. C\textsubscript{4'C\textsubscript{5}} conformations are described in terms of a time-averaged distribution over the staggered rotamers gauche\textsuperscript{(+) (g\textsuperscript{+})}, gauche\textsuperscript{-trans (g\textsuperscript{t})}, and gauche\textsuperscript{(-) (g\textsuperscript{-})}. The rotamer populations were calculated from the experimental proton-proton coupling constants J\textsubscript{4'5'} and J\textsubscript{4'5'} with the help of the empirically generalized Karplus equation of Altona et al.\textsuperscript{7} The conformation of the sugar rings in nucleotides is generally treated as a two-state equilibrium between a C\textsubscript{4}-endo and a C\textsubscript{5}-endo type puckered ring form.\textsuperscript{8} In principle, five vicinal proton-proton coupling constants are available to monitor the sugar conformation (J\textsubscript{4,5}, J\textsubscript{4',5'}, J\textsubscript{4',5'}, J\textsubscript{4',5'}, and J\textsubscript{4,5'}). In various cases, however, it proved impossible to determine accurate values for J\textsubscript{4',5'}, J\textsubscript{4',5'}, and/or J\textsubscript{4,5'}, due to one of the following reasons: (i) collapse of H\textsubscript{2} and H\textsubscript{2} in the NMR spectra; (ii) overlap of the H\textsubscript{3} and H\textsubscript{3} spectral pattern with the residual signal of the solvent DMSO-d\textsubscript{6}; (iii) overlap of H\textsubscript{5} and the H\textsubscript{5}/H\textsubscript{5'} spectral pattern. In order to arrive at a uniform treatment for all model compounds, we used the formula x(C\textsubscript{2j}-endo) = (J\textsubscript{4,5} + J\textsubscript{4',5'} - 9.8)/5.9, as developed by Rinkel et al.\textsuperscript{9} This method allows one to estimate the conformational equilibrium of the sugar ring in DNA nucleotides with a fair accuracy, on the basis of J\textsubscript{4,5} and J\textsubscript{4',5'} exclusively. For the nucleotides 5, 6, and 12, the assignment of the H\textsubscript{5} patterns to the upper and lower residue was performed with homonuclear decoupling experiments, based on the fact that the connectivity sequence phosphorus-H\textsubscript{1}H\textsubscript{2'/2}/H\textsubscript{1}/H\textsubscript{1} only exists for the upper residue.

**Results and Discussion**

The solvents acetone-d\textsubscript{4} and DMSO-d\textsubscript{6} have been chosen to study the conformational aspects of the model systems 5-16. Acetone-d\textsubscript{4} was found to be an unsuitable solvent to study conformational transmission, since hydrogen bonding between the backbone atom O\textsubscript{5} and H\textsubscript{4} of thymidine or cytosine, or H\textsubscript{8} of adenine, strongly fixes the C\textsubscript{4'-C\textsubscript{5}} conformation in the g\textsuperscript{+} rotamer (Figure 1).\textsuperscript{10} The formation of the O\textsubscript{5}-base hydrogen bond was perfectly prevented in DMSO-d\textsubscript{6}, which enabled us to establish the impact of conformational transmission on the molecular structure of our model systems in an unequivocal way.

**Conformation of 5-16 in DMSO-d\textsubscript{6}** Table 1 (left) summarizes the experimental coupling constants J\textsubscript{4V} and J\textsubscript{4V}, and the calculated rotamer distributions around the C\textsubscript{4'-C\textsubscript{5}} bond for 5-16 in the solvent DMSO-d\textsubscript{6}.

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### Table I. Experimental Coupling Constants J\textsubscript{4V} and J\textsubscript{4V} Measured in DMSO-d\textsubscript{6} (Left) or Acetone-d\textsubscript{4} (Right) and the Calculated Time-Averaged Rotamer Populations around the C\textsubscript{4'-C\textsubscript{5}} Bond\textsuperscript{a}

<table>
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<tr>
<th>compd</th>
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<th>J\textsubscript{4V}, Hz</th>
<th>x(g\textsuperscript{+})</th>
<th>x(g\textsuperscript{t})</th>
<th>x(g\textsuperscript{-})</th>
<th>J\textsubscript{4V}, Hz</th>
<th>J\textsubscript{4V}, Hz</th>
<th>x(g\textsuperscript{+})</th>
<th>x(g\textsuperscript{t})</th>
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\textsuperscript{a} Data refer to the 3'-residue in the case of the nucleotides 5-8 and 12, 13.
Conformational Transmission in Nucleotides

Table II. Experimental Coupling Constants \( J_{12} \) and \( J_{13} \) Measured in DMSO-\( d_6 \) (Left) or Acetone-\( d_6 \) (Right) and the Calculated Population of the \( C_2 \)-Endo Puckered Form of the 2'-Deoxyribose Ring

<table>
<thead>
<tr>
<th>compd</th>
<th>DMSO-( d_6 )</th>
<th>acetone-( d_6 )</th>
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<td></td>
<td>( J_{12} ), Hz</td>
<td>( J_{13} ), Hz</td>
</tr>
<tr>
<td>5 5'-residue</td>
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<td>5 3'-residue</td>
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<td>6 5'-residue</td>
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</table>

Figure 1. Part of the X-ray crystal structure of 3',5'-di-O-acetylthymidine, in which the \( g^+ \) conformation is stabilized via hydrogen bonding between \( O_5 \) and \( H_6 \). Hetero atoms (O, N) are shaded, and hydrogen atoms have been omitted for clarity.

of these data shows that the \( P^V \) TBP nucleotides 5–8 have dominant populations of \( g^+ \), which corresponds with trans orientation of \( O_5 \) and \( O_4 \) (vide supra); \( x(g^+) \) varies form 0.48 to 0.65 for 5–8. The \( P^V \) structures 12 and 13, on the other hand, display a clear preference for the well-known \( g^+ \) conformation, in which \( O_5 \) is gauche with respect to \( O_1 \) (\( x(g^+) = 0.71 \) and 0.63 for 12 and 13, respectively). The occurrence of conformational transmission in 5–8 implies that \( O_5 \) is preferentially located in the axis of the \( P^V \) TBP, i.e., structure I (\( O_5 \) axial, \( O_3 \) equatorial) prevails over the two possible alternatives, II (\( O_5 \) axial, \( O_3 \) equatorial) and III (\( O_5 \) and \( O_3 \) equatorial). The preference of I over II correlates with quantum chemical model calculations by van Lier et al.\(^{11}\) which showed that \( O_5 \) axial, \( O_3 \) equatorial is approximately 8 kJ/mol more stable than \( O_5 \) axial, \( O_3 \) equatorial. From Dreiding molecular models, it seems clear that III is unfavorable with respect to I and II (no quantum chemical calculations have been performed). These results provide strong support for our original proposition\(^{12}\) that formation of \( P^V \) TBP in the DNA backbone can substantially perturb the DNA secondary structure via a rotation around the \( C_4-C_5 \) linkage from \( g^+ \) toward \( g^- \). The \( P^V \) TBP systems 7 and 8, in which base stacking is eliminated since the 5'-base is replaced by hydrogen, are of further interest. Comparison with 5 and 6 reveals that the preference for \( g^+ \) is most pronounced in the absence of stacking (7 and 8; \( x(g^+) = 0.59 \) and 0.65, respectively; 5 and 6, \( x(g^+) = 0.48 \) and 0.50, respectively), i.e., conformational transmission opposes the regular stacking of adjacent bases.

The data on the \( P^V \) TBP nucleotides 9–11 show that a high preference exists for the \( g^+ \) conformation (Table I). The explanation for the absence of conformational transmission in these systems rests on the fact that \( O_5 \) is preferentially located in an equatorial position in the TBP.\(^{13}\) The similarity of the \( C_4-C_5 \) rotamer populations of 9–11 and the \( P^V \) counterparts 14–16 is in line with our earlier work, in which a close resemblance was found for 5'-tetrahydrofurfuryl, and tetrahydrofurfuryl in an equatorial location in a \( P^V \) TBP.\(^{14}\) It must be concluded that the 5'-\( P^V \) TBP nucleotides 9–11 are in fact inadequate models to study conformational transmission in DNA structures.

The conformational data on the sugar rings in 5–16 are summarized in Table II (left). These data clearly show a preference for the \( C_2 \)-endo puckered conformation of the ring. Conformational transmission upon going from \( P^{IV} \) (12, 13) toward \( P^V \) TBP (5–8) results in a slight increase of \( x \) (\( C_2 \)-endo) for the 3'-residue. The apparent preference for the conformational combination \( g^- \) (\( C_4-C_5 \) bond) and \( C_2 \)-endo (sugar ring) corresponds with the conclusion of Remin\(^{14}\) that a \( g^-/C_2 \)-endo conformation is highly unfavorable.

Conformation of 5–16 in Acetone-\( d_6 \). The experimental coupling constants \( J_{15} \) and \( J_{45} \) measured in acetone-\( d_6 \), as well as the calculated rotamer populations of \( g^+ \), \( g^- \), and \( g^0 \), are listed in Table I (right). Inspection of these data shows that none of the \( P^V \) TBP systems display conformational transmission. In fact, it appears that increasing the phosphorus coordination from \( P^{IV} \) to \( P^V \) TBP results in a slight increase of the \( g^0 \) rotamer populations. For example, it is found for the \( P^V \) TBP systems 5–8 in acetone-\( d_6 \) that \( x(g^0) \) ranges from 0.85 to 0.91, while \( x(g^0) \)


\(^{13}\) A single bulky substituent on a \( P^V \) TBP structure prefers an equatorial location. See, for instance: Luckenbach, R. Dynamic Stereoochemistry of Pentacoordinated Phosphorus and Related Elements; Georg Thieme Verlag: Stuttgart, 1975.


respectively. These data suggest that conformational transmission is prevented by the formation of a hydrogen bond between O₃ and H₅ of thymine (vide supra). The extreme situation represents the 5'-PV TBP compound 9 with 〈x⟩= 0.90. The data in Table II (right) show that the conformational equilibria of the sugar rings in 5'-16 in aceton-d₆ are heavily biased toward the C₂,endo form. 

Concluding Remarks

The results obtained with the model compounds 5-11 illustrate several novel and revealing aspects of conformational transmission in nucleotide structures. First, it is clear that the solvent is of importance in determining whether or not conformational transmission will occur. Apparently, it is a prerequisite for conformational transmission to occur in both charged and neutral PV TBPs. It follows from a comparison of the data on TBP structures (which are stable enough for experimental studies) with those of TBP (N,N-diisopropylamino) methoxyphosphonyl) 5'-O-acyethylthymidine. 5'-O-Acetylthymidine (1.42 g, 5 mmol) was added with stirring to a mixture of 100 mL of dry chloroform and 10 mL of dry diisopropylamine. After the addition, the reaction flask was thoroughly flushed with argon and sealed with a rubber septum. After the mixture was stirred for 2 h, dropwise addition of chloro(N,N-diisopropylamino)methoxyphosphonyl (1.03 g, 5.2 mmol) was started. The resulting yellow solution was stirred for 2 h and diluted with 250 mL of ethyl acetate (prewashed with NaHCO₃). Repeated washing with 100-mL portions of a saturated NaCl solution in water, and finally with pure water, drying on Na₂SO₄, and evaporation of all volatile material afforded an oily product with R₃ 0.34. Coevaporation with dry dichloromethane yielded the desired product as a slightly colored foam (1.52 g, 68%): [³¹P NMR (acetone-δ) δ 0.90-1.25 (1H, m, δH₂,₁₆), 1.58 (3H, s, δH₅,₅₀)]. Quantum chemical calculations performed by van Lier et al. with a model of the solvent isopropylamine and the solvent acetone-d₆.

Spectroscopic studies were performed by van Lier et al. on a Bruker HX 200 (36.4 MHz) or a Bruker AC 200 (80.9 MHz) spectrometer. Woelm silica gel was used for column chromatography. All melting and boiling points are uncorrected. 31P NMR spectra were recorded in the Fourier transform (FT) mode on a Bruker AC 200 (36.4 MHz) or a Bruker AM 500 (500 MHz) spectrometer. Tetramethylsilane was used as the internal standard. Appropriate spectral windows (10-15 ppm) were chosen, and Fourier transformation was usually performed with 32K data points. 3PD NMR spectra were run in the FT mode on a Bruker HX 200 (36.4 MHz) or a Bruker AC 200 (80.9 MHz) spectrometer. Woelm silica gel was used for column chromatography. All melting and boiling points are uncorrected. 5'-O-Acetylthymidine. Acetic anhydride (2.45 g, 24 mmol) was added, and the reaction mixture was stirred for 4 h. Thorough evaporation of the pyridine afforded a yellow syrup, which was transferred to a 10-cm-long silica gel column. Elution with butanone yielded a slightly colored foam (0.32 g, 32% yield). 3PD NMR indicated the presence of two diastereomers with δ 145.8 and 145.2 (acetone δ) 15.0 and 15.8 (2H, s, δH₄,₅₀) (acetone δ) 15.0 and 15.8 (2H, s, δH₄,₅₀). However, since it is known that hydrogen-bonding interactions in aqueous solution are relatively weak due to competition of water molecules for hydrogen-bonding donor and acceptor sites (ref 8, p 126), it must be expected that the conformational transmission effect is also operative in water as the solvent.

Experimental Section

1H NMR spectra were recorded in the Fourier transform (FT) mode on a Bruker AC 200 (36.4 MHz) or a Bruker AM 500 (500 MHz) spectrometer. Tetramethylsilane was used as the internal standard. Appropriate spectral windows (10-15 ppm) were chosen, and Fourier transformation was usually performed with 32K data points. 3PD NMR spectra were run in the FT mode on a Bruker HX 90 (36.4 MHz) or on a Bruker AC 200 (80.9 MHz) spectrometer. Woelm silica gel was used for column chromatography. All melting and boiling points are uncorrected. 5'-O-Acetylthymidine. Acetic anhydride (2.45 g, 24 mmol) was added over 30 min to a magnetically stirred solution of thymidine (4.84 g, 20 mmol) in 150 mL of dry pyridine. The reaction mixture was stirred for 3 h, after which the solvent was evaporated under reduced pressure with moderate heating (40 °C). The last traces of pyridine were removed by coevaporation with toluene. Thin-layer chromatography (TLC) of the residual gum, using butanone as eluent, revealed the presence of four different compounds, i.e., 3',5'-di-O-acyethylthymidine (R₃ 0.51), 3',5'-O-acyethylthymidine (R₃ 0.37), 5'-O-acyethylthymidine (R₃ 0.17), and unreacted thymidine (R₃ 0.95). Repeated column chromatography afforded 5'-O-acyethylthymidine as a white solid in 28% yield (1.60 g): [³¹P NMR (acetone-δ) δ 1.87 (2H, s, δH₃,₅₀), 2.38 (2H, s, δH₃,₅₀)]. The last traces of pyridine were removed by coevaporation with toluene. Thin-layer chromatography (TLC) of the residual gum, using butanone as eluent, revealed the presence of four different compounds, i.e., 3',5'-di-O-acyethylthymidine (R₃ 0.51), 3',5'-O-acyethylthymidine (R₃ 0.37), 5'-O-acyethylthymidine (R₃ 0.17), and unreacted thymidine (R₃ 0.95). Repeated column chromatography afforded 5'-O-acyethylthymidine as a white solid in 28% yield (1.60 g): [³¹P NMR (acetone-δ) δ 1.87 (2H, s, δH₃,₅₀), 2.38 (2H, s, δH₃,₅₀)].
conversion of the phosphate into 12. 31P NMR (acetone-d6) δ 0.2 and 0.8.

2-(3'-O-(5'-O-Tritylthymidyl))-2-(5'-O-(3'-O-acetylthymidyl))-2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole (6). This compound was prepared by the addition of 1 equiv of freshly distilled butanedione to a cooled (0 °C) solution of 5'-O-(3'-O-acetylthymidyl) 3'-O-(5'-O-tritylthymidyl) methyl phosphate in a 5-mm NMR sample tube. After 20 min, 31P NMR indicated quantitative conversion of the phosphate into the pentacoordinated phosphorus structure of 7. 31P NMR (acetone-d6) δ -50.3 (s); ²H NMR (acetone-d6) δ 8.2 (2 H, br s, NH), 7.52 and 7.51 (2 H, m, H5, aromatic H), 6.21 (1 H, t, H5-(3's-residue)), 6.16 (1 H, t, H3-(3's-residue)), 5.78 (1 H, m, H5-(3's-residue)), 5.22 (1 H, m, H7-(3's-residue)), 4.20 (2 H, m, H2, H7-(3's-residue)), 4.17-4.12 (2 H, m, H5p, H7p-(3's-residue)), 3.72 (3 H, d, OCH3, δ 12.8 Htz), 3.40 (2 H, m, H5p, H7p-(3's-residue)), 1.90 (6 H, s, CH3 dioxaphosphole), 2.25-2.20 (4 H, m, H2a,-2b), 2.10 (3 H, s, acet), 1.88 and 1.84 (2 × 3 H, 5, CH3).

5'-O-Acetyl-1',2'-dideoxyribosyl 1',2'-Dideoxyribosyl (5.9 g, 55 mmol) was reacted with acetic anhydride (6.1 g, 60 mmol) according to the procedure that was described for 5'-O-acetylthymidine (vide supra). Repeated column chromatography using butanone as eluent finally afforded the desired product as a yellowish oil with Rf 0.38 in 17% yield (1.32 g). Detection was effected by exposure to iodine vapor: ¹H NMR (acetone-d6) δ 1.58-2.35 (2 H, m, H2a, H2b), 2.13 (3 H, s, Ac), 3.16-4.30 (6 H, m, Hlt, Htt, H3, H4, H5, H6, H7, 5'-CH3). Anal. Calcd for C14H28PN05: C, 52.34; H, 8.72; N, 4.36. Found: C, 51.6; H, 8.4; N, 5.0.

3'-O-(5'-O-Diisopropylamino)methoxyphosphino)-5'-O-acetylthymidyl (9). This compound was prepared by the addition of 1 equiv of freshly distilled butanedione to a cooled (0 °C) solution of 5'-O-(3'-O-acetylthymidyl) 3'-O-(5'-O-trityl-1',2'-dideoxyribosyl) methyl phosphate (vide supra). The product was obtained as a foam. 31P NMR indicated the presence of two diastereomers with δ 145.9 and 145.0 (acetone-d6). After 30 min, 31P NMR proved complete conversion into 8; 31P NMR (acetone-d6) δ -50.3 (s); ²H NMR (acetone-d6) δ 8.17-7.20 (15 H, m, aromatic H), 6.13 (1 H, t, H1-(3's-residue)), 5.72 (1 H, m, H3-(3's-residue)), 5.22 (1 H, m, H5, H7-(3's-residue)), 4.22 (1 H, m, H5-(3's-residue)), 3.80 (3 H, d, OCH3, δ 12.3 Htz), 3.78-3.70 (2 H, m, H5p, H7p-(3's-residue)), 1.81 (6 H, s, dioxaphosphole), 2.41-2.19 (4 H, m, H2a,-2b), 2.13 (3 H, s, acet), 1.88 (3 H, s, 5'-CH3).

3'-O-Acetylthymidine 5'-Dime thylphosphite. A solution of dimethoxy(N,N-dimethylamino)phosphine (14.9 mmol, 1.95 g) in 25 mL of dry 1,4-dioxane was added dropwise to a stirred and heated (80 °C) solution of 3'-O-acetylthymidine (2.00 g, 7.1 mmol) and tetrazole (250 mg) in 50 mL of dry 1,4-dioxane. After 3 h, TLC using butanone as eluent indicated complete conversion into a product with Rf 0.64. The reaction mixture was concentrated in vacuo, and the resulting glass was chromatographed on a silica gel column: yield, 1.6 g, 60%; ¹H NMR (acetone-d6) δ 1.87 (6 H, d, OMe), 2.12 (3 H, s, Ac), 2.65 (1 H, m, H2a), 3.12 (1 H, m, H2), 3.38 (6 H, dd, OMe), 4.10 (2 H, m, H5, H7, 5'-CH3). Anal. Calcd for C9H14N2O5P: C, 52.3; H, 7.7; N, 2.9. Found: C, 51.6; H, 8.4; N, 5.0.

1',2'-Dideoxyribosyl methyl phosphite. This compound was prepared in a coupling reaction of 3'-O-acetyl-1',2'-dideoxyribosyl methyl phosphite according to the procedure that was described for 3'-O-(N,N-diisopropylamino)methoxyphosphino)-5'-O-acetylthymidyl methyl phosphite (vide supra). Purification as described yielded the desired product as a foam, mp 96-101 °C, in 52% yield (0.78 g); ²H NMR (acetone-d6) δ 1.12 (12 H, m, isopropyl), 1.4-2.4 (2 H, m, H2a, H2b), 2.10 (3 H, s, Ac), 3.0-4.40 (8 H, m, H1, H5, H6, H7, 5'-CH3). 31P NMR (acetone-d6) δ 154.2 and 153.7 (ratio 1:0.88). Anal. Calcd for C12H20N2O6P2 C, 52.34; H, 7.57; N, 4.36. Found: C, 51.6; H, 8.4; N, 5.0.

2-(3'-O-(5'-O-Acetylthymidyl))-2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole (7). This compound was prepared by the addition of 1 equiv of freshly distilled butanedione to a cooled (0 °C) solution of 5'-O-(3'-O-acetylthymidyl) 3'-O-(5'-O-acetyl-1',2'-dideoxyribosyl) methyl phosphite in a 5-mm NMR sample tube. After 30 min, 31P NMR indicated complete conversion of the phosphate into the pentacoordinated phosphorus structure of 8; 31P NMR (acetone-d6) δ -44.41; ²H NMR (acetone-d6) δ 8.9 (1 H, br s, NH), 7.68 (1 H, s, Hs), 6.16 (1 H, t, H1, H3-(3's-residue)), 5.30 (1 H, m, H5, H7-(3's-residue)), 4.30 (1 H, m, H5, H7), 4.28-4.30 (2 H, m, H2a,-2b), 2.96 (6 H, s, CH3 dioxaphosphole), 2.30-2.20 (2 H, m, H5, H7), 1.95 and 1.90 (2 × 3 H, 5, CH3).

1',2'-Dideoxyribosyl methyl phosphite (13). This compound was obtained by bubbling a stream of oxygen/argon through a cooled (0 °C) solution of 5'-O-(5'-O-acetylthymidyl) 3'-O-(5'-O-acetyl-1',2'-dideoxyribosyl) methyl phosphite in a 5-mm NMR sample tube.
described for 9: "P NMR (acetone-d6) δ = -45.7; "H NMR (acetone-d6) δ = 5.81 (1 H, br, s, NH), 7.55 (1 H, d, H5), 6.18 (1 H, dd, H3), 5.83 (1 H, d, H2), 5.32 (1 H, m, H4), 4.29 (2 H, m, H2/3). 2.45-4.30 (2 H, m, H5, H6), 3.80 (6 H, d, OCH3, J = 13.0 Hz), 2.41-2.28 (2 H, m, H2/3), 1.90 (6 H, s, CH3 dioxaphosphole).

3'-O-Acetylmethylidyne 5'-Dimethyl phosphate) (14). An ozone/oxygen stream was passed through a cooled (0 °C) solution of 500 mg of 3'-O-acetylmethylidyne 5'-dimethyl phosphate in 10 mL of anhydrous dichloromethane. After 20 min, TLC using a solvent system of n-butanol/acetone/methanol/water (90:10:10:5) showed complete conversion of the phosphate into 14 (Rf = 0.30). "P NMR (acetone-d6) δ 6.49; "H NMR (acetone-d6) δ 6.49; "H NMR (acetone-d6) δ 8.8 (1 H, br, s, NH), 7.04 (2 H, br, s, NH), 5.61 (1 H, d, H2), 5.07 (1 H, m, H3), 4.47-4.07 (2 H, m, H4/5), 3.78 (6 H, d, OCH3, J = 13.0 Hz), 2.80-2.27 (2 H, m, H2/3), 2.18 (3 H, s, acetyl).

2'-Deoxy-3'-O-acetylmethylidyne 5'-Dimethyl phosphate) (15). This compound was prepared from 2'-deoxy-3'-O-acetylmethylidyne 5'-dimethyl phosphate) according to the procedure that was given for 14. The product was obtained as a colorless glass (Rf = 0.14, eluent butanone/triethylamine, 9:5:5 v/v). "P NMR (acetone-d6) δ 6.49; "H NMR (acetone-d6) δ 8.85 and 8.25 (2 x 1 H, s, H2/3), 7.04 (2 H, br, s, NH), 6.12 (1 H, dd, H5), 5.55 (1 H, m, H4), 4.37 (1 H, m, H4), 4.20-4.07 (2 H, m, H3/4), 3.78 (6 H, d, OCH3, J = 11.2 Hz), 2.80-2.27 (2 H, m, H2/3), 2.18 (3 H, s, acetyl).

2'-Deoxy-3'-O,N,N-diacetylcytidine 5'-Dimethyl phosphate) (16). This compound was prepared from 2'-deoxy-3'-O,N,N-diacetylcytidine 5'-dimethyl phosphate), according to the procedure that was given for 14. This product was isolated as a slightly colored glass (Rf = 0.12; eluent butanone): "P NMR (acetone-d6) δ 6.49; "H NMR (acetone-d6) δ 8.3 (1 H, br, s, NH), 7.15 (1 H, d, H2), 6.20 (1 H, dd, H5), 5.90 (1 H, d, H6), 5.42 (1 H, m, H4), 4.38 (1 H, m, H3), 4.19-4.06 (2 H, m, H2/3), 3.81 (6 H, d, OCH3, J = 11.3 Hz), 2.41-2.17 (2 H, m, H2/3).

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Studies on the Conformation of 5,15-Diarylporphyrins with (Arylsulfonyloxy)oxy Substituents1

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Dimeso-substituted octaaethylporphyrins, carrying an (arylsulfonyloxy)oxy group at the ortho position of the two (meso) phenyl groups, were synthesized from dipyrrolylmethanes and aldehydes. On account of a 1H NMR upfield shift in CDC13 solution of 2.5 ppm for the aryl protons, a folded conformation is assumed in which the substituted aryl groups lie right above and below the porphyrin plane. In CDC13/CF3COOH solution the upfield shifts are 10 ppm. In this article different models of these porphyrins are presented: 1. The porphyrin and the substituted aryl groups are coplanar; 2. The porphyrin and the substituted aryl groups are noncoplanar. The results of low-temperature 1H NMR measurements and ring-current calculations agreed with our assumptions. The sulfonyloxy group promotes folding of the molecule more than the ester, sulfonyl, sulfinyl, thio, or methylene group. In zinc porphyrins carrying anthraquinone substituents, intramolecular coordination was observed.

The mechanism of the charge separation step in photosynthesis is the subject of continuing investigations, mostly on porphyrins, preferably with well-defined geometries. In the course of our synthetic work in this field we prepared a 5,15-diaryl-2,7,8,12,13,17,18-octamethylporphyrin, carrying a tosylate group in the 0-position, i.e. 6b (Figure 1). The 1H NMR spectrum of this compound in CDC13 solution showed an unexpectedly large upfield shift for the aromatic tosylate protons: 2.63 and 3.06 ppm for H2, H6 and H2, H5, respectively, compared to the 6 values of a reference compound, the corresponding aldehyde RCHO (7b) used in the synthesis (Scheme 1). In the following we use 6 values, defined as 6 for a proton in the aldehyde 7, ~6 for the corresponding proton in the porphyrin 6 (see for numbering of the protons Figure 1). Since upon 10-fold dilution of a solution of 6b we did not observe a significant change of 6 values, we exclude intermolecular association and explain the observed shifts of 6 by a contribution of charge transfer as the driving force for the folding of the molecule.

1 Part of this work has been described in a preliminary communication: Sanders, G. M.; van Dijk, M.; van Veldhuizen, A.; van der Plas, H. C. J. Chem. Commun. 1986, 1311.


(3) The use of, e.g., the p-(mesoary1)-substituted isomer of 6a as reference compound instead of the aldehyde RCHO 7a did not make a significant difference.