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Conformational Transmission in Pentacoordinated Phosphorus Systems, Modelling the Activated State of Cyclic AMP

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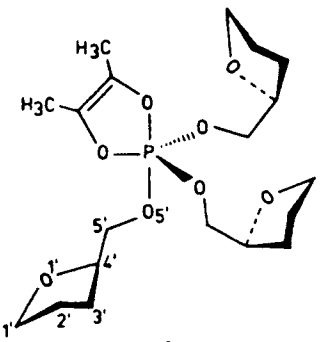
ABSTRACT

The proposed activated state of cyclic adenosine 3',5'-monophosphate (cAMP) is modelled by two nucleoside cyclic 3',5' P^V-TBP compounds **3** *and* **4**. *The reason for the design of compound* **3**, *in which a probe fragment (O—CH_2—CH_2—OCH_3 group) is linked to phosphorus, was reflected in a conformational transmission effect, which occurs when the probe is located in the axis of a P^V-TBP. This means that the six-membered 3',5'-dioxaphosphorinane ring predominantly remains in a diequatorial (e,e) orientation. In the absence of conformational transmission, as in compound* **4**, *the 3',5'-dioxaphosphorinane ring favors an equatorial-axial (e,a) orientation. From this we conclude that the occurrence of conformational transmission can stabilize the (e,e) orientation of the 3',5'-ring. This can be of relevance to the activation of protein kinase by cAMP. In order to obtain more structural information from* **3** *and* **4**, *we performed MNDO calculations on the models* **8–10**. *These calculations revealed that the (e,e) orientation of the 3',5'-ring is destabilized by 3–4 kcal/mol compared to the (e,a) orientation. For the (e,a) geometry, the 3',5'-ring adopts a twist conformation, whereas the (e,e) orientated 3',5'-ring shows a half-chair geometry.*

INTRODUCTION

In the past decade, we have extensively studied conformational transmission in stabilized five-coordinated phosphorus (P^V) model compounds [1, 2]. A clear visualization of the conformational transmission effect is obtained by comparing the trigonal bipyramidal (TBP) P^V system **1** with its four-coordinated phosphorus (P^{IV}) counterpart **2** (Scheme 1).



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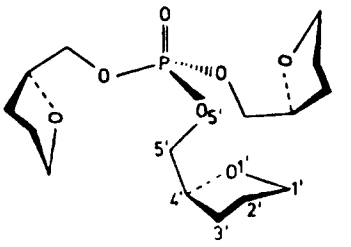

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SCHEME 1

Variable temperature ^1H NMR experiments on compound **1** have revealed that trans orientation of $O_{5'}$ and $O_{1'}$, clearly predominates for the axially located tetrahydrofurfuryl group in **1**, as a result of enhanced electrostatic repulsion between $O_{5'}$ (axial in the TBP), and $O_{1'}$ [3]. The two equatorial tetra-

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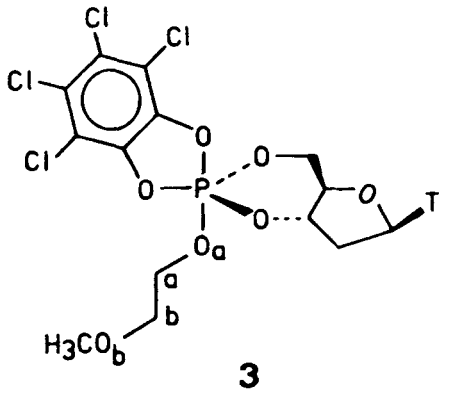
hydrofurfuryl groups in **1**, as well as the three equivalent tetrahydrofurfuryl groups in **2**, showed a highly comparable preference for a $O_{5'}$-$O_{1'}$ gauche conformation [4]. The results on **1** unequivocally revealed that the intrinsic bonding properties of pentacoordinated phosphorus in the TBP geometry (leading to increased electron density for the axial sites, in comparison with the equatorial sites [1d]) are actually reflected in the conformational properties of the three tetrahydrofurfuryl substituents. Subsequent experiments have shown that the conformational transmission effect is not restricted to tetrahydrofurfuryl groups; e.g., the occurrence of conformational transmission was also clearly established for P^V-TBP systems that entail one or more O—CH_2—CH_2—X substituents (X = OR, SR, NR_2) [1j], as well as for P^V-TBP compounds modelling an activated state of phospholipids [1g, n] and phosphorylated sugars [1f, i].

In this paper, we focus on the P^V-TBP compounds **3** and **4**, which are model systems for the P^V-TBP activated state of 3',5'-cyclic adenosine monophosphate (cAMP) [2, 5] (Scheme 2).



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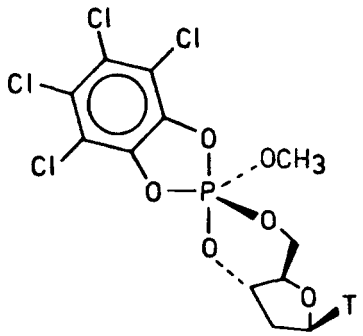

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SCHEME 2

We observed conformational transmission within the O—CH_2—CH_2—OCH_3 group in **3** (vide infra), from which it can be concluded that the O—CH_2—CH_2—OCH_3 group resides mostly in the axis of the TBP. Bearing in mind the ring strain rule [6] (stating that the tetrachloro-1,2-benzoquinone ring in **3** is in equatorial-axial (e,a) location), it then follows that the 3',5'-dioxaphosphorinane ring part of the time occupies a diequatorial (e,e) location in the TBP [2]. We feel that this application of the conformational transmission effect provides a unique clue in order to establish the location of the 3',5'-ring. For compound **4**, in which evidently no conformational transmission can occur, we derived from the three-bond phosphorus-proton *J*-coupling measured for the methoxy protons that the 3',5'-ring is predominantly in equatorial-axial (e,a) location [1j, 2].

These experimental results are of relevance with respect to the original model description for the mechanism of activation of cAMP, as proposed by van Ool and Buck [5b]. It was proposed that activation of protein kinases by cAMP occurs via a diequatorial location of the 3',5'-dioxaphosphorinane ring (compare **3**), whereas hydrolysis of cAMP by phosphodiesterases proceeds through a P^V-TBP intermediate with (e,a) orientation of the 3',5'-ring (compare **4**). Our present results on **3** and **4** confirm the idea that formation of a P^V-TBP structure by a $P^{IV} \rightarrow P^V$ activation within a 3',5'-cyclic nucleotide can result in two isomeric structures, i.e. (e,a) and (e,e), respectively.

In the following, we will briefly outline the experimental data that were obtained for **3** and **4**. Moreover, the results of a set of MNDO model calculations on (e,a) and (e,e) P^V-TBP systems will be described.

CONFORMATION OF THE P^V-TBPs **3** *AND* **4**

Location of the 3',5'-Dioxaphosphorinane Ring

The conformational analysis of the C_a–C_b bond in **3** was based on the four vicinal H–H *J*-couplings ($J_{H_1H_3}$, $J_{H_1H_4}$, $J_{H_2H_3}$, and $J_{H_2H_4}$), obtained from the 400 MHz ^1H NMR spectrum of **3** in CD_2Cl_2 at −41°C. Iterative simulation of the subspectra was performed with a standard computer program (see Figure 1). The conformation around C_a–C_b can be described as an equilibrium between one O_a–O_b trans and two approximately degenerate O_a–O_b gauche rotamers (+,−) (see Figure 2).

The value of $\Sigma J = J_{H_1H_3} + J_{H_1H_4} + J_{H_2H_3} + J_{H_2H_4}$ can be calculated as a function of the O_a–O_b torsion angle, using the empirically parametrized Karplus equation developed by Altona et al. [7]. The ΣJ values calculated for the trans rotamer and for the gauche(+) and gauche(−) rotamers are 30.0 Hz and 16.4 Hz respectively, leading to the formula:

$$x(O_a\text{–}O_b \text{ trans}) = \frac{\Sigma J^{exp} - 16.4}{30.0 - 16.4} \times 100\%.$$

The conformational analysis of the C_a–C_b bond in **3** showed a 51% population of the O_a–O_b trans rotamer, and a total of 49% population of the O_a–O_b

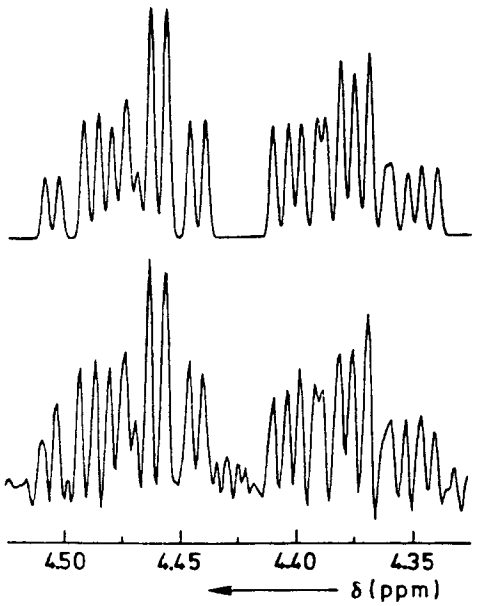
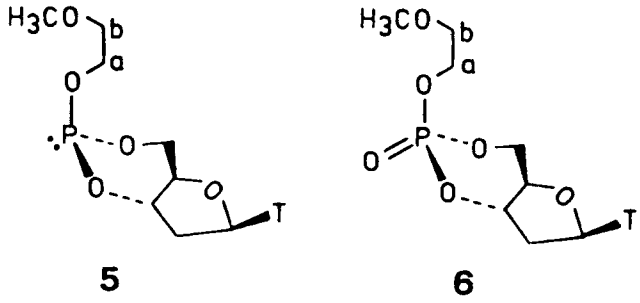


FIGURE 1 Computer Simulated (upper trace) and Experimental (lower trace) Expansion of the H_1/H_2 Pattern in the 400 MHz ^1H NMR Spectrum of Compound **3** at −41°C.



SCHEME 3

gauche rotamers. For comparison, an analogous conformational analysis was performed for the *cis*-phosphite and *cis*-phosphate counterparts of **3** (i.e., compounds **5** and **6**, respectively) (Scheme 3).

In comparison with **3**, these data (see Table 1) show considerably diminished O_a–O_b trans populations (10% and 9% O–O trans for **5** and **6**, respectively).

The location of the 3′,5′-ring in compound **4** was determined qualitatively on the basis of the NMR coupling constant between phosphorus and the methoxy protons ($^3J_{POMe}$) [1j]. As a reference system for **4**, we used compound **7** (Scheme 4). Due to pseudorotation around the P^V center the experimental $^3J_{POMe}$ (**7**) represents a time-averaged value, i.e., the three methoxy groups are rapidly exchanged over one axial and two equatorial sites in the TBP. Thus,

$$^3J_{POMe}(\mathbf{7}) = \tfrac{1}{3}[^3J_{POMe}(ax) + 2\ ^3J_{POMe}(eq)]$$

For the equatorial bonds the hybridization of phosphorus in a TBP results in an enlarged s-character in comparison with the axial ones [8], i.e., $^3J_{POMe}$(equatorial) > $^3J_{POMe}$(axial). We measured $^3J_{POMe}$(**4**) = 14.3 Hz, and $^3J_{POMe}$(**7**) = 13.6 Hz (400 MHz ^1H NMR at 20°C; solvent CD_2Cl_2); i.e., the methoxy group in **4** has a preference for equatorial location. Combining this with the well-known ring strain rule, which states that five-membered rings preferentially adopt an (e,a) location in the TBP [6], reveals that the 3′,5′-ring of **4** predominantly remains in an (e,a) location. Our experimental data on **4** do not discriminate between the possibilities of either rapid pseudorotation (on the NMR timescale), or complete absence of pseudorotation around the P^V-TBP. However, if pseudorotation does occur according to the well-known Berry mechanism [9], it is the methoxy group that will be acting as the pivot. In that case, the methoxy group will remain equatorial during the dynamic exchange of the other four ligands over the axial and equatorial sites in the TBP.

The conformational analysis of **3**, **5**, and **6** strongly indicates that conformational transmission occurs in **3**. From this, we conclude that the dynamic equilibrium of phosphorus pseudorota-

FIGURE 2 Newman Projections of the Rotamers around the C_a–C_b Bond.

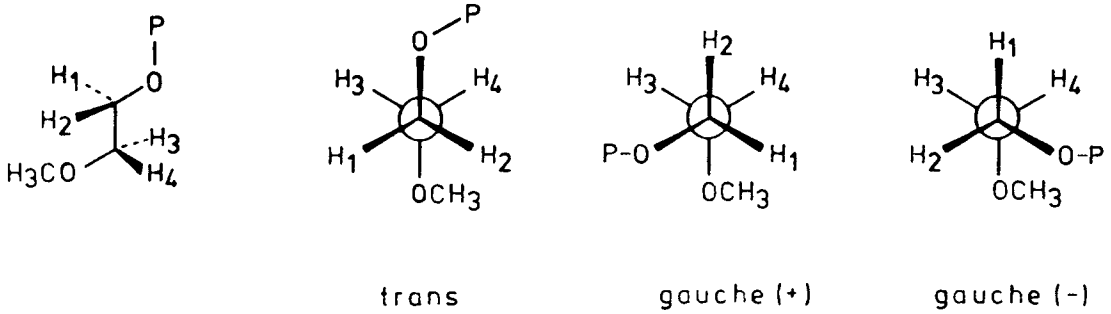


TABLE 1 Values of $J_{H_1H_3}$, $J_{H_1H_4}$, $J_{H_2H_3}$, and $J_{H_2H_4}$, Measured for the Conformational Probe System in the Compounds **3**, **5** and **6** at −41°C in CD_2Cl_2, along with the Percentages of O_a–O_b trans Orientation.

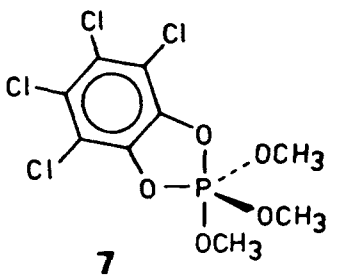
Compound	$J_{H_1H_3}$	$J_{H_1H_4}$	$J_{H_2H_3}$	$J_{H_2H_4}$	ΣJ	% *O–O trans*
3	2.2	7.1	4.7	9.4	23.4	51
5	5.7	3.2	3.2	5.7	17.8	10
6	5.3	3.5	3.5	5.3	17.6	9

tion in **3** is such that the O—CH_2—CH_2—OCH_3 group remains most of the time in the axis of the P^V-TBP. Combining this with the ring rule (vide supra) [6], it follows that the 3',5'-ring in **3** 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 [9], using either $O_{3'}$ or $O_{5'}$ as the pivot.

Conformation of the 2'-Deoxyribose Ring

The conformation of the sugar ring of **3–6** was performed with use of the PSEUROT program [10]. As input data, the sets of vicinal H–H coupling constants ($J_{H_1'H_2'}$, $J_{H_1'H_2''}$, $J_{H_2'H_3'}$, $J_{H_2''H_3'}$, and $J_{H_3'H_4'}$) measured for each compound (see Table 2) were used. The best-fit conformational parameters of two sugar structures participating in a rapid conformational equilibrium was calculated, as well as the equilibrium composition.

Using the present data as basis, PSEUROT rapidly converged toward a single conformation that is characterized by a phase angle (P) of 35.9°, and a maximum puckering amplitude (ν_{max}) of 39.9° [11]. The five endocyclic torsion angles $\nu_0 \ldots \nu_4$ can be calculated from P and ν_{max} according to the formula $\nu_j = \nu_{max} \cdot \cos(P + (j\text{-}2) \cdot 144°)$ [12], i.e., $\nu_0[C_{4'}\text{–}O_{4'}\text{–}C_{1'}\text{–}C_{2'}] = -12.2°$; $\nu_1[O_{4'}\text{–}C_{1'}\text{–}C_{2'}\text{–}C_{3'}] = -12.4°$; $\nu_2[C_{1'}\text{–}C_{2'}\text{–}C_{3'}\text{–}C_{4'}] = 32.3°$; $\nu_3[C_{2'}\text{–}C_{3'}\text{–}C_{4'}\text{–}O_{4'}] = -39.9°$; $\nu_4[C_{3'}\text{–}C_{4'}\text{–}O_{4'}\text{–}C_{1'}] = 32.2°$. From these results, we conclude that the structure of the 2'-deoxyribose ring in **3–6** resides in a twist ($^4_3$T) geometry (vide infra), which perfectly agrees with X-ray crystallographic studies on 3',5'-cyclic phosphites and phosphates [13].



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SCHEME 4

Conformation of the 3',5'-Dioxaphosphorinane Ring

There is substantial interest in the conformational properties of dioxaphosphorinane rings attached to a P^V-TBP structure, 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 P^V-TBP intermediate [14]. The conformational analysis of the 3',5'-ring in **5** and **6** is based on the work of Bentrude et al. [15]. These studies showed 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 conformation results in $J_{PH_{5'}} \simeq 2.5$ Hz, $J_{PH_{5''}} \simeq 10.7$ Hz for *cis*-phosphites [16] and $J_{PH_{5'}} \simeq 1$ Hz, $J_{PH_{5''}} \simeq 22.5$ Hz for *cis*-phosphates [17]. The vicinal H–P coupling constants fit into classical Karplus type relations with quite different parameterizations for phosphite and phosphate structures [15, 16]. Table 2 shows that $J_{PH_{5'}}$ and $J_{PH_{5''}}$ measured for the *cis*-phosphite **5** closely resembles the standard values for a chair conformation. Also the $J_{PH_{5'}}$, $J_{PH_{5''}}$ data as obtained for the *cis*-phosphate **6** corresponds to a chair geometry.

Recent studies of Bentrude et al. [14] are the basis for our conformational analysis of the 3',5'-ring in **3** and **4**. The validity of a Karplus type equation for $^3J_{PH}$ scalar couplings in P^V-TBP systems is strongly suggested by these studies [14]. Antiperiplanar orientation of H and P across H–C–O–P and H–C–N–P coupling paths was found to result in large $^3J_{PH}$ couplings (26.1 and 25.0 Hz, respectively), while much smaller values of $^3J_{PH}$ were found for gauche orientations (8.7 and 5.5 Hz for H–C–O–P and H–C–N–P respectively). Large $^3J_{PH}$ coupling constants ($\simeq$ 27 Hz) observed for **3** and **4** were interpreted as evidence for antiperiplanar orientation of P and H. We conclude from the data in Table 2 that phosphorus and $H_{5'}$ are antiperiplanar in **3** and **4**, while phosphorus and $H_{5''}$ exist in a gauche conformation. *It is clearly demonstrated that* **3** *and* **4** *populate a nonchair structure for the 3',5'-dioxaphosphorinane ring.*

MNDO CALCULATIONS ON (e,a) AND (e,e) P^V-TPBs

A better insight could be obtained into the molecular conformation of the P^V-TBPs **3** and **4** by per-

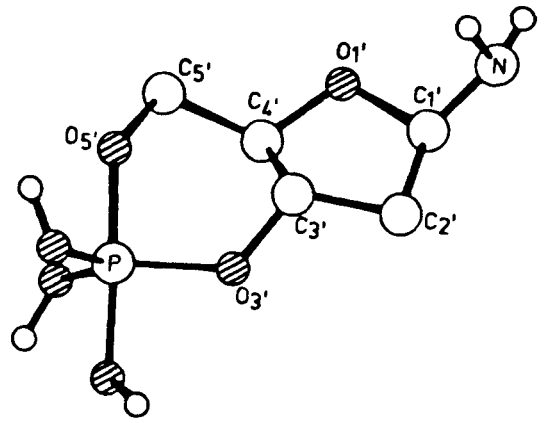
TABLE 2 Vicinal $^1H-^1H$ and $^{31}P-^1H$ Coupling Constants Measured for Compound **3, 4, 5,** and **6** at $-41°C$ in CD_2Cl_2.

Compound	$J_{H_1H_2}$	$J_{H_1H_2}$	$J_{H_2H_3}$	$J_{H_2H_3}$	$J_{H_3H_4}$	$J_{H_4H_5}$	$J_{H_4H_5}$	J_{H_5P}	J_{H_5P}
3	2.6	9.0	8.1	—	9.1	9.1	7.3	27.4	0.6
4	3.3	8.4	8.4	10.1	9.2	9.2	7.2	27.0	1.3
5	2.5	9.0	8.0	11.0	9.2	10.7	4.4	2.3	10.5
6	2.6	9.2	8.3	10.4	9.2	10.6	4.7	<1	22.4

forming a set of MNDO semi-empirical calculations [18] on the isomeric model systems **8**, **9** (both (e,a)), and **10** (e,e). The experimental data describing the structure of the 2'-deoxyribose ring, the torsion angle [$P-O_{5'}-C_{5'}-H_{5''}$], and the torsion angle [$O_{5'}-C_{5'}-C_{4'}-O_{1'}$] (vide supra) were used as input values for the MNDO calculations. During the calculations, only the bond angles and torsion angles defining the TBP geometry were fixed. The obtained structures are illustrated in Figure 3; the calculated heats of formation of **8–10** are −263.7, −262.6, and −259.8 kcal/mol, respectively. From this, it should be noted that both (e,a) forms are almost equally stable, while the (e,e)-isomer is destabilized by approximately 3–4 kcal/mol.

In all three calculations the resulting optimized

FIGURE 3 MNDO Optimized Geometries for the P^V-TBP Isomeric Model Systems **8,9** (both (e,a)), and **10** (e,e). The heat of formation is almost the same for **8** and **9** (ΔH_f = −263.7 and −262.6 kcal/mol, respectively). The (e,e) system **10** is only slightly destabilized in comparison with **8** and **9** (ΔH_f = −259.8 kcal/mol).



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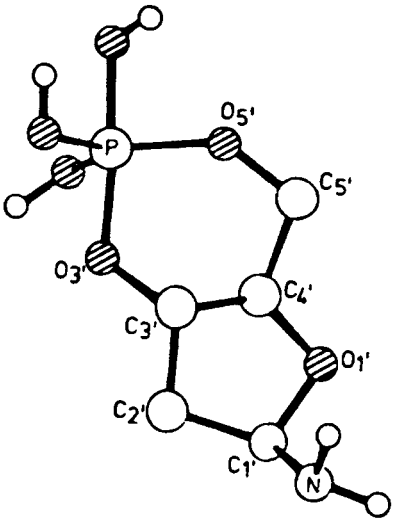

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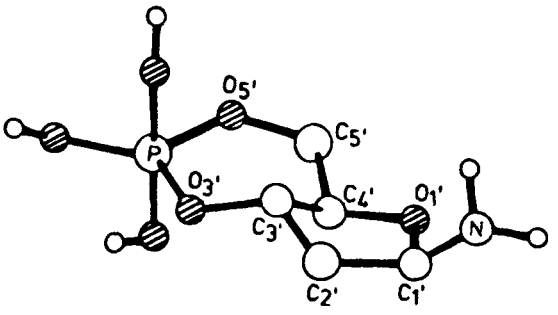

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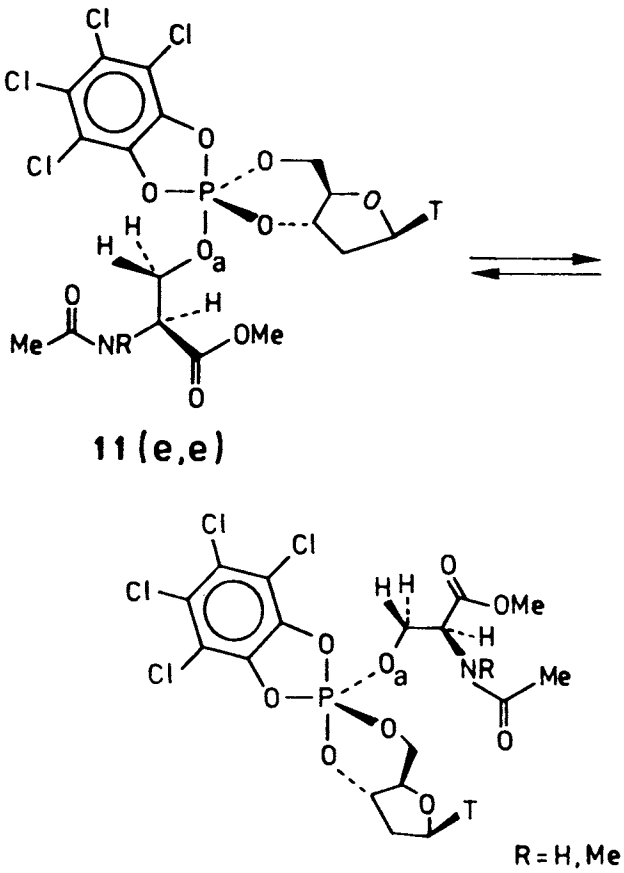
conformations showed that the 2'-deoxyribose ring remained almost unchanged. Most probably, the limited structural freedom of the 2'-deoxyribose ring can be attributed to the trans fusion in our systems. However, the 3',5'-dioxaphosphorinane ring showed slight structural variations. For the (e,a)-isomers **8** and **9**, it is found that the ring predominantly remains in a twist structure in which $O_{5'}$, $C_{5'}$, $C_{4'}$, and $O_{3'}$ are approximately in the same plane; the P atom is bent toward the exo side of this plane, while $C_{3'}$ is located on the endo side. At the phosphorus end the dioxaphosphorinane ring of the (e,e) system **10** is flattened, as is obvious from the low values of the torsion angles [$C_{4'}$–$C_{5'}$–$O_{5'}$–P] (−5.0° for **10**, −31.8° and −27.3° for **8** and **9**, respectively), and [$C_{5'}$–$O_{5'}$–P–$O_{3'}$] (19.8° for **10**, 50.6° and 40.6° for **8** and **9**, respectively) (see Table 3) [19]. The conformation of the dioxaphosphorinane ring in **10** seems to fit best with a half-chair (chaise longue) in which $C_{3'}$ acts as the back.

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. [14]. Furthermore, our experimental data show 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 reveal that an (e,a) orientation is slightly energetically favorable, it appears from the data on **3** 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.

Based on the X-ray studies of the cAMP binding domain in the crystal structure of the bacterial catabolite gene activator protein (CAP) dimer [20], we have synthesized the P^V-TBP model system **11**, in which a serine group is linked to the P^V-TBP (Scheme 5). The design of compound **11** was based on the close proximity of the CH_2—OH side-chain of serine-83 to the phosphorus atom of cAMP, i.e. the formation of a P^V-TBP activated state in which the CH_2–OH of serine serves as the additional fifth ligand appears to be plausible. The resulting P^V-TBP



SCHEME 5

may show conformational transmission by virtue of enhanced charge repulsion between O_a and N [1j]; i.e., (e,e) orientation of the 3',5'-ring could be stabilized in this way. At present, the conformation of the P^V-TBP **11** is not solved completely, but we succeeded in synthesizing compound **11** (R = H), as was evident from the ^{31}P NMR spectrum (162 MHz; −20°C; solvent CD_2Cl_2; δ −44.2).

TABLE 3 Torsion Angles Describing the Conformation of the 3',5'-Dioxaphosphorinane Ring in the MNDO-Optimized Structures of the Model Systems **8–10**.

Torsion Angle	**8** (*e,a*)$_1$	**9** (*e,a*)$_2$	**10** (*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

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REFERENCES AND NOTES

[1] (a) H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 99,* 1980, 181. (b) J. J. C. van Lier, L. H. Koole, H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 102,* 1983, 148. (c) J. J. C. van Lier, M. T. Smits, H. M. Buck, *Eur. J. Biochem., 132,* 1983, 55. (d) L. H. Koole, E. J. Lanters, H. M. Buck, *J. Am. Chem. Soc., 106,* 1984, 5451. (e)

L. H. Koole, R. J. L. van Kooyk, H. M. Buck, *J. Am. Chem. Soc., 107,* 1985, 4032. (f) N. K. de Vries, H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 105,* 1986, 150. (g) G. H. W. M. Meulendijks, W. van Es, J. W. de Haan, H. M. Buck, *Eur. J. Biochem., 157,* 1986, 421. (h) H. M. Buck, L. H. Koole, M. H. P. van Genderen, *Phosphorus and Sulfur, 30,* 1987, 545. (i) N. K. de Vries, H. M. Buck, *Carbohydrates, 165,* 1987, 1. (j) M. H. P. van Genderen, L. H. Koole, B. C. C. M. olde Scheper, L. J. M. van de Ven, H. M. Buck, *Phosphorus and Sulfur, 32,* 1987, 73. (k) A. E. H. de Keijzer, L. H. Koole, H. M. Buck, *J. Am. Chem. Soc., 110,* 1988, 5995. (l) A. E. H. de Keijzer, H. M. Buck, *J. Org. Chem., 53,* 1988, 4827. (m) L. H. Koole, M. H. P. van Genderen, H. M. Buck, *J. Org. Chem., 53,* 1988, 5226. (n) G. H. W. M. Meulendijks, J. W. de Haan, M. H. P. van Genderen, H. M. Buck, *Eur. J. Biochem., 182,* 1989, 531. (o) A. E. H. de Keijzer, L. H. Koole, W. J. M. van der Hofstad, H. M. Buck, *J. Org. Chem., 54,* 1989, 1432. (p) L. H. Koole, A. T. A. Olders, M. Opresnik, H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 109,* 1990, 55.

[2] N. L. H. L. Broeders, L. H. Koole, H. M. Buck, *J. Am. Chem. Soc., 112,* 1990, 7475.

[3] Equatorial tetrahydrofurfuryl groups have a preference for O–O gauche (g^+, g^t) conformation (318 K: $x(g^+) = 0.37$, $x(g^t) = 0.39$, $x(g^-) = 0.24$; 217 K: $x(g^+) = 0.43$, $x(g^t) = 0.44$, $x(g^-) = 0.13$). Axial tetrahydrofurfuryl ligands predominantly adopt an O–O trans (g^-) conformation (318 K: $x(g^+) = 0.25$, $x(g^t) = 0.14$, $x(g^-) = 0.61$; 217 K: $x(g^+) = 0.14$, $x(g^t) = 0.06$, $x(g^-) = 0.80$) [1d].

[4] (a) S. Wolfe, *Acc. Chem. Res., 5,* 1972, 102. (b) W. K. Olson, *J. Am. Chem. Soc., 104,* 1982, 285.

[5] (a) P. J. J. M. van Ool, H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 100,* 1981, 79. (b) P. J. J. M. van Ool, H. M. Buck, *Eur. J. Biochem., 121,* 1982, 329. (c) P. J. J. M. van Ool, H. M. Buck, *Recl. Trav. Chim. Pays-Bas, 103,* 1984, 119.

[6] Five-membered dioxaphospholene rings have a pronounced preference for (e,a) location in a P^V-TBP. (R. R. Holmes, *J. Am. Chem. Soc., 100,* 1978, 433; Pentacoordinated Phosphorus; American Chemical Society: Washington, D.C., 1980; Vols I, II; ACS Monograph No. 175, 176).

[7] C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron, 36,* 1980, 2783.

[8] (a) R. F. Hudson, M. Green, *Angew. Chem., 75,* 1963, 47. (b) J. H. H. Hamerlinck, P. Schipper, H. M. Buck, *J. Org. Chem., 48,* 1983, 306. (c) G. Buono, J. R. Llinas, *J. Am. Chem. Soc., 103,* 1981, 4532.

[9] P. S. Berry, *J. Chem. Phys., 32,* 1960, 933.

[10] (a) *Quantum Chemistry Program Exchange 463.* (b) F. A. A. M. de Leeuw, C. Altona, *J. Chem. Soc., Perkin Trans. 2,* 1988, 375.

[11] C. Altona, M. Sundaralingam, *J. Am. Chem. Soc., 94,* 1972, 8205.

[12] H. P. M. de Leeuw, C. A. G. Haasnoot, C. Altona, *Isr. J. Chem., 20,* 1980, 108.

[13] (a) W. G. Bentrude, A. E. Sopchik, G. S. Bajwa, W. N. Setzer, W. S. Sheldrick, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun., C42,* 1986, 1027. (b) W. Depmeier, J. Engels, K. H. Klaska, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem., 33,* 1977, 2436. (c) A. Ku Chwang, M. Sundaralingam, *Acta Crystallogr., B30,* 1974, 1233. (d) C. L. Coulter, *Acta Crystallogr., B25,* 1969, 2055 and *B26,* 1970, 441.

[14] (a) J. H. Yu, W. G. Bentrude, *Tetrahedron Lett., 30,* 1989, 2195. (b) J. H. Yu, W. G. Bentrude, *J. Am. Chem. Soc., 110,* 1988, 7897.

[15] (a) W. G. Bentrude, A. E. Sopchik, T. Gajda, *J. Am. Chem. Soc., 111,* 1989, 3981. (b) K. A. Nelson, A. E. Sopchik, W. G. Bentrude, *J. Am. Chem. Soc., 105,* 1983, 7752.

[16] (a) G. S. Bajwa, W. G. Bentrude, *Tetrahedron Lett., 5,* 1978, 421. (b) R. J. M. Hermans, H. M. Buck, *Phosphorus and Sulfur, 31,* 1987, 255. (c) M. Kainosho, A. Nakamura, *Tetrahedron, 25,* 1969, 4071.

[17] (a) K. A. Nelson, W. G. Bentrude, W. N. Setzer, J. P. Hutchinson, *J. Am. Chem. Soc., 109,* 1987, 4058. (b) P. P. Lankhorst, C. A. G. Haasnoot, C. Erkelens, C. Altona, *J. Biomol. Struct. Dyns., 1,* 1984, 1387. (c) R. J. M. Hermans, H. M. Buck, *J. Org. Chem., 52,* 1987, 5150.

[18] (a) M. J. S. Dewar, W. Thiele, *J. Am. Chem. Soc., 67,* 1977, 4899. (b) M. N. D. O.: *Quantum Chemical Program Exchange 353* (1978).

[19] A half chair 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. 14a.

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