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NEW SILA-ANALOGUES OF CYCLIC NUCLEOTIDES, 3',5'-O-SILANEDIYL NUCLEOSIDES

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ABSTRACT: Treatment of nucleosides with di-tert-butyldichlorosilane in the presence of imidazole in DMF gave new sila-analogues of cyclic nucleotides which contain a rigid trans(1,2)-fused 6 to 5 membered ring system.

Silyl groups play important roles as protecting groups and become reactive sites in synthetic organic chemistry as well.[1] However, they have attracted little attention to their usefulness in the preparation of analogues (sila-analogue) of naturally occurring compounds.

We have recently reported[2] the synthesis of N-acylated deoxyribonucleosides by the use of bifunctional silanes such as dimethyldichlorosilane and methylphenyldichlorosilane: the treatment of a deoxyribonucleoside with 1.1 equiv of a dialkyldichlorosilane was effective for the protection of both hydroxyl groups in the sugar moiety against subsequent acylation, and the formation of hitherto unknown 3',5'-O-dialkylsilanediyl derivatives has been postulated.

This postulated compound contains a trans-fused 6 to 5 membered ring system similar to the one in the biologically important cyclic nucleotides. In cyclic nucleotides, the exocyclic phosphate ring makes the furanose ring comformationally restricted.[3] The rigid bicyclic structure of these compounds facilitates the conformational studies in solution and solid state. Furthermore, conversion of ribofuranosyl compounds to the corresponding cyclic 3',5'-monophosphates provides a useful means of determining the anomeric configuration by NMR spectroscopy.[4]

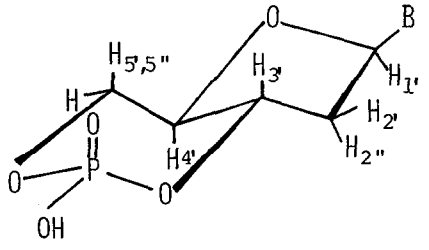
In the present study, the formation of stable cyclic silyl derivatives of thymidine and deoxyadenosine has been confirmed in the reaction with dichlorosilanes having large substituents such as tert-butyl group on the silicon atom. These cyclic compounds contain a conformationally rigid trans-fused ring system similar to the one in the cyclic nucleotides.

Thymidine (dT) in dry N,N-dimethylformamide was treated at 30°C with 1.1 equiv of di-tert-butyldichlorosilane in the presence of 4.4 equiv of imidazole. Analysis of the reaction mixture by TLC (silica-gel plates, Merck) in $CHCl_3$/MeOH (10:1,v/v) showed that the reaction proceeded slowly: after 16 h, nearly half of the starting material (dT) remained intact and two products increasing with the reaction time were detected (Rf=0.35 and 0.64).

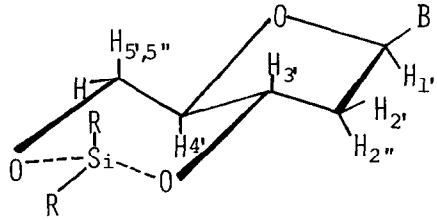
The compound with the smaller Rf value was proved to be a 5'-silylated thymidine by comparison with an authentic material.[5] After evaporating the solvent in vacuo, the other product was isolated by silica gel column chromatography using $CHCl_3$ as eluent and assigned as a 3',5'-cyclic silyl derivative by IR, NMR, and mass spectrometry. All the results obtained support this assignment. The infrared spectrum lacked the absorption due to OH-stretching vibrations, indicating the involvement of both hydroxyl groups in the formation of this derivative. The mass spectrum exhibited peaks corresponding to the molecular ion and the fragment ions arising from the loss of a tert-butyl group.

Fig.1 shows a 360 MHz proton magnetic resonance spectrum determined in $CDCl_3$. The proton NMR signals of the 2-deoxy-D-ribofuranosyl moiety were assigned by the two-dimensional J-correlation NMR technique and analyzed for NMR constants by computer simulation. One of the remarkable results obtained is the large discrepancy ($\Delta\delta$=0.43 ppm) between the chemical shifts of both protons on 5'-carbon, indicating the lack of free rotation due to its rigid structure. This phenomenon was also observed for 3',5'-cyclic deoxyribonucleotides ($\Delta\delta\simeq$0.16 ppm) but not for deoxyribonucleotides[6] and it can be accounted for as well by the rigid conformation of the exocyclic six-membered ring. Coupling constants are also useful criteria for structure determinations. Thus, the magnitude of the geminal coupling between the protons at the 5'-position is -9.5, -9.3 and -12.5 Hz for this product, thymidine cyclic 3',5'-(hydrogen phosphate),[7] and acyclic thymidine 5'-phosphate,[6] respectively. The similarity of the values of our product and the cyclic nucleotide suggests the existence of an analogous cyclic structure in the former. As seen in Table 1, the other coupling constants of the product agree very closely with those of cyclic nucleotides, indicating the restricted cyclic structure of 3',5'-O-(di-tert-butylsilanediyl)thymidine (DtBSdT). The isolated yield of DtBSdT was 42% after two days of reaction. When 2.2 equiv of di-tert-butyldichlorosilane and 8.8 equiv of imidazole were used, the yield was nearly doubled.

Similar treatment of thymidine with diisopropyldichlorosilane, tert-butylmethyldichlorosilane, and tert-butylphenyldichlorosilane gave the corresponding cyclic silyl derivatives in 76, 68 and 80% yield, respectively. Here, the reactions were completed in 30 minutes.



3',5'-cyclic deoxyribonucleotide



3',5'-O-silanediyl deoxyribonucleoside

B = thymin-1-yl (DtBSdT)

B = adenin-9-yl (DtBSdA)

Needless to say, these silanediyl groups are useful for the protection of hydroxyl groups.[2,8] Di-tert-butylsilanediyl derivative of thymidine was more stable in acidic conditions (80% AcOH) than the corresponding tetraisopropyldisiloxanediyl derivative[9] which contained a disiloxane group in the place of a silyl group, and the latter more stable than the diisopropylsilanediyl derivative.

Application of the above cyclization procedure to deoxyadenosine gave 3',5'-O-(di-tert-butylsilanediyl)deoxyadenosine (DtBSdA) in 46% yield. The proton NMR spectrum of DtBSdA was determined in $CDCl_3$ with Me_4Si as internal standard. The difference in the chemical shifts between the two protons at 5'-position was 0.40 ppm (chemical shifts: 4.041 and 4.439 ppm) and its geminal coupling constant of -9.4 Hz was in good agreement with -9.7 Hz for deoxyadenosine cyclic 3',5'-(hydrogen phosphate)[7] (-12.5 Hz for deoxyadenosine 5'-phosphate). The coupling constants are summarized in Table 1.

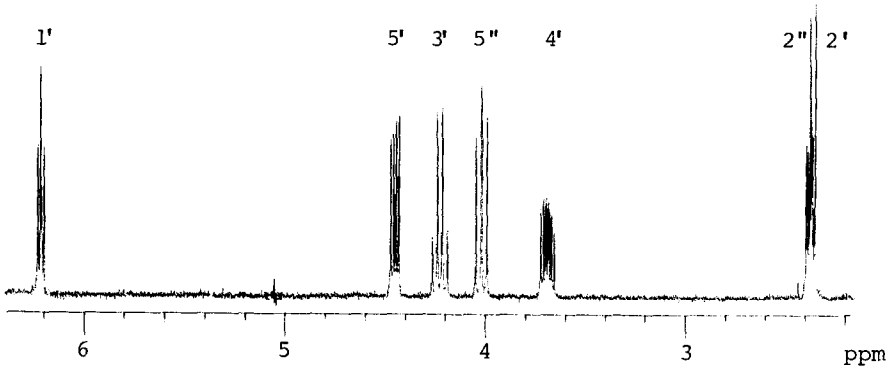


Fig.1 360 MHz proton NMR spectrum of DtBSdT in $CDCl_3$ at 30°C (2-deoxy-D-ribofuranosyl moiety).

Table 1. Proton spin-spin coupling constants of cyclic derivatives of deoxyribonucleosides*

	DtBSdT	cdTMP**	DtBSdA	cdAMP**	2'-D-cdAMP**
J(1',2')	2.2	2.4	1.6	–	1.4
J(1',2")	8.9	8.7	8.5	–	8.5
J(2',3')	7.7	7.8	7.3	–	–
J(2",3')	10.4	10.9	10.6	–	–
J(3',4')	8.9	9.6	9.0	9.4	–
J(4',5')	5.0	4.7	5.0	4.6	–
J(4',5")	10.3	10.7	10.4	10.7	–
J(2',2")	-13.6	-13.4	-13.1	–	–
J(5',5")	-9.5	-9.3	-9.4	-9.7	–

* Coupling constants in Hz.

** cdTMP= thymidine cyclic 3',5'-(hydrogen phosphate), (from ref. 7)
cdAMP= deoxyadenosine cyclic 3',5'-(hydrogen phosphate), (from ref. 7)
2'-D-cdAMP= ribo-2'-deuterio-2'-deoxyadenosine cyclic 3',5'-(hydrogen phosphate). (from ref.10)

The coupling values of the cyclic nucleotides in Table 1 are obtained in D_2O. The values of cyclic silanediyl derivatives are in good agreement with those of the corresponding cyclic nucleotides regardless of the solvent (the former/$CDCl_3$ and the latter/D_2O) and the substituents at C-1' (thymin-1-yl for DtBSdT and adenin-9-yl for DtBSdA) have little effect on the values. These facts support the conclusion that the 2-deoxy-D-ribofuranosyl moiety of these cyclic silyl compounds exists in exactly the same conformation as that of cyclic deoxyribonucleotides.

The ease of formation and the rigid ring system of 3',5'-O-silanediyl derivatives suggest that these bifunctional silyl groups will be useful not only as protecting groups but also in the preparation of conformational analogues of cyclic nucleotides.

X-ray crystallographic analysis of the cyclic silanediyl derivatives and the extended work to the case of ribonucleosides are currently in progress.

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