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A 400- and 600-MHz 1H NMR Conformational Study on Nucleoside Cyclic 3',5'-P^V-TBP Systems. Conformational Transmission Induces Diequatorial Orientation of the 3',5'-Dioxaphosphorinane Ring in a Nonchair Conformation

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Abstract: The novel nucleoside cyclic 3',5'-P^V-TBP compounds 4 and 5 were studied as models for the proposed activated state of cyclic adenosine 3',5'-monophosphate (cAMP). Compound 4 features equatorial-axial (e,a) orientation of the 3',5'-dioxaphosphorinane ring. The design of compound 5, which incorporates OCH_2CH_2OME as a conformational probe, was essentially based on our previous work on conformational transmission in P^V-TBP compounds. 1H NMR analysis of compound 5 showed conformational transmission in the probe fragment, which indicates that the molecular structure with diequatorial (e,e) orientation of the 3',5'-ring, and axial location of OCH_2CH_2OME contribute significantly to the pseudorotational equilibrium. Conformational transmission in 5 was clearly established via comparison with the P^V-TBP compounds 13, in which O-nBu replaces the OCH_2CH_2OME group, 14, in which the furanose ring of thymidine, and 15, in which the OCH_2CH_2OME group is locked in an equatorial position of the P^V-TBP. The results reveal that conformational transmission can help to stabilize diequatorial orientation of the 3',5'-dioxaphosphorinane ring, which may be of relevance for the trigger function of cAMP with respect to protein kinases. The detailed conformational properties of 4 and 5 were investigated further on the basis of MNDO calculations on the models 22-24. Structural data as obtained from 1H NMR were used in the context of the optimizations. The calculations showed that axial-equatorial orientation of the 3',5'-dioxaphosphorinane ring is favored by 3-4 kcal/mol over diequatorial orientation. The optimized structures show a twist conformation of the e,a-oriented 3',5'-dioxaphosphorinane ring, whereas the e,e orientation corresponds with a half-chair geometry.

Introduction

Cyclic adenosine 3',5'-monophosphate (cAMP, 1) plays a central role as a second messenger in the regulation of cell metabolism.1 Binding of cAMP with the regulatory subunit of a protein kinase initiates a cascade of enzymatic reactions that ultimately lead to the breakdown of glycogen and release of glucose to the blood stream. The intracellular concentration of cAMP represents a balance between the action of adenylate cyclase (which produces cAMP from adenosine triphosphate in response to a hormone signal) and 3',5'-cyclic nucleotide phosphodiesterase (which catalyzes the hydrolysis of cAMP into 5'-AMP). The structural requirements for the binding of cAMP to the regulatory subunit of protein kinases as well as to phosphodiesterases have been investigated in detail.2 Several years ago, the idea was put forward that cAMP may react via an activated state in which phosphorus is in a five-coordinated (P^I) state with a trigonal-bipyramidal (TBP) geometry.3 This P^V-TBP intermediate can be generated via attack of a nucleophile on phosphorus, thereby forcing the 3',5'-dioxaphosphorinane ring into diequatorial (e,e) or equatorial-axial (e,a) orientation. It was proposed by van Ool and Buck that an e,e P^V-TBP intermediate is involved in the triggering of protein kinases, whereas an e,a P^V-TBP controls the hydrolysis of cAMP into 5'-AMP.4 This dynamic model of the mechanism of action of cAMP has reinforced the interest in the structural properties of stable P^V-TBP compounds with a 1,3,2-dioxaphosphorinane ring or a related six-membered ring fragment. The present structural knowledge of these systems is largely based on X-ray crystallographic and NMR studies. The available X-ray data reveal that a six-membered ring favors e,a orientation in the P^V-TBP, thereby accommodating a nonchair conformation.4 These structural features also prevail in solution, as is apparent from numerous NMR studies. For example, van Ool and Buck used low-temperature 13C NMR in order to assess e,a or e,e orientation of the dioxaphosphorinane ring in the phosphoranes 2 and 3 which were studied as models for the P^V-TBP activated state of cAMP.5a For compound 2, it was found that retardation of phosphorus pseudorotation yields an e,a P^V-TBP structure. Pseudorotation of 3 could not be frozen, indicating that the stability difference between e,a and e,e is diminished in comparison with 2.6a (See Note Added in Proof in ref 34.) Furthermore, Bentrude et al. have recently used NMR techniques to study a number of P^V-TBPs with a 1,3,2-dioxo- or 1,3,2-oxazaphosphorinane ring.5 These systems show a nonchair conformation of the six-membered ring, implying that the formation of P^V-TBP activated cAMP is associated with a substantial conformational change of the 3',5'-ring.


In this paper, we report the results of a $^1$H- and $^{31}$P-NMR structural study on two novel P$^4$-TBPs which may be regarded as representative models for cAMP in its activated state (4, 5, see Chart I). In the case of 4, the location of the 3',5'-dioxaphosphorinane ring was assessed via the vicinal proton-phosphorus coupling constant $J_{pOMe}$. The design of the P$^4$-TBP compound 5 was based on our previous work on, e.g., 10 and 11, which give a visualization of the conformational transmission effect: the axial and equatorial ligands adopt O=O trans and O-O gauche conformations, respectively.6 The conformational transmission effect finds its origin in the intrinsic bonding properties of trigonal-bipyramidal phosphorus, resulting in electron attraction from the substituents in the equatorial plane, along with release of electron density toward the axial substituents.7 The latter effect leads to the conclusion that the probe system is partially axial in the bipyramidal phosphorus, resulting in electron attraction from the substituents in the equatorial plane, along with release of electron density toward the axial substituents.8

Results and Discussion

Preparation of 4–9. Our synthesis of the cis phosphites 6 and 7 differs from the two-step method reported by Nelson et al.9 for the preparation of cis-thymidine 3',5'-cyclic phenyl phosphate (overall yield 14%). We prepared compound 6 and 7 directly in a 1H tetrazole-catalyzed reaction of thymidine annelated (N,N-diisopropyloxy)methoxyphosphine (leading to 6) or bis(N,N-diisopropyloxy)(2-methoxyethoxy)phosphine (leading to 7). An NMR study of 18C6 solutions showed formation of an isomer with a 1:1 ratio. Subsequent chromatographic purification exclusively yielded 6 and 7 as pure white solids (yields 23% and 33%, respectively). Oxidation of 6 and 7 into the cis phosphates 8 and 9, respectively, was accomplished by treatment with NO$_2$/NO$_3$, which is known to proceed with retention of configuration.10 The P$^4$-TBP target compounds 4 and 5 were prepared through reaction with 1 equiv of tetra-chloro-1,2-benzoquinone at ~80 °C in a 5-mm NMR tube (solvent CD$_2$Cl$_2$).

Conformational Analysis. A. Location of the 3',5'-Dioxaphosphorinane Ring in the P$^4$-TBPs 4 and 5. For compound 4, we qualitatively determined the location of the 3',5'-ring on the basis of the NMR coupling constant between phosphorus and the methoxy protons ($J_{pOMe}$). Compound 12 was used as a reference system with respect to 4. It should be noted that the experimental $J_{pOMe}$ (12) represents a time-averaged value as a result of pseudorotation around the P$^4$ center, i.e., the three methoxy groups are rapidly exchanged over one axial and two equatorial sites in the TBP. Thus,

$J_{pOMe}(12) = \frac{1}{2} J_{pOMe(axial)} + 2 J_{pOMe(equatorial)}$

The hybridization of phosphoranes in a TBP results in an enlarged s-character for the equatorial bonds in comparison with the axial ones,11 i.e., $J_{pOMe(equatorial)} > J_{pOMe(axial)}$. We found that $J_{pOMe}(4) = 14.3$ Hz and $J_{pOMe}(12) = 13.6$ Hz (400-MHz $^1$H NMR at 20 °C; solvent CD$_2$Cl$_2$), i.e., the methoxy group in 4 is predominantly in equatorial location. Combination of this result with the well-known ring strain rule, which states that five-membered rings have high preference for e,a location in the TBP, reveals that the 3',5'-ring preferentially adopts an e,a location in 4. It should be noted that our experimental data on 4 are not conclusive with respect to pseudorotation around the P$^4$-TBP; i.e., no discrimination can be made between the possibilities...


(12) Koole, L. H.; van Genderen, M. H.; Koole, L. H.; Buck, H. M. J. Org. Chem. 1988, 53, 5206. (c) de Keijzer, A. E. H.; Koole, L. H.; Buck, H. M. J. Am. Chem. Soc. 1988, 110, 5996. (7) Ramirez, F.; Ugi, I. Advances in Physical Organic Chemistry; Academic: London, 1973; Vol. 9, pp 25–126. Although almost no phosphoranes possess a perfect TBP geometry, the ones studied in the present work are expected to show no more than 15% distortion toward the square-pyramidal geometry (see also ref 8). This is confirmed by the available X-ray data (ref 4) as well as by very recent X-ray studies on a set of spirocyclic pentaoxyphosphoranes varying in ring size (Kumara Swamy, K. C.; Day, R. G.; Holmes, R. R. J. Am. Chem. Soc. In press).
The conformation around C9-C10 can be described in terms of one O1-O2 trans and two approximately degenerate O1-O2 gauche rotamers (+, -). The magnitude of \((J_{H1H2} + J_{H1H3} + J_{H2H3})\) was calculated as a function of the O1-O2 torsion angle, by using the empirically parametrized Karplus equation developed by Altona et al.\(^{15}\) This showed that \((J_{H1H2} + J_{H1H3} + J_{H2H3})\) amounts to 30.0 Hz in the trans rotamer and 16.4 for gauche (+) and gauche (-), leading to the formula

$$x(O1-O2 \text{ trans}) = \frac{(J_{H1H2} + J_{H1H3} + J_{H2H3}) - 16.4}{13.6} \times 100\%$$

The conformational analysis of the C9-C10 bond in 5 resulted in 51\% population of the O1-O2 trans rotamer and a total of 49\% population of the O1-O2 gauche rotamers. For comparison, we performed an analogous conformational analysis for the cis phosphate and cis phosphite counterparts of 5 (i.e., compounds 7 and 9, respectively). These data (Table I) show substantially diminished O1-O2 trans populations in comparison with 5.

![Figure 1](image)

Figure 1. Computer-simulated (upper trace) and experimental (lower trace) expansion of the H1/H2 pattern in the 400-MHz 1H-NMR spectrum of compound 5 at -41°C. Note that H1 and H2 are diastereotopic, with \(\Delta\delta \approx 0.1 \text{ ppm.} \) The patterns of H1 and H2 each consist of 16 lines, which are partly resolved.

### Table 1. Values of \(J_{H1H2}, J_{H1H3}, J_{H2H3}, J_{H1H4}, \) and \(J_{H2H4}\)

<table>
<thead>
<tr>
<th>compd</th>
<th>(J_{H1H2})</th>
<th>(J_{H1H3})</th>
<th>(J_{H2H3})</th>
<th>(J_{H1H4})</th>
<th>(J_{H2H4})</th>
<th>(\sum J)</th>
<th>% O-O trans</th>
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<tr>
<td>5</td>
<td>2.2</td>
<td>7.1</td>
<td>4.7</td>
<td>9.4</td>
<td>23.4</td>
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<td>7</td>
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<td>17.6</td>
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<tr>
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<td>6.5</td>
<td>18.0</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*Measured for the conformational probe system in the compounds 5, 7, and 9 at -41°C in CD2Cl2 and 14 and 15 at 20°C in CD2Cl2, along with the calculated percentages of O2-O2 trans orientation.

Furthermore, we compared 5 with three other P5-TBP systems, i.e., 13–15. Compound 13 represents the absence of conformational transmission (O1 in 5 substituted by C(H2) in 13). As expected, 13 and its cis-phosphate counterpart 13a displayed a highly similar conformational equilibrium around the C9-C10 linkage.\(^{12}\) From this analysis of the C9-C10 bond in 14 showed that \((J_{H1H2} + J_{H1H3} + J_{H2H3} + J_{H1H4}) = 25.4\) Hz, i.e., 66\% O1-O2 trans orientation exists. Compounds 5 and 14 show virtually analogous conformational characteristics, revealing that substitution of O1 by C(H2) has no predominant impact on the preferred e,e or e,a orientation in the present set of model systems. Finally, we compared the data on 5 with those measured for compound 15, in which the OCH2CH2OMe probe is in fact locked in an equatorial position in the P5-TBP.\(^{16}\) Conformational analysis of C9-C10 in 15 indeed showed a reduced preference for O1-O2 trans (12\%), see Table 1.

The results on 5, 7, 9, and 13–15 strongly indicate that conformational transmission occurs in 5 and 14. Thus, the dynamic equilibrium of phosphorus pseudorotation in 5 and 14 is such that the OCH2CH2OMe group resides most of the time in the axis of the P5-TBP. Combining this work with the ring strain rule (vide supra)\(^{11}\) it follows that the 3',5'-ring in 5 and 14 is engaged in an equilibrium between e,a and e,e orientations in the P5-TBP. The interconversion between e,a and e,e orientation of the ring can occur via the Berry pseudorotation mechanism,\(^{14}\) by using either O2 or O2 as the pivot.\(^{17}\)

### Axiophlicity of the OCH2CH2OMe Group

Our observation of conformational transmission in compounds 5 and 14 and the

(15) Haasnoot, C. A. G.; de Leeuw, F. A. M.; Altona, C. Tetrahedron 1980, 36, 2783. The graph shows \(\sum J = (J_{H1H2} + J_{H1H3} + J_{H2H3} + J_{H1H4})\) as a function of the O-O torsion angle, relevant for compounds 5, 7, 9, 14, and 15, is given in the Supplementary Material.

(16) Both the dioxaphospholene ring and the dioxaphospholane rings in 15 display a marked preference for e,a orientation (ref 8). The OCH2CH2OMe probe acts as the pivot pseudorotation of 15 (compare the methoxy group in 5).

(17) Our observation of conformational transmission for 5 and 14 provides indirect evidence for e,a location of the 3',5'-diophosphorinane ring. In fact, explicit determination of the molecular conformation of 5 or 14 would require an X-ray diffraction study. Some additional indication concerning the possibility of e,a orientation of the 3',5'-ring follows by comparing the proton-phosphorus couplings of the probe fragment (J_{H1H2}, J_{H1H3}, J_{H2H3}) in 5 with those of compound 15 (J_{H1H2} = 6.8 Hz, J_{H1H3} = 2.6 Hz; 15: J_{H1H2} = J_{H1H3} = 10.7 Hz). The reduced proton-phosphorus coupling constants of 5 are in agreement with a dynamic equilibrium between an axial and equatorial orientation of the OCH2CH2OMe fragment.\(^{13}\) From a previous study on conformational transmission in P5-TBP compounds is known that the OCH2CH2OMe fragment in an axial location results in a maximum O1-O2 trans population of approximately 50\%, which is close to the value of 51\% found for compound 5.\(^{11}\) Furthermore, we wish to point out that the occurrence of conformational transmission appears to be an exclusive feature of the axial sites in the P5-TBP, as based on all P5 model compounds studied so far.\(^{12,13}\) For these reasons, our conclusion that an e,a and an e,e P5-TBP intermediate can be formed during the activation of CAMP appears to be justified.
conclusion of concomitant e.e location of the 3',5'-ring implicitly show that axial locations of the OCH2CH2OMe group in the PV-TBP is preferred (increased axiophilicity). This is in agreement phosphates and ethyl groups. The data on expulsions of the cyclopentanemethyl group occurs with a probability Le., the cyclopentanemethyl group (absence of conformational transmission) displays a probability, respectively, the PV-TBPs 2-4 in comparison with the ethyl groups. Furthermore, our studies on the pseudorotational dynamics of, e.g., the PV-TBPs 17a,b-19a,b, also showed a clear axiophilicity in the case of a substituent that can show conformational transmission.26

![Diagram of cyclopentanemethyl phosphate](image)

It was found that pseudorotation of 17a-19a is accelerated by a factor 2-4 in comparison with 17b-19b, which can be attributed to conformational transmission occurring on the pseudorotational pathway.26 Thus, pseudorotation of 17a-19a proceeds via a low-energy TBP intermediate, whereas 17b-19b pseudorotate via a high-energy square-pyramidal intermediate. On the basis of data obtained with the systems 5, 14, and 16a,b-19a,b, one might anticipate that a substituent that is capable of showing conformational transmission will also display an increased preference for axial location in a PV-TBP. B. Conformation of the 2'-Deoxyribose Ring. Conformational analysis of the sugar ring of 4-9 was performed with the PSEUROT program.21 The sets of vicinal H-H coupling constants (JH1H2, JH2H3, JH3H4, JH4H5, JH5H1) measured for each compound (Table II) were used as input data. PSEUROT calculates the best-fit conformational parameters of two sugar structures participating in a rapid conformational equilibrium as well as the equilibrium composition.

On the basis of the present data, PSEUROT rapidly converged to a single conformation which is characterized by a phase angle (P) of 35.9° and a maximum puckering amplitude (vmax) of 39.9°.22 As is well-known, the five endocyclic torsion angles ϕi=ϕi+60° can be calculated from P and ϕ1 according to the formula: ϕi=ϕi+60°=ϕi+60°+60°. The data on phosphite and sulfoxide 3'-5'-cyclic nucleotides are in agreement with our models23 as given in Table II and 2135 and 2136.

![Image of a table](image)

**Table II.** Vicinal H-H and 3P-H Coupling Constants Measured for Compounds 4-9 in CD2Cl2

<table>
<thead>
<tr>
<th>compd</th>
<th>JH1H2</th>
<th>JH2H3</th>
<th>JH3H4</th>
<th>JH4H5</th>
<th>JH5H1</th>
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<th>JH2H3</th>
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</tr>
</tbody>
</table>

* Spectra of compounds 4, 6, and 8 were recorded at 20 °C; spectra of 5, 7, and 9 were taken at -41 °C.


(19) The second-order rate constants for alkaline hydrolysis of compounds 6a and 6b at 335 K are 0.006 and 0.0031 mol/s, respectively (ref 19). These values dropped to 0.000394 and 0.000344 /mol/s at 277 K for 6a and 6b, respectively.


The data on 20 and 21 strongly suggest that a Karplus type equation is valid for \( J_{PH} \) scalar couplings in \( P^2 \)-TBP systems.\(^6\) Antiperiplanar orientation of H and P across H-C-O-P and H-C-N-P coupling paths was found to result in large \( J_{PH} \) couplings (26.1 and 25.0 Hz, respectively), while much smaller values of \( J_{PH} \) were found for gauche orientations (8.7 and 5.5 Hz for H-C-O-P and H-C-N-P, respectively). We have interpreted large \( J_{PH} \) coupling constants (\( \approx 27 \) Hz) observed for 4 and 5 as evidence for antiperiplanar orientation of P and H. Thus, it is concluded from the data in Table II that phosphorus and H are antiperiplanar in 4 and 5, while gauche orientation exists for phosphorus and H. These results are in close agreement with the data reported for 20 and 21.\(^7\) Thus, it is clearly demonstrated that 4 and 5 populate a nonchair structure for the 3',5'-dioxaphosphorinane ring.

A second clue for characterization of the 3',5'-ring is provided by the coupling constants \( J_{HH} \) and \( J_{HP} \) from which the conformation around the C4',C5' (\( \gamma \)) bond can be deduced.\(^8\) By using the generalized Karplus equation of Altona et al.,\(^15\) we calculated \( J_{HH} \) and \( J_{HP} \) as a function of the torsion angle \( \delta \) (vide supra) as input values. During the calculations, only the bond angles and torsion angles defining the TBP geometry were fixed. The resulting structures are depicted in Figure 3; the calculated heats of formation of the \( P^2 \)-TBP systems correspond with a torsion angle of approximately 180°. The \( P^2 \)-TBP systems 4 and 5, on the other hand, appear to correspond with a rotation around C4'-C5' bond in such a way that the torsion angle has increased to approximately 200°.

In order to obtain a better insight into the molecular conformation of the \( P^2 \)-TBPs 4 and 5, we performed a set of MNDO semiempirical calculations\(^9\) on the isomeric model systems 22, 23, 24 (both e,a), and 24 (e,e). The calculations were started by using the experimental data concerning the structure of the 2'-deoxyribose ring. The torsion angle \( \alpha \) (vide supra) as input values. The MNDO calculations, only the bond angles and torsion angles defining the TBP geometry were fixed. The resulting structures are depicted in Figure 3; the calculated heats of formation of the \( P^2 \)-TBP systems correspond with a torsion angle of approximately 180°. The \( P^2 \)-TBP systems 4 and 5, on the other hand, appear to correspond with a rotation around C4'-C5' bond in such a way that the torsion angle has increased to approximately 200°.


A chaise lounge conformation of the 3',5'-dioxaphosphorinane ring in the case of e,a orientation in the \( P^2 \)-TBP was also predicted by Yu and Broduce. See ref 3b.

Figure 2. Calculated variation of \( J_{HH} \) and \( J_{HP} \) with the torsion angle \( \phi \). The Karplus equation described in ref 15 was used. Filled circles represent data points for the 3',5'-cyclic phosphites 6 and 7, and the 3',5'-cyclic phosphates 8 and 9 (Table II), corresponding with \( \phi \approx 180^\circ \). The data measured for the \( P^2 \)-TBPs 4 and 5 (open circles) point toward a \( \phi \) value of \( \approx 200^\circ \), i.e., the \( P^2 \)-TBP structure forces a rotation around the C4'-C5' bond of approximately 20°, irrespective of e,a or e,e orientation of the 3',5'-dioxaphosphorinane ring.

Table III. Torsion Angles Describing the Conformation of the 3',5'-Dioxaphosphorinane Ring in the MNDO-Optimized Structures of the Model Systems 22-24

<table>
<thead>
<tr>
<th>Torsion Angle</th>
<th>22 (e,a)</th>
<th>23 (e,a)</th>
<th>24 (e,e)</th>
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</tbody>
</table>

Note the relatively low values of the torsion angles \( |\theta_c-C_5'-O_3'| \) and \( |P-O_3'-C_5'| \) for 24 in comparison with 22 and 23 (see text).

These calculations led to the following heats of formation: (i) e,a isomer with \( O_3' \) equatorial and \( O_5' \) axial, -230.0 kcal/mol; (ii) e,a isomer with \( O_5' \) equatorial and \( O_3' \) axial, -230.8 kcal/mol; (iii) e,e isomer, -225.2 kcal/mol.\(^{20}\) It appears from these data that substitution of \( O_2' \) by \( C(H_2) \) does not significantly alter the relative stabilities of e,a and e,e orientation. This result correlates well with the observed conformational similarity of compounds 5 and 14, based on NMR J couplings.

The present experimental and theoretical data clearly show that activation of cAMP via formation of a \( P^2 \)-TBP intermediate will induce a nonchair conformation of the 3',5'-dioxaphosphorinane ring, which is in complete agreement with the results of Broduce et al.\(^13\) Furthermore, our experimental data reveal that formation of a \( P^2 \)-TBP structure may lead to e,a or e,e orientation of the 3',5'-dioxaphosphorinane ring. Although the MNDO calculations show that an e,a orientation is slightly energetically favorable, it appears from the data on 5 that conformational transmission in one of the ligands will help to stabilize the e,e isomer.

This effect may be of importance with respect to the binding of cAMP to the regulatory subunit of protein kinases. X-ray studies of the cAMP binding domain in the crystal structure of the bacterial catabolite gene activator protein (CAP) dimer reveal that the CH_3OH side chain of a serine residue (Ser-83) is in the right position for nucleophilic attack on the phosphorus of cAMP.\(^21\)

The resulting \( P^2 \)-TBP may show conformational transmission by virtue of enhanced charge repulsion between O and N in the atom sequence \( O^2'-OCH_2CHRN_3 \) i.e., e,e orientation of the 3',5'-ring.

(30) Substitution of \( O_2' \) in 22-24 has only a minor impact on the structural details: i.e., the 3',5'-dioxaphosphorinane ring of both e,a isomers shows a twist conformation reminiscent of the structures 22 and 23. The e,e isomer again shows a half-chair conformation, analogous to 24.

could be stabilized in this way. Clearly, this would exactly fit
with the model description of van Ool and Buck.16

Experimental Section

Material and Methods. The 1H NMR spectra were recorded on
Bruker AM 600,15 AM 400, or AC 200 NMR spectrometers. Tetra-
methylsilane (TMS) was used as the internal standard for NMR samples.
13P NMR spectra were recorded at 162 or 81 MHz on the AM 400 or
AC 200 instruments, respectively, and referenced against 85% H3PO4 as
external standard. 13C NMR spectra were recorded at 100.6 or 50.3
MHz on the AM 400 or AC 200 instruments, respectively. For all

(32) Bruker AM 600 NMR spectrometer of the Dutch National hf NMR
facility at Nijmegen. The Netherlands.


(34) Note Added in Proof: Very recently, it was reported by Bentrude et al. (Yu, J. H.; Sopchik, A. E.; Arif, A. M.; Bentrude, W. G. J. Org. Chem. 1990, 55, 3444) that decaesalence phenomena due to retarded pseudorotation can be observed for 3 if a stronger magnetic field is used (14C NMR 125 MHz; compared with 32.6 MHz used by van Ool and Buck). From the 13C NMR spectrum at -113 °C it could be concluded that the dioxaphosphorinane ring in 3 prefers e,a orientation in the P7-TBP. Furthermore, the predicted twist
gyrometric geometry of the e,a oriented 3',5'-dioxaphosphorinane ring in a P7-TBP was
in agreement with X-ray crystallographic data reported by Bentrude et al. in the same paper.
absorbed in a gas trap containing a sodium bicarbonate solution. After distillation (bp 60 °C at 30 mmHg) pure 2-chloro-1,3,2-dioxaphospholane (3P NMR (162 MHz, CDCl₃) δ 20.7 ppm) was obtained (30.6 g, 0.24 mol). This compound was added dropwise during 2 h to a solution of 2-methyoxyethanol (18.4 g, 0.24 mol) and triethylamine (24.4 g, 0.24 mol) in 200 mL of dry pyridine at room temperature. After 2 h at room temperature, the ammonium salt was removed by filtration, and the solution was concentrated in vacuo. Pure 2-(2-methoxyethoxy)-1,3,2-dioxaphospholane was obtained by distillation of the residue at 0.01 mmHg (bp 80 °C) as a colorless liquid: yield 25.6 g (31%).

The mixture was concentrated in vacuo (at room temperature) and coevaporated with toluene and dichloromethane. A white solid was obtained which was chromatographed on a silica gel column with methanol/dichloromethane 8:92 v/v as eluent, yielding 57 mg (34%) of 6-4.4 ppm) the mixture was evaporated under vacuo. A white foam appeared, which was chromatographed on a silica gel column with ethyl acetate/dichloromethane 1:1 v/v as eluent, yielding 57 mg (34%) of 6-4.4 ppm).

cis-Thymidine 3',5'-Cyclic Methyl Phosphite (9). cis-Thymidine 3',5'-cyclic methyl phosphate (7) (300 mg, 1.45 mmol) was dissolved in dichloromethane (40 mL) at −20 °C. Dichloromethane, saturated with N₂O₅/N₂O₄, was added until a greenish color appeared. After complete conversion of 7 (3P NMR (81 MHz, CH₂Cl₂/CD₂Cl₂ 1:1) δ 4.4 ppm) the mixture was evaporated under vacuo. A white foam appeared, which was chromatographed on a silica gel column with methanol/dichloromethane 6:94 v/v as eluent, yielding 75 mg (34%) of 8 as a white solid: Rf 0.21 (methanol/dichloromethane 1:1) δ 4.4 ppm.)

cis-Thymidine 3',5'-Cyclic 1-Butyl Phosphate (13). cis-Thymidine 3',5'-cyclic one-butyl phosphate (12) (300 mg, 1.45 mmol) was dissolved in dichloromethane (40 mL) at −20 °C. Dichloromethane, saturated with N₂O₅/N₂O₄, was added until a greenish color appeared. After complete conversion of 12 (3P NMR (162 MHz, CH₂Cl₂/CD₂Cl₂ 1:1) δ 4.4 ppm) the mixture was evaporated under vacuo. A white foam appeared, which was chromatographed on a silica gel column with methanol/dichloromethane 6:94 v/v as eluent, yielding 75 mg (34%) of 13 as a white solid: Rf 0.21 (methanol/dichloromethane 1:1) δ 4.4 ppm.)
Multinuclear NMR Study of the Crystal Field Strength of the Nitro Ligand and the Empirical Estimation of the $^{59}$Co NMR Chemical Shifts of Cobalt–Nitro Complexes

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Abstract: The variable ligand field strength of the nitro ligand has been reexamined on the basis of a steric model. An improved empirical method is proposed for the estimation of nitro ligand field strength in terms of a single correction parameter $\Delta_0$ (1.82 $\times 10^4$ ppm) to the shift parameter $\Delta_{CO}$ (3.075 $\times 10^4$ ppm) for the estimation of the $^{59}$Co NMR chemical shifts of cobalt–nitro complexes. The reversed chemical shift trend of geometrical isomers of cobalt–nitro complexes are attributed to variations in the $^{109}$Co of the nitro ligands. The model is applied to the assignment of different isomers of cobalt–nitro compounds obtained from ligand exchange reactions of the cobalt(III)–anion with the $N_2$ and SCN$^-$ ions. In all the ligand exchange reactions studied, it was found that mixed nitro complexes formed in the reaction predominantly adopted the trans configuration.

Introduction

Some time ago, it was demonstrated$^1$ that the isotropic $^{59}$Co NMR chemical shift for the entire range of orthoaxial six-coordinated diamagnetic cobalt(III) complexes relative to $[\text{Co} (\text{CN})_6]^2-$ could be reasonably estimated by using the empirical equation

$$\delta (\text{ppm}) = \frac{1}{3} \left( \frac{1}{S_1 + S_2} + \frac{S_1 + S_4}{S_1 + S_4} \right) - 11000$$

where $S_1$ and $S_2$, $S_1$ and $S_4$, and $S_1$ and $S_4$ are parameters characteristic of the ligands on the $x$, $y$, and $z$ axis, respectively. This expression calculates the chemical shift of any cobalt complex with a given set of $S_i$ parameters$^1$ for all the different ligands encountered and was developed based on the well-established inverse relationship between the $^{59}$Co chemical shifts and the energies of the first spin-allowed ($^{4}T_{1g}$) electronic transition of octahedral Co$^{2+}$ complexes.$^{23}$ The model successfully predicts the order of the chemical shifts for a large variety of low-symmetry geometrical isomers, i.e., cis is more shielded than trans, and similarly fac is more shielded than mer isomers, which have been demonstrated experimentally both by $^{59}$Co NMR$^2$ as well as by optical data.$^5$ But the model fails to predict the correct chemical shifts and shielding trend when cobalt(III)–nitro complexes were encountered. In another article,$^6$ an empirical formula was

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