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TWIST CONFORMATION FOR THE CIS N,N-DIMETHYLPHOSPHORAMIDATE OF THYMIDINE 3',5'-CYCLIC PHOSPHATE

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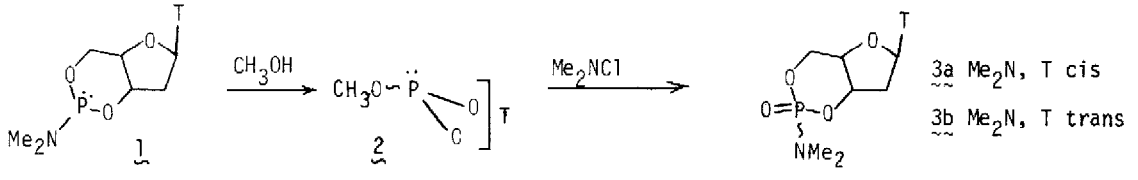
Abstract. PMR analysis assigns twist and chair predominant conformations to the R_P and S_P diastereomers, respectively (3a and 3b), of thymidine 3',5'-cyclic N,N-dimethylphosphoramidate, 3. The twist conformer population of 3a is about 64 (acetone) to 75% (toluene).

3',5'-Cyclic nucleoside monophosphates, e.g. cAMP and cGMP, are important bioregulator molecules. Phosphorus-derivatized cyclic nucleotides (e.g. 1-3) have potential as mimics or antagonists of the natural molecules.[1] Furthermore, they have been used recently[2] as precursors to the individual diastereomers of the stereochemically valuable molecules cAMPS and (O^{18})-cAMP. We wish to point out here the usefulness of P-derivatized cyclic nucleotides to probe the conformational properties of the phosphate ring. Clearly, the known strain[3] engendered by the trans fusion of the phosphate and ribose rings could lead to geometry changes effecting the chair-twist equilibrium available to the phosphorus-containing ring. We report what is to our knowledge the first PMR-based conformational analysis of the 1,3,2-dioxaphosphorinane ring of a P-derivatized cyclic nucleotide. Of special interest is the finding that for the cis diastereomer of N,N-dimethylphosphoramidate (3) a twist conformer is largely populated in solution.

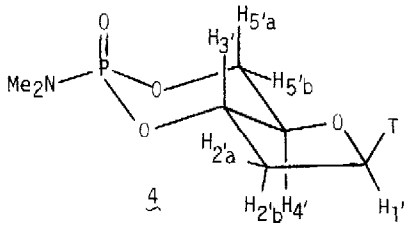
Trans phosphoramidate 3b (Me_2N and base ring trans, S configuration at P) was reported earlier and characterized by X-ray crystallography.[4] Preparation of the cis isomer, 3a, has now been accomplished by reaction of Me_2NCl with methyl phosphite 2, available[5] as an approximately 50/50 diastereomeric mixture from phosphoramidite 1. The overall yield of diastereomeric dimethylphosphoramidates by ^{31}P NMR was 90% based on phosphite 2. Isolation of the cis isomer, 3a, from a 71/29 trans/cis mixture of diastereomers was accomplished by medium-pressure liquid chromatography on SiO_2 with 92:8 $CHCl_3$/MeOH as eluant. Isomer 3a was readily characterized by comparison of its



T=thyminyl

^{13}C NMR spectrum to that of 3b[4,6] and by quantitative elemental analysis for C, H, and P. Starting with 1g of 2, 150 mg of 3a and 500 mg of 3b, diastereomerically pure, are isolated from one MPLC pass of crude product.

The proton couplingsfor the 1,3,2-dioxaphosphorinane ring of cis- and trans-3 are given in Table I. Spectra were recorded at 300 MHz and iteratively refined by LAOCN3 techniques. The 1,3,2-dioxaphosphorinane ring of the trans isomer, 3b, is readily assigned the chair conformation,



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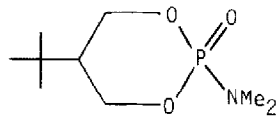

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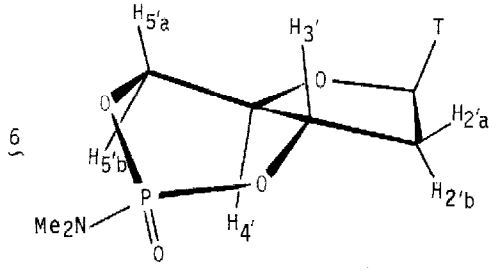
4, on the basis of the similarity of its J values to those for underivatized cyclic nucleotides, for instance 3',5'-cyclic thymidine,[7-9] cytidine,[7] and deoxyadenosine monophosphates,[7,10] which unquestionably possess chair-form phosphate rings. Most diagnostic is the large value (21.64 Hz) for $J_{H_{5'b}P}$ which is clearly indicative of the large (160-180°) $H_{5'b}COP$ dihedral angle. That trans-3 populates a chair conformation, structure 4, both in solution and in the crystal, is consistent with the relatively large size of the dimethylamino group and its consequent equatorial preference in 5 and related compounds.[11,12]

Table I. PMR Coupling Constants for 3a and 3b.

			J, Hz[d]									
Comp.[c]	Solvent	T, °C	2'a3'	2'b3'	3'4'	4'5'a	4'5'b	5'a5'b	3'P	4'P	5'aP	5'bP
3a	acetone-d_6	28	~9.1[b]	~9.1[b]	9.1	10.4	5.9	-9.2	~1.0[b]	-3.2	12.3	8.3
3a	toluene-d_8	26	8.2	9.8	9.1	10.1	6.0	-9.1	~0.2	-0.4	14.4	6.0
3b	acetone-d_6	28	8.4	10.31	9.3	10.8	4.8	-9.3	1.5	0.4	0.9	21.6

[a]At 300 MHz. LAOCN3-iterated except as noted. [b]Non-iterated value.
[c]Chemical shifts in ppm downfield from TMS. 3a (acetone-d_6): $H_{3'}$, 4.94; $H_{4'}$, 4.20; $H_{5'a}$, 4.31; $H_{5'b}$, 4.61. 3a (toluene-d_8): $H_{3'}$, 4.60; $H_{4'}$, 3.90; $H_{5'a}$, 4.11; $H_{5'b}$, 3.78. 3b (acetone-d_6): $H_{3'}$, 4.92; $H_{4'}$, 3.93; $H_{5'a}$, 4.48; $H_{5'b}$, 4.49. [d]Average errors about ±0.03Hz (cis), ±0.05 (trans).

By contrast, it is certain from the data of Table I that cis-3 is primarily in a non-chair conformation.[6] Dreiding models make it evident that because of the ring fusion, only one twist form, 6, should be energetically accessible. The skewing of the ring in 6 is such that the coupling $J_{5'aP}$ must be larger than $J_{5'bP}$ since, depending on the extent of twisting, dihedral angle $H_{5'a}COP$ in 6 could be as large as 180°, reducing that for $H_{5'b}COP$ to as low as 60°. At the



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same time, the angle $H_{5'a}CCH_{4'}$ remains of the order 160-180°. This situation leads to the combination of large coupling of $H_{5'a}$ to both phosphorus and $H_{4'}$ which is not possible in a chair form and is diagnostic of a twist conformation.[13] The couplings in acetone of $H_{3'}$ to $H_{4'}$ (9.10 Hz) and to phosphorus (~1 Hz) are quite consistent with structure 6 since the $C_{4'}C_{3'}OP$ side of the ring maintains the chairlike arrangement it would have in the true chair, e.g. 4.

The coupling $J_{5'bP}$(8.26 Hz) for 3a is anomalously high if one assumes that only conformation 6 is populated. Based on the Karplus curve of Kainosho[14] for such couplings in six-membered phosphate rings, the 12.3 Hz value for $J_{5'aP}$ corresponds to an approximate 140° HCOP dihedral angle for $H_{5'a}$. Thus, for $J_{5'b}$ the analogous angle is 100° for which a value of $J_{5'bP}$ of 1-2 Hz would be predicted.[9] Use of the 0.9 Hz and 21.6 Hz values of $J_{5'aP}$ and $J_{5'bP}$, respectively, found for 3b for the corresponding couplings of the cis-chair conformation of 3a along with assumed, reasonable values[15] of 19.0 and 0.5 Hz for these parameters for the same hydrogens in 6 allows time-averaged values for $J_{5'aP}$ and $J_{5'bP}$ to be calculated. J values within 0.1 Hz of the experimental ones of Table I result if the mole fraction of 6 is 0.64 in acetone and 0.75 in toluene.

The above suggests that: 1) the dimethylamino group of 3a is highly destabilizing in the axial position of the chair conformation; or 2) the chair to twist interconversion is accompanied by a relatively small increase in free energy easily overcome by even small 1,3-synaxial repulsions involving the dimethylamino group. The latter energy change has been estimated to be 1 kcal/mol or less in model ring systems such as cis-5.[11,16] The 60% estimated twist population for cis-5 emphasizes the similarities of these two ring systems.[10] (Cf. the 64-75% twist population for 6.) Thus, ΔG^{o} for the chair to twist interconversion of the phosphate ring of underivatized cyclic nucleotides (e.g. cAMP and cGMP) themselves may be relatively small, in which case there is no intrinsic energetic reason why they could not be bound in a receptor cite in a twist conformation. It must be emphasized that there is no evidence at present that this in fact occurs. The possible chemical advantages of such binding are not presently evident but may become so as the details of receptor-site structures are unraveled.

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