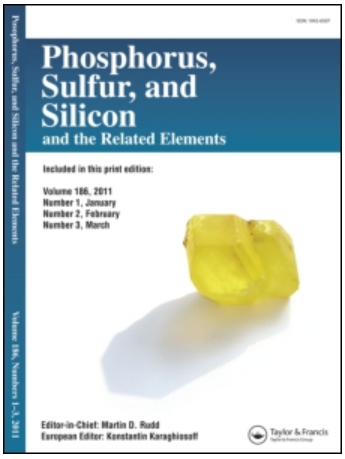

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
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Conformations of Bioorganic P(V) Cyclic Nucleotide Model Compounds

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To cite this Article Bentrude, Wesley G. , Yu, Jaehoon H. and Sopchik, Alan E.(1990) 'Conformations of Bioorganic P(V) Cyclic Nucleotide Model Compounds', Phosphorus, Sulfur, and Silicon and the Related Elements, 51: 1, 73 — 76
To link to this Article: DOI: 10.1080/10426509008040685
URL: http://dx.doi.org/10.1080/10426509008040685

Phosphorus, Sulfur, and Silicon, 1990, Vols. 51/52, pp. 73-76
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CONFORMATIONS OF BIOORGANIC P(V) CYCLIC NUCLEOTIDE MODEL COMPOUNDS

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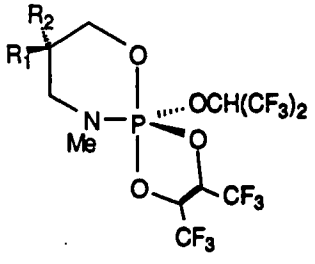
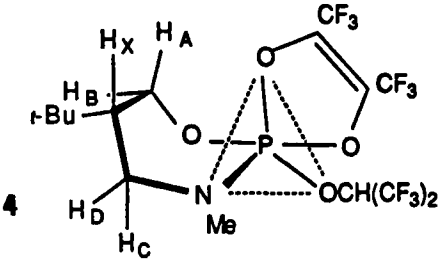
Abstract Compounds containing pentacovalent phosphorus in six-member rings have been synthesized. These are structural models for potential enzyme or substrate adducts of cAMP. The presence of twist rather than chair form P(V) containing rings was demonstrated by ^{1}H NMR analysis.

It has been suggested that in the reactions of cAMP with various phosphodiesterases or on its interaction with the regulator subunit of protein kinases I and II, pentacovalent, i.e. P(V), cAMP-enzyme or cAMP-substrate intermediates are formed.[1] We showed earlier[2] that the free energy difference between the chair and twist forms of the phosphate ring of cAMP itself likely is small enough that enzyme binding forces could readily convert that ring to the twist form, if it were chemically advantageous to do so. However, the question of the corresponding conformation of the P(V) adducts potentially formed has not been addressed.

With the above in mind, we examined first the ^{1}H NMR spectra of a series of P(V) compounds containing the 1,3,2-oxazaphosphorinane. The primary goal was to establish the presence of a Karplus-like relationship for $^3J_{HP}$ for P(V) systems. Second, we sought to apply such a relationship to the $^3J_{HP}$ values of the P(V)-containing 1,3,2-dioxaphosphorinane rings of certain molecules which were prepared as models of P(V) cAMP derivatives in enzymatic systems. The overall goal was to assess the relative stabilities of chair and twist conformations of the 1,3,2-dioxaphosphorinane rings. Indeed, these ring systems, attached apical/equatorial to phosphorus, were found to be very largely, if not entirely, in the twist conformation.

The 1,3,2-oxazaphosphorinanes studied were 1 - 3,[3] prepared by standard means. ^{1}H NMR spectra taken at 300, 400, or 500 MHz gave a clear indication of a Karplus-like relationship as seen in the large disparity between the J_{AP} and J_{BP} (also J_{CP} and J_{DP}) values listed below. These rings are known to be attached to P(V) in an apical/equatorial fashion. Diagnostic of a very predominant population of twist conformation, approximated by 4, are the combination of large J_{BP}, J_{AX}, and J_{BX} along with large J_{DP} and J_{CX}. These parameters are quite analogous to what we reported previously for twist-form P(IV) 1,3,2-oxazaphosphorinanes,[4] and P(III),[5] and P(IV)[6] 1,3,2-dioxaphosphorinanes, and also for 1.[3]





4

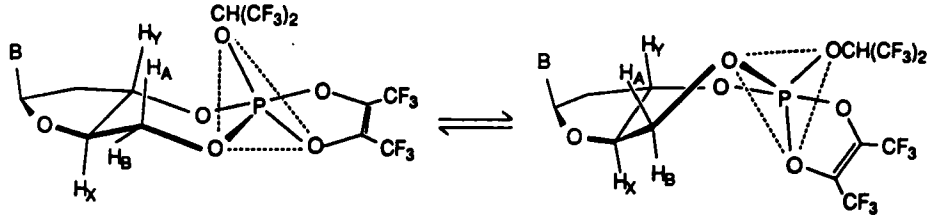
1 $R^1 = R^2 = H$

2 $R^1 = \underline{t}$-Bu, $R^2 = H$

3 $R^1 = H$, $R^2 = \underline{t}$-Bu

J_{AP} = 5.8 Hz J_{BP} = 29.4 Hz
J_{DP} = 29.8 Hz J_{CP} = 2.2 Hz
J_{AX} = 8.7 Hz J_{DX} = 4.6 Hz
J_{CX} = 11.8 Hz J_{BX} = 7.3 Hz

The 1,3,2-dioxaphosphorinane model systems of interest are those shown below based on thymidine, 5, and the corresponding fused ring system without the pyrimidine base (diastereomers 6 and 7). In these cases (see Table) the combination of large J_{AP} coupled with the small size of J_{BX} indicate that 5 - 7 are almost entirely in the twist conformation in solution.[7] (8 is believed to be the diastereomer corresponding to 5 and 6). Earlier X-ray structures of closely related 1,3,2-oxazaphosphorinanes[8] and 1,3,2-dioxaphosphorinanes[9] showed their rings to be attached apical/equatorial and in non-chair(boat/twist) conformations. Our NMR work appears to be the



8a 8b

5 B = 1-thyminyl, major diastereomer
6 B = H, major diastereomer
7 B = H, minor diastereomer

first to present evidence for the presence of a dominant twist conformation in solution.

TABLE I Coupling Constants (Hz) for 5 - 7 in $CDCl_3$.

Compound	J_{AX}	J_{AP}	J_{BP}	J_{BX}
5[a]	9.3	26.5	2.6	7.0
6[b]	9.2	29.3	~.0	6.8
7[b]	9.5	26.5	2.6	7.0

[a] At 300 MHz. [b]At 400 MHz.

Of course the results for 5 - 7 do not demand that P(V) adducts in enzymic systems also be in the boat or twist conformation. However, it can be strongly suggested that an unknown amount of enzyme-substrate binding energy may be required if such adducts are to remain in the chair conformation. The possible stereoelectronic advantages of both chair and twist conformations relative to the details of the enzymatic processes should be considered.

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