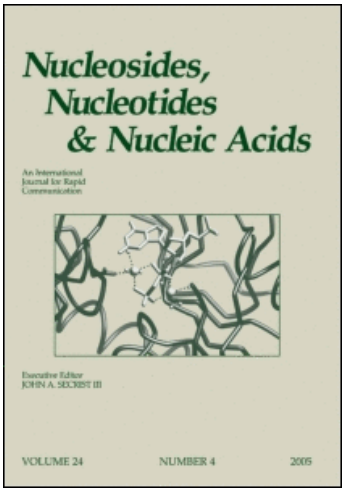

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EVIDENCE FOR THE STEREOELECTRONIC CONTROL OF THE ACID HYDROLYSIS OF ADENOSINE CYCLIC 3',5'-PHOSPHORAMIDATE DIASTEREOISOMERS

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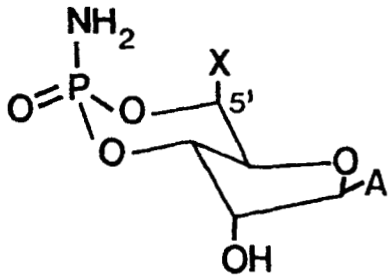
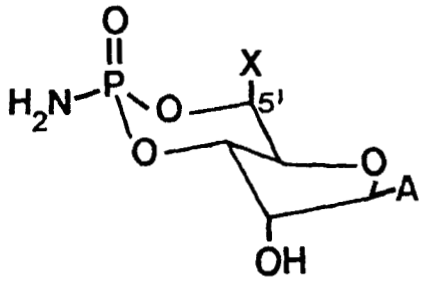
Abstract. The substitution by a methyl group of the axial 5'hydrogen atom of adenosine cyclic 3',5'-phosphoramidate diastereoisomers significantly increases the P-N bond breaking for the $\underline{R}_P$ diastereoisomer, but does not change that for the $\underline{S}_P$ diastereoisomer as anticipated on the basis of ground state stereoelectronic effects.

Recently, we reported the anomalous behavior in acid hydrolysis of adenosine cyclic 3',5'-phosphoramidate diastereoisomers derived from ammonia ($\underline{R}_P$-**1** and $\underline{S}_P$-**1**).[1] Contrary to the well-known sensitivity of P-N bonds towards acid,[2,3] $\underline{R}_P$-**1** and $\underline{S}_P$-**1** hydrolyzed with dominant ester bond breakings (91.4% for $\underline{R}_P$-**1** and 97.8% for $\underline{S}_P$-**1**), and the P-N bond breaking was unimportant (8.6% for $\underline{R}_P$-**1** and 3.2% for $\underline{S}_P$-**1**).[4]



R_P

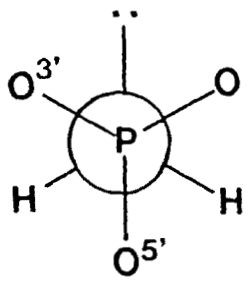


S_P

	X
1	H
6	CH_3

A = adenin-9-yl

The above results were interpreted[4] in terms of ground state stereoelectronic effects due to the overlap between the lone pair of the amide nitrogen atom of pyramidal geometry[5] and the σ^* antibonding orbital of one of the two P-O ester bonds. This n_N <--> σ^*_{PO} orbital mixing can be attained in two of the three possible staggered conformations about the P-N bond (2 and 3), in which the orientation of the lone pair on nitrogen is antiperiplanar to one of the two P-O ester bonds.



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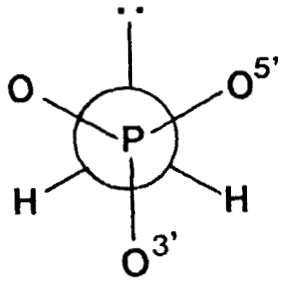

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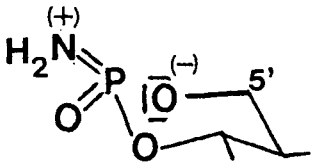
No-bond-double-bond resonance structures 4 and 5 evidently demonstrate the weakening of the P-O-ester bonds and the strengthening of the P-N linkage for conformations 2 and 3, respectively. Therefore, from these stereoelectronically



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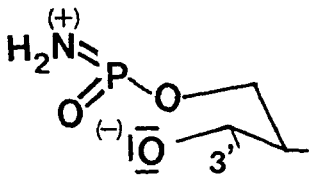


5

favored conformations, dominant ester bond breakings and unimportant P-N bond breaking can be expected. Dreiding molecular models show clearly that for $\underline{S_P}$-1, this stereoelectronic effect cannot be influenced by the conformation of the dioxaphosphorinane ring: it may equally be effective for rings of both chair and twist conformations.[6] The same is true also for $\underline{R_P}$-1 molecules with dioxaphosphorinane ring of twist conformation. On the other hand, for $\underline{R_P}$-1 molecules with chair-shaped dioxaphosphorinane ring, the 1,3-synaxial steric repulsion between the amino group and the 3'and/or 5' hydrogen atom may destabilize the stereoelectronically favored conformations 2 and 3 resulting in an increase of P-N bond breaking. The approximately threefold P-N bond breaking of $\underline{R_P}$-1 compared to $\underline{S_P}$-1 was interpreted on this basis.[4]

The synaxial steric repulsion could be increased further by substituting e.g. a methyl group for the axial 5' hydrogen atom. Therefore, an additional increase of P-N bond breaking in the acid hydrolysis of $\underline{R_P}$-9(6-deoxy- α -L-talofuranosyl)adenine cyclic 3',5'-phosphoramidate ($\underline{R_P}$-6) is expected, provided that, similarly to $\underline{R_P}$-1,[9] the dioxaphosphorinane ring of $\underline{R_P}$-6 is of chair conformation or a mixture of chair and twist conformations in solution. On the other hand, the above mentioned H→CH_3 substitution should have no effect on P-N bond breaking in the acid hydrolysis of $\underline{S_P}$-9(6-deoxy- α -L-talofuranosyl)adenine cyclic 3',5'-phosphoramidate ($\underline{S_P}$-6).

To test the validity of the outlined suggestion, $\underline{R_P}$-6 and $\underline{S_P}$-6 were prepared and the conformation of their dioxa-

phosphorinane ring in solution was determined. Acid hydrolysis of $\underline{R_P}$-6 and $\underline{S_P}$-6 was studied and compared with that of $\underline{R_P}$-1 and $\underline{S_P}$-1. The results are summarized in the present paper.

RESULTS AND DISCUSSION

Synthesis and solution conformation of $\underline{R_P}$- and $\underline{S_P}$-9(6-deoxy- α-L-talofuranosyl)adenine cyclic 3',5'-phosphoramidates ($\underline{R_P}$-6 and $\underline{S_P}$-6)

Diastereomeric phosphoramidates $\underline{R_P}$-6 and $\underline{S_P}$-6 were synthesized from 9(6-deoxy-α-L-talofuranosyl)adenine cyclic 3',5'-monophosphate (7) with $POCl_3$ in trimethyl phosphate at 0^oC followed by *in situ* treatment of the reactive intermediate with a suspension of $(NH_4)_2CO_3$ in a mixture of DMF/pyridine (9:1) at 25^oC exactly in the same way as described for the preparation of $\underline{R_P}$-1 and $\underline{S_P}$-1.[1] After two succesive purifications on reversed phase MPLC and HPLC columns, the compounds were obtained in yields of 8.9% ($\underline{R_P}$-6) and 24.0% ($\underline{S_P}$-6), respectively. The structure of compounds was verified by NMR and mass spectrometry. Diastereoisomers $\underline{R_P}$-6 and $\underline{S_P}$-6 were distinguished by ^{31}P NMR. On the basis of literature data,[10] $\underline{R_P}$-6 (axial amino group) is expected to absorb at higher field.

Solution conformation of the dioxaphosphorinane ring of $\underline{R_P}$-6 and $\underline{S_P}$-6 was determined by NMR. ^1H, ^{13}C and ^{31}P NMR data in DMSO-d_6 solution at ambient temperature are summarized in TABLE 1. Vicinal proton-phosphorus and carbon-phosphorus coupling constants, $^3J(PH5')$, $^3J(PC4')$ and $^3J(PC6')$ as well as the difference between the ^{31}P chemical shift values ($\Delta\delta^{31}P = \delta^{31}P(\underline{R_P}\text{-6}) - \delta^{31}P(\underline{S_P}\text{-6})$) indicate that $\underline{R_P}$-6 and $\underline{S_P}$-6 possess dioxaphosphorinane rings as equilibrium mixtures of chair (8) and twist (9) conformations. In the equilibrium mixture, the twist form dominates for $\underline{R_P}$-6, while $\underline{S_P}$-6 is highly biased toward the chair form.

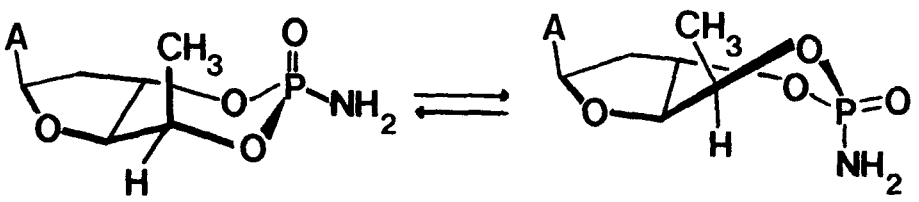
The values of 7.8 Hz (for $\underline{R_P}$-6) and 18.4 Hz (for $\underline{S_P}$-6) obtained for coupling $^3J(PH5')$ are less than expected for chair-shaped dioxaphosphorinane rings and larger than if

TABLE 1. NMR spectral parameters[a] of $\underline{R}_P$- and $\underline{S}_P$-9(6-deoxy-α-L-talofuranosyl)adenine cyclic 3',5'-phosphoramidates (6) and 9(6-deoxy-α-L-talofuranosyl)adenine cyclic 3',5'-monophosphate (7)

Compound	$\underline{R}_P$-6		$\underline{S}_P$-6		7	
Site	$\delta(^1H)$	$\delta(^{13}C)$	$\delta(^1H)$	$\delta(^{13}C)$	$\delta(^1H)$	$\delta(^{13}C)$
2	8.177	152.74	8.203	152.79	8.942	151.78
4		148.64		148.68		148.53
5		119.11		119.04		119.05
6		156.09		156.08		155.32
8	8.317	140.19	8.378	140.29	8.419	140.58
6-NH_2	7.384		7.389		7.792	
1'	5.995	91.63	5.994	91.51	5.997	91.51
2'	4.670	71.22	4.710	71.38	4.673	71.35
3'	5.246	72.41	5.390	70.59	5.337	71.76
4'	4.504	72.69	4.309	72.81	4.356	72.79
5'	4.875	73.52	4.815	74.07	4.848	74.23
6'	1.251	14.27	1.352	14.44	1.319	13.72
2'-OH	6.143		6.195		b)	
P-NH_2	4.980		5.060			
$^3J(1'2')$	∿0.5		∿0.5		∿0.5	
$^3J(2'3')$	5.5		5.5		5.5	
$^3J(3'4')$	10.2		10.2		10.2	
$^3J(4'5')$	6.4		6.0		6.0	
$^3J(5'6')$	6.7		6.8		6.8	
$^3J(2'OH)$	4.6		4.7		b)	
$\delta(^{31}P)$	8.56		9.16		-4.52	
$^4J(PH2')$	1.2		0.7		<0.3	
$^3J(PH3')$	1.0		2.7		2.0	
$^4J(PH4')$	0.7		0.6		0.6	
$^3J(PH5')$	7.8		18.4		17.7	
$^4J(PH6')$	<0.3		<0.3		<0.3	
$^2J(PNH)$	6.0		7.1			
$^3J(PC2')$	7.2		8.3		8.2	
$^2J(PC3')$	4.7		4.0		4.8	
$^3J(PC4')$	10.1		5.9		6.6	
$^2J(PC5')$	8.3		8.1		8.5	
$^3J(PC6')$	4.8		1.2		1.5	

[a]Chemical shifts are in ppm relative to internal TMS for ^1H and ^{13}C resonances. External 85% H_3PO_4 was used for the 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 EXPERIMENTAL).

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



8 9

only a twist conformation were populated.[11] Approximate mole fractions of the twist conformer populations of 0.65 (for $\underline{R_P}$-$\underline{6}$) and 0.15 (for $\underline{S_P}$-$\underline{6}$) were estimated by using $^3J(PH5')$ values of 21.6 Hz and 0.5 Hz as suggested by Bentrude for the chair and the twist conformations of thymidine cyclic 3',5'-dimethylphosphoramidate diastereoisomers.[7]

The increase of coupling $^3J(PC4')$ in going from $\underline{S_P}$-$\underline{6}$ ($^3J(PC4')$=5.9 Hz)) to $\underline{R_P}$-$\underline{6}$ (J(PC4')=10.1 Hz) corroborates an increase of twist conformer population.[11-14] Coupling $^3J(PC6')$ is expected to alter similarly, since the C6'C5'O5'P torsional angle changes from gauche into the direction of trans during a chair-to-twist transformation. The coupling $^3J(PC6')$ of $\underline{R_P}$-$\underline{6}$ (4.8 Hz) is, indeed, remarkably larger than that of $\underline{S_P}$-$\underline{6}$ (1.2 Hz).

The relatively small value of $\Delta\delta^{31}P$ = 0.60 ppm indicates a highly populated twist conformation for the dioxaphosphorinane ring of $\underline{R_P}$-$\underline{6}$, since the greater the $\Delta\delta^{31}P$ value the greater is the proportion of the chair conformation in the equilibrium mixture of diastereoisomers.[13,15] For thymidine cyclic 3',5'-N,N-dimethylphosphoramidate diastereoisomers a $\Delta\delta^{31}P$ value of 0.62 ppm,[12] and for the $\underline{R_P}$ diastereoisomer, a dioxaphosphorinane ring of about 65-75% in twist conformation were established.[7] On the other hand, $\Delta\delta^{31}P$ = 3.64 ppm was observed for adenosine cyclic 3',5'-phosphoramidate diastereoisomers having chair-shaped dioxaphosphorinane rings.[9]

The above results show that the substitution of a methyl group for the axial 5' hydrogen atom in adenosine cyclic 3',5'-monophosphate partly forces the chair-shaped dioxaphosphorinane ring[16,17] into the twist conformation. Methyl substituted cyclic phosphate 7 is about 18% in twist conformation (calculated from $^3J(PH5')$ = 17.7 Hz as above). The twist conformer population increases to about 65% for R_P-6 in which the amino group of larger size substitutes for the axial oxygen atom. In diastereoisomer S_P-6, in which the amino and the methyl substituents are located on the opposite side of the dioxaphosphorinane ring, the twist conformer population (about 15%) is practically the same as in 7 (about 18%).

On the basis of the above results a single flattened-chair at phosphorus, as an alternative conformation for the dioxaphosphorinane ring of S_P-6, cannot be unequivocally excluded, since $^3J(PH)$ couplings modestly depend on factors other than torsional angle.[18] In this case, an H5'C5'O5'P torsional angle of about 150° would correspond to the coupling of $^3J(PH5')$ = 18.4 Hz according to the Karplus type equation derived by Lee and Sarma for phosphates.[19]

Acid hydrolysis of R_P- and S_P-9(6-deoxy- α-L-talofuranosyl)adenine cyclic 3',5'-phosphoramidates (R_P-6 and S_P-6)

Diastereomeric phosphoramidates R_P-6 and S_P-6 were hydrolyzed in 0.1 N hydrochloric acid at 37°C. Percentage bond breakings and approximate half lives together with those of R_P-1 and S_P-1 are displayed in TABLE 2.

As shown in TABLE 2, the percent P-N bond breaking significantly increased for R_P-6, but did not change for S_P-6 in comparison with R_P-1 and S_P-1, respectively. These results are in good agreement with our suggestion that formed the basis of the present work and was described in the introduction. Accordingly, for R_P molecules having chair-shaped dioxaphosphorinane ring, the 1,3-synaxial steric repulsion between the amino group and the 5' hydrogen atom (for 1) or the 5' methyl group (for 6) depopulates the

TABLE 2.
Hydrolysis of $\underline{R}_P$ and $\underline{S}_P$ diastereoisomers of 9(6-deoxy- α -L-talofuranosyl)adenine cyclic phosphoramidate (6) and of adenosine cyclic 3',5'-phosphoramidate (1)[a] in 0.1N hydrochloric acid at 37°C.

Compound	Bond breaking (%)			$t_{1/2}$(min)
	P-N	P-O-C5'	P-O-C3'	
$\underline{R}_P$-6	15.5	78.5	6.0	41
$\underline{S}_P$-6	3.2	89.6	7.2	48
$\underline{R}_P$-1	8.6	80.8	10.6	27
$\underline{S}_P$-1	3.2	86.1	10.7	32

[a]Data for $\underline{R}_P$-1 and $\underline{S}_P$-1 are taken from Ref. 4

stereoelectronically favored conformations of ester bond breakings (2 and 3). This leads to a relative increase of P-N bond breaking, obviously to a greater extent for $\underline{R}_P$-6 than for $\underline{R}_P$-1. To compare the increments of P-N bond breaking, defined as (% P-N bond breaking of $\underline{R}_P$) - (% P-N bond breaking of $\underline{S}_P$), the chair conformer populations in $\underline{R}_P$-1 (about 90%[9]) and in $\underline{R}_P$-6 (about 35%) should be taken into account. In such a way, approximate values of 6% (for $\underline{R}_P$-1) and 35% (for $\underline{R}_P$-6) can be estimated for the proportion of the $\underline{R}_P$ molecules with chair-shaped dioxaphosphorinane ring that are decomposed with P-N bond breaking. This means that the substitution by a methyl group of the axial 5' hydrogen atom of $\underline{R}_P$ adenosine cyclic 3',5'-phosphoramidate molecules having chair-shaped dioxaphosphorinane ring, causes an about sixfold increase of P-N bond breaking in the acid hydrolysis.

The stability toward acid of 6 compared to 1 increased by a factor of about 1.5. The ratio of ester bond breakings P-O-C5'/P-C-3' increased by approximate factors of 1.5 (for

S_P-6) and 1.7 (for R_P-6). These findings may be due to intrinsic properties of the dioxaphosphorinane ring in 6 diastereoisomers and will be further studied.

The increase of P-N bond breaking for R_P-6 compared to R_P-1 and the constancy of the same bond breaking for S_P-1 and S_P-6 fit nicely with our suggestion[4] about the role of ground state stereoelectronic effects in the acid hydrolysis of R_P-1 and S_P-1 and may thus be regarded as indirect proofs for the stereoelectronic control of this hydrolysis.

EXPERIMENTAL

Synthesis

9(6-Deoxy- α-L-talofuranosyl)adenine cyclic 3',5'-monophosphate (7) was prepared from adenosine via 2',3'-O-isopropylideneadenosine[20] and N^6-benzoyl-2',3'-O-isopropylideneadenosine[21] according to a literature procedure[22] and was characterized by NMR (TABLE 1).

9(6-Deoxy- α-L-talofuranosyl)adenine cyclic 3',5'-phosphoramidate diastereoisomers (R_P-6 and S_P-6) were prepared from tri-n-butylammonium salt of 7 (0.5 mmol)[23] in exactly the same way as described[1] for the synthesis of adenosine cyclic 3',5'-phoshoramidate diastereoisomers (R_P-1 and S_P-1) by using a suspension of $(NH_4)_2CO_3$ (2 g) in a mixture of DMF/pyridine (9:1,v/v, 150 mL) for ammonolysis. The reaction mixture was purified by MPLC on a LiChroprep RP-18 (25-40 μm, Merck) column (2.5x92.0 cm) in water/tetrahydrofuran (97:7, v/v) mixture. (Elution rate: 20.0 mL/4 min/fraction.) Diastereoisomers appeared, partly resolved, in fractions 88-93 (R_P-6) and 94-110 (S_P-6) and were further purified by semi-preparative HPLC on a LiChrosorb RP-18 (5 μm, Merck) column (250x10 mm I.D.) in a water/tetrahydrofuran (97.5:2.5, v/v) mixture. About 200-400 A_{260} units of the diastereomeric mixture were separated in one run. After concentrating and freeze-drying the appropriate fractions, HPLC homogeneous diastereoisomers were isolated as white solids in yields of 8.9% (R_P-6) and 24.0% (S_P-6) as deter-

mined by UV. For NMR parameters see TABLE 1. MS; m/z (relative abundance of $\underline{R_P}$-6 and $\underline{S_P}$-6,%): 343 (86 and 88) $(M+H)^+$, 263 (8.5 and 7.3) $(M-PO_2NH_2)^+$, 136 (100 and 100) $(B+2H)^+$, 107 (95 and 73) $NH_2PO(OCHCH_3)^+$. The positive fast atom bombardment (+FAB) spectra were taken by using an MS-902 type mass spectrometer equipped with FAB ion source. Operating conditions were as follows: source temperature: 25°C, matrix: glycerol, gun: Ar, 8 keV.

NMR and conformation

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. Conventional (1D) spectra were recorded to obtain the values of ^1H (400 MHz), ^{13}C (100.6 MHz) and ^{31}P (162 MHz) chemical shifts and coupling constants J(HH), J(PH) and J(PC). The assignment of the closely spaced ^{13}C resonances to individual sites of the sugar moiety was conveniently inferred from two-dimensional (2D) carbon-proton chemical shift correlation experiments. Owing to J(PC) and/or J(PH) couplings, correlations involving phosphorus-coupled nucleus (nuclei) give rise to two cross-peaks in the correlation map: the distances measured along F1 and F2 between the two peaks afford the first-order values of J(PH) and J(PC), respectively. Run with high digital resolution, these experiments have provided straightforward means to obtain the accurate magnitude of some P-H couplings that appeared masked by unresolved long-range interproton couplings in the ^1H spectra. NMR data are summarized in TABLE 1.

Twist and chair conformer populations were calculated according to the following equations:

$$^3J(PH5')^{obs} = {}^3J(PH5')_{chair} \cdot n_c + {}^3J(PH5')_{twist} \cdot n_t$$

$$n_c + n_t = 1,$$

where n_c and n_t are the mole fractions of the chair and the twist conformations, respectively, $^3J(PH5')_{chair} = 21.6$ Hz and $^3J(PH5')_{twist} = 0.5$ Hz.[7]

Acid hydrolysis

Acid hydrolysis was performed with 0.4 mM solutions of R_P-6 or S_P-6 in 0.1 N HCl (2.0 mL) at 37°C for 2 h or 72 h. After neutralization with triethylamine, aliquots of the hydrolysates were analyzed by HPLC on a Hypersil ODS (5 μm, Shandon) column (250x4 mm I.D.) in a methanol/0.1 M aqueous triethylammonium acetate, pH 7.2 (1:9, v/v) mixture. (Elution rate: 2mL/min.) UV absorbing hydrolysis products (7 for P-N bond breaking, 9(6-deoxy-α-L-talofuranosyl)adenine 5'-monophosphate (10) for P-O-C3' bond breaking and 9(6-deoxy-α-L-talofuranosyl)adenine 2'(3')-monophosphate (11) for P-O-C5' bond breaking)[24] were identified by establishing the appropriate peak intensities before and after successive addition of authentic samples to the hydrolysates. Of the control compounds, 7 and 10 were synthesized according to Ref. 22. Phosphate 11 was prepared by the barium hydroxide catalyzed hydrolysis of 7 followed by acid treatment.[26] Retention times (min) were: 4.2 (adenine, 1.2% after 2 h, neglected for calculation), 5.5 (10), 8.3 (3'-phosphate) and 13.6 (2'-phosphate) (11), 16.3 (7), 19.1 (R_P-6) and 20.2 (S_P-6). Approximate half lives were determined on exactly the same way as in the case of R_P-1 and S_P-1.[4]

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