

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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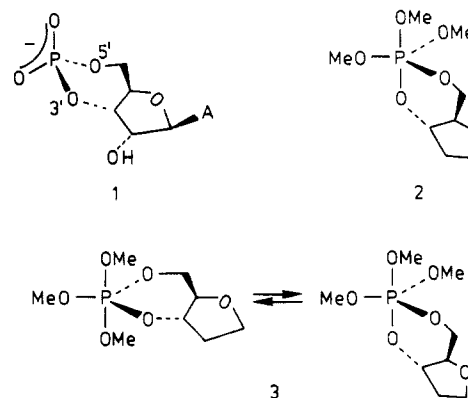
Abstract: The novel nucleoside cyclic 3',5' P^{V} -TBP compounds **4** and **5** were studied as models for the proposed activated state of cyclic adenosine 3',5'-monophosphate (cAMP). Compound **4** features equatorial-axial (e,a) orientation of the 3',5'-dioxaphosphorinane ring. The design of compound **5**, which incorporates $\text{OCH}_2\text{CH}_2\text{OMe}$ 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 $\text{OCH}_2\text{CH}_2\text{OMe}$ 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*-*n*Bu replaces the $\text{OCH}_2\text{CH}_2\text{OMe}$ group, **14**, in which a trans-fused cyclopentane ring replaces the furanose ring of thymidine, and **15**, in which the $\text{OCH}_2\text{CH}_2\text{OMe}$ 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 start 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'-adenosine monophosphate (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^{V}) 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.^{3b} 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 ^{13}C 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.^{3a} For compound **2**, it was found that retardation

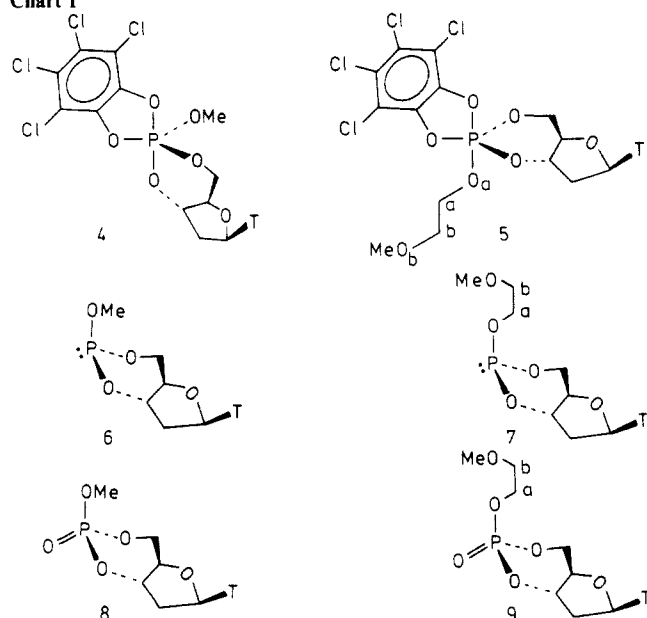


of phosphorus pseudorotation yields an e,a P^{V} -TBP structure. Pseudorotation of **3** could not be frozen, indicating that the stability difference between e,a and e,e is diminished in comparison with **2**.^{3a} (See Note Added in Proof in ref 34.) Furthermore, Bentrude et al. have recently used 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.

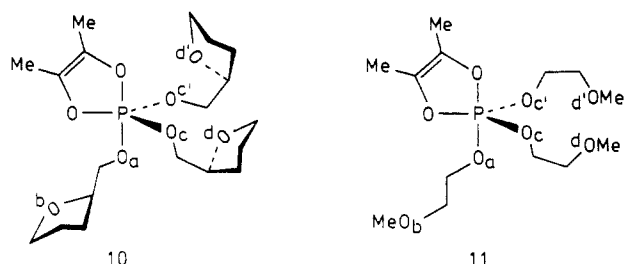
(1) (a) Stryer, L. In *Biochemistry*; Freeman and Co.: San Francisco, 1980. (b) Review series: *Advances in Cyclic Nucleotide Research*; Greengard, P., Robinson, G. A., Sr., Eds.; Raven Press: New York, 1980-1986; Vols. 11-17. (2) (a) Miller, J. P. *Adv. Cyclic Nucl. Res.* **1981**, *14*, 335. (b) Revenkar, G. R.; Robins, R. K. In *Handbook of Experimental Pharmacology*; Nathanson, J. A., Keabian, J. W., Eds.; Springer-Verlag: Berlin-Heidelberg, FRG, 1982; Vol. 58/1, Chapter 2. (c) van Haastert, P. J. M.; Dijkgraaf, P. A. M.; Konijn, T. M.; Abbad, E. G.; Petridis, G.; Jastorff, B. *Eur. J. Biochem.* **1983**, *131*, 659. (3) (a) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 79. (b) van Ool, P. J. J. M.; Buck, H. M. *Eur. J. Biochem.* **1982**, *121*, 329. (c) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 119.

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Chart I



In this paper, we report the results of a ^1H - and ^{31}P -NMR structural study on two novel P^{V} -TBP's 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 $^3J_{\text{POMe}}$. The design of the P^{V} -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



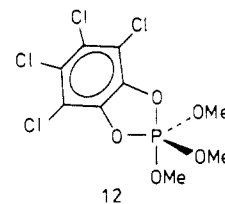
finds its origin in the intrinsic bonding properties of trigonal-bipyramidal phosphorus, resulting in electron attraction from the substituents in the equatorial plane, along with release of electron density toward the axial substituents.⁷ The latter effect leads to an increased electron density on O_a of the P^{V} -TBP's 10 and 11 in comparison with the tetracoordinated counterparts, i.e., trans orientation of O_a and O_b becomes preferred. *Mutatis mutandis*, the equatorial ligands display gauche orientation of $\text{O}_{c(c')}$ and $\text{O}_{d(d')}$. With respect to 5, we could utilize the $\text{OCH}_2\text{CH}_2\text{OMe}$ group as a conformational probe. The experimental observation (vide infra) of a substantial amount of $\text{O}_a\text{-O}_b$ trans orientation in 5 first leads to the conclusion that the probe system is partially axial in the P^{V} -TBP system 5. Since the tetrachloro-1,2-benzoquinone fragment is e,a,⁸ it follows that the 3',5'-ring has a partial diequatorial

orientation. Our present results on 4 and 5 indicate that both intermediates (i.e., an e,a and an e,e P^{V} -TBP) can be formed upon activation of cAMP.

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 phosphite (overall yield 14%). We prepared compound 6 and 7 directly in a 1H tetrazole-catalyzed reaction of thymidine and bis(*N,N*-diisopropylamino)methoxyphosphine¹⁰ (leading to 6) or bis(*N,N*-diisopropylamino)(2-methoxyethoxy)phosphine (leading to 7). ^{31}P NMR showed formation of 6 and its trans isomer in the ratio 2:3; 7 and its trans isomer were formed in 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 through reaction with $\text{NO}_2/\text{N}_2\text{O}_4$, which is known to proceed with retention of configuration.¹¹ The P^{V} -TBP target compounds 4 and 5 were prepared through reaction with 1 equiv of tetrachloro-1,2-benzoquinone at -80°C in a 5-mm NMR tube (solvent CD_2Cl_2).

Conformational Analysis. A. Location of the 3',5'-Dioxaphosphorinane Ring in the P^{V} -TBP's 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 ($^3J_{\text{POMe}}$).¹² Compound 12 was used as a reference system with respect to 4. It should be noted that the



experimental $^3J_{\text{POMe}}$ (12) represents a time-averaged value as a result of pseudorotation around the P^{V} center, i.e., the three methoxy groups are rapidly exchanged over one axial and two equatorial sites in the TBP. Thus,

$$^3J_{\text{POMe}}(12) = \frac{1}{3}[^3J_{\text{POMe}}(\text{axial}) + 2^3J_{\text{POMe}}(\text{equatorial})]$$

The hybridization of phosphorus in a TBP results in an enlarged s-character for the equatorial bonds in comparison with the axial ones,¹³ i.e., $^3J_{\text{POMe}}(\text{equatorial}) > ^3J_{\text{POMe}}(\text{axial})$. We found that $^3J_{\text{POMe}}(4) = 14.3 \text{ Hz}$ and $^3J_{\text{POMe}}(12) = 13.6 \text{ Hz}$ (400-MHz ^1H NMR at 20°C ; solvent CD_2Cl_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 strong preference for e,a location in the TBP,⁸ 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^{V} -TBP; i.e., no discrimination can be made between the possi-

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(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. O.; Holmes, R. R. *J. Am. Chem. Soc.* In press).

(8) Five-membered dioxaphospholene rings have a pronounced preference for e,a location in a P^{V} -TBP. The difference in ring strain between e,a and e,e location amounts to approximately 21 kcal/mol (Holmes, R. R. *J. Am. Chem. Soc.* **1978**, *100*, 433. Holmes, R. R. *Pentacoordinated Phosphorus*; American Chemical Society: Washington, DC, 1980; Vols. I, II; ACS Monograph No. 175, 176). Nevertheless, diequatorial location of the dioxaphospholene ring may occur as an intermediate during pseudorotation around pentacoordinated phosphorus (Koole, L. H.; van der Hofstad, W. J. M.; Buck, H. M. *J. Org. Chem.* **1985**, *50*, 4381).

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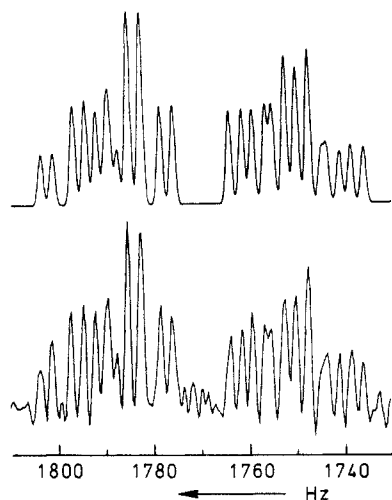
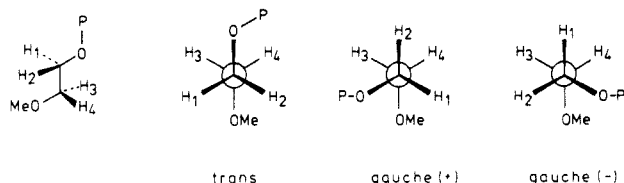


Figure 1. Computer-simulated (upper trace) and experimental (lower trace) expansion of the H_1/H_2 pattern in the 400-MHz ^1H -NMR spectrum of compound **5** at -41°C . Note that H_1 and H_2 are diastereotopic, with $\Delta\delta \approx 0.1$ ppm. The patterns of H_1 and H_2 each consist of 16 lines, which are partly resolved.

bilities of either rapid pseudorotation (on the NMR time scale) or complete absence of pseudorotation. Clearly, if pseudorotation occurs according to the well-known Berry mechanism,¹⁴ it is the methoxy group which acts as the pivot. In this case, the methoxy group remains equatorial during the dynamic exchange of the other four ligands over the axial and equatorial sites in the TBP.

In order to investigate the orientation of the 3',5'-dioxaphosphorinane ring in **5**, we performed a conformational analysis of the $\text{C}_a\text{--C}_b$ bond. The four vicinal H-H J couplings ($J_{H_1H_3}$, $J_{H_1H_4}$, $J_{H_2H_3}$, and $J_{H_2H_4}$) were abstracted from the 400-MHz ^1H -NMR spectrum of **5** in CD_2Cl_2 at -41°C . A standard computer program was used for iterative simulation of the subspectra (see Figure 1).



The conformation around $\text{C}_a\text{--C}_b$ can be described in terms of one $\text{O}_a\text{--O}_b$ trans and two approximately degenerate $\text{O}_a\text{--O}_b$ gauche rotamers (+, -). The magnitude of ($J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4}$) was calculated as a function of the $\text{O}_a\text{--O}_b$ torsion angle, by using the empirically parametrized Karplus equation developed by Altona et al.¹⁵ This showed that ($J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4}$) amounts to 30.0 Hz in the trans rotamer and 16.4 for gauche (+) and gauche (-), leading to the formula

$$x(\text{O}_a\text{--O}_b \text{ trans}) = \frac{(J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4})^{\text{exp}} - 16.4}{13.6} \times 100\%$$

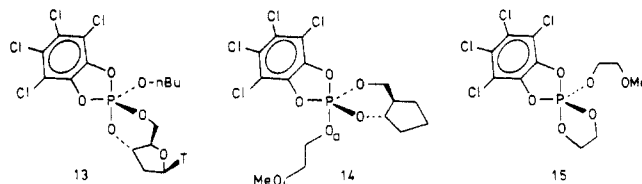
The conformational analysis of the $\text{C}_a\text{--C}_b$ bond in **5** resulted in 51% population of the $\text{O}_a\text{--O}_b$ trans rotamer and a total of 49% population of the $\text{O}_a\text{--O}_b$ gauche rotamers. For comparison, we performed an analogous conformational analysis for the cis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

Table I. Values of $J_{H_1H_3}$, $J_{H_1H_4}$, $J_{H_2H_3}$, and $J_{H_2H_4}$ ^a

compd	$J_{H_1H_3}$	$J_{H_1H_4}$	$J_{H_2H_3}$	$J_{H_2H_4}$	ΣJ	% O-O trans
5	2.2	7.1	4.7	9.4	23.4	51
7	5.7	3.2	3.2	5.7	17.8	10
9	5.3	3.5	3.5	5.3	17.6	9
14	3.9	5.9	4.6	11.0	25.4	66
15	6.5	2.5	2.5	6.5	18.0	12

^a Measured for the conformational probe system in the compounds **5**, **7**, and **9** at -41°C in CD_2Cl_2 and **14** and **15** at 20°C in CD_2Cl_2 , along with the calculated percentages of $\text{O}_a\text{--O}_b$ trans orientation.

Furthermore, we compared **5** with three other P^V-TBP systems, i.e., **13–15**. Compound **13** represents the absence of conformational transmission (O_b in **5** substituted by $\text{C}(\text{H}_2)$ in **13**). As expected, **13** and its *cis*-phosphate counterpart **13a** displayed a highly similar conformational equilibrium around the $\text{C}_a\text{--C}_b$ linkage^{6a,b} (**13**: $x(\text{O}_a\text{--C}_c \text{ trans}) = 80\%$; **13a**: $x(\text{O}_a\text{--C}_c \text{ trans}) = 79\%$). Our interest in compound **14** was primarily based on our previous work on the models **2** and **3** (vide supra), which indicated that substitution of O_1' (i.e., the endocyclic furan oxygen) by $\text{C}(\text{H}_2)$ changes the preferred orientation of the 3',5'-dioxaphosphorinane ring from e,e toward e,a. Conformational analysis of the $\text{C}_a\text{--C}_b$ bond in **14** showed that ($J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4}$) = 25.4 Hz, i.e., 66% $\text{O}_a\text{--O}_b$ trans orientation exists. Compounds **5** and **14** show virtually analogous conformational characteristics, revealing that substitution of O_1' by $\text{C}(\text{H}_2)$ 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 $\text{OCH}_2\text{CH}_2\text{OMe}$ probe is in fact locked in an equatorial position in the P^V-TBP.¹⁶ Conformational analysis of $\text{C}_a\text{--C}_b$ in **15** indeed showed a reduced preference for $\text{O}_a\text{--O}_b$ trans (12%, see Table I).



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 $\text{OCH}_2\text{CH}_2\text{OMe}$ group resides most of the time in the axis of the P^V-TBP. Combining this work with the ring strain rule (vide supra),⁸ 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 P^V-TBP. The interconversion between e,a and e,e orientation of the ring can occur via the Berry pseudorotation mechanism,¹⁴ by using either O_3' or O_5' as the pivot.¹⁷

Axiophilicity of the $\text{OCH}_2\text{CH}_2\text{OMe}$ Group. Our observation of conformational transmission in compounds **5** and **14** and the

(16) Both the dioxaphospholane ring and the dioxaphospholane rings in **15** display a marked preference for e,a orientation (ref 8). The $\text{OCH}_2\text{CH}_2\text{OMe}$ probe acts as the pivot pseudorotation of **15** (compare the methoxy group in **4**).

(17) Our observation of conformational transmission for **5** and **14** provides indirect evidence for e,e location of the 3',5'-dioxaphosphorinane 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 an e,e orientation of the 3',5'-ring follows by comparing the proton-phosphorus couplings of the probe fragment (J_{PH_1} , J_{PH_2} (drawing 4)) in **5** with those of compound **15** (**5**: $J_{\text{PH}_1} = 6.8$ Hz, $J_{\text{PH}_2} = 2.6$ Hz; **15**: $J_{\text{PH}_1} = J_{\text{PH}_2} = 10.7$ Hz). The reduced proton-phosphorus coupling constants of **5** are in agreement with a dynamic equilibrium between an axial and equatorial orientation of the $\text{OCH}_2\text{CH}_2\text{OMe}$ fragment.¹³ From a previous study on conformational transmission in P^V-TBP compounds is known that the $\text{OCH}_2\text{CH}_2\text{OMe}$ fragment in an axial location results in a maximum $\text{O}_a\text{--O}_b$ trans population of approximately 50%, which is close to the value of 51% found for compound **5**.¹² Furthermore, we wish to point out that the occurrence of conformational transmission appears to be an exclusive feature of the axial sites in the P^V-TBP, as based on all P^V model compounds studied so far.^{6,12} For these reasons, our conclusion that an e,a and an e,e P^V-TBP intermediate can be formed during the activation of cAMP appears to be justified.

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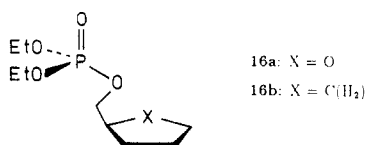
(15) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783. The graph showing $\Sigma J = (J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4})$ as a function of the O-O torsion angle, relevant for compounds **5**, **7**, **9**, **14**, and **15**, is given in the Supplementary Material.

Table II. Vicinal ^1H - ^1H and ^{31}P - ^1H Coupling Constants Measured for Compounds 4-9 in CD_2Cl_2^a

compd	$J_{\text{H}_1'\text{H}_2'}$	$J_{\text{H}_1'\text{H}_2''}$	$J_{\text{H}_2'\text{H}_3'}$	$J_{\text{H}_2''\text{H}_3'}$	$J_{\text{H}_3'\text{H}_4'}$	$J_{\text{H}_4'\text{H}_5'}$	$J_{\text{H}_4'\text{H}_5''}$	$J_{\text{H}_5'\text{P}}$	$J_{\text{H}_5''\text{P}}$
4	3.3	8.4	8.4	10.1	9.2	9.2	7.2	27.0	1.3
5	2.6	9.0	8.1		9.1	9.1	7.3	27.4	0.6
6	2.5	8.9	8.0	10.9	9.3	10.7	4.4	2.3	10.4
7	2.5	9.0	8.0	11.0	9.2	10.7	4.4	2.3	10.5
8	3.0	8.9	8.4	10.1	9.2	10.7	4.7	1.1	21.7
9	2.6	9.2	8.3	10.4	9.2	10.6	4.7	<1	22.4

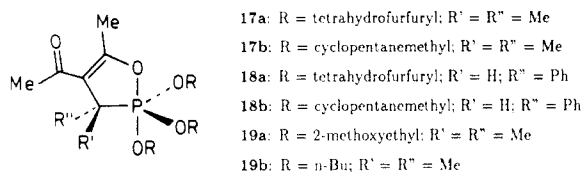
^aSpectra of compounds 4, 6, and 8 were recorded at 20 °C; spectra of 5, 7, and 9 were taken at -41 °C.

conclusion of concomitant e,e location of the 3',5'-ring implicitly show that axial locations of the $\text{OCH}_2\text{CH}_2\text{OMe}$ group in the $\text{P}^V\text{-TBP}$ is preferred (increased axiophilicity). This is in agreement with a recent kinetic study concerning alkaline hydrolysis of the phosphates **16a** and **16b**.¹⁸ Compound **16a** displayed faster kinetics¹⁹ and a different distribution of reaction products, in comparison with **16b**.



Compound **16a** produced tetrahydrofurfuryl ethyl phosphate and diethyl phosphate in the ratios 1.85:1 (335 K) and 1.52:1 (277 K), while compound **16b** led to cyclopentanemethyl ethyl phosphate and diethyl phosphate in the ratios 2.47:1 (334 K) and 2.76:1 (277 K). These data reveal that expulsion of the tetrahydrofurfuryloxy group in the reaction of **16a** occurs with a probability of $>1/3$. Thus, it follows that the tetrahydrofurfuryl group (capable of conformational transmission) is more axiophilic than the ethyl groups. The data on **16b**, on the other hand, show that expulsion of the cyclopentanemethyl group occurs with a probability $<1/3$, i.e., the cyclopentanemethyl group (absence of conformational transmission) displays a *smaller* axiophilicity in comparison with the ethyl groups.

Furthermore, our studies on the pseudorotational dynamics of, e.g., the $\text{P}^V\text{-TBP}$ s **17a,b-19a,b**, also showed a clear axiophilicity in the case of a substituent that can show conformational transmission.^{6a,20}



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.^{6c} 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 $\text{P}^V\text{-TBP}$.

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 ($J_{\text{H}_1'\text{H}_2'}$, $J_{\text{H}_1'\text{H}_2''}$, $J_{\text{H}_2'\text{H}_3'}$, $J_{\text{H}_2''\text{H}_3'}$, and $J_{\text{H}_3'\text{H}_4'}$) measured for each compound (Table II) were used as input data. PSEUROT calculates the best-fit

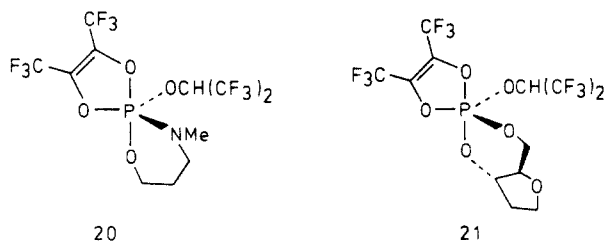
conformational parameters of two sugar structures participating in a rapid conformational equilibrium as well as the equilibrium composition.

On the basis of the present data, PSEUROT rapidly converged toward a single conformation which is characterized by a phase angle (P) of 35.9° and a maximum puckering amplitude (ν_{max}) of 39.9°. As is well-known, the five endocyclic torsion angles $\nu_0 \dots \nu_4$ can be calculated from P and ν_{max} according to the formula $\nu_j = \nu_{\text{max}} \cos(P + (j-2) \cdot 144^\circ)$,²³ i.e., $\nu_0[\text{C}_4\text{-O}_1\text{-C}_1\text{-C}_2] = -12.2^\circ$, $\nu_1[\text{O}_1\text{-C}_1\text{-C}_2\text{-C}_3] = -12.4^\circ$, $\nu_2[\text{C}_1\text{-C}_2\text{-C}_3\text{-C}_4] = 32.3^\circ$, $\nu_3[\text{C}_2\text{-C}_3\text{-C}_4\text{-O}_1] = -39.9^\circ$, and $\nu_4[\text{C}_3\text{-C}_4\text{-O}_1\text{-C}_1] = 32.2^\circ$. It follows from these results that the structure of the 2'-deoxyribose ring in 4-9 resides in a twist (^4_3T) geometry (vide infra), which is in excellent agreement with X-ray crystallographic studies on 3',5'-cyclic phosphites and phosphates.²⁴

C. Conformation of the 3',5'-Dioxaphosphorinane Ring in 4 and 5. The conformational properties of dioxaphosphorinane rings attached to a $\text{P}^V\text{-TBP}$ structure have attracted considerable attention, especially since the 3',5'-ring in cAMP is likely to undergo a chair into nonchair (boat and/or twist) conformation prior to, or concerted with, the formation of a $\text{P}^V\text{-TBP}$ intermediate.⁵ Our method for conformational analysis of the 3',5'-ring in 4-9 is abstracted from the work of Bentrude et al.²⁵ These studies revealed that *cis* 3',5'-cyclic nucleotides normally have a chair geometry in which phosphorus and H_5 are antiperiplanar, while phosphorus and H_5 are in a gauche orientation. This geometry results in $J_{\text{PH}_5} \approx 2.5$ Hz, $J_{\text{PH}_5''} \approx 10.7$ Hz for *cis*-phosphites²⁶ and $J_{\text{PH}_5} \approx 1$ Hz, $J_{\text{PH}_5''} \approx 22.5$ Hz for *cis*-phosphates.^{9,27} The vicinal H-P coupling constants fit into classical Karplus type relations with quite different parametrizations for phosphite and phosphate structures.^{26,27} Inspection of the data in Table II shows that J_{PH_5} and $J_{\text{PH}_5''}$ measured for the *cis*-phosphites **6** and **7** closely resemble the standard values for a chair conformation. Similarly, the J_{PH_5} , $J_{\text{PH}_5''}$ data as obtained for the *cis*-phosphates **8** and **9** also correspond to a chair geometry.

Conformational analysis of the 3',5'-ring in **4** and **5** is based on recent studies of Bentrude et al. on the $\text{P}^V\text{-TBP}$ systems **20**^{5a} and **21**;^{5b} compound **21** is closely related to our models **4** and **5**.

(22) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205.(23) de Leeuw, H. P. M.; Haasnoot, C. A. G.; Altona, C. *Isr. J. Chem.* **1980**, *20*, 108.(24) (a) Coulter, C. L. *Acta Crystallogr.* **1969**, *B25*, 2055; **1970**, *B26*, 441.(b) Ku Chwang, A.; Sundaralingam, M. *Acta Crystallogr.* **1974**, *B30*, 1233.(c) Bentrude, W. G.; Sopchik, A. E.; Bajwa, G. S.; Setzer, W. N.; Sheldrick, W. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 1027.(d) Depmeier, W.; Engels, J.; Klaska, K. H. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *33*, 2436.(25) It should be noted that the preparation and conformational analysis of compounds **6** and **8** have been described previously (**6**, **8**: Bentrude, W. G.; Sopchik, A. E.; Gajda, T. *J. Am. Chem. Soc.* **1989**, *111*, 3981. **6**: Nelson, K. A.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 7752. **8**: Sopchik, A. E.; Bajwa, G. S.; Nelson, K. A.; Bentrude, W. G. In *Phosphorus Chemistry*; Quin, L. D.; Verkade, J. G., Eds.; ACS Symposium Series 171; American Chemical Society: Washington, DC, 1981; pp 217-220.). The NMR data are in agreement with 0.2 Hz with our results as given in Table II.(26) (a) Bajwa, G. S.; Bentrude, W. G. *Tetrahedron Lett.* **1978**, *5*, 421.(b) Hermans, R. J. M.; Buck, H. M. *Phosphorus and Sulfur* **1987**, *31*, 255.(c) Kainosho, M.; Nakamura, A. *Tetrahedron* **1969**, *25*, 4071.(27) (a) Lankhorst, P. P.; Haasnoot, C. A. G.; Erkelens, C.; Altona, C. J. *Biomol. Struct. Dyn.* **1984**, *1*, 1387. (b) Bentrude, W. G.; Setzer, W. N. In *³¹P NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes*; Verkade, J. G.; Quin, L., Eds.; VCH Publishers, Inc.: Deerfield Beach, FL, 1987; Chapter 11. (c) Hermans, R. J. M.; Buck, H. M. *J. Org. Chem.* **1987**, *52*, 5150.(18) Koole, L. H.; Olders, A. T. A.; Opresnik, M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 55.(19) The second-order rate constants for alkaline hydrolysis of compounds **6a** and **6b** at 335 K are 0.008 and 0.003 1/mol s, respectively (ref 19). These values dropped to 0.00009 and 0.00004 1/mol s at 277 K, for **6a** and **6b**, respectively.(20) de Keijzer, A. E. H.; Buck, H. M. *J. Org. Chem.* **1988**, *53*, 4827.(21) (a) Quantum Chemistry Program Exchange 463. (b) de Leeuw, F. A. A. M.; Altona, C. J. *Chem. Soc., Perkin Trans. 2* **1982**, 375.



The data on **20** and **21** strongly suggest that a Karplus type equation is valid for $^3J_{\text{PH}}$ scalar couplings in P^V-TBP systems.⁵ Antiperiplanar orientation of H and P across H-C-O-P and H-C-N-P coupling paths was found to result in large $^3J_{\text{PH}}$ couplings (26.1 and 25.0 Hz, respectively), while much smaller values of $^3J_{\text{PH}}$ 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 $^3J_{\text{PH}}$ coupling constants (≈ 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_{5'} are antiperiplanar in **4** and **5**, while gauche orientation exists for phosphorus and H_{5'}. These results are in close agreement with the data reported for **20** and **21**.⁵ 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 $J_{\text{H}_4\text{H}_5'}$ and $J_{\text{H}_4\text{H}_5''}$ from which the conformation around the C₄-C_{5'} (γ) bond can be deduced.^{6a-d} By using the generalized Karplus equation of Altona et al.,¹⁵ we calculated $J_{\text{H}_4\text{H}_5'}$ and $J_{\text{H}_4\text{H}_5''}$ as a function of the torsion angle [O₅-C₅-C₄-O_{1'}] (see Figure 2). This graph indicates that the P^{III} and P^{IV} systems correspond with a torsion angle of approximately 180°. The P^V-TBP systems **4** and **5**, on the other hand, appear to correspond with a rotation around C₄-C_{5'} 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^V-TBPs **4** and **5**, we performed a set of MNDO semiempirical calculations²⁸ on the isomeric model systems **22**, **23** (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 [P-O₅-C₅-H_{5'}], and the torsion angle [O₅-C₅-C₄-O_{1'}] (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 **22-24** are -263.7, -262.6, and -259.8 kcal/mol, respectively. Thus, both e,a forms are almost equally stable, while the e,e isomer is destabilized by approximately 3-4 kcal/mol.

Inspection of the resulting optimized conformations revealed that the 2'-deoxyribose ring remained almost unchanged in all three calculations. Most probably, the limited structural freedom of the 2'-deoxyribose ring can be attributed to the trans fusion in our systems. The 3',5'-dioxaphosphorinane ring, on the other hand, showed slight structural variations (Figure 4).

For the e,a isomers **22** and **23**, it is found that the ring preferentially adopts a twist structure in which O₅, C_{5'}, C_{4'}, and O_{3'} are approximately in the same plane; the P atom is bent toward the exo face of this plane, while C_{3'} is located on the endo side. The dioxaphosphorinane ring of the e,e system **24** is flattened at the phosphorus end, as is obvious from the low values of the torsion angles [C₄-C₅-O₅-P] (-5.0° for **24**, -31.8° and -27.3° for **22** and **23**, respectively) and [C₅-O₅-P-O_{3'}] (19.8° for **24**, 50.6° and 40.6° for **22** and **23**, respectively) (Table III).²⁹ The dioxaphosphorinane ring in **24** can probably be best described as a half-chair (chaise longue) in which C_{3'} acts as the back.

Additional MNDO calculations have been performed on the analogues of the systems **22-24**, in which O_{1'} is replaced by C(H₂).

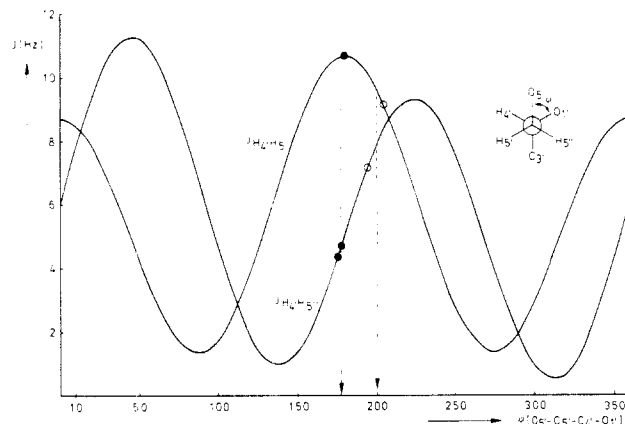


Figure 2. Calculated variation of $J_{\text{H}_4\text{H}_5'}$ and $J_{\text{H}_4\text{H}_5''}$ with the torsion angle $\phi[\text{O}_5\text{-C}_5\text{-C}_4\text{-O}_{1'}]$. The Karplus equation described in ref 15 was used. Filled circles represent data points for the 3',5'-cyclic phosphites **6** and **7**, and the 3',5'-cyclic phosphates **8** and **9** (Table II), corresponding with $\phi \approx 180^\circ$. The data measured for the P^V-TBPs **4** and **5** (open circles) point toward a ϕ value of $\approx 200^\circ$, i.e., the P^V-TBP structure forces a rotation around the C₄-C_{5'} 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**^a

torsion angle	22 (e,a) ₁	23 (e,a) ₂	24 (e,e)
P-O ₃ -C ₃ -C ₄	-47.8	-54.2	-50.1
O ₃ -C ₃ -C ₄ -C _{5'}	68.3	67.5	67.8
C ₃ -C ₄ -C ₅ -O _{5'}	-30.4	-29.5	-35.7
C ₄ -C ₅ -O ₅ -P	-31.8	-27.3	-5.0
C ₅ -O ₅ -P-O _{3'}	50.6	40.6	19.8
O ₅ -P-O ₃ -C _{3'}	-3.3	6.4	11.0

^a Note the relatively low values of the torsion angles [C₄-C₅-O₅-P] and [C₅-O₅-P-O_{3'}] for **24** in comparison with **22** and **23** (see text).

These calculations led to the following heats of formation: (i) e,a isomer with O₃ equatorial and O₅ axial, -230.0 kcal/mol; (ii) e,a isomer with O₃ equatorial and O₅ axial, -230.8 kcal/mol; (iii) e,e isomer, -225.2 kcal/mol.³⁰ It appears from these data that substitution of O_{1'} by C(H₂) 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^V-TBP intermediate will induce a nonchair conformation of the 3',5'-dioxaphosphorinane ring, which is in complete agreement with the results of Bentrude et al.⁵ Furthermore, our experimental data reveal that formation of a P^V-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 CH₂OH side chain of a serine residue (Ser-83) is in the right position for nucleophilic attack on the phosphorus of cAMP.³¹ The resulting P^V-TBP may show conformational transmission by virtue of enhanced charge repulsion between O and N in the atom sequence P^V-OCH₂CHRN,¹² i.e., e,e orientation of the 3',5'-ring

(30) Substitution of O_{1'} 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 showed a half-chair conformation, analogous to **24**.

(31) (a) Weber, I. T.; Takio, K.; Titani, K.; Steitz, T. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 7679. (b) Takio, K.; Wade, R. D.; Smith, S. B.; Krebs, E. G.; Walsh, K. A.; Titani, K. *Biochemistry* **1984**, *23*, 4207. (c) Weber, I. T.; Shabb, J. B.; Corbin, J. D. *Biochemistry* **1989**, *28*, 6122.

(28) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) M.N.D.O.: Quantum Chemical Program Exchange 353, 1978.

(29) A chaise longue conformation of the 3',5'-dioxaphosphorinane ring in the case of e,e orientation in the P^V-TBP was also predicted by Yu and Bentrude. See ref 5b.

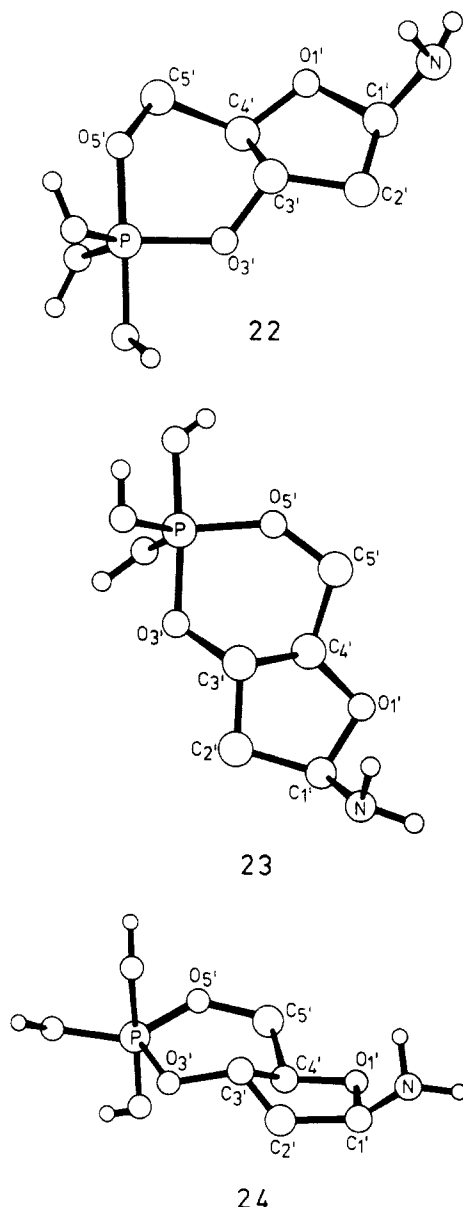


Figure 3. MNDO-optimized geometries for the P^V -TBP isomeric model systems **22**, **23** (both (a,e)), and **24** (e,e). Structures **22** and **23** have virtually identical heats of formation ($\Delta H_f^\circ = -263.7$ and -262.6 kcal/mol, respectively). The e,e system **24** is only slightly destabilized in comparison with **22** and **23** (ΔH_f° (**24**) = -259.8 kcal/mol).

could be stabilized in this way. Clearly, this would exactly fit with the model description of van Ool and Buck.^{3b}

Experimental Section

Material and Methods. The ^1H NMR spectra were recorded on Bruker AM 600,³² AM 400, or AC 200 NMR spectrometers. Tetramethylsilane (TMS) was used as the internal standard for NMR samples. ^{31}P NMR spectra were recorded at 162 or 81 MHz on the AM 400 or AC 200 instruments, respectively, and referenced against 85% H_3PO_4 as external standard. ^{13}C NMR spectra were recorded at 100.6 or 50.3 MHz on the AM 400 or AC 200 instruments, respectively. For all

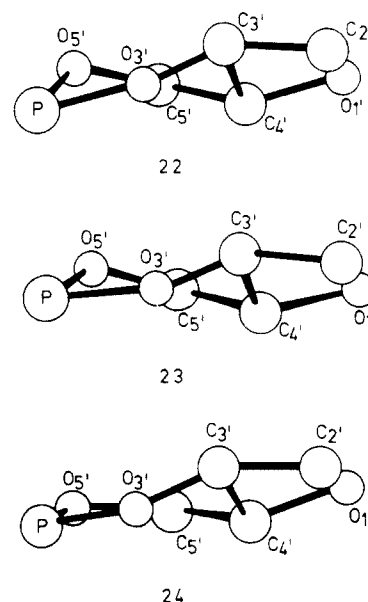


Figure 4. Detailed view of the conformation of the 3',5'-dioxaphosphorinane ring in the MNDO-optimized structures **22**–**24**. For the e,a systems **22** and **23**, a twist conformation is encountered, in which O_5 , C_5 , C_4 , and O_3 are approximately in the same plane; P and C_3 are located on the exo and endo face of this plane, respectively. The e,e isomer **24** shows a half-chair conformation of the 3',5'-ring; P resides approximately in the plane through O_5 , C_5 , C_4 , and O_3 ; C_3 is bent toward the endo face of this plane.

column separations, we used Merck silica gel 60 (particle size 0.063–0.200 mm). Pyridine was distilled from KOH pellets and dried on 4-Å molecular sieves. 1*H*-Tetrazole was purified through sublimation. Reactions were routinely run in an inert atmosphere of dry nitrogen or dry argon. Prior to the reaction step, in which thymidine was cyclized, the last traces of water were removed from the nucleoside via coevaporation with small portions of dry pyridine. Unless otherwise noted, reactions were run at ambient temperature.

Synthesis. Bis(*N,N*-diisopropylamino)(2-methoxyethoxy)phosphine. 2-Methoxyethanol (79.8 g, 1.05 mol) was added dropwise to phosphorus trichloride (137.5 g, 1.00 mol) over 2 h while stirring. The inner temperature of the reaction flask was kept between 20 and 30 °C, and the produced hydrochloric acid was absorbed in a gas trap containing a sodium bicarbonate solution. After distillation (bp 67 °C at 20 mmHg), pure (2-methoxyethoxy)dichlorophosphine (^{31}P NMR (81 MHz, CDCl_3) δ 179.5 ppm) was obtained (101.9 g, 0.58 mol). This compound was added dropwise during 2 h to a solution of *N,N*-diisopropylamine (348.9 g, 3.45 mol) in 750 mL of dry ether at 0 °C, and the solution was stirred overnight at room temperature. Then, the ammonium salt was removed by filtration, and the solution was concentrated in vacuo. Pure bis(*N,N*-diisopropylamino)(2-methoxyethoxy)phosphine was obtained by distillation of the residue at 0.7 mmHg (bp 105 °C) as a colorless liquid: yield 126.4 g (41%); ^{31}P NMR (81 MHz, CDCl_3) δ 127.6; ^1H NMR (200 MHz, CDCl_3) δ 3.60 (8 H, m, 4 H-C-N and 4 H-C-O), 3.38 (3 H, s, OCH_3), 1.16 (24 H, m, CH_3).

Bis(*N,N*-diisopropylamino)-1-butoxyphosphine. 1-Butanol (74.0 g, 1.00 mol) was added dropwise to phosphorus trichloride (137.5 g, 1.00 mol) over 5 h while stirring. The inner temperature of the reaction flask was kept between 20 and 30 °C, and the produced hydrochloric acid was absorbed in a gas trap containing aqueous sodium bicarbonate. After distillation (bp 64 °C at 20 mmHg) pure 1-butoxydichlorophosphine (^{31}P NMR (162 MHz, CDCl_3) δ 178.4 ppm) was obtained (69.9 g, 0.40 mol). This compound was added dropwise during 3 h to a solution of *N,N*-diisopropylamine (242.4 g, 2.40 mol) in 600 mL of dry ether at 0 °C, and the solution was stirred overnight at room temperature. Then, the ammonium salt was removed by filtration, and the solution was concentrated in vacuo. Pure bis(*N,N*-diisopropylamino)-1-butoxyphosphine was obtained by distillation of the residue at 0.03 mmHg (bp 80 °C) as a colorless liquid: yield 25.8 g (9%); ^{31}P NMR (162 MHz, CDCl_3) δ 127.0; ^1H NMR (400 MHz, CDCl_3) δ 3.55 (4 H, m, 4 H-C-N and 2 H-C-O), 1.58 (2 H, m, CH_2), 1.42 (2 H, m, CH_2), 1.18 (24 H, m, CH_3), 0.93 (3 H, t, CH_3).

2-(2'-Methoxyethoxy)-1,3,2-dioxaphospholane. Ethylene glycol (31.0 g, 0.50 mol) was added dropwise to phosphorus trichloride (68.8 g, 0.50 mol) over 2 h while stirring. The inner temperature of the reaction flask was kept between 20 and 30 °C, and the produced hydrochloric acid was

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

(33) Penney, C. L.; Belleau, B. *Can. J. Chem.* **1978**, *56*, 2396.

(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 decoalescence phenomena due to retarded pseudorotation can be observed for **3** if a stronger magnetic field is used (^{13}C NMR 125 MHz; compared with 22.6 MHz used by van Ool and Buck). From the ^{13}C NMR spectrum at -113 °C it could be concluded that the dioxaphosphorinane ring in **3** prefers e,a orientation in the P^V -TBP. Furthermore, the predicted twist geometry of the e,a oriented 3',5'-dioxaphosphorinane ring in a P^V -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 (³¹P NMR (162 MHz, CDCl₃) δ 168.1 ppm) was obtained (30.6 g, 0.24 mol). This compound was added dropwise during 2 h to a solution of 2-methoxyethanol (18.4 g, 0.24 mol) and triethylamine (24.4 g, 0.24 mol) in 250 mL of dry ether at 0 °C, and the solution was stirred for 1 h at room temperature. Then, 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 0.6 mmHg (bp 76 °C) as a colorless liquid: yield 25.6 g (31%); ³¹P NMR (162 MHz, CDCl₃) δ 135.8; ¹H NMR (400 MHz, CDCl₃) δ 4.22 (2 H, m, Hs of the 5-ring), 4.01 (2 H, m, Hs of the 5-ring), 3.91 (2 H, m, H_a), 3.52 (2 H, m, H_b), 3.40 (3 H, s, OCH₃).

3β-(2'-Methoxyethoxy)-trans-2,4-dioxo-3-phosphabicyclo[4.3.0]nonane. Bis(*N,N*-diisopropylamino)(2-methoxyethoxy)phosphine (8.71 g, 28.4 mmol) was added to a solution of (1*R*,2*S*)-2-hydroxycyclopentanemethanol (prepared as described by Penney and Belleau^{26b,33}) (3.00 g, 25.9 mmol) and 1*H*-tetrazole (3.62 g, 51.7 mmol) in 250 mL of dry pyridine, and the reaction mixture was stirred for about 1 h. Formation of the cyclic phosphite was evident from the ³¹P NMR spectrum (pyridine/pyridine-*d*₅ 1:1) δ 3(β) 122.6 and 3(α) 128.4. The 3(β)/3(α) ratio was approximately 1:1. The mixture was concentrated in vacuo (at room temperature) and coevaporated with toluene and dichloromethane. The obtained oil was diluted with 200 mL of ethyl acetate, resulting in sedimentation of 1*H*-tetrazole and ammonium salts. After filtration, the filtrate was concentrated in vacuo. Distillation of the residue at 0.01 mmHg (bp 80 °C) yielded 2.44 g of 3-(2'-methoxyethoxy)-trans-2,4-dioxo-3-phosphabicyclo[4.3.0]nonane (60% 3(β) and 40% 3(α)). Almost pure 3β-(2'-methoxyethoxy)-trans-2,4-dioxo-3-phosphabicyclo[4.3.0]nonane was obtained as a colorless liquid by chromatography on a silica gel column with ethyl acetate as eluent (*R*_f 0.62): yield 1.54 g (26%); ³¹P NMR (162 MHz, CDCl₃) δ 123.8 (3(α) 130.0), 3(β)/3(α) ratio approximately 98:2; ¹H NMR (400 MHz, CDCl₃) δ 4.27 (1 H, m, H_{5a} or H_{5b}), 4.12 (1 H, m, H₁), 4.05 (1 H, m, H_{5b} or H_{5a}), 3.90 (2 H, m, H_a), 3.58 (2 H, m, H_b), 3.40 (3 H, s, OCH₃), 2.05–1.10 (7 H, m, H₆, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}).^{26b}

cis-Thymidine 3',5'-Cyclic Methyl Phosphite (6).²⁵ Bis(*N,N*-diisopropylamino)methoxyphosphine⁹ (3.90 g, 14.9 mmol) was added to a suspension of thymidine (3.00 g, 12.4 mmol) and 1*H*-tetrazole (2.17 g, 31.0 mmol) in 300 mL of dry pyridine, and the reaction mixture was stirred for 2 h. Formation of the cyclic phosphite was evident from the ³¹P NMR spectrum (pyridine/pyridine-*d*₅ 1:1) δ *cis* 122.9 and *trans* 129.0. The *cis*/*trans* ratio was approximately 2:3. The mixture was concentrated in vacuo (at room temperature) and coevaporated with toluene and dichloromethane. A white solid was obtained which was suspended in 400 mL of ethyl acetate (3 times). After sedimentation of 1*H*-tetrazole and ammonium salt, the clear upper layer was separated. The collected layers were concentrated in vacuo and coevaporated with dichloromethane. A white foam appeared which was chromatographed rapidly on a short silica gel column. First, impurities were eluted with dichloromethane, and then with a gradient of dichloromethane/ethyl acetate (1:1 v/v → 1:4 v/v) as eluent we obtained 6 as a white solid: yield 0.85 g (23%); mp 127–129 °C; *R*_f 0.42 (ethyl acetate); ³¹P NMR (81 MHz, CD₂Cl₂) δ 125.7 (*trans* 132.5), *cis*/*trans* ratio approximately 95:5; ¹H NMR (600 MHz, CD₂Cl₂) δ 9.45 (1 H, br s, NH), 7.07 (1 H, q, H₆ of T), 6.16 (1 H, dd, H₁), 4.48 (1 H, m, H₃), 4.42 (1 H, m, H₅), 4.28 (1 H, m, H_{5'}), 3.64 (1 H, m, H₄), 3.58 (3 H, d, OCH₃, ³*J*_{POCH} = 12.3 Hz), 2.45 (1 H, m, H_{2'}), 2.33 (1 H, m, H₂), 1.94 (3 H, d, CH₃ of T); ¹³C NMR (50.32 MHz, CD₂Cl₂) δ 164.6 (C₂ or C₄ of T), 151.0 (C₄ or C₂ of T), 135.8 (C₆ of T), 111.9 (C₅ of T), 82.3 (C₁), 75.4 (C_{4'}, ³*J*_{POCC} = 7.2 Hz), 68.9 (C₃), 66.2 (C₅, ²*J*_{POC} = 3.1 Hz), 50.5 (OCH₃, ²*J*_{POC} = 18.9 Hz), 36.3 (C₂), 12.6 (CH₃ of T). Anal. Calcd for C₁₁H₁₅N₂O₆P: C, 43.71; H, 4.97; N, 9.27. Found: C, 43.78; H, 4.74; N, 9.97.

cis-Thymidine 3',5'-Cyclic 2-Methoxyethyl Phosphite (7). Bis(*N,N*-diisopropylamino)(2-methoxyethoxy)phosphine (2.78 g, 9.1 mmol) was added to a suspension of thymidine (2.00 g, 8.3 mmol) and 1*H*-tetrazole (1.45 g, 20.7 mmol) in 200 mL of dry pyridine, and the reaction mixture was stirred for about 2 h. Formation of the cyclic phosphite was evident from the ³¹P NMR spectrum (pyridine/pyridine-*d*₅ 1:1) δ *cis* 123.1 and *trans* 129.8. The *cis*/*trans* ratio was approximately 1:1. The mixture was concentrated in vacuo (at room temperature) and coevaporated with toluene and dichloromethane. The obtained oil was diluted with 500 mL of ethyl acetate, resulting in sedimentation of 1*H*-tetrazole and ammonium salt. After filtration, the filtrate was concentrated in vacuo and chromatographed on a silica gel column with ethyl acetate/dichloromethane 1:1 v/v as eluent. A white solid of 7 was obtained in 33% yield (0.95 g): mp 51–55 °C; *R*_f 0.32 (ethyl acetate); ³¹P NMR (81 MHz, CD₂Cl₂) δ 124.3 (*trans* 131.3), *cis*/*trans* ratio approximately 95:5; ¹H NMR (600 MHz, CD₂Cl₂) δ 9.89 (1 H, br s, NH), 7.11 (1 H, q, H₆ of T), 6.19 (1 H, dd, H₁), 4.55 (1 H, m, H₃), 4.49 (1 H, m, H₅), 4.28 (1

H, m, H_{5'}), 3.97 (2 H, m, H_a), 3.63 (1 H, m, H₄), 3.60 (2 H, m, H_b), 3.40 (3 H, s, OCH₃), 2.46 (1 H, m, H_{2'}), 2.32 (1 H, m, H₂), 1.93 (3 H, d, CH₃ of T); ¹³C NMR (50.32 MHz, CD₂Cl₂) δ 164.6 (C₂ or C₄ of T), 151.0 (C₄ or C₂ of T), 135.8 (C₆ of T), 111.9 (C₅ of T), 82.2 (C₁), 75.4 (C_{4'}, ³*J*_{POCC} = 6.9 Hz), 72.5 (C₃, ³*J*_{POCC} = 5.3 Hz), 68.8 (C₃), 66.3 (C₅, ²*J*_{POC} = 3.5 Hz), 62.8 (C_a, ²*J*_{POC} = 16.6 Hz), 58.9 (OCH₃), 36.3 (C₂), 12.6 (CH₃ of T). Anal. Calcd for C₁₃H₁₉N₂O₇P: C, 45.09; H, 5.49; N, 8.09. Found: C, 43.1; H, 5.8; N, 9.9.

cis-Thymidine 3',5'-Cyclic Methyl Phosphate (8).²⁵ *cis*-Thymidine 3',5'-cyclic methyl phosphite (6) (100 mg, 0.33 mmol) was dissolved in dichloromethane (30 mL) at –20 °C. Dichloromethane, saturated with NO₂/N₂O₄, was added until a greenish color appeared. After complete conversion of 6 (³¹P NMR (162 MHz, CH₂Cl₂/CD₂Cl₂ 1:1) δ –3.1 ppm) the mixture was evaporated under vacuo. A white foam appeared, which was chromatographed on a silica gel column with methanol/dichloromethane 8:92 v/v as eluent, yielding 57 mg (54%) of 8 as a white solid: mp 97–102 °C; *R*_f 0.23 (methanol/dichloromethane 8:92 v/v); ³¹P NMR (162 MHz, CD₂Cl₂) δ –3.2; ¹H NMR (400 MHz, CD₂Cl₂) δ 9.70 (1 H, br s, NH), 7.08 (1 H, q, H₆ of T), 6.23 (1 H, dd, H₁), 4.74 (1 H, m, H₃), 4.62 (1 H, m, H₅), 4.40 (1 H, m, H_{5'}), 3.96 (1 H, m, H₄), 3.90 (3 H, d, OCH₃, ³*J*_{POCH} = 11.2 Hz), 2.65 (1 H, m, H_{2'}), 2.54 (1 H, m, H₂), 1.98 (3 H, d, CH₃ of T); ¹³C NMR (100.64 MHz, CD₂Cl₂) δ 164.3 (C₂ or C₄ of T), 150.5 (C₄ or C₂ of T), 136.6 (C₆ of T), 112.2 (C₅ of T), 86.5 (C₁), 78.4 (C₃, ²*J*_{POC} = 5.5 Hz), 74.2 (C_{4'}, ³*J*_{POCC} = 5.6 Hz), 69.9 (C₅, ²*J*_{POC} = 8.9 Hz), 54.7 (OCH₃), 35.4 (C₂, ³*J*_{POCC} = 8.3 Hz), 12.5 (CH₃ of T). Anal. Calcd for C₁₁H₁₅N₂O₇P: C, 41.51; H, 4.72; N, 8.81. Found: C, 40.74; H, 5.02; N, 8.85.

cis-Thymidine 3',5'-Cyclic 2-Methoxyethyl Phosphate (9). *cis*-Thymidine 3',5'-cyclic 2-methoxyethyl phosphite (7) (500 mg, 1.45 mmol) was dissolved in dichloromethane (40 mL) at –20 °C. Dichloromethane, saturated with NO₂/N₂O₄, was added until a greenish color appeared. After complete conversion of 7 (³¹P 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 270 mg (52%) of 9 as a white solid: mp 70–71 °C; *R*_f 0.22 (methanol/dichloromethane 6:94 v/v); ³¹P NMR (162 MHz, CD₂Cl₂) δ –4.4; ¹H NMR (400 MHz, CD₂Cl₂) δ 9.45 (1 H, br s, NH), 7.04 (1 H, q, H₆ of T), 6.27 (1 H, dd, H₁), 4.68 (1 H, m, H₃), 4.59 (1 H, m, H₅), 4.46 (1 H, m, H_{5'}), 4.28 (2 H, m, H_a), 3.93 (1 H, m, H₄), 3.68 (2 H, m, H_b), 3.41 (3 H, s, OCH₃), 2.62 (1 H, m, H_{2'}), 2.50 (1 H, m, H₂), 1.93 (3 H, d, CH₃ of T); ¹³C NMR (100.64 MHz, CD₂Cl₂) δ 163.9 (C₂ or C₄ of T), 150.4 (C₄ or C₂ of T), 136.2 (C₆ of T), 112.3 (C₅ of T), 85.9 (C₁), 78.3 (C₃, ²*J*_{POC} = 5.4 Hz), 74.3 (C_{4'}, ³*J*_{POCC} = 5.5 Hz), 71.5 (C₅, ³*J*_{POCC} = 6.0 Hz), 70.0 (C₅, ²*J*_{POC} = 9.0 Hz), 67.1 (C_a, ²*J*_{POC} = 5.4 Hz), 59.1 (OCH₃), 35.5 (C₂, ³*J*_{POCC} = 8.3 Hz), 12.6 (CH₃ of T). Anal. Calcd for C₁₃H₁₉N₂O₈P: C, 43.09; H, 5.25; N, 7.73. Found: C, 42.2; H, 5.4; N, 9.4.

cis-Thymidine 3',5'-Cyclic 1-Butyl Phosphite. Bis(*N,N*-diisopropylamino)-1-butoxyphosphine (2.77 g, 9.1 mmol) was added to a suspension of thymidine (2.00 g, 8.3 mmol) and 1*H*-tetrazole (1.45 g, 20.7 mmol) in 200 mL of dry pyridine, and the reaction mixture was stirred for about 2 h. Formation of the cyclic phosphite was evident from the ³¹P NMR spectrum (pyridine/pyridine-*d*₅ 1:1) δ *cis* 122.8 and *trans* 129.7. The *cis*/*trans* ratio was approximately 1:1. The mixture was concentrated in vacuo (at room temperature) and coevaporated with toluene and dichloromethane. The obtained oil was diluted with 450 mL of ethyl acetate, resulting in sedimentation of 1*H*-tetrazole and ammonium salt. After filtration, the filtrate was concentrated in vacuo and chromatographed on a silica gel column with ethyl acetate/dichloromethane 1:1 v/v as eluent. An oil of *cis*-thymidine 3',5'-cyclic 1-butyl phosphite was obtained in 21% yield (0.59 g): *R*_f 0.40 (ethyl acetate/dichloromethane 1:1 v/v); ³¹P NMR (162 MHz, CD₂Cl₂) δ 124.5 (*trans* 131.6), *cis*/*trans* ratio approximately 93:7; ¹H NMR (400 MHz, CD₂Cl₂) δ 9.78 (1 H, br s, NH), 7.07 (1 H, q, H₆ of T), 6.18 (1 H, dd, H₁), 4.47 (1 H, m, H₃), 4.43 (1 H, m, H₅), 4.28 (1 H, m, H_{5'}), 3.84 (2 H, m, H_a), 3.63 (1 H, m, H₄), 2.43 (1 H, m, H_{2'}), 2.42 (1 H, m, H₂), 1.93 (3 H, d, CH₃ of T), 1.67 (2 H, m, H_b), 1.43 (2 H, m, H_c), 0.97 (3 H, t, H_d); ¹³C NMR (100.64 MHz, CD₂Cl₂) δ 164.3 (C₂ or C₄ of T), 150.8 (C₄ or C₂ of T), 135.6 (C₆ of T), 111.9 (C₅ of T), 82.3 (C₁), 75.5 (C_{4'}, ³*J*_{POCC} = 6.9 Hz), 68.9 (C₃), 66.2 (C₅, ²*J*_{POC} = 3.6 Hz), 63.7 (C_a, ²*J*_{POC} = 18.1 Hz), 36.5 (C₂), 33.5 (C_b, ³*J*_{POCC} = 5.4 Hz), 19.4 (C_c), 13.8 (C_d), 12.7 (CH₃ of T).

cis-Thymidine 3',5'-Cyclic 1-Butyl Phosphate (13a). *cis*-Thymidine 3',5'-cyclic 1-butyl phosphite (250 mg, 0.73 mmol) was dissolved in dichloromethane (30 mL) at –20 °C. Dichloromethane, saturated with NO₂/N₂O₄, was added until a greenish color appeared. After complete conversion of *cis*-thymidine 3',5'-cyclic 1-butyl phosphite (³¹P NMR (162 MHz, CH₂Cl₂/CD₂Cl₂ 1:1) δ –4.3 ppm) the mixture was evaporated under vacuo. A white foam appeared, which was chromatographed on a silica gel column with methanol/dichloromethane 5:95 v/v as eluent, yielding 100 mg (38%) of 14 as a white solid: *R*_f 0.23 (methanol/di-

chloromethane 5:95 v/v); ^{31}P NMR (162 MHz, CD_2Cl_2) δ -4.3; ^1H NMR (400 MHz, CD_2Cl_2) δ 9.30 (1 H, br s, NH), 7.02 (1 H, q, H_6 of T), 6.18 (1 H, dd, $\text{H}_{1'}$), 4.68 (1 H, m, $\text{H}_{3'}$), 4.58 (1 H, m, $\text{H}_{5'}$), 4.35 (1 H, m, $\text{H}_{5'}$), 4.16 (2 H, m, H_4), 3.91 (1 H, m, H_4), 2.61 (1 H, m, $\text{H}_{2'}$), 2.54 (1 H, m, $\text{H}_{2'}$), 1.93 (3 H, d, CH_3 of T), 1.75 (2 H, m, H_6), 1.47 (2 H, m, H_6), 0.98 (3 H, t, H_4); ^{13}C NMR (100.64 MHz, CD_2Cl_2) δ 164.3 (C_2 or C_4 of T), 150.5 (C_4 or C_2 of T), 136.6 (C_6 of T), 112.1 (C_5 of T), 86.4 ($\text{C}_{1'}$), 78.3 ($\text{C}_{3'}$, $^2J_{\text{POC}} = 5.5$ Hz), 74.3 ($\text{C}_{4'}$, $^3J_{\text{POCC}} = 7.7$ Hz), 69.8 ($\text{C}_{5'}$, $^2J_{\text{POC}} = 9.0$ Hz), 68.4 (C_8 , $^2J_{\text{POC}} = 5.9$ Hz), 35.4 ($\text{C}_{2'}$, $^3J_{\text{POCC}} = 8.4$ Hz), 32.5 (C_6 , $^3J_{\text{POCC}} = 9.9$ Hz), 19.1 (C_6), 13.7 (C_4), 12.5 (CH_3 of T).

Pentacoordinated Compounds 4, 5, and 13–15. In order to avoid decomposition during handling and purification, we prepared the P^{V} compounds 4, 5, and 13–15 in situ in NMR tubes. These syntheses were carried out by addition of 1 equiv of tetrachloro-1,2-benzoquinone to the corresponding phosphites, dissolved in CD_2Cl_2 at -80°C . The NMR tubes were flushed with dry argon and sealed. After 1 h, the NMR samples were transferred into the NMR instrument, which had been stabilized at constant temperature (20°C for 4, 14, and 15; -41°C for 5 and 13), and the ^1H - and ^{31}P -NMR spectra were recorded. The identity of the P^{V} -TBP systems was established on the basis of ^1H - and ^{31}P -NMR spectroscopy, which showed >95% purity in each case.

Compound 4: ^{31}P NMR (81 MHz, CD_2Cl_2 , 20°C) δ -43.3; ^1H NMR (600 MHz, CD_2Cl_2 , 20°C) δ 9.00 (1 H, br s, NH), 7.05 (1 H, q, H_6 of T), 6.17 (1 H, dd, $\text{H}_{1'}$), 4.76 (1 H, m, $\text{H}_{3'}$), 4.73 (1 H, m, $\text{H}_{5'}$), 4.20 (1 H, m, $\text{H}_{5'}$), 3.98 (1 H, m, H_4), 3.93 (3 H, d, OCH_3 , $^3J_{\text{POCH}} = 14.3$ Hz), 2.48 (1 H, m, $\text{H}_{2'}$), 2.44 (1 H, m, $\text{H}_{2'}$), 1.93 (3 H, d, CH_3 of T).

Compound 5: ^{31}P NMR (162 MHz, CD_2Cl_2 , -41°C) δ -44.7; ^1H NMR (400 MHz, CD_2Cl_2 , -41°C) δ 10.29 (1 H, br s, NH), 7.12 (1 H,

q, H_6 of T), 6.31 (1 H, dd, $\text{H}_{1'}$), 4.82 (1 H, m, $\text{H}_{3'}$), 4.75 (1 H, m, $\text{H}_{5'}$), 4.53–4.32 (2 H, m, H_4), 4.23 (1 H, m, $\text{H}_{5'}$), 4.00 (1 H, m, H_4), 3.74–3.55 (2 H, m, H_6), 3.38 (3 H, s, OCH_3), 2.53 (1 H, m, $\text{H}_{2'}$), 2.43 (1 H, m, $\text{H}_{2'}$), 1.96 (3 H, d, CH_3 of T).

Compound 13: ^{31}P NMR (162 MHz, CD_2Cl_2 , -41°C) δ -44.7; ^1H NMR (400 MHz, CD_2Cl_2 , -41°C) δ 10.84 (1 H, br s, NH), 7.12 (1 H, q, H_6 of T), 6.30 (1 H, dd, $\text{H}_{1'}$), 4.78 (1 H, m, $\text{H}_{3'}$), 4.74 (1 H, m, $\text{H}_{5'}$), 4.28 (2 H, m, H_4), 4.20 (1 H, m, $\text{H}_{5'}$), 4.03 (1 H, m, H_4), 2.52 (1 H, m, $\text{H}_{2'}$), 2.44 (1 H, m, $\text{H}_{2'}$), 1.97 (3 H, d, CH_3 of T), 1.67 (2 H, m, H_6), 1.39 (2 H, m, H_6), 0.96 (3 H, t, H_4).

Compound 14: ^{31}P NMR (162 MHz, CD_2Cl_2 , 20°C) δ -46.3; ^1H NMR (400 MHz, CD_2Cl_2) δ 4.58 (1 H, m, H_{5b}), 4.30 (3 H, m, H_1 and H_4), 3.96 (1 H, m, H_{5a}), 3.56 (2 H, m, H_6), 3.36 (3 H, s, OCH_3), 2.25–1.20 (7 H, m, H_6 , H_7 , H_{7b} , H_{8a} , H_{8b} , H_{9a} , H_{9b}).^{25b}

Compound 15: ^{31}P NMR (162 MHz, CD_2Cl_2 , 20°C) δ -22.6; ^1H NMR (400 MHz, CD_2Cl_2 , 20°C) δ 4.20 (2 H, m, H_4), 4.15 (4 H, m, H_5 of the 5-ring), 3.52 (2 H, m, H_6), 3.30 (3 H, s, OCH_3).

Acknowledgment. The authors thank Mr. L. J. M. van de Ven for his help in the analysis of the ^1H NMR spectra.

Supplementary Material Available: Two-dimensional ^{31}P - ^1H and ^{13}C - ^1H correlation maps measured for the cyclic 3',5'-phosphites and cyclic 3',5'-phosphates 6–9 and a calculated graph of $J_{\text{H}_1\text{H}_3} + J_{\text{H}_1\text{H}_4} + J_{\text{H}_2\text{H}_3} + J_{\text{H}_2\text{H}_4}$ vs torsion angle [$\text{H}_1\text{--C}_a\text{--C}_b\text{--H}_3$] (10 pages). Ordering information is given on any current masthead.

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 Δ_{N} ($1.824 \times 10^{-6} \text{ ppm}^{-1}$) to the shift parameter S_{NO_2} ($3.075 \times 10^{-5} \text{ ppm}^{-1}$) 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 $10Dq$ 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 cobaltinitrite anion with the N_3^- and SCN^- ions. In all the ligand exchange reactions studied, it was found that mixed nitro complexes formed in the reaction predominately adopted the trans configuration.

Introduction

Some time ago, it was demonstrated¹ that the isotropic ^{59}Co NMR chemical shift for the entire range of orthoaxial six-coordinated diamagnetic cobalt(III) complexes relative to $[\text{Co}(\text{CN})_6]^{3-}$, could be reasonably estimated by using the empirical equation

$$\delta(\text{ppm}) = \frac{1}{3} \left(\frac{1}{S_1 + S_2} + \frac{1}{S_3 + S_4} + \frac{1}{S_5 + S_6} \right) - 11000 \quad (1)$$

where S_1 and S_2 , S_3 and S_4 , S_5 and S_6 are parameters characteristic of the ligands on the x , y , and z axis, respectively. This expression calculates the chemical shift of any cobalt complexes with a given set of S_L parameters¹ 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 ($^1\text{T}_{1g}$) electronic transition of octahedral CoA_6 complexes.^{2,3} 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 NMR⁴ 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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