of analogously substituted alkenyl radicals. It was reported that a substituent at position 3 of 5-hexenyl radicals favors the formation of the *Z* product of 5-exo cyclizations[17] while a substituent at position 3 of a 6-heptenyl radical favors the *E* product of 6-exo cyclizations.[18] These observations were supported by force field calculations.[19]

In summary, the *n*-Bu_3SnH/AIBN-induced cyclization of alkenylisothiocyanates constitutes a general and efficient method for the preparation of γ-thiolactams, and a useful method for the preparation of suitably substituted δ-thiolactams.

Acknowledgment. We thank the Minerva Foundation (Munich, Germany) for financial support.

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Apical-Equatorial Orientation of the Six-Membered Ring in P(V) Models of Enzymatically Formed cAMP-Nucleophile Adducts. Relationship to the Basic Hydrolysis of cAMP

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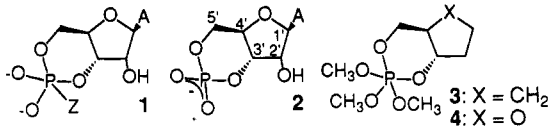
Received February 23, 1990

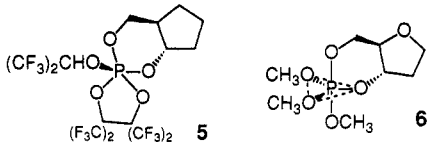
Summary: Results of a low-temperature ^{13}C NMR study of **4**, an X-ray crystal structure of **5**, and ^1H NMR results for **4** and **5** which show both model compounds to have the P(V) 1,3,2-dioxaphosphorinane ring attached apical/equatorial to phosphorus and in a twist rather than chair conformation are reported and discussed relative to the enzymic and particularly the basic chemical hydrolysis of cAMP.

Pentacovalent phosphorus, P(V), adducts (**1**) have been proposed as intermediates both in the phosphodiesterase-catalyzed hydrolysis[1] of cAMP (**2**) to 5′-AMP and in the activation by cAMP of protein kinases[2] on coordination of cAMP with the active site of the regulatory subunit. As a guide to an understanding of the biological systems, several nonenzymic P(V) model systems have been prepared[3,4] of which one can ask: (1) Is the structure trigonal bipyramidal or square pyramidal about phosphorus? (2) Is the six-membered (1,3,2-dioxaphosphorinane) ring attached to P(V) diequatorial or apical/equatorial? (3) For apical/equatorial attachment, is the O5′ or O3′ atom apical? (4) What is the conformation (chair or nonchair) of that ring?



Puzzlingly different answers to question **2** have been presented in certain systems. Thus, it has been calculated by CNDO/2 methods that a pentacovalent adduct from cAMP with ring *diequatorial* is about 25 kcal/mol *lower* in energy than its apical/equatorial alternative.[2c] Furthermore, in a ^{13}C NMR study[2a] the MeO signals of **4** (X = O) failed to decoalesce at −88 °C, whereas, at the same temperature, **3** (X = CH_2) showed two MeO resonances, the lower field one (two equatorial MeO's) being of twice the intensity of the higher field peak (one apical MeO). The result for **3** is clearly indicative of *apical/equatorial* 1,3,2-dioxaphosphorinane ring attachment. The lack of decoalescence for **4**, which with X = O more closely resembles a cAMP P(V) adduct, was interpreted[2a] to mean that the corresponding ring of **4** is by contrast quite likely *diequatorial*. This conclusion is consistent with the CNDO/2 calculations.[2c]

In this report we present high-field variable-temperature studies of **4** which dispel the notion that its P(V)-containing 1,3,2-dioxaphosphorinane ring is diequatorial. Also reported is an X-ray structure[5] of the model system **5**



which shows the apical and equatorial positions of the O5′ and O3′ ring atoms, respectively, to be attached to near-TBP P(V) contained in a *twist* form 1,3,2-dioxaphosphorinane ring. These findings, although important by themselves, lead as well to a better understanding of the regiochemistry of the nonenzymic, base-catalyzed ring opening of cAMP.

Selected ^{13}C NMR spectra for **4**[5] obtained at 125 MHz over the temperature range 25 to −113 °C in CD_2Cl_2 are displayed in Figure 1. Just as was found with **3** at 22.6 MHz,[2a] **4** also reaches a slow exchange limit at which the low-field equatorial MeO's are twice as intense as the higher field, apical one[6] which means that *the 1,3,2-diox-*

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(3) For recent work, see: (a) Reference 2a. (b) Yu, J. H.; Bentrude, W. G. *J. Am. Chem. Soc.* **1988**, *110*, 7897. (c) Yu, J. H.; Bentrude, W. G. *Tetrahedron Lett.* **1989**, *30*, 2195. (d) Swamy, K. C. K.; Day, R. O.; Holmes, R. R. *Abstracts of Lectures, XI*, International Conference on Phosphorus Chemistry, Tallinn, USSR, July 3-7, 1989; abstract 2-22. (e) Bentrude, W. G.; Yu, J. H.; Sopchik, A. E. *Ibid.* abstract 4-19.
(4) Ramirez, F.; Maracek, J. F.; Ugi, I.; Lemmen, P.; Marquarding, D. *Phosphorus* **1975**, *5*, 73. Chang, B. C.; Conrad, W. E.; Denney, D. B.; Denney, D. Z.; Edelman, R.; Powell, R. L.; White, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 4004.
(5) Phosphorane **5** was prepared by the method of ref 2a in >95% purity as assessed by ^1H and ^{13}C NMR spectroscopy.
(6) This chemical shift relationship between apical and equatorial methoxy groups has been defined in van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 215.

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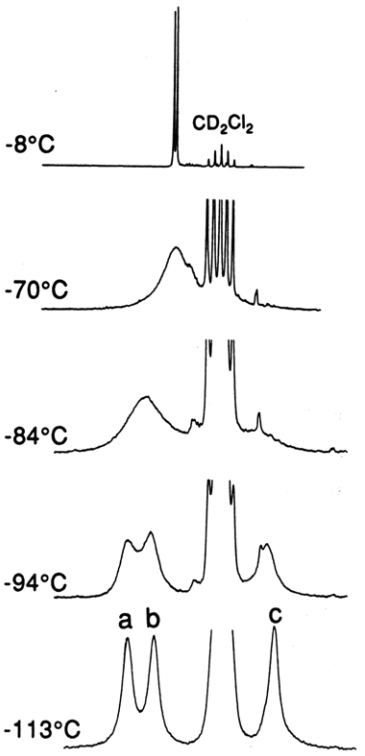


Figure 1. Temperature-dependent ^{13}C NMR spectrum of CH_3O resonances of **4** in CD_2Cl_2 at 125 MHz: a, b = 2 equatorial CH_3O (δ 57.7, 56.8); c = 1 apical CH_3O (δ 52.8).

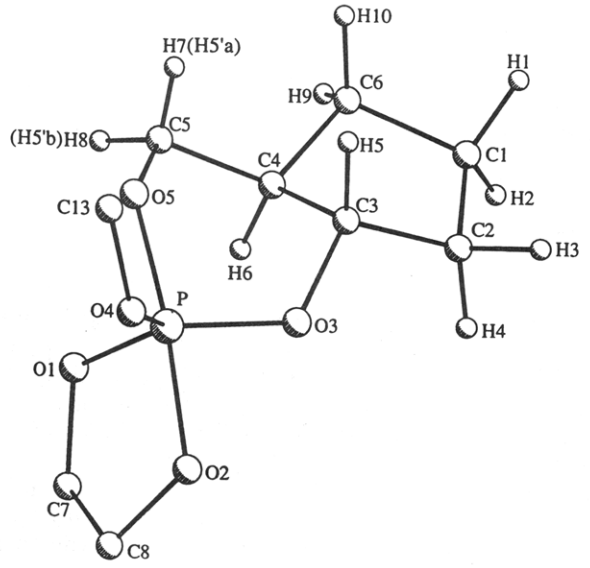
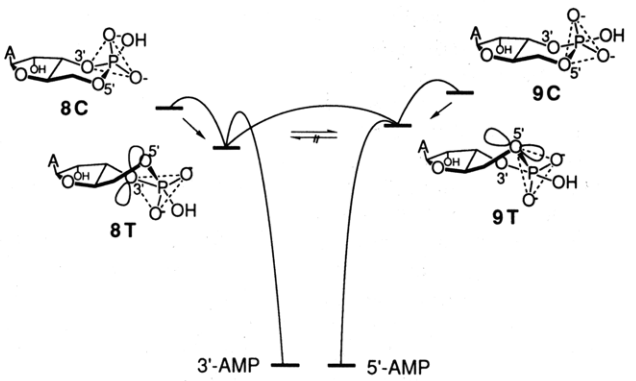


Figure 2. PLUTO plot for **5** (CF_3 and $(CF_3)_2CH$ groups removed).

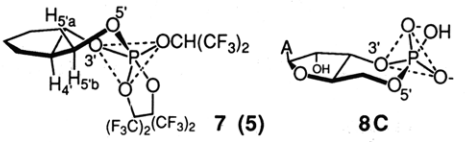
aphosphorinane ring is unmistakably attached apical/equatorial to phosphorus, structure ***6***. Any effect on the relative thermodynamic stabilities of equatorial/equatorial and apical/equatorial ring isomers of substituting O (**2**) for CH_2 (**1**) is not great enough to override the intrinsic preference for such rings to be apical/equatorial for which increasing evidence exists in monocyclic systems.[2a,3d,6,7] Thus the possibility[2a] that ring system **4**, and those P(V) systems derived from cAMP (**1**), have a preference for the 1,3,2-dioxaphosphorinane ring to be diequatorial rather than apical/equatorial on P(V) can be discarded.

Scheme I



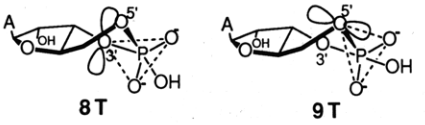
In Figure 2 is displayed a PLUTO drawing of the X-ray crystal structure of **5**.[8] This represents to our knowledge *the first structure* of such a model system, and provides the first X-ray evidence for the *near-TBP geometry* for this sort of trans ring-fused, bicyclic P(V) 1,3,2-dioxaphosphorinane. The positions of the apical/equatorial ring oxygens are of particular significance, since the P–O3′ bond is expected[1] to be apical when cleaved to form 5′-AMP in the phosphodiesterase-catalysed hydrolysis of cAMP. *In Figure 2 the P–O5′ bond is apical.* If the form with O5′ apical is the thermodynamically favored one in solution as well, then an important role of phosphodiesterase must be to form the cAMP–H_2O adduct with O3′ instead of O5′ in the apical position.

Another important feature seen in Figure 2 is the *twist conformation of the phosphorus-containing ring* of ***5***, also depicted by **7**. The increasingly recognized propensity of



monocyclic P(V) 1,3,2-dioxaphosphorinane rings attached apical/equatorial to phosphorus to be in nonchair conformations[3d,7a] is evidently unaffected by the fused-ring feature of **5**. The nonchair conformation for **4** and **5** in solution was clearly demonstrated, as shown[3b,8] for other P(V) 1,3,2-dioxaphosphorinanes, by the observed combination of simultaneously large $J_{5'aP}$ and $J_{5'a4'}$. These splittings are for **4** (500 MHz, CD_2Cl_2) $J_{5'aP}$ = 26.4 Hz, $J_{5'a4'}$ = 8.8 Hz, $J_{5'bP}$ = 0.8 Hz, $J_{5'b4'}$ = 7.2 Hz; and for **5** (300 MHz, C_6D_6) $J_{5'aP}$ = 29.4 Hz, $J_{5'a4'}$ = 10.6 Hz, $J_{5'bP}$ = 0.2 Hz, $J_{5'b4'}$ = 7.9 Hz.

The above results allow further insight into the mechanism of the basic hydrolysis of cAMP which proceeds, like its enzymic counterpart, with inversion of configuration at phosphorus,[1c] but gives predominantly 3′-AMP rather than 5′-AMP (3′-AMP/5′-AMP = 4/1). A conformation for cAMP which approximates that of **5** is given by **8T**. The O5′ analogue is depicted in **9T**. Phosphoranes **8** and **9** potentially can be interconverted by a single Berry pseudorotation. In **8T** the lone pair on O3′ is optimally



(7) (a) Schomburg, D.; Hacklin, H.; Roeschenthaler, G. V. *Phosphorus Sulfur* **1988**, *35*, 241. (b) Barlow, J. H.; Bone, S. A.; Russell, D. R.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 1031. See also Figure 1.

(8) A complete description of this structure and its relationship to ^1H NMR evidence for the twist structure in solution for a series of P(V) 1,3,2-dioxaphosphorinanes has been submitted for publication. Yu, J. H.; Arif, A. M.; Bentrude, W. G.

located in the equatorial plane.[9] This, along with the probable slightly greater apicophilicity of the primary OC5′ group over that of the secondary OC3′ substituent,[11] imparts the *thermodynamic* stability to the O5′ apical structure which results in its being lower in energy than its O3′ apical counterpart. This difference is depicted in Scheme I (structures **8T** and **9T**).

On the other hand **9T** should be *kinetically* more labile towards scission of the apical O–P bond than **8T**, because the p orbital electron pair on O5′ in **9T** is lined up parallel to the apical bonding system to assist *stereoelectronically*[10] with the scission of the O3′–P bond to give 5′-AMP. In this view **9T** would immediately give 5′-AMP, and pseudorotation to form **8T** would not occur (see the scheme). The predominance of 3′-AMP then most likely results from the kinetically as well as thermodynamically more favored formation of 5′O apical **8T**, generated concertedly on attack by HO^- or immediately from kinetically favored chair form **8**, **8C** (5′O apical).[12] In that case, and if **8T** decays rapidly to 3′-AMP, the difference of activation energy for the two pathways ($\Delta\Delta G^{\ddagger}$) is 0.8 kcal/mol. Indeed, since **8T** and especially **9T** are both set up for apical departure of good leaving groups, there is no reason to think that they should be rapidly equilibrated prior to scission (Hammett–Curtin-based product distribution). Nonetheless, it is conceivable that some of the 5′-AMP results from conversion of **8T** to **9T** in competition with scission of **9T** to 5-AMP. In that instance the selectivity for **8** vs **9** formation would be greater than 0.8 kcal/mol.

These ideas are at variance with those expressed recently[13] concerning the relative amounts of P–O3′ and P–O5′ scission on hydrolysis of cyclic 3′,5′-phosphoramidate ($P(O)NMe_2$) derivatives of cAMP and its 5′-Me-substituted analogues. Those studies, however, certainly appear to show the sensitivity of product distribution to small changes in stabilities of intermediates.

Acknowledgment. Support of this research by Grant R01 CA11045 from the NCI of the PHS is gratefully acknowledged.

Supplementary Material Available: Preparation of **5** and tables for the X-ray structure of **5** of crystal data, positional parameters, bond lengths, bond distances, torsional angles, and thermal parameters (19 pages); listing of structure factors (10 pages). Ordering information given on any current masthead page.

(9) Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047.
(10) For an extensive converage of such ideas see Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047. Transition-state effects are normally greater than ground-state effects.
(11) Trippett, S. *Phosphorus Sulfur* **1976**, *1*, 89.
(12) Although **8C** does not benefit energetically from the placement of the O3′ lone pair equatorial, it nonetheless has the primary, presumably more apicophilic, O5′–C bond apical.
(13) Radics, L.; Bottka, S.; Tomasz, J. *Nucleosides Nucleotides* **1989**, *8*, 1305.

Enantioselective Wittig–Horner Reaction in the Solid State

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Received February 13, 1990

Summary: Wittig–Horner reactions in the solid state of the inclusion compound of 4-methyl- or 3,5-dimethylcyclohexanone and an optically active host compound with (carbethoxymethylene)triphenylphosphorane gave optically active 4-methyl- and 3,5-dimethyl-1-carbethoxymethylene)cyclohexane, respectively.

We have previously presented very efficient enantioselective photoreactions of prochiral compounds in inclusion complexes with optically active host compounds in the solid state.[1] We recently also reported that usual organic reactions such as pinacol rearrangement,[2] Baeyer–Villiger oxidation,[3] $NaBH_4$ reduction,[4] and $FeCl_3$-assisted phenol coupling[5] occur efficiently in the solid state and that even enantioselective reactions occur in the solid state when the reactant is complexed with an optically active host.

For example, treatment of the inclusion compound of ketones and (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**1b**),[6] (−)-1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**2**),[6] or β-cyclodextrin[7] with a borane–ethylenediamine complex or $NaBH_4$ in the solid state gave optically active alcohols of up to 59% ee. These reactions involve enantioselective hydride attack. We have further found that the Wittig–Horner reagent **3** also attacks prochiral ketones enantioselectively when the substrates are included in an optically active host, giving optically active olefins.

For example, when a mixture of finely powdered 1:1 inclusion compound of **1b** and 4-methylcyclohexanone (**4a**) (1.5 g) and (carbethoxymethyl)triphenylphosphorane (**3**) (2.59 g) was kept at 70 °C, the Wittig–Horner reaction was completed within 4 h. To the reaction mixture was added ether–petroleum (1:1), and the precipitated solid (triphenylphosphine oxide and excess **3**) was removed by filtration. The crude product left after evaporation of the solvent of the filtrate was distilled in vacuo to give (−)-4-methyl-1-(carbethoxymethylene)cyclohexane (**5a**) of 42.3% ee in 73.0% yield (Table I). The optical purity of **5a** was determined by measuring the ^1H NMR spectrum in the presence of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).[8]

(1) Toda, F. *Top. Curr. Chem.* **1988**, *149*, 211.
(2) Toda, F.; Shigemasa, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 209.
(3) Toda, F.; Yagi, M.; Kiyoshige, K. *J. Chem. Soc., Chem. Commun.* **1988**, 958.
(4) Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 320.
(5) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007.
(6) Toda, F.; Mori, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1245.
(7) Toda, F.; Shigemasa, T. *Carbohydr. Res.* **1989**, *192*, 363.
(8) $En(hfc)_3$ (99+%) is available from Aldrich Co. Ltd., Milwaukee, WI. The methylene proton signal of the carbethoxy group of **5a** and its (+)-enantiomer appeared at δ 5.24 and 5.28 ppm in $CDCl_3$, respectively, in the presence of 0.1 molar equiv of $Eu(hfc)_3$.

0022-3263/90/1955-3446$02.50/0