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'-bicyclo[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, CH₂); 13C NMR (see Table IV). Anal. Calcd for C₂₅H₂₄F₂: C, 75.59; H, 9.45. Found: C, 75.29; H, 9.84.

Preparation of Some 4-Substituted 4'-Fluoro-1,1'-bicyclo[2.2.2]octanes as Mixtures (6, X = H, CI, Br, I, and CH₃). Initially, we set out to prepare 4-iodo-4'-fluoro-1,1'-bicyclo[2.2.2]octane (6, X = I) as an appropriate precursor for synthesizing a fairly extensive series of systems. However, this goal was thwarted when an attempt to prepare this compound in quantity by treatment of 4-hydroxy-4'-iodo-1,1'-bicyclo[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'-bicyclo[2.2.2]octane was treated with ca. 1 equiv of iodotrimethylsilane to afford a mixture containing 4-iodo-4'-fluoro-1,1'-bicyclo[2.2.2]octane (6, X = I; ca. 32%), 4,4'-diiodo-1,1'-bicyclo[2.2.2]octane (ca. 4%), and unreacted starting material (ca. 64%). Samples of the sublimed mixture were then treated appropriately with Li/3-BuOH/THF:2 ICl:3 or Br₂54 to provide mixtures containing the parent system (6, X = H), the chloro- or bromo-fluoro (6, X = Cl or Br) derivatives, respectively. Treatment of the difluoro precursor (6, X = F) with a limited quantity of trimethylaluminum as previously described gave a mixture containing the methyl-fluoro derivative (6, X = CH₃), 4,4'-dimethyl-1,1'-bicyclo[2.2.2]octane, and unreacted starting material. All the aforementioned mixtures were unambiguously characterized by VPC analysis and 13C NMR (Table IV). Spectra assignments for the various compounds were facilitated by the characteristic 13C-19F coupling constants in the bicyclo[2.2.2]octane ring system as well as by the fact that, except for bridgehead positions, additivity of substituent effects on chemical shifts work very well for 1,1'-bicyclo[2.2.2]octanes. The availability of authentic samples of 1,1'-bicyclo[2.2.2]octane (mp 234-236 °C; 13C NMR (CDCl₃, relative MeSi) δ 34.06 (C(1,1)), 24.75 (C(2,2)), 26.18 (C(3,3)), 23.79 (C(4,4)'), and 4,4'-dimethyl-1,1'-bicyclo[2.2.2]octane (mp 182-184 °C (lit. 56 mp 184-185 °C); 13C NMR (CDCl₃, relative MeSi) δ 34.48 (C(1,1)'), 25.59 (C(2,2)'), 33.55 (C(3,3)'), 27.16 (C(4,4)'), 28.14 (CH₃) allowed 13C NMR spectra to be calculated for all the appropriately substituted bicyclo[2.2.2]octanes. These agreed well with all the observed spectra.

Registry No. 5 (X = H), 116263-68-4; 5 (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 = I), 116263-95-7; 5 (X = NH₂), 116263-96-8; 5 (X = Sn(CH₃)₂), 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-acetoxytriptycene, 97735-14-7; 9-hydroxytriptycene, 73597-16-7; 9,10-dibromoanthracene, 523-27-3; 9,10-dibromotriptycene, 795-42-6; 9-bromo-10-hydroxytriptycene, 116263-69-5; 9-bromo-10-chloroanthracene, 22722-73-9; 9-bromo-10-chlorotriptycene, 116263-71-9; 9-chloro-10-hydroxytriptycene, 116263-72-0; 9-methyl-10-methoxyanthracene, 21992-33-5; 9-methyl-10-methoxytriptycene, 116263-74-2; 9-hydroxy-10-methy triptycene, 116263-75-3; 1-acetyl-4-methoxybicyclo[2.2.2]octane, 116263-77-5; 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid, 773-34-2; 1-acetoxy-4-methoxybicyclo[2.2.2]octane, 116263-78-6; 1,4-diiodo bicyclo[2.2.2]octane, 10364-05-3; 1-iodo-4-methoxybicyclo[2.2.2]octane, 74467-18-8; 1-acetoxy-4-iodobicyclo[2.2.2]octane, 74467-17-7; 4,4'-dimethoxy-1,1'-bicyclo[2.2.2]octane, 116263-79-9; 4,4'-di hydroxy-1,1'-bicyclo[2.2.2]octane, 116263-79-7.


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

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Received April 29, 1988

A set of nucleotide analogues containing a stable trigonal bipyramidal phosphorus (Pv TBP) 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 O₆ and the base proton H₈ (pyrimidine base) or H₇ (purine base), resulting in a preference for the standard gauche(+) conformation around the C₅-C₆ bond. In the hydrogen bond disrupting solvent DMSO-d₆, the Pv TBP nucleotides 5-8 clearly show conformational transmission, i.e., a preference for the unusual gauche(-) (g') rotamer around the C₅-C₆ 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 Pv 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 (Pv TBP) compounds. It was shown that the construction of specific ligands
Conformational Transmission in Nucleotides

Chart I

Chart II. Pγ Nucleotide Structures Studied in This Work and Their Pν Counterparts

was established that pseudorotation in 3a and 4a is 2–4 times faster than in 3b and 4b. With the acceptance of the intermedancy 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.10,11 in their studies on conformational transmission in model systems for phospholipids. For monomeric phospholipid models in solution, it was found that going from Pν toward Pγ TBP results in a structural change in the glyceryl fragment leading to stronger van der Waals interaction between the two acyl chains.12 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.5

Now we will offer a detailed study of the impact of Pγ TBP locations in the backbone of nucleotides for conformational transmission on the level of single-strand phosphate-methylated DNAs in various solvents. The Pγ TBP nucleotides 5–11 (Chart II) were chosen as representative model systems. The selection of phosphate-methylated DNAs is necessary to guarantee stable Pγ TBP. The presentation of the results will be discussed with the

References:
2. For 1 in acetone-d6 at 276 K, it was shown that axial and equatorial locations in the Pγ TBP correspond with 68 and 20% O-O trans, respectively. See ref 1a.
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^{iv}) were synthesized from the corresponding phosphate triester (P^{iii}) nucleotides via reaction with butanediol, and ozone/oxygen, respectively. The precursor P^{iii} nucleotides were prepared from 5'-protected thymidine 3'-(methyldiisopropylphosphoramidite) (in the case of 5, 6, and 12), or 5'-protected 1',2'-dideoxyribose 3'-(methyldiisopropylphosphoramidite) (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 the pure form in moderate yields (vide infra). In various cases, however, it proved impossible to determine accurate values for J_{2y}, J_{3y}, and/or J_{4y}, due to one of the following reasons: (i) collapse of H_2 and H_5 in the NMR spectra; (ii) overlap of the H_4 or H_5 spectral pattern with the residual signal of the solvent DMSO-d_6; (iii) overlap of H_4 and the H_5/H_4 spectral pattern. In order to arrive at a uniform treatment for all model compounds, we used the formula x(C_2^{endo}) = (J_{1y} + J_{2y} - 9.8)/5.9, as developed by Rinkel et al. 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_{1y} and J_{2y} exclusively. For the nucleotides 5, 6, and 12, the assignment of the H_4 patterns to the upper and lower residue was performed with homonuclear decoupling experiments, based on the fact that the connectivity sequence phosphorus-H_4-H_5/H_4-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_5 of thymidine or cytosine, or H_4 of adenine, strongly fixes the C_4-C_5 conformation in the g^t rotamer (Figure 1). The formation of the O_5^-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_{2y} and J_{3y} and the calculated rotamer distributions around the C_4-C_5 bond for 5-16 in the solvent DMSO-d_6.

<table>
<thead>
<tr>
<th>compd</th>
<th>J_{2y}, Hz</th>
<th>J_{3y}, Hz</th>
<th>x(g^t)</th>
<th>x(g^t)</th>
<th>x(g^-)</th>
<th>J_{2y}, Hz</th>
<th>J_{3y}, Hz</th>
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<td>3.5</td>
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<td>2.9</td>
<td>0.80</td>
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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 $J_{13}$ 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>
</tr>
</thead>
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<tr>
<td>$J_{12}$, Hz</td>
<td>$J_{13}$, Hz</td>
<td>$x(C_2$-endo)</td>
</tr>
<tr>
<td>5 5'-residue</td>
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<tr>
<td>5 3'-residue</td>
<td>7.9</td>
<td>7.5</td>
</tr>
<tr>
<td>6 5'-residue</td>
<td>8.0</td>
<td>7.5</td>
</tr>
<tr>
<td>6 3'-residue</td>
<td>7.3</td>
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</tr>
<tr>
<td>7 3'-residue</td>
<td>8.0</td>
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<td>16</td>
<td>7.5</td>
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</tbody>
</table>

Figure 1. Part of the X-ray crystal structure of 3',5'-di-O-acetylthymidine,18 in which the $g^+$ conformation is stabilized via hydrogen bonding between $O_2$ 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 $O_2$ and $O_4$ (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 $O_2$ is gauche with respect to $O_4$. The occurrence of conformational transmission in 5–8 implies that $O_2$ is preferentially located in the axis of the $P^V$ TBP, i.e., structure I ($O_2$ axial, $O_4$ equatorial) prevails over the two possible alternatives, II ($O_2$ axial, $O_4$ equatorial) and III ($O_2$ and $O_4$ equatorial). The preference of I over II correlates with quantum chemical model calculations by van Lier et al.11 which showed that $O_2$ axial, $O_4$ equatorial is approximately 8 kJ/mol more stable than $O_2$ axial, $O_4$ 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 proposition12 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 $O_2$ 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 $P^V$ (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 $g_1$ ($C_4$-$C_5$ bond) and $C_2$-endo (sugar ring) corresponds with the conclusion of Remin14 that a $g$'/$C_2$-endo conformation is highly unfavorable.

Conformation of 5–16 in Acetone-$d_6$. The experimental coupling constants $J_{45}$ and $J_{49}$ measured in acetone-$d_6$, 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 $PI^V$ 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-$d_6$ that $x(g^+)$ ranges from 0.85 to 0.91, while $x(g^-)$(12) Buck, H. M. Recl. Trav. Chim. Pays-Bas 1980, 99, 181.

respectively. These data suggest that conformational transmission is prevented by the formation of a hydrogen bond between O₆ and H₂ of thymine (vide supra). The extreme situation represents the 5'-P7 TBP compound 9 with χ(2*) = 0.90. The data in Table II (right) show that the conformational equilibria of the sugar rings in 5'→16 in acetone-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 that a hydrogen bond disrupting solvent such as DMSO is used. 15 Otherwise, the mission that a hydrogen bond disrupting solvent such as acetone-d₆ are heavily biased toward the C₂,-endo form. 5270

It follows from a comparison of the data on the TBP system formed in natural DNA has two negatively charged groups which are neutral species, whereas the transient TBP is a slightly colored foam (1.52 g, 68%): mp 155-109 °C; 1H NMR (acetone-d₆) δ 0.90-1.25 (12 H, m, Me diisopropyl), 1.58-1.69 (6 H, s, Ac), 2.12 and 2.10 (2 H, s, CH₃ dioxaphosphole), 2.42-2.21 (4 H, m, H₂,Ac), 3.36-3.52 (4 H, m, H₂,Ac), 4.80 (1 H, m, H₂,Ac), 6.44 (1 H, dd, H₂,Ac), 7.68 (1 H, s, H₂,Ac). 31P NMR (acetone-d₆) δ 154.8 and 154.1 (ratio 1.0:1). Anal. Calcd for CₙHₙOₙPₙOₙ: C, 50.7; H, 5.2; P, 9.7. 5'-O-(3'→5'-Acetylthymidyl)-2-(3'→5'-Acetylthymidyl) methyl phosphate (12). This compound was prepared by the 15 additional step of a cooled 15 mm NMR sample tube. After 30 min, 31P NMR (acetone-d₆) δ 0.90-1.25 (12 H, m, Me diisopropyl), 1.58 (6 H, s, Ac). 1H NMR (acetone-d₆) δ 0.90-1.25 (12 H, m, Me diisopropyl).
conversion of the phosphate into $^{31}$P NMR (acetone-$d_6$) δ 0.2 and 0.8. 2-(3′-O-(5′-O-Tritylthymidyl))-2-(3′-O-(3′-O-acetylthymidyl)-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, $^{31}$P NMR indicated quantitative conversion of the phosphate into the pentacoordinated phosphorus structure of 6: $^{31}$P NMR (acetone-$d_6$) δ -50.3 (s); $^1$H NMR (acetone-$d_6$) δ 8.2 (2 H, br s, NH), 7.69 and 7.51 (2 H, m, aromatic H), 6.21 (1 H, t, H$_7$ (5′-residue)), 6.16 (1 H, t, H$_7$ (3′-residue)), 5.78 (1 H, m, H$_5$ (3′-residue)), 5.22 (1 H, m, H$_5$ (5′-residue)), 4.20 (2 H, m, H$_6$), 4.17–4.12 (2 H, m, H$_5$, H$_{5r}$ (3′-residue)), 3.72 (3 H, d, OCH$_3$ δ = 12.8 Hz), 3.40 (2 H, m, H$_{5r}$ (5′-residue)), 1.90 (6 H, s, CH$_3$ dioxaphosphole), 2.25–2.20 (4 H, m, H$_{2r}$/2t), 2.10 (1 H, s, acetyl), 1.88 and 1.84 (2 × 5 H, s, 5-CH$_3$).

5′-O-Acetyl-1′,2′-dideoxyribose 1′,2′-Dideoxyribose (5.9 g, 50 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 CH$_3$ dioxaphosphole, 2.28–2.20 (4 H, m, H$_{2r}$/2t), 2.10 (1 H, s, acetyl), 1.88 and 1.84 (2 × 5 H, s, 5-CH$_3$).

3′-O-((N,N-Diisopropylamino)methoxyphosphino)-5′-O-acetyl-1′,2′-dideoxyribose. This compound was synthesized from 5′-O-acetyl-1′,2′-dideoxyribose (1.20 g, 7.5 mmol) and chloro(N,N-diisopropylamino)methoxyphosphino (1.58 g, 8.0 mmol) according to the procedure that was given for 3′-O-(N,N-diisopropylamino)methoxyphosphino)-5′-O-acetylthymidine (vide supra). Purification was achieved by crystallization of the product as a foam, mp 96–101 °C, in 52% yield (0.78 g).

$^1$H NMR (acetone-$d_6$) δ 8.9 (1 H, br s, NH), 6.04 (1 H, d, OMe), 4.92 (1 H, m, H$_5$), 3.89–3.82 (2 H, m, H$_{5r}$/5t, H$_{5t}$/5r), 3.78 (3 H, s, CH$_3$), 1.89 (6 H, s, CH$_3$ dioxaphosphole), 2.30–2.19 (4 × 1 H, m, H$_{2r}$/2t). Anal. Calcd for C$_{14}$H$_{28}$PN$_2$O$_5$: C, 52.34; H, 8.72; N, 4.36. Found: C, 51.6; H, 8.4; N, 5.0.

3′-O-((N,N-Diisopropylamino)methoxyphosphino)-5′-O-acetyl-1′,2′-dideoxyribose (602 mg, 2.2 mmol) and 3′-O-((N,N-diisopropylamino)methoxyphosphino)-5′-O-acetyl-1′,2′-dideoxyribose (640 mg, 2 mmol) as described for 5′-O-(3′-O-acetylthymidyl) 3′-O-(5′-O-acetylthymidyl) methyl phosphate (vide supra). The product was obtained as a colorless glass.

This compound was prepared from dimethoxy(N,N-dimethyl)methoxyphosphine (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%; $^1$H NMR (acetone-$d_6$) δ 1.87 (3 H, d, CH$_3$ base), 2.12 (3 H, s, Ac), 2.65 (1 H, m, H$_2$/2t), 3.12 (1 H, m, H$_2$/2t), 4.31–3.92 (2 H, m, H$_{5t}$/5r), 3.78 (6 H, d, OCH$_3$ δ = 13.2 Hz), 2.10 (3 H, s, Ac), 3.0–4.40 (8 H, m, H$_{5t}$/5r, H$_5$/H$_{5r}$, H$_{5t}$/5r, 2′ × isopropyl); $^3$P NMR (acetone-$d_6$) δ 154.2 and 153.7 (ratio 10:88). Anal. Calcd for C$_{14}$H$_{28}$P$_2$O$_5$: C, 52.34; H, 8.72; N, 4.36. Found: C, 51.6; H, 8.4; N, 5.0.

2-(3′-O-(5′-O-Acetyl-1′,2′-dideoxyriboyl))-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 3′-O-(5′-O-acetylthymidyl) 3′-O-(5′-O-acetylthymidyl) methyl phosphate in a 5-mm NMR sample tube. After 30 min, $^3$P NMR indicated complete conversion of the methyl phosphate into the pentacoordinated phosphorus structure of 7: $^3$P NMR (acetone-$d_6$) δ -44.1; $^1$H NMR (acetone-$d_6$) δ 8.9 (1 H, br s, NH), 7.68 (1 H, s, H$_7$), 6.16 (1 H, t, H$_7$), 5.30 (1 H, m, H$_5$), 4.30 (1 H, m, H$_5$), 4.25–3.23 (2 × 1 H, m, H$_{5t}$/5r), 2.80 (6 H, m, CH$_3$/CH$_2$/2t) 1.82 (6 H, s, CH$_3$ dioxaphosphole), 1.30 (3 H, s, 5-CH$_3$).

2′-Deoxy-3′-O-acetyladenosine 5′-(Dimethyl phosphate). A solution of dimethoxy(N,N-dimethyl)methoxyphosphine (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-acetyladenosine (2.05 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%; $^1$H NMR (acetone-$d_6$) δ 1.87 (3 H, d, CH$_3$ base), 2.12 (3 H, s, Ac), 2.65 (1 H, m, H$_2$/2t), 3.12 (1 H, m, H$_2$/2t), 4.31–3.92 (2 H, m, H$_{5t}$/5r), 3.78 (6 H, d, OCH$_3$ δ = 13.2 Hz), 2.10 (3 H, s, Ac), 3.0–4.40 (8 H, m, H$_{5t}$/5r, H$_5$/H$_{5r}$, H$_{5t}$/5r, 2′ × isopropyl); $^3$P NMR (acetone-$d_6$) δ 154.2 and 153.7 (ratio 10:88). Anal. Calcd for C$_{14}$H$_{28}$P$_2$O$_5$: C, 52.34; H, 8.72; N, 4.36. Found: C, 51.6; H, 8.4; N, 5.0.
described for 9: $^{31}$P NMR (acetone-$d_6$) $\delta$ -45.7; $^1$H NMR (acetone-$d_6$) $\delta$ 0.14 (1 H, br, s, NH), 7.5 (1 H, d, H$_2$), 6.18 (1 H, dd, H$_2$), 5.83 (1 H, d, H$_2$), 5.32 (1 H, m, H$_2$), 4.23 (1 H, m, H$_2$), 4.35-4.30 (2 H, m, H$_5$/H$_6$), 3.80 (6 H, d, OCH$_3$, J = 2.18 (3 H, s, acetyl). $^2$-Deoxy-3'-O-acetyladenosine 5'-dimethylphosphite). Chromatography on a Woelm silica gel column using dry butanones as eluent yielded the product as a colorless glass (R$_f$ 0.46): yield, 420 mg (55%).

2'-Deoxy-3'-O,N$^4$-diacetylcytidine 5'-dimethylphosphite). This compound was prepared from 2'-deoxy-3'-O,N$^4$-diacetylcytidine 5'-dimethylphosphite, according to the procedure that was given for 3'-O-acetylamidinylidine 5'-dimethylphosphite). This product was isolated as a slightly colored glass (R$_f$ 0.12; eluent butanone): $^{31}$P NMR (acetone-$d_6$) $\delta$ 0.12 (acetone-$d_6$) $\delta$ 6.9; $^1$H NMR (acetone-$d_6$) $\delta$ 8.3 and 8.25 (2 H, m, H$_2$). This product was prepared from 2'-deoxy-3'-O,N$^4$-diacetylcytidine 5'-dimethylphosphite, according to the procedure that was given for 14. This product was obtained as a colorless glass (R$_f$ 0.14, eluent butanone/triethylamine, 95:5 v/v): $^{31}$P NMR (acetone-$d_6$) $\delta$ 6.7; $^1$H NMR (acetone-$d_6$) $\delta$ 8.3 and 8.25 (2 x 1 H, s, H$_2$). This compound was prepared from 2'-deoxy-3'-O,N$^4$-diacetylcytidine 5'-dimethylphosphite, according to the procedure that was given for 14. This product was obtained as a colorless glass (R$_f$ 0.14, eluent butanone/triethylamine, 95:5 v/v): $^{31}$P NMR (acetone-$d_6$) $\delta$ 6.7; $^1$H NMR (acetone-$d_6$) $\delta$ 8.3 and 8.25 (2 x 1 H, s, H$_2$).

Studies on the Conformation of 5,18-Diarylporphyrins with (Arylsulfonyloxy)oxy Substituents

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Dimeso-substituted octaalkylporphyrins, 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 $^1$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 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. $\Delta$G, $\Delta$H, and $\Delta$S values for the various conformational equilibria were calculated from the NMR data. We suggest van der Waals 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 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-2,7,12,13,17,18-octamethylporphyrin, carrying a tosylate group in the $\beta$-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$_2$,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 $\Delta\delta$ 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). 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


(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.