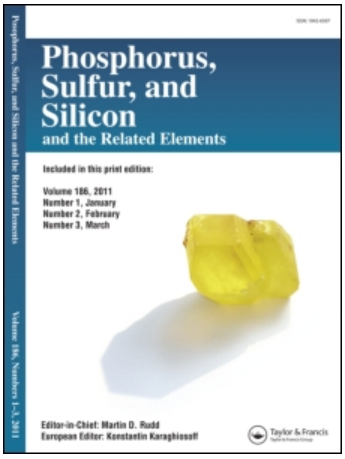

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Conformational studies of phosphorus-containing ring systems of pharmacological and biochemical importance-derivatives of cyclophosphamide and cyclic nucleotides

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CONFORMATIONAL STUDIES OF PHOSPHORUS-CONTAINING RING SYSTEMS OF PHARMACOLOGICAL AND BIOCHEMICAL IMPORTANCE--DERIVATIVES OF CYCLOPHOSPHAMIDE AND CYCLIC NUCLEOTIDES

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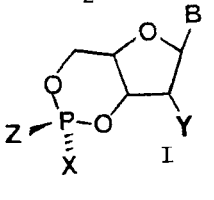
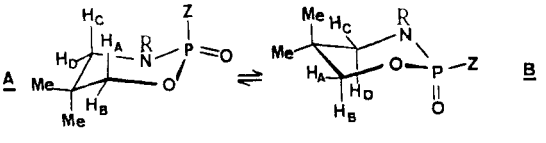
Abstract Results of a systematic study of the conformational features of the 1,3,2-oxazaphosphorinane ring system characteristic of the antitumor drug cyclophosphamide and its congeners are reported. Comparisons are made to the related 1,3,2-dioxaphosphorinane ring system of nucleoside cyclic 3',5'-monophosphates, e.g. cAMP and cTMP, and their neutral derivatives, I.

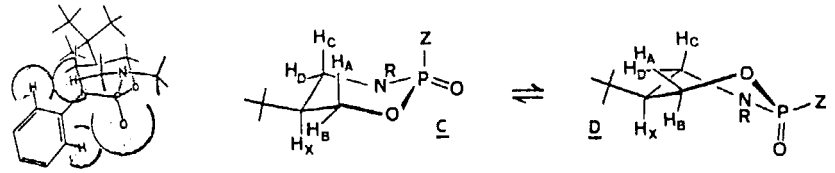
The equilibrium A ⇄ B (R = H) is found to be very sensitive to changes in the apparent effective steric size of Z for a series of dialkylamino substituents on phosphorus.[3,4] The population of A in C_6D_6 (parentheses) decreases in the order Me_2N (60%), Et_2N (40%) $(ClCH_2CH_2)_2N$ (30%), $isoPr_2N$ (12%). (Based on J_{AP}, J_{BP}, etc. and relative chemical shift changes for H_A, H_B, H_C, and H_D.) The axial preference of the Me_2N in solution and in the crystal (X-ray study)[5] is in surprising contrast to the corresponding 5,5-dimethyl-1,3,2-dioxaphosphorinane (Me_2N >90% equatorial)[6] and cTMP derivative (I, B = thyminyl, Y = H, Z = Me_2N, X = O, 50-75% twist populated[7]). The greater effective steric size of $isoPr_2N$ is confirmed by the shift in equilibrium C ⇄ D (R = H) from ca. 80% in favor of C with Z = Me_2N to an approximate 65% population of D for Z = $isoPr_2N$.[4]



I



The equilibrium C ⇌ D, as earlier reported[8], is strongly shifted to the right for Z = Me_2N on change of R from H to Ph ($\Delta\Delta G^0 \simeq 1.5$ kcal/mol). An effect of ca. the same magnitude has now been noted for A ⇌ B.[4] Its likely origin[8] (II) in destabilizing steric interactions between NR and $PNMe_2$ in A and C is supported by the strong shift towards D (>95%) of the equilibrium C ⇌ D in the case R = Ph, Z = mesityl compared to that for R = Z = Ph (60%).[9]

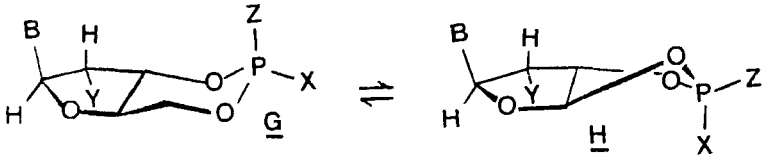
II 

Replacement of the t-butyl of the above system by phenyl fails to result in measurable population of the chair conformer with phenyl axial and Me_2N equatorial (X-ray and ^1H NMR).[10] This is likely a result of the very low free energy change (ΔG^0_{CT}) associated with the chair to twist interconversion E→F which can be estimated to be 0.5 to 1.0 kcal/mol.[4] This value is at least as low as that for the 1,3,2-dioxaphosphorinanes and is unusually small for a saturated six-membered ring.

These findings mean that cyclophosphamide itself can readily assume any of the conformations analogous to A, B(E) or F as might be required for its biological oxidative activation by the P450 enzyme system. The same can be said conformationally for the oxidation product, 4-hydroxycyclophosphamide, with regard to its breakdown to cytotoxic metabolites.

The chair-twist equilibrium available to I, which was earlier found[7] to be displaced 50-75% towards the twist form for the case B = thyminyl, Y = H, Z = Me_2N, X = O, favors the twist conforma-

tion (H) by only 0.5 kcal/mol less (DMSO) with the corresponding compound based on adenosine.[11] The 5-iodo- and 5-isopropyldeoxyuridine analogs of I with Z = $PhCH_2NH$ and X = O also populate twist forms[12] though to a lesser extent (∿33%, DMSO-d_6) than does the above Z = Me_2N case based on thymidine. Phosphites derived from thymidine (I, Z = lone pair; X = MeO, PhO) are 75%-95% in the twist conformation[13] with RO pseudoaxial, which demonstrates the energetic ease of the chair to twist interconversion in tervalent as well as pentavalent 1,3,2-dioxaphosphorinane rings trans-fused to a ribose or deoxyribose ring as in I. The potential biochemical significance is that the diesters, cyclic AMP and cyclic GMP, likely can be readily converted from the chair to the twist conformation on formation of enzyme-substrate complexes, although there is as yet no experimental evidence that this occurs.



Though structurally similar, the 1,3,2-oxaza- and 1,3,2-dioxaphosphorinane ring systems differ significantly in several respects. First, while ΔG^0_{CT} is very small for both systems, it may well be lower for the 1,3,2-oxazaphosphorinanes. Second, the 1,3,2-oxazaphosphorinane system is subject to apparent NR/PZ steric effects. Third, Me_2N and perhaps other substituents, have an effective steric size which is smaller in the 1,3,2-oxazaphosphorinane system. Finally, the 1,3,2-oxaza compounds undergo NH...O=P hydrogen bonding in the crystal[5] which if persistent in solution could influence conformational energies.

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