Conformational transmission in nucleotides containing trigonal bipyramidal phosphorus as the internucleoside linkage
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recrystallization from a hexane/ethanol (1:1 v/v) mixture, afforded 4,4'-difluoro-1,1'-bibicyclo[2.2.2]octane (6, X = F) as a white microcrystalline solid (2.3 g, 90.6%): mp 278-280°C; 1H NMR (CDCl₃) δ 1.63 (24 H, s, CH₂CH₂); 13C NMR (CDCl₃) δ (see Table IV). Anal. Calcd for C₁₆H₂₄F₂: C, 75.59; H, 9.45. Found: C, 75.29; H, 9.84.

Preparation of Some 4-Substituted 4'-Fluoro-1,1'-bibicyclo[2.2.2]octanes as Mixtures (6, X = H, Cl, Br, I, and CH₃). Initially, we set out to prepare 4-iodo-4'-fluoro-1,1'-bibicyclo[2.2.2]octane (6, X = I) as an appropriate precursor for synthesizing a fairly extensive series of system 6. However, this goal was thwarted when an attempt to prepare this compound in quantity by treatment of 4-hydroxy-4'-iodo-1,1'-bibicyclo[2.2.2]octane with sulfur tetrafluoride at room temperature in the usual manner afforded the difluoro derivative (6, X = F) almost quantitatively. At this stage of our investigation, a cost-benefit analysis led us to restrict our efforts to a more limited range of compounds obtainable as mixtures from the readily available difluoro compound (6, X = F).

By use of the procedure of Olah et al., 4,4'-difluoro-1,1'-bibicyclo[2.2.2]octane was treated with ca. 1 equiv of iodotriphenylphosphine in benzene to afford the difluoro derivative (6, X = F) (ca. 64%). Samples of the sublimed mixture were then treated with a limited quantity of trimethylaluminium as previously described.

Registry No. 5 (X = H), 116263-68-5; 4 (X = Br), 116263-70-8; 5 (X = Cl), 116263-73-1; 5 (X = CH₃), 116263-76-4; 5 (X = NO₂), 116263-86-6; 5 (X = CN), 116263-87-7; 5 (X = COOH), 116263-88-8; 5 (X = COOCH₃), 116263-89-9; 5 (X = COCH₃), 116263-90-2; 5 (X = CHO), 116263-91-3; 5 (X = CH₂OH), 116263-92-4; 5 (X = COCl), 116263-93-5; 5 (X = OH), 116263-94-6; 5 (X = Cl), 116263-95-7; 5 (X = NH₂), 116263-96-8; 5 (X = Sn(CH₃)₄), 116263-97-9; 5 (X = D), 116278-40-1; 6 (X = F), 116263-80-0; 6 (X = I), 116263-81-1; 6 (X = Cl), 116263-83-3; 6 (X = H), 116263-82-2; 6 (X = CH₃), 116263-84-4; 6 (X = Br), 116263-85-6; 9-acetoxytripyrtene, 97735-14-7; 9-hydroxytripyrtene, 73597-16-7; 9,10-dibromoantracen, 523-27-3; 9,10-dibromotripyrtene, 795-42-6; 9-bromo-10-hydroxytripyrtene, 116263-69-5; 9-bromo-10-chloroantracen, 22273-72-9; 9-bromo-10-chlorotripyrtene, 116263-71-9; 9-chloro-10-hydroxytripyrtene, 116263-72-0; 9-methyl-10-methoxyantracen, 21992-33-5; 9-methyl-10-methoxytripyrtene, 116263-74-2; 9-hydroxy-10-methytripyrtene, 116263-75-3; 1-acethyl-4-methoxy-1,1'-bibicyclo[2.2.2]octane; 116263-77-5; 4-methoxy-1,1'-bibicyclo[2.2.2]octane-1-carboxylic acid, 773-34-2; 1-acetoxy-4-methoxy-1,1'-bibicyclo[2.2.2]octane, 116263-78-6; 1,4-diodo-1,1'-bibicyclo[2.2.2]octane, 13884-05-3; 1-iodo-4-methoxy-1,1'-bibicyclo[2.2.2]octane, 74467-18-8; 1-acetoxy-4-iodo-1,1'-bibicyclo[2.2.2]octane, 74467-16-6; 4-iodobicyclo[2.2.2]octane-1-carboxylic acid, 74467-17-7; 4,4'-dihydroxy-1,1'-bibicyclo[2.2.2]octane, 116278-39-8; 4,4'-dihydroxy-1,1'-bibicyclo[2.2.2]octane, 116263-79-7.


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

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A set of nucleotide analogues containing a stable trigonal bipyramidal phosphorus (PVTB) moiety (5-11) has been developed, and their conformational properties were studied with 300- and 500-MHz 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 O₆₈ and the base proton H₆₈ (pyrimidine base) or H₇₅ (purine base), resulting in a preference for the standard gauche(+) conformation around the C₆₈-C₇₈ bond. In the hydrogen bond disrupting solvent DMSO-d₆, the PVTB nucleotides 5-8 clearly show conformational transmission, i.e., a preference for the unusual gauche(−) (g') rotamer around the C₆₈-C₇₈ bond is found. This structural distortion opposes stacking 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 PVTB locations in DNA can lead to a marked change of the secondary structure (Buck, H. M. Real. Fun. Chem. Phys.-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 (PVTB) compounds. It was shown that the construction of specific ligands...
Conformational Transmission in Nucleotides

Chart I

Chart II. P V Nucleotide Structures Studied in This Work and Their P V Counterparts

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 13C 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 13C NMR. It was observed that conformational transmission results in a more downfield 13C chemical shift for the ω-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

References:
different contributions of the bioorganic ligands leading to a relaxed $P^V$ TBP structure.

**Methods**

**Synthesis of 5'-16.** The model compounds 5'-8 ($P^V$ TBP) and 12 and 13 ($P^V$) were synthesized from the corresponding phosphate triester ($P^I$) nucleotides via reaction with butanediol, and ozone/oxygen, respectively. The precursor $P^I$ nucleotides were prepared from 5'-1'-2'-dideoxyribose ($P^I$) and dry butanone as eluent afforded these compounds in scale.6 The model compounds were investigated with 300- and 500-MHz $^1$H NMR.

Conformational analysis of the structural aspects of 5'-16 were investigated with 300- and 500-MHz $^1$H NMR. Conformational analysis was focused on the $C_4-C_5$ bonds, as well as on the sugar moieties. $C_4-C_5$ conformations are described in terms of a time-averaged distribution over the staggered rotamers gauche (+) ($g^+$), gauche- trans ($g^t$), and gauche (-) ($g^-$). The rotamer populations were calculated from the experimental proton-proton coupling constants $J_{4.5}$ and $J_{4.5'}$ with the help of the empirically generalized Karplus equation of Altona et al.7 The configuration of the sugar rings in nucleotides is generally treated as a two-state equilibrium between a $C_5$-endo and a $C_5$-endo type puckered ring form.8 In principle, five vicinal proton-proton coupling constants are available to monitor the sugar conformation ($J_{1.2}$, $J_{1.3}$, $J_{2.3}$, $J_{3.4}$, and $J_{3.4'}$). In various cases, however, it proved impossible to determine accurate values for $J_{2.3}$, $J_{3.4}$, and/or $J_{3.4'}$ due to one of the following reasons: (i) collapse of $H_2$ and $H_5$ in the NMR spectra; (ii) overlap of the $H_2$ or $H_5$ spectral pattern with the residual signal of the solvent DMSO-$d_6$; (iii) overlap of $H_2$ and the $H_5$/$H_5'$ spectral pattern. In order to arrive at a uniform treatment for all model compounds, we used the formula $x(C_5$-endo) = ($J_{1.2} + J_{1.3} - 9.8$)/5.9, as developed by Rinkel et al.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 $J_{1.2}$ and $J_{1.3}$ exclusively. For the nucleotides 5'-8, and 12, the assignment of the $H_2$ patterns to the upper and lower residue was performed with homonuclear decoupling experiments, based on the fact that the connectivity sequence phosphorus-$H_2$-$H_5$-$H_5'$ only exists for the upper residue.

**Results and Discussion**

The solvents acetone-$d_6$ and DMSO-$d_6$ have been chosen to study the conformational aspects of the model systems 5'-16. Acetone-$d_6$ was found to be an unsuitable solvent to study conformational transmission, since hydrogen bonding between the backbone atom $O_6$ and $H_6$ of thymidine or cytosine, or $H_8$ of adenine, strongly fixes the $C_4-C_5$ conformation in the $g^+$ rotamer (Figure 1).10 The formation of the $O_6$-base hydrogen bond was perfectly prevented in DMSO-$d_6$, 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-$d_6$.** Table 1 (left) summarizes the experimental coupling constants $J_{4.5}$ and $J_{4.5'}$ and the calculated rotamer distributions around the $C_4-C_5$ bond for 5'-16 in the solvent DMSO-$d_6$. Inspection

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<th>$J_{4.5'}$, Hz</th>
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<th>$x(g^t)$</th>
<th>$x(g^-)$</th>
<th>$J_{4.5}$, Hz</th>
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*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 $J_{1'}$, Measured in DMSO-$d_6$ (Left) or Acetone-$d_4$ (Right) and the Calculated Population of the C$_2$-Endo Puckered Form of the 2'-Deoxyribose Ring

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<td>5 3'-residue</td>
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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$_Y$ 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$_Y$ and O$_Z$ (vide supra); $x$(g$^+$) varies from 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$_Y$ is gauche with respect to O$_Z$ ($x$(g$^+$) $= 0.71$ and 0.63 for 12 and 13, respectively). The occurrence of conformational transmission in 5–8 implies that O$_Y$ is preferentially located in the axis of the P$_V$ TBP, i.e., structure I (O$_Y$ axial, O$_Z$ equatorial) prevails over the two possible alternatives, II (O$_Y$ axial, O$_Z$ equatorial) and III (O$_Y$ and O$_Z$ equatorial). The preference of I over II correlates with quantum chemical model calculations by van Lier et al.$^{11}$ which showed that O$_Y$ axial, O$_Z$ equatorial is approximately 8 kJ/mol more stable than O$_Y$ axial, O$_Z$ 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$_Z$ 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 form 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-$d_4$. The experimental coupling constants $J_{12}$ and $J_{1'}$ measured in acetone-$d_4$, as well as the calculated rotamer populations of g$^+$, g$^*$, and g$^*$, 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$^*$ rotamer populations. For example, it is found for the P$_V$ TBP systems 5–8 in acetone-$d_4$ that $x$(g$^*$) ranges from 0.85 to 0.91, while $x$(g$^*$)

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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 via a PIV into PIV TBP transition. Two points must be made in extrapolating the present data to conformational transitions in natural DNA: (i) The PIV TBP compounds 5-11 are neutral species, whereas the transient PIV TBP system formed in natural DNA has two negatively charged oxygens bound to phosphorus. Quantum chemical calculations performed by van Lier et al., have shown that conformational transmission occurs in both charged and neutral PIV TBP complexes. These data strengthen our original point that neutral PIV TBP structures (which are stable enough for experimental studies) can be used as models for unstable transient PIV TBP's as formed in our proposed mechanism for conformational transmission in natural DNA. (ii) The present study refers to DMSO-d6 or acetylated DNA as the solvent, whereas natural DNA is usually in an aqueous environment. The instability of the systems 5-11 has precluded direct conformational studies in prootic media (e.g., CD3OD or D2O). 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 HX 90 (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. 31P NMR spectra were run in the FT mode on a Bruker AM 200 (200 MHz) spectrometer. Woelm silica gel was used for column chromatography. All melting and boiling points are uncorrected.

5'-O-Acetylation
Acetic anhydride (2.45 g, 24 mmol) was added over 30 min to a magnetically stirred solution of 5'-O-acetylthymidine (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., 5',5'-di-O-acetyltymidylide (Rf 0.51), 3'-O-acetyltymidylide (Rf 0.37), 5'-O-acetyltymidylide (Rf 0.17), and unreacted thymidine (Rf 0.0). Repeat column chromatography afforded 5'-O-acetyltymidylide as a white solid in 28% yield (1.60 g): mp 194-197 °C; 1H NMR (acetone-d6) δ 1.87 (3 H, s, Me), 2.82 (3 H, s, Ac), 3.94-4.09 (4 H, m, H2, H3, H4, H5), 4.19 (1 H, t, H6'), 5.32 (1 H, m, H7), 6.33 (1 H, d, H8), 7.66 (1 H, s, H8). Anal. Calc. for C9H14NO4P: C, 50.7; H, 5.8; N, 9.8. Found: C, 50.5; H, 5.8; N, 10.1.
3'-O-((N,N-Diisopropylamino)methoxyphosphino)-5'-O-acetyltymidylide.
5'-O-Acetyltymidylide (1.42 g, 5 mmol) was added with stirring to a mixture of 100 mL of dry chloroform and 10 mL of dry diisopropylethylamine. 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)methoxyphosphine (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 a yellowish oil, which was transferred to a silica gel column. Elution with a mixture of n-hexane/dichloromethane/triethylamine (45:45:5 v/v/v) yielded an oily product with Rf 0.34. Coevaporation with dry dichloromethane yielded the desired product as a slightly colored foam (1.52 g, 68%): mp 106-109 °C; 1H NMR (acetone-d6) δ 0.90-1.25 (12 H, m, Me diisopropyl), 1.58 (3 H, s, Me), 1.93 (3 H, s, Ac), 2.12 (3 H, s, Ac), 2.52-2.56 (2 H, m, H5', H6'), 3.37 (3 H, d, OMe, J = 11 Hz), 3.98 (1 H, d, H2'), 4.08 (1 H, d, H3'), 4.44 (2 H, d, Ac), 4.80 (1 H, t, H1') 5.45 and 5.61 (1 H, d, H2'), 7.68 (1 H, s, H8); 31P NMR (acetone-d6) δ 154.8 and 154.1 (ratio 1:1). Anal. Calc. for C19H24N3P13O7: C, 51.23; H, 7.19; N, 9.44. Found: C, 50.7; H, 7.2; N, 9.7.
5'-O-(3'-O-Acetylthymidyl) 3'-O-(5'-O-Acetylthymidyl)
Methyl Phosphate. 3'-O-Acetylthymidyl (0.80 g, 2.46 mmol) and 3'-O-((N,N-diisopropylamino)methoxyphosphono)-5'-O-acetyltymidylide (0.94 g, 2.11 mmol) were dissolved with stirring in 15 mL of dry pyridine. 1H-Tetrazole (0.24 g, 3.2 mmol) was added, and the reaction mixture was stirred for 4 h. Thorough evaporation of the pyridine afforded a yellowish syrup, which was transferred to a 10-cm-long silica gel column. Elution with butane yielded a slightly colored foam (Rf 0.32). 31P NMR indicated the presence of two diastereomers with δ 145.8 and 145.2 (acetone-d6) δ 1.95 and 1.98 (2 X, s, Me), 2.19 (3 H, s, Ac), 2.25 (3 H, s, Me), 3.22 (3 H, d, OMe, J = 11 Hz), 3.40-3.52 (2 H, m, H5', H6'), 4.06 and 4.16 (2 X, 1 H, m, H2', H3'), 4.56 and 4.71 (2 X, 1 H, m, H2', H3'), 6.35 and 6.42 (2 X, 1 H, d, H8), 7.58 and 7.62 (2 X, 1 H, s, H8). Anal. Calc. for C19H24N3P13O7: C, 52.08; H, 5.73; N, 9.72. Found: C, 51.9; H, 5.6; N, 9.6.
2-(3'-O-(5'-O-Acetylthymidyl)-2-(3'-O-(3'-acetylthymidyl))-2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole (5).
This compound was prepared by the addition of 1 equiv of freshly distilled butaneone to a cooled (0 °C) solution of 5'-O-(3'-O-(3'-acetylthymidylyl)-3'-O-(5'-O-(2'-acetylthymidylyl)) methyl phosphate in a 5-mm NMR sample tube. After 30 min, 31P NMR indicated complete conversion of the phosphate into the penta-coordinated phosphorus structure of 5.

(15) Conformational transmission was also observed with the model compounds 5-8 in the hydrogen bond disrupting solvent [(CH3)2N]P=O. See: Normant, H. Bull. Soc. Chim. Fr. 1965, 2, 791.
(16) NMR facility at the Eindhoven University of Technology.
(17) Dutch National hf 500/200 NMR facility at Nijmegen, The Netherlands.
conversion of the phosphate into 12: 31P NMR (acetone-d6) δ 0.2 and 0.8.

(3'-O-(5'-O-Tritylthymidy1))-2-(5'-O-(3'-O-acetylthymidy1)-2-methoxy-4,5-dimethyl-1,3,2X5-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-acetylthymidy1) 3'-O-(5'-O-tritylthymidy1) methyl phosphite in a 5-mm NMR sample tube. After 20 min, 31P NMR indicated quantitative conversion of the phosphate into the pentacoordinated phosphorus structure of 6: 31P NMR (acetone-d6) δ -50.3 (s); 1H NMR (acetone-d6) δ 8.2 (2 H, br s, NH), 7.52 and 7.51 (2 H, m, aromatic H), 6.21 (1 H, t, H5 (3'-residue)), 6.16 (1 H, t, H5 (3'-residue)), 5.78 (1 H, m, H5 (3'-residue)), 5.22 (1 H, m, H2 (5'-residue)), 4.20 (2 H, m, H5, H4), 4.17-4.12 (2 H, m, H5, H3 (3'-residue)), 3.72 (3 H, d, OCH3, J = 12.8 Hz), 3.40 (2 H, m, H5 (3'-residue)), 1.90 (6 H, s, CH3 dioxaphosphole), 2.25-2.20 (4 H, m, H2, 2j, 2h), 2.10 (3 H, s, acetyl), 1.88 and 1.84 (2 × 3 H, s, 5-CH3).

3'-O-Acetyl-1',2'-dideoxyribose. 1',2'-Dideoxyribose19 (5.9 g, 50 mmol) was reacted with acetic anhydride (6.1 g, 60 mmol) as described in vacuo, and the resulting glass was chromatographed on a Woelm silica gel column using dry butanone/triethylamine (95:5 v/v) afforded the product as a foam. 31P NMR (acetone-d6) δ -50.3 (s); 1H NMR (acetone-d6) δ 8.7 (1 H, br s, NH), 7.58 (1 H, s, H5), 7.44-7.20 (15 H, m, aromatic H), 6.13 (1 H, t, H5 (3'-residue)), 5.72 (1 H, m, H2 (5'-residue)), 5.22 (1 H, m, H5 (3'-residue)), 4.33 (1 H, m, H4 (5'-residue)), 4.22 (1 H, m, H3 (5'-residue)), 3.80 (3 H, d, OCH3, J = 13.2 Hz), 3.78-3.70 (2 H, m, H2 (3'-residue)), 3.41 (2 H, m, H5 (5'-residue)), 1.80 (6 H, s, dioxaphosphole), 2.41-2.19 (4 H, m, H2, 2j, 2h), 2.14 (3 H, s, acetyl), 1.88 (3 H, s, 5-CH3), 1.12 (12 H, m, isopropyl), 1.26-2.4 (2 H, m, H2, 2j).

3'-O-Acetyl-1',2'-dideoxyribose (6) was reacted with acetic anhydride (6.1 g, 60 mmol) as described for 31P NMR (acetone-d6) δ -46.2; 1H NMR (acetone-d6) δ 8.2 and 8.1 (2 × 1 H, H5, H3), 7.2 (2 H, br s, NH), 6.04 (1 H, t, H5), 5.22 (1 H, m, H2 (3'-residue)), 4.31-3.92 (2 H, m, H5, H3 (3'-residue)), 3.78 (6 H, d, OMe), 4.10 (2 H, m, H5, H3), 4.33 (1 H, m, H4 (5'-residue)), 4.28 (1 H, m, H3 (5'-residue)), 3.80 (3 H, d, OCH3, J = 13.0 Hz), 2.68 (1 H, m, H5, H3), 1.80 (6 H, s, dioxaphosphole), 1.80 (3 H, s, acetyl), 1.12 (12 H, m, isopropyl), 1.26-2.4 (2 H, m, H2, 2j).

This compound was obtained from 3'-O-(5'-triethylphosphite) 2'- deoxyribose as described in vacuo, and the resulting glass was chromatographed on a Woelm silica gel column using dry butanone/triethylamine (95:5 v/v) afforded the product as a foam. 31P NMR (acetone-d6) δ -46.2; 1H NMR (acetone-d6) δ 8.2 and 8.1 (2 × 1 H, H5, H3), 7.2 (2 H, br s, NH), 6.04 (1 H, t, H5), 5.22 (1 H, m, H2 (3'-residue)), 4.31-3.92 (2 H, m, H5, H3 (3'-residue)), 3.78 (6 H, d, OMe), 4.10 (2 H, m, H5, H3), 4.33 (1 H, m, H4 (5'-residue)), 4.28 (1 H, m, H3 (5'-residue)), 3.80 (3 H, d, OCH3, J = 13.2 Hz), 3.63 (6 H, s, dioxaphosphole), 2.14 (3 H, s, acetyl), 1.88 (3 H, s, 5-CH3), 1.12 (12 H, m, isopropyl), 1.26-2.4 (2 H, m, H2, 2j).

Conformational Transmission in Nucleotides

(18) The synthesis of this phosphite was described previously. See: Koole, L. H.; van Genderen, M. H. P.; Buck, H. M. J. Am. Chem. Soc. 1987, 109, 3916.

described for 9: $^{31}$P NMR (acetone-d$_6$) $\delta$ = 45.7; $^1$H NMR (acetone-d$_6$) $\delta$ = 2.18 (3 H, s, acetyl), 2.38-2.27 (2 H, m, $H_2$t/2$_3$), 2.05 (3 H, s, acetyl), 1.87 (3 H, s, 5-CH$_3$).

3'-O-Acetylthymidine 5'-(Dimethyl phosphate) (14). An ozone/oxygen stream was passed through a cooled (0 °C) solution of 500 mg of 3'-O-acetylthymidine 5'-(dimethyl phosphate) in 10 mL of anhydrous dichloromethane. After 20 min, TLC using butanol as eluent indicated complete conversion of the phosphate into 14 ($R_f$ 0.30). $^1$H NMR (acetone-d$_6$) $\delta$ 6.9; $^{31}$P NMR (acetone-d$_6$) $\delta$ 6.7; $^1$H NMR (acetone-d$_6$) $\delta$ 8.3 and 8.25 (2 × 1 H, s, $H_2$/$H_8$), 7.04 (2 H, br s, NH), 6.12 (1 H, dd, $H_2$), 5.55 (1 H, m, $H_8$), 4.37 (1 H, m, $H_5$), 4.20-4.07 (2 H, m, $H_2$/1$H_5$), 3.78 (6 H, d, OCH$_3$, $J$ 11.2 Hz), 2.32-2.17 (2 H, m, $H_2$/2$H_3$), 2.18 (3 H, s, acetyl).

2'-Deoxy-3'-O-acetylthymidine 5'-(Dimethyl phosphate) (15). This compound was prepared from 2'-deoxy-3'-O,N$_4$-diacetylthymidine 5'-(dimethyl phosphate) according to the procedure that was described for 9. $^1$H NMR (acetone-d$_6$) $\delta$ 8.3 (1 H, br s, NH), 7.75 (1 H, d, $H_6$), 6.02 (1 H, dd, $H_2$), 5.90 (1 H, d, $H_8$), 5.42 (1 H, m, $H_3$), 4.38 (1 H, m, $H_5$), 4.19-4.06 (2 H, m, $H_2$/1$H_5$), 3.81 (6 H, d, OCH$_3$, $J$ 11.3 Hz), 2.41-2.17 (2 H, m, $H_2$/2$H_3$).

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Studies on the Conformation of 5,15-Diarylporphyrins with (Arylsulfonyl)oxy Substituents$^1$

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Dimeeso-substituted octaalkylyporphyrins, carrying an (arylsulfonyl)oxy group at the ortho position of the two (meso) phenyl groups, were synthesized from dipyrromethanes and aldehydes. On account of a $^1$H NMR upfield shift in CDC$_3$ 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 CDC$_3$/CF$_3$COOH solution the upfield shifts are absent. The results of low-temperature $^1$H NMR measurements and ring-current calculations agreed with our assumptions. The sulfonloxy group promotes folding of the molecule more than the ester, sulfonyl, sulfanyl, thio, or methylene group. In zinc porphyrins carrying anthraquinone substituents, intramolecular coordination was observed. $\Delta$G, $\Delta$H, and $\Delta$S values for the various conformational equilibria were calculated from the NMR data. We suggest van der Wals interactions with a contribution of charge transfer as the driving force for the folding of the molecule.

The mechanism of the charge separation step in photoysisynthesis 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-2,7,12,15,17,18-octamethylporphyrin, carrying a tosylate group in the 8-position of an ethoxy side chain, attached at the ortho (meso) aryl position, i.e. 6b (Figure 1). The $^1$H NMR spectrum of this compound in CDC$_3$ solution showed an unexpectedly large upfield shift for the aromatic tosylate protons: 2.03 and 3.06 ppm for H$_2'$H$_6'$ and H$_5'$H$_5'$, respectively, compared to the $\delta$ values of a reference compound, the corresponding aldehyde RCHO (7b) used in the synthesis (Scheme 1). In the following we use $\Delta$ values, defined as $\delta$ for a proton in the aldehyde 7, $-\delta$, for the corresponding proton in the porphyrin 6 (see for numbering of the protons Figure 1).$^3$ Since upon 10-fold dilution of a solution of 6b we did not observe a significant change of $\delta$ values, we exclude intermolecular association and explain the observed shifts

$^1$Part of this work has been described in a preliminary communication: Sanders, G. M.; van Dijk, M.; Koning, G. P.; van Veldhuizen, A.; van der Plas, H. C. J. Org. Chem. 1988, 53, 5272-5281.


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