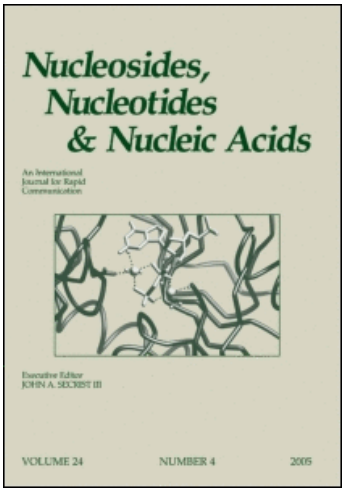

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9-(6-Deoxy- β -D-Allofuranosyl)Adenine Cyclic 3',5' -Phosphor-Amidate: A New Cyclic AMP Amide Derivative Containing an Equatorial Methyl Group at the 5'-Position

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9-(6-DEOXY-β-D-ALLOFURANOSYL)ADENINE CYCLIC 3',5'-PHOSPHORAMIDATE: A NEW CYCLIC AMP AMIDE DERIVATIVE CONTAINING AN EQUATORIAL METHYL GROUP AT THE 5'-POSITION

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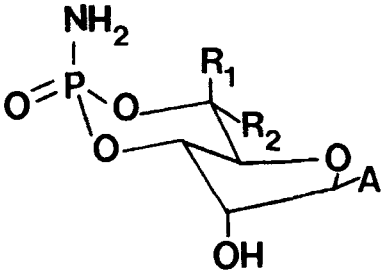
Abstract. R_P and S_P phosphorus diastereoisomers of the title compound (**2**) are prepared from the corresponding cyclic monophosphate. Solution conformation of the dioxaphosphorinane ring and hydrolysis of R_P-**2** and S_P-**2** are studied and compared with those of the phosphorus diastereoisomers of the isomeric compound that contains the 5'-methyl group in the axial position.

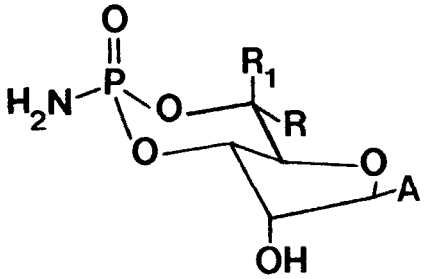
Phosphoramidate derivatives of adenosine cyclic 3',5'-monophosphate (cyclic AMP), a fundamental intracellular mediator and regulatory molecule of living systems, possess chiral phosphorus atom. Therefore, these compounds appear in the form of two phosphorus diastereoisomers, R_P and S_P. Biochemical studies on the separated diastereoisomers yielded valuable informations about the binding sites and the activation requirements of cyclic AMP metabolizing enzymes.[1,2] NMR investigations on the same diastereoisomers led to a better understanding of the chair⇌twist conformational equilibrium of the 1,3,2-dioxaphosphorinane ring in nucleoside cyclic 3',5'-monophosphates.[3-5]

Extensive studies on the phosphoramidate derivatives of cyclic AMP were performed in our laboratory in the past five years.[6] A part of these studies was directed to the preparation of new compounds that may be of chemical and/or bio-

chemical interest. Most recently, $\underline{R}_P$ and $\underline{S}_P$ diastereoisomers of 9(6-deoxy- α -L-talofuranosyl)adenine cyclic 3',5'-phosphoramidate (**1**), a sugar-modified cylic AMP-amide derivative that contains a methyl group in place of the axial 5'-hydrogen atom, have been described.[7] Solution conformation of the dioxaphosphorinane ring in $\underline{R}_P$-**1** and $\underline{S}_P$-**1** and acid hydrolysis of the diastereoisomers have also been investigated.



$\underline{R}_P$



$\underline{S}_P$

	$\underline{R}_1$	$\underline{R}_2$	$\underline{A}$
1	CH_3	H	adenin-9-yl
2	H	CH_3	adenin-9-yl

The substitution by a methyl group of the equatorial 5'-hydrogen atom of cyclic AMP-amide would result in the isomeric $\underline{R}_P$- and $\underline{S}_P$-9(6-deoxy- β -D-allofuranosyl)adenine cyclic 3',5'-phosphoramidate (**2**). Of the four compounds, $\underline{R}_P$-**1**, $\underline{S}_P$-**1**, $\underline{R}_P$-**2** and $\underline{S}_P$-**2**, the $\underline{R}_P$ and $\underline{S}_P$ pairs are phosphorus, while the **1** and **2** pairs are carbon diastereoisomers. Studies of these pairs of diastereoisomers offer the possibility of comparing the effect of the orientation (axial or equatorial) of both the amino and the 5'-methyl groups on the conformation and hydrolytic reactivity of cyclic AMP-amides. To perform these investigations of stereochemical interest, $\underline{R}_P$-**2** and $\underline{S}_P$-**2** have been prepared, the conformation of their dioxaphosphorinane ring in solution and their hydrolysis have been studied and compared with those of $\underline{R}_P$-**1** and $\underline{S}_P$-**1**. The results are presented in this paper.

RESULTS AND DISCUSSION

Synthesis and solution conformation of R_P- and S_P-9(6-deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-phosphoramidates (R_P-**2** and S_P-**2**)

The method described earlier for the preparation of R_P- and S_P-adenosine 3',5'-phosphoramidates[6b] as well as of R_P-**1** and S_P-**1**[7] was adapted to the synthesis of R_P-**2** and S_P-**2**. 9(6-Deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-monophosphate (**3**) was activated with $POCl_3$ in anhydrous trimethyl phosphate at 0°C. The reactive intermediate was treated *in situ* with a suspension of $(NH_4)_2CO_3$ in a mixture of DMF/pyridine (9:1) at 25°C. After two successive purifications on reversed phase MPLC and HPLC columns, R_P-**2** and S_P-**2** were obtained in yields of 6.3% and 22.5%, respectively. The structure of products was confirmed by ^1H, ^{13}C and ^{31}P NMR and mass spectrometry. Diastereoisomers R_P-**2** and S_P-**2** were distinguished by ^{31}P NMR. On the basis of literature data,[8] S_P-**2** (equatorial amino group) is expected to absorb at lower field. NMR data are collected in TABLE 1.

One chair and only one single twist conformation are energetically accessible for the dioxaphosphorinane ring of nucleoside cyclic 3',5'-monophosphates and their derivatives. This is a result of the transoid five-to-six-membered ring fusion.[3,5] Therefore, in solution the dioxaphosphorinane ring of the above mentioned compounds is an equilibrium mixture of chair and twist conformations. NMR data in TABLE 1 reveal that both for R_P-**2** and for S_P-**2** the equilibrium mixture is highly biased toward the chair form in DMSO-d_6 solution. On the contrary, approximate twist conformer populations of 65% and 15% were estimated for the dioxaphosphorinane ring of R_P-**1** and S_P-**1**, respectively, under the same conditions.[7]

In the chair-shaped dioxaphosphorinane ring of **2**, the conformation is gauche about the PO5'C5'H5' and the PO5'C5'C4' torsional angles, while it is trans about the PO5'C5'C6' angle. The small value for coupling ^3J(PH5') (1.4

TABLE 1. NMR spectral parameters[a] of R_P- and S_P-9(6-deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-phosphoramidates (2) and 9(6-deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-monophosphate (3)

Compound	R_P-2		S_P-2		3	
Site	(^{1}H)	(^{13}C)	(^{1}H)	(^{13}C)	(^{1}H)	(^{13}C)
2	8.169	152.82	8.191	152.84	8.276	150.70
4		148.69		148.68		148.38
5		118.86		119.01		118.99
6		156.02		156.04		154.43
8	8.299	139.67	8.374	140.12	8.471	140.74
6-NH_2	7.351		7.359		8.065	
1'	6.000	91.15	5.995	91.46	6.003	91.47
2'	4.676	71.46	4.700	71.47	4.661	71.50
3'	4.917	76.33	5.061	75.43	4.940	76.57
4'	3.793	76.51	3.732	76.68	3.771	76.90
5'	4.565	76.10	4.562	75.07	4.488	75.42
6'	1.323	19.49	1.321	19.56	1.310	19.41
2'-OH	6.220		6.220		b)	
P-NH_2	5.040		5.213			
^3J(1'2')	~0.5		~0.5		~0.5	
^3J(2'3')	5.1		5.3		5.25	
^3J(3'4')	9.8		9.8		9.9	
^3J(4'5')	9.5		9.8		9.5	
^3J(5'6')	6.1		6.1		6.1	
^3J(2'OH)	4.6		4.4		b)	
$\delta(^{31}P)$	7.40		11.34		-3.99	
^4J(PH2')	1.0		0.8		0.9	
^3J(PH3')	2.2		2.4		1.9	
^4J(PH4')	0.2		0.7		<0.1	
^3J(PH5')	1.4		1.2		1.2	
^4J(PH6')	1.8		1.6		1.95	
^2J(PNH)	6.0		7.3			
^3J(PC2')	8.5		8.8		8.5	
^2J(PC3')	5.2		4.1		4.7	
^3J(PC4')	5.1		3.4		3.8	
^2J(PC5')	8.3		6.4		7.5	
^3J(PC6')	7.6		8.3		8.5	

[a]Chemical shifts are in ppm relative to internal TMS for ^{1}H and ^{13}C resonances. External 85% H_3PO_4 was used for referencing of ^{31}P signals. Coupling constants are in Hz. Interproton couplings are based on first-order approximation. Phosphorus-proton couplings were inferred from 2D heteronuclear C-H chemical shift correlation experiments.For details see Ref. 7.

[b]These resonances are exchange-averaged in this sample.

Hz for $\underline{R_P}$-**2** and 1.2 Hz for $\underline{S_P}$-**2**) is indicative of a gauche arrangement of the phosphorus to the axial 5' proton about the O5'C5' bond.[9] Of vicinal carbon-phosphorus couplings, ^3J(PC6')(7.6 Hz for $\underline{R_P}$-**2** and 8.3 Hz for $\underline{S_P}$-**2**) is larger than ^3J(PC4')(5.1 Hz for $\underline{R_P}$-**2** and 3.4 Hz for $\underline{S_P}$-**2**) in the case of both diastereoisomers. Inspection of Dreiding models shows, that this relationship supports the existence of a trans POS'C5'C6' and a gauche POS'C5'C4' torsional angle. An increase in coupling ^3J(PC4') and a decrease of coupling ^3J(PC6') can be found in going from $\underline{S_P}$-**2** to $\underline{R_P}$-**2**. This trend corresponds to slight changes of the torsional angles from the gauche into the direction of the cis (for POS'C5'C4') and from the trans into the direction of the gauche conformation (for POS'C5'C6') and suggests somewhat higher populated chair conformation for the dioxaphosphorinane ring of $\underline{S_P}$-**2** than for that of $\underline{R_P}$-**2**. The slight depopulation of the chair conformation for $\underline{R_P}$-**2** may be caused by the 1,3-syn-axial steric repulsion between the amino group and the 5'(or 3')hydrogen atom.[3] The relatively large ^{31}P chemical shift difference between $\underline{S_P}$-**2** and $\underline{R_P}$-**2** (3.94 ppm) also indicates a conformational equilibrium biased highly toward the chair form, since the greater the shift difference the greater is the proportion of the chair conformer population in the equilibrium mixture of diastereoisomers.[10,11]

Hydrolysis of $\underline{R_P}$- and $\underline{S_P}$-9(6-deoxy-β-D-allofuranosyl)-adenine cyclic 3',5'-phosphoramidates ($\underline{R_P}$-**2** and $\underline{S_P}$-**2**)

Diastereomeric phosphoramidates $\underline{R_P}$-**2** and $\underline{S_P}$-**2** were hydrolyzed in 0.1 N hydrochloric acid and in 0.1 N sodium hydroxide at 37°C. Percentage bond breakings and approximate half-lives together with those of $\underline{R_P}$-**1** and $\underline{S_P}$-**1** are collected in TABLE 2.

As shown in TABLE 2, the two diastereomeric pairs of phosphoramidates **1** and **2** hydrolyze with dominant ester bond breakings both in acid and in alkali. A preferential fission of the P-O-C5' linkage occurs in **1**. On the contrary, the two ester bond breakings are commensurable for **2**. The degree of

TABLE 2.
Hydrolysis of $\underline{R}_P$ and $\underline{S}_P$ diastereoisomers of 9(6-deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-phosphoramidate (**2**) and of 9(6-deoxy-α-L-talofuranosyl)adenine cyclic 3',5'-phosphoramidate (**1**) in 0.1 N hydrochloric acid (H^+) and in 0.1 N sodium hydroxide (OH^-) at 37°C.

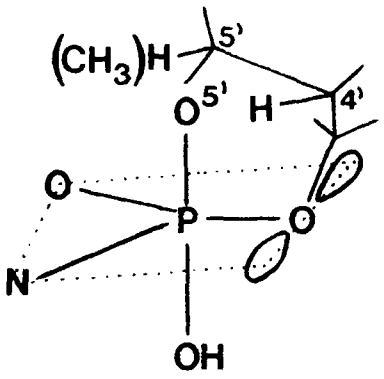
Compound		Bond breaking (%)			$t_{1/2}$ (min)
		P-N	P-O-C5'	P-O-C3'	
$\underline{R}_P$-**2**	H^+	4.6	53.6	41.8	149
	OH^-	-	66.3	33.7	0.04
$\underline{S}_P$-**2**	H^+	13.4	35.4	51.2	212
	OH^-	-	46.6	53.4	0.1
$\underline{R}_P$-**1**	H^+	15.5	78.5	6.0	41
	OH^-	-	80.7	19.3	0.04
$\underline{S}_P$-**1**	H^+	3.2	89.6	7.2	48
	OH^-	-	74.5	25.5	0.06

Data for $\underline{R}_P$-**1** and $\underline{S}_P$-**1** in acid are taken from Ref. 7, those in alkali are unpublished results of S. Bottka.

P-O-C3' bond breaking is always greater for a given $\underline{S}_P$ than for the respective $\underline{R}_P$ diastereoisomer. Fission of the P-N bond occurs in a small degree in acid.

For the interpretation of ester bond breakings we should recall that nucleophilic displacement at phosphorus

according to an $S_N2(P)$ mechanism proceeds via a trigonal bipyramidal transition state with apical attack of the entering group and apical departure of the leaving group.[12,13] On the basis of the lone pair orientation effect,[14] a boat-shaped dioxaphosphorinane ring occupying apical-equatorial situations of the trigonal bipyramid is expected to be the energetically most favorable transition state for the hydrolytic fission of the ester bonds in 1 and 2. Only an apical-equatorial boat dioxaphosphorinane ring provides for the lone pair on the equatorial sp^2 hybridized ring oxygen atom[15] to be in the favored equatorial plane.[16] Examination of Dreiding models shows that in the transition state of P-O-C5' bond breaking (4) the lone pair on the p_z orbital of the equatorial O3' atom is located in the equatorial plane. On the contrary, in the transition state of P-O-C3' bond breaking (5), the lone pair on the p_z orbital of the equatorial O5' atom is perpendicular to the equatorial plane. On this basis the preferential fission of the P-O-C5' linkage of 1 can be understood. The increased P-O-C3' bond breaking observed for 2 may be interpreted on steric grounds. Steric repulsion between the cis H4' and H5' protons of 1 acts against the lone pair orientation effect in the transition state. This steric effect should be greater for 2 than for 1, since 2 contains a methyl group of larger size instead of the H5' proton. Consequently, the transition state energy of P-O-C5' bond breaking should be larger for 2 than for 1. The greater P-O-C3'bond breaking observed for a given S_P diastereomer in comparison with the respective R_P diastereomer, may be interpreted similarly, by considering the steric repulsion between the cis-oriented substituents NH_2, H4' and H5' (for S_P-1) or NH_2, H4' and 5'CH_3 (for S_P-2). The effect is obviously greater for S_P-2 than for S_P-1. The result is a greater difference between S_P-2 and R_P-2, than between S_P-1 and R_P-1 in percentage P-O-C3' bond breaking.



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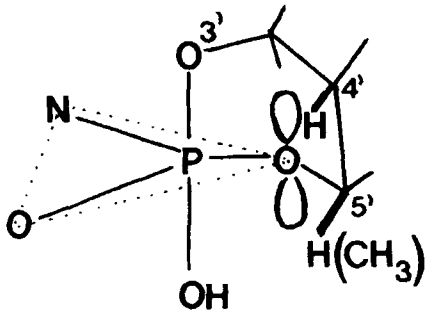

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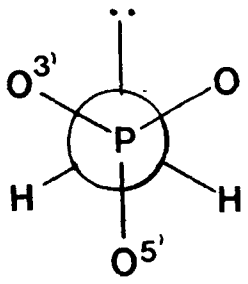
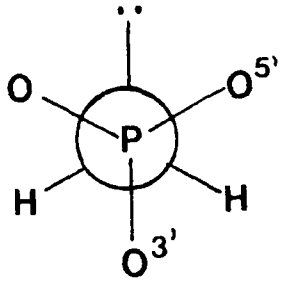
The unexpectedly[17,18] low degree of P-N bond breaking in the acid hydrolysis of 1 was interpreted in terms of ground state stereoelectronic effects due to the overlap between the lone pair of the amide nitrogen atom of pyramidal geometry and the σ^* antibonding orbital of one of the two P-O ester bonds.[6f,7] This orbital overlap requires the antiperiplanar orientation of the lone pair to the ester bond which can be attained in two of the three possible staggered conformations about the P-N bond (6 and 7). The



6



7

$n_N(--)\sigma^*_{PO}$ orbital mixing weakens the ester bonds and strengthens the P-N linkage in the stereoelectronically favored conformations 6 and 7 and may, thus, be responsible

for the observed low degree of P-N bond breaking and for the dominant cleavage of the ester bonds. The approximately fivefold P-N bond breaking found for $\underline{R_P}$-**1** compared to $\underline{S_P}$-**1** was explained by considering the 1,3-synaxial steric repulsion between the amino and the 5'-methyl groups and the H3' proton of the $\underline{R_P}$-**1** molecules with chair-shaped dioxaphosphorinane ring. This steric repulsion may increase the extent of P-N bond breaking by destabilizing the stereoelectronically favored conformations **6** and **7**. The reverse correlation observed for the diastereoisomers of **2** may be interpreted similarly, since the boat-shaped dioxaphosphorinane ring of $\underline{S_P}$-**2** molecules in the transition state possesses the same cis arrangement for the amino and the 5'-methyl groups and the H3' proton, as the chair-shaped dioxaphosphorinane ring of $\underline{R_P}$-**1** molecules have in the ground state.

EXPERIMENTAL

9(6-Deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-monophosphate (**3**) was prepared from adenosine *via* 2',3'-O-isopropylideneadenosine[19] and N^6-benzoyl-2',3'-O-isopropylideneadenosine[20] according to a literature procedure[21] and was characterized by NMR.

9-(6-Deoxy-β-D-allofuranosyl)adenine cyclic 3',5'-phosphoramidate diastereoisomers ($\underline{R_P}$-**2** and $\underline{S_P}$-**2**) were synthesized from tri-n-butylammonium salt of **3** (0.5 mmol)[6a] in exactly the same way as described for the preparation of $\underline{R_P}$-**1** and $\underline{S_P}$-**1**.[7] After MPLC purification on a LiChroprep RP-18 (25-40 μm, Merck) column (2.5x92.0 cm) in water/tetrahydrofuran (97.5:2.5, v/v) mixture (elution rate: 20.0 mL/4 min/fraction), the diastereoisomers appeared, partly resolved, in fractions 120-130 ($\underline{R_P}$-**2**) and 131-157 ($\underline{S_P}$-**2**). About 200-400 A_{260} units of these mixtures were further purified by semi-preparative HPLC on a LiChrosorb RP-18 (5 μm, Merck) column (250x10 mm I.D.) in the same eluent described above for MPLC. The diastereoisomers were isolated

as white solids by concentrating and freeze-drying the appropriate pooled fractions in total yields of 6.3% ($\underline{R_P}$-**2**) and 22.5% ($\underline{S_P}$-**2**) as determined by UV. For NMR parameters see TABLE 1. MS; m/z (relative abundance of $\underline{R_P}$-**2** and S_P-**2**, %): 343 (100 and 100) $(M+H)^+$, 263 (9.3 and 3.8) $(M-PO_2NH_2)^+$, 136 (82 and 79) $(B+2H)^+$, 107 (89 and 32) $NH_2PO(OCHCH_3)^+$.

NMR spectra were run with dilute (10-20 mg in 0.6 mL) DMSO-d_6 solutions at ambient temperature using a Varian Associates model XL-400 instrument. For details of NMR and MS studies see Ref. 7.

Hydrolysis studies were performed with 0.4 mM solutions of $\underline{R_P}$-**2** and $\underline{S_P}$-**2** in 0.1 N HCl for 2h or 72h and in 0.1 N NaOH (2.0 mL of each) for 15 min at 37°C. The acidic samples were neutralized with triethylamine. The alkaline hydrolysates were acidified by 0.2 N HCl (2.0 mL) and kept for 24h at 37°C, then neutralized with triethylamine. Aliquots of the hydrolysates were analyzed by HPLC on a Hypersil ODS (5 μm, Shandon) column (250x4 mm I.D.) in an acetonitrile/0.1 M aqueous triethylammonium acetate, pH 7.2 (6:94, v/v) mixture (elution rate: 2 mL/min). UV absorbing stable products of hydrolyis (**3** for P-N bond breaking, 9-(6-deoxy- β-D-allofuranosyl)adenine 5'-monophosphate (**8**) for P-O-C3' bond breaking and 9-(6-deoxy- β-D-allofuranosyl)adenine 2'(3')-monophosphate (**9**) for P-O-C5' bond breaking) were identified by establishing the appropriate peak intensities before and after successive addition of authentic samples to the hydrolysates. The primary products of ester bond breakings, 9(6-deoxy- β-D-allofuranosyl)adenine 5'-phosphoramidate and 9-(6-deoxy-β-D-allofuranosyl)adenine 3'-phosphoramidate were unstable in acid and converted to **8** and **9**, respectively, as expected on the basis of literature data.[17,18,22] Of the control compounds, **3** and **8** were prepared according to Ref. 21. Phosphate **9** was prepared by the barium hydroxide catalyzed hydrolysis of **3** followed by acid treatment.[23] Retention times (min) were: (1.6, adenine, 1.0% after 2 h, neglected for calculation), 1.9 (**8**), 4.2 (3'-phosphate) and 9.0 (2'-phosphate) (**9**), 13.0 (**3**), 16.0 (R_P-**2**) and 16.9 ($\underline{S_P}$-**2**). Ap-

proximate half-lives were calculated from the pseudo-first-order rate constants that had been obtained by measuring the decrease of the concentration of R_P-2 and S_P-2 at four different points of time close to the half-life. Alkaline hydrolysis of R_P-1 and S_P-1 was performed analogously, but for HPLC analyis, the system described for analyzing the acid hydrolysates of R_P-1 and S_P-1,[7] was used.

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