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^{31}P-^{15}N SPIN-SPIN COUPLING AS A PROBE FOR THE ASSIGNMENT OF ABSOLUTE CONFIGURATION IN R_P- AND S_P-THYMIDINE CYCLIC 3',5'-PHOSPHORDIMETHYLAMIDATES

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Abstract: The synthesis of both diastereomeric ^{15}N-labelled on the dimethylamino function thymidine 3',5' cyclic N,N-dimethylphosphoramidates is described. The applicability of $^{1}J_{^{31}P-^{15}N}$ to the configurational assignments at P-atom is demonstrated.

We previously reported that configurational assignments at the P-atom in the diastereomeric 2-X-2-Y-4-methyl-1,3,2-dioxaphosphorinanes (I, X≠Y) can be achieved by means of direct spin-spin coupling constants ($^{1}J_{P-X}$) between phosphorus and X, where X represents the magnetically active nuclei (spin quantum number = ½, X = ^{1}H, ^{13}C, ^{19}F and ^{77}Se)[1]. An axially oriented atom X possesses a lower absolute value of $^{1}J_{P-X}$ than that when X occupies an equatorial position in six membered dioxaphosphorinanyl chair-ring systems:

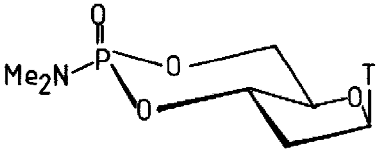
$$|^{1}J_{P-X}|_{ax} < |^{1}J_{P-X}|_{eq}$$

The spatial orientation of X in the pair of diastereomers of I (X=Se) was

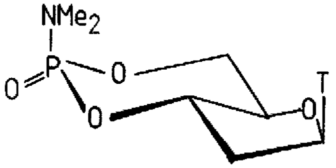
a I b

unambigously proved by means of X-ray analysis of two 2-t-butylamino-2-seleno-4-methyl-1,3,2-dioxaphosphorinanes[2b-c].

Only recently, it became apparent that the diastereoisomeric nucleoside 3',5'-cyclic phosphoranilidates are key intermediates in the synthesis of nucleoside 3',5'-cyclic phosphorothioates of biological interest[3]. Thus the possibility for the assignment of the absolute configuration at P-atom by analysis of spin-spin interactions between phosphorus-31 and nitrogen-15 of the amidate function contributes significantly to this area of research. We choose thymidine 3',5'-cyclic N,N-dimethylphosphoramidates II as the model system for investigating the dependence of the magnitude of $^{1}J_{^{31}P-^{15}N}$ on the spatial orientation of the exocyclic ^{15}N-bearing substituent on the phosphorus in diastereoisomeric 1,3,2-dioxaphosphorinanyl ring system. This was quite obviously the system of choice since the synthesis of IIa was already described[4a-b] and its structure recently proved by means of X-ray crystallography[5].



IIa (S_P)



IIb (R_P)

T-thymidin-1-yl

^{15}N-labelling of the dimethylamino function of both IIa and IIb was accomplished by reaction of the triethylammonium salt of thymidine 3',5'-cyclic phosphate (2.5 mmole) with ^{15}N-dimethylamine (25 mmole, 53% isotopic enrichment) in the presence of triphenylphosphine (7.5 mmole) and carbon tetrachloride (7.5 mmole). This Appel-type reaction[6] was carried out in dry pyridine as solvent at room temperature. Both IIa and IIb were present in the reaction mixture in the ratio of ca. 45:55. The products were isolated and separated by means of preparative tlc |IIa R_f 0.38; IIb R_f 0.32; silica gel GF_{254}; developing system: $CHCl_3$-MeOH (9:1)| in 71% yield. The spectral and physicochemical data of IIa and IIb are given in Table 1.

Comp.	UV[b)] λ_{max} nm	MS[c)] $M^{+\cdot}$ amu	^{31}P[d)] nmr	|α| in MeOH (c 0.4)		^{13}C nmr[e)] Carbon atoms no.					
				589 nm	435 nm	1'	2'	3'	4'	5'	$(CH_3)_2N$-
IIa[a)]	264 *10.4*	332 *1.47*	-7.53 *53*	-50.0	-86.6	85.4 *<1.5*	35.5 *7.4*	76.9 *4.4*	74.9 *4.4*	68.9 *7.4*	36.2 *4.4*[f)]
IIb	264 *8.5*	332 *6.05*	-6.91 *42*	-53.6	-98.3	86.7 *<1.5*	35.5 *7.4*	78.4 *4.4*	74.2 *11.8*	69.1 *8.8*	36.3 *2.9*[f)]

a) the easily crystallized diastereoizomer m.p. 220°; b) in MeOH, $E \times 10^{-2}$ values (in italics); c) intensity of molecular ion (in italics); d) in DMSO-d_6, δ values in ppm downfield from external 85% H_3PO_4, $|^1J_{^{31}P-^{15}N}|$ values in Hz (in italics), estimated error ±0.5 Hz; e) in pyridine-d_5, shift values in ppm downfield from internal TMS, $|J_{C-P}|$ values in Hz (in italics), estimated error ±1.5 Hz; f) J_{C-N-P} values.

Compound IIa was identical with that described *by Bajwa and Bentrude*[4b]. *Additionally* the following arguments support the assignment of trans- and cis-geometry for IIa and IIb respectively:

i) The isomer with equatorially oriented Me_2N group, as expected[7], absorbs at lower field in the ^{31}P nmr spectra than that with Me_2N substituent in the axial position.

ii) The coupling constant ($^3J_{P-C4'}$) of compound IIa is nearly the same as that reported by Bajwa and Bentrude (4.0 Hz). The coupling constant in IIb is substantially higher (11.8 Hz).

It is assumed that the 1,3,2-dioxaphosphorinanyl ring of IIb exists in the chair conformation. This assumption is based on the known facts that in nucleoside 3',5'-cyclic phosphates[8] and in phosphoranilidates[9] the dioxaphosphorinanyl part fused with ribose or deoxyribose moiety exists predominantly in the chair conformation. The assigned order of the $^1J_{^{31}P-^{15}N}$ values agrees with our empirical observations and demonstrates further the applicability of the direct spin-spin coupling criterion for configurational analysis about a P-atom incorporated in 1,3,2-dioxaphosphorinanyl ring systems. Therefore axially oriented $Me_2{}^{15}N$ has a lower absolute value of $^1J_{^{31}P-^{15}N}$ than that in equatorial disposition.

Other than conformational elucidation these observations also demonstrate the *differences between hybridization* of the nitrogen atoms depending upon their spatial orientation to the P-ring system. Equatorial nitrogen contains more

sp^2 character as reflected in the higher absolute $|^1J_{^{31}P-^{15}N}|$ value as compared to an axial nitrogen which has a lower absolute value of $|^1J_{^{31}P-^{15}N}|$ and therefore more sp^3 character.

This conclusion is fully consistent with our previously reported data[2a] demonstrating that in the pair of 2-t-butylamino-2-seleno-4-methyl-1,3,2-dioxaphosphorinanes the P-N bond in the isomer with the axial t-BuNH group is longer (1.665 and 1.648 A)[2c] as compared to the isomer where t-BuNH group occupies the equatorial position (1.619 A)[2b]. Further discussion of stereoelectronic effects in cyclic phosphoramidates and phosphoramidites will be published separately[10].

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10. In the case of diastereomeric 2-dimethylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes I (X=Me_2N-, Y=O) the isomer Ia possesses $^1J_{^{31}P-^{15}N}$=37.6 Hz (benzene) and IIb has $^1J_{^{31}P-^{15}N}$=54.7 Hz (benzene); R.W.Kinas and W.J.Stec - manuscript in preparation.

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