KINETICS AND MECHANISMS FOR THE ISOMERIZATION OF INTERNUCLEOSIDIC 3′-O-P-CH_2-5′ AND 3′-O-P-CH(OH)-5′ LINKAGES TO THEIR 2′,5′-COUNTERPARTS

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Dedicated to Professor Antonín Holý on the occasion of his 70th birthday.

Isomerization of internucleosidic 3′-O-P-CH_2-5′ and 3′-O-P-CH(OH)-5′ phosphonate linkages to their 2′,5′-counterparts has been studied over a wide pH-range. The model compounds employed are phosphonate analogs of adenylyl-(3′,5′)-adenosine and adenylyl-(2′,5′)-adenosine having either adenosine ((*R*,*S*)-**1**, (*R*,*S*)-**2**) or 5′-deoxyadenosine (**3**, **4**) bonded to the phosphorus atom through the C5′-atom. For comparative purposes, the hydrolytic stability of C5′-hydroxyphosphonate analogs derived from 2′-deoxyadenosine ((*R*,*S*)-**5**) has also been studied. In addition to the expected acid-catalyzed (pH < 3) and pH-independent reactions (pH 3–9), the diastereomeric C5′-hydroxyphosphonate analogs ((*R*,*S*)-**1**, (*R*,*S*)-**2**), but not their deoxy counterparts (**3**, **4**), have been observed to undergo a hydroxide-ion-catalyzed isomerization around pH 11 (90 °C). Evidently a hydrogen bond between the dianionic phosphorane and the C5′-hydroxy group stabilize the phosphorane to such an extent that isomerization via kinetically invisible protonation to monoanion becomes possible. The mechanisms of the isomerization reactions taking place under various conditions are discussed.

Keywords: Nucleosides; Nucleotides; RNA; Dinucleoside phosphonates; Phosphonate migration; Kinetics; Mechanisms; Hydrolysis; Isomerizations.

The phosphodiester bonds of RNA are hydrolyzed under physiological conditions at least 10^{10} times as fast as the corresponding linkages in DNA [1,2]. The reason for this enormous difference in hydrolytic stability is the extreme efficiency with which the neighboring 2′-hydroxy group attacks on the phosphorus atom. Species derived from solvent water have never been

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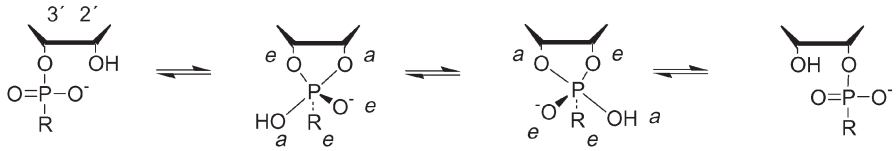
observed to compete with the 2′-hydroxy group as a nucleophile. The reaction may proceed spontaneously, but it is greatly accelerated by Brönsted acids and bases[3–8] and by metal ions[9–12]. The cleavage of RNA phosphodiester bonds accelerated by protein enzymes (ribonucleases)[13] or catalytic ribonucleic acids (so-called small ribozymes)[14] proceeds by a similar intramolecular nucleophilic attack of the 2′-hydroxy group on the phosphorus atom. Accordingly, the mechanistic details of this reaction are of considerable interest.

A possible way to stabilize oligoribonucleotides against enzymatic degradation is replacement of the 5′-linked oxygen with a carbon atom. Such phosphonate analogs have been hoped to find applications as antisense oligonucleotides in antiviral chemotherapy. Independently of their possible applications, the C5′-phosphonate analogs of diribonucleoside-(3′,5′)-monophosphates are useful model compounds for mechanistic studies. While the stable P–C5′ bond prevents the cleavage reaction, i.e. the departure of the 5′-linked nucleoside upon the attack of the 2′-hydroxy group on the phosphorus atom, it does not prevent the nucleophilic attack and, hence, formation of a pentacoordinated phosphorane intermediate. The intermediate obtained may collapse back to the starting material, but it can also undergo isomerization to a 2′,5′-bond via pseudorotation[15], as depicted in Scheme 1. This isomerization closely resembles the isomerization of RNA phosphodiester bonds that competes with the chain cleavage under acidic and neutral conditions[2]. With C5′-phosphonates, the catalysis of the isomerization reaction can be studied over a wide pH-range without any complications arising from concurrent cleavage.



SCHEME 1

We now report on kinetic studies with a set of phosphonate analogs (**1**–**4**) of adenylyl-(3′,5′)-adenosine and their 2′-deoxyadenosine counterparts (**5**) (Chart 1). Most of the compounds bear a hydroxy group on C5′ of the 5′-linked nucleoside (**1**, **2** and **5**). This is an interesting structural modification from the mechanistic point of view, since previous studies suggest that an appropriately situated hydroxy[16,17] or amino group[18] may as a hydrogen-

bond donor considerably stabilize the phosphorane intermediate. In particular, the effect on the stability of a dianionic phosphorane, known otherwise to be only marginally stable[4,19,20], is of interest.

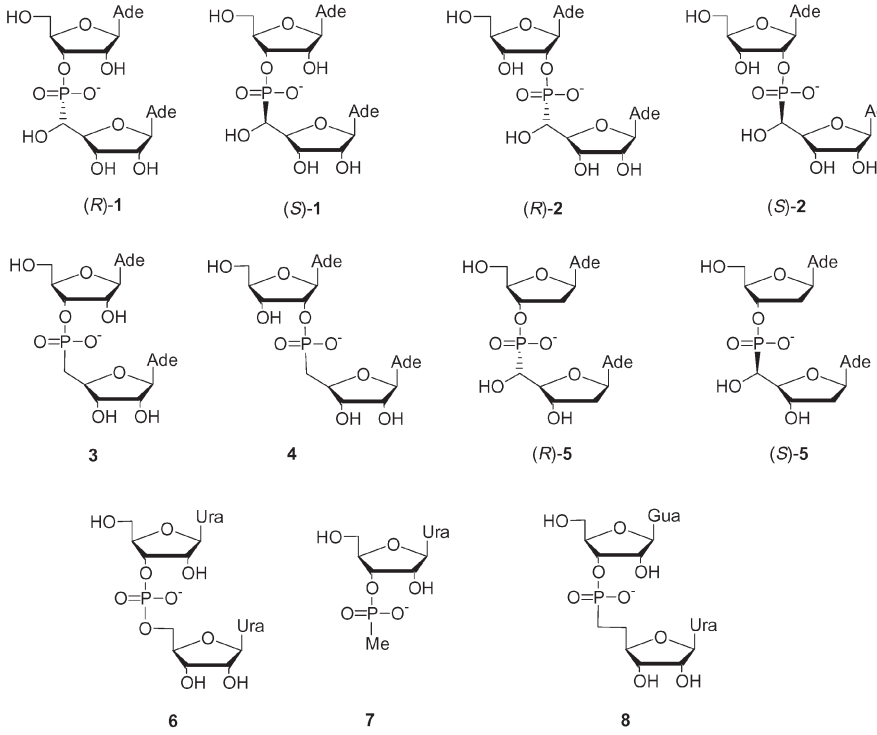


CHART 1
Structures of the compounds discussed

EXPERIMENTAL

Materials

Preparation of the dinucleoside C5′-phosphonates **1**–**5** used in the kinetic measurements will be described elsewhere[21].

Kinetic Measurements

Reactions were carried out in sealed tubes immersed in a thermostatted water bath, the temperature of which was adjusted to 90.0 ± 0.1 °C. The hydronium ion concentration in the reaction solutions was adjusted with nitric acid, sodium hydroxide and formate[22,23], acetate[23,24], MES [25], HEPES [25] and glycine[26] buffers. The pH values of the buffers were calcu-

lated from the literature data of the pK_a values of the buffer acids under the experimental conditions. The ionic strength of the solutions was adjusted to 1.0 mol l^{-1} with $NaNO_3$. The effect of buffer concentration on the reaction rate was determined at two different buffer concentrations. As no buffer catalysis was observed, a constant low buffer concentration of 0.05 mol l^{-1} was used for the rest of the runs.

The initial substrate concentration in the kinetic runs was ca. 10^{-4} mol l^{-1}. The composition of the samples withdrawn at appropriate time intervals was analyzed by HPLC on a Hypersil–Keystone Aquasil C18 column (4 × 150 mm, 5 μm) using 0.06 M acetic acid buffer (pH 4.3) containing 4–8% MeCN (v/v) as an eluent.

The pseudo-first-order rate constants for the mutual isomerization between the 2′- and 3′-isomers, viz. (*R*)-**1** and (*R*)-**2**, (*S*)-**1** and (*S*)-**2**, and **3** and **4**, were obtained by Eq. (*1*) applying a two-parameter (k_{obs} and x_{eq}) least-squares fitting to the time-dependent decrease in the concentration of the starting material. Here k_f and k_r denote the

$$k_{obs} = k_f + k_r = -\frac{1}{t} \ln \frac{1 - x_{eq}}{x_t - x_{eq}} \qquad (1)$$

the first-order rate constants of the forward and reverse reactions, respectively, and x_t and x_{eq} stand for the mole fraction of the starting material at time t and at equilibrium of the two isomers under consideration. The values for k_f and k_r were then calculated by Eqs (*2*) and (*3*).

$$k_f = (1 - x_{eq})\, k_{obs} \qquad (2)$$

$$k_r = x_{eq}\, k_{obs} \qquad (3)$$

The pseudo-first-order rate constants for the acid-catalyzed depurination of the starting material (pH < 4) and for the base-catalyzed degradation of either of the adenine moieties (pH > 10) were obtained by applying integrated first-order rate equation to the decrease in the sum concentration of the 2′,5′- and 3′,5′-isomers of the starting material.

RESULTS

The reactions of dinucleoside C5′-phosphonates **1**–**5** were followed by analyzing the composition of the aliquots withdrawn at suitable intervals from the reaction solution by reversed-phase HPLC. Around neutrality, the only reaction observed with the C5′-hydroxyphosphonate analogs, (*R*,*S*)-**1**, of adenylyl-3′,5′-adenosine (ApA) was migration of the phosphonate group between the 2′- and 3′-hydroxy functions, i.e. equilibration of (*R*)-**1** with (*R*)-**2** and (*S*)-**1** with (*S*)-**2**. Both diastereomers ((*R*)-**1** and (*S*)-**1**) reacted at equal rate. As seen from Table I and the pH-rate profile in Fig. 1, the interconversion is pH-independent at pH 3–9. At pH < 3, the isomerization turns acid-catalyzed and depurination of the starting material starts to compete with the isomerization. The rate constants indicated in Table I and Fig. 1 re-

TABLE I

Observed first-order rate constants for the mutual isomerization (k_f, k_r), depurination (k_{dp}) and adenine moiety degradation (k_{deg}) of the C5′-hydroxyphosphonate analogs of ApA (*R*,*S*)-**1** and (*R*,*S*)-**2**, and their unsubstituted counterparts **3** and **4** at 90.0 ± 0.1 °C (*I* = 1.0 mol l^{-1} with $NaNO_3$). k_f and k_r refer to 3′→2′ and 2′→3′ migration, respectively

Compd.	pH	k_f, 10^{-5} s^{-1}	k_r, 10^{-5} s^{-1}	k_f/k_r	k_{dp}, 10^{-5} s^{-1}	k_{deg}, 10^{-5} s^{-1}
(*R*)-**1**	0.01	2710	1840	1.47	420	
	0.96	124	105	1.18	82.2	
	1.16	58.9	50.6	1.16	73.3	
	1.40	21.6	27.2	0.79	49.9	
	1.96	6.48	4.89	1.33	13.4	
	3.00	2.76	2.35	1.17	1.2	
	4.50	1.77	1.74	1.02		
	6.00	1.84	1.68	1.10		
	7.00	1.85	1.67	1.11		
	8.00	1.56	1.55	1.01		
	9.00	1.73	1.76	0.98		
	10.42	5.05	4.49	1.12		0.786
	10.63	8.19	6.58	1.24		1.81
	10.82	12.4	9.13	1.36		2.65
	11.42	13.2	10.5	1.26		4.48
	12.42	13.6	10.1	1.35		34.9
(*S*)-**1**	1.96	6.38	6.92	0.92		
	5.00	2.26	2.08	1.09		
	10.42	5.71	4.49	1.27		
3	0.01	1790	1530	1.17	308	
	0.96	145	128	1.13	112	
	1.16	60.7	47.7	1.27	85.6	
	1.40	28.4	26.9	1.06	59.6	
	1.96	4.22	9.60	0.44	21.3	
	4.50	0.474	0.476	1.00		
	6.00	0.480	0.542	0.89		
	7.00	0.448	0.461	0.97		
	10.63	0.517	0.429	1.21		

fer to the cleavage of the first adenine base from the starting material. Around pH 11, a hydroxide-ion-catalyzed isomerization takes place over a narrow pH-range and at pH > 12, the reaction again turns pH-independent. Degradation of the adenine moieties starts to compete with the isomerization at pH > 10. This reaction is first-order in hydroxide ion concentration. Again the rate constants given in Table I refer to disappearance of the isomeric phosphonate dimers, i.e. modification of one of the adenine moieties. It is worth noting that hydroxide-ion-catalyzed isomerization of ribonucleoside 3′-phosphodiesters has not been reported.

In contrast to their C5′-hydroxyphosphonate counterparts ((*R*,*S*)-**1**; (*R*,*S*)-**2**), the C5′-unsubstituted phosphonate analogs of ApA (**3** and **4**) do not undergo a hydroxide-ion-catalyzed isomerization, but the reaction remains pH-independent at pH 4–11. In more alkaline solutions, degradation of the adenine moieties becomes so fast that the isomerization rate cannot be measured. The rate of the pH-independent interconversion of **3** and **4** is one fourth of the rate of the corresponding reaction of the C5′-hydroxyphosphonate analogs ((*R*,*S*)-**1**; (*R*,*S*)-**2**). The acid-catalyzed reactions, in turn, take place approximately as readily with phosphonate (**3** and **4**) as with hydroxyphosphonate ((*R*,*S*)-**1**; (*R*,*S*)-**2**) analogs. The C5′-hydroxyphosphon-

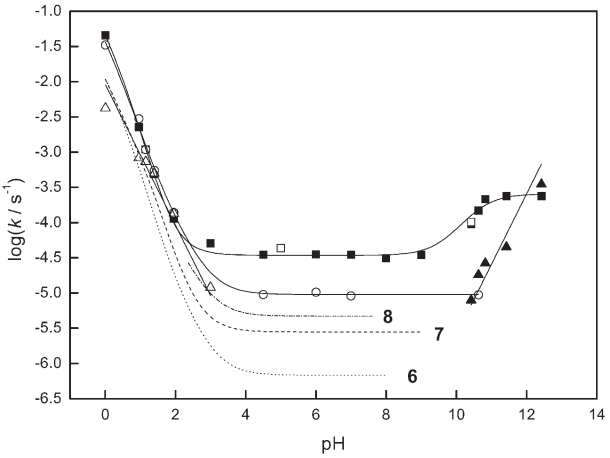


FIG. 1

pH-rate profiles for the mutual isomerization of C5′-hydroxyphosphonates (*R*)-**1** and (*R*)-**2** (■) and (*S*)-**1** and (*S*)-**2** (□), and their deoxy counterparts **3** and **4** (○). △ refer to depurination of (*R*)-**1** and (*R*)-**2** and ▲ to adenine moiety degradation of the same compounds. The data refer to 90 °C (I = 1.0 mol l^{-1} with $NaNO_3$). The dotted lines refer to isomerization of UpU (**6**)[2], uridine 3′-methylphosphonate (**7**)[28] and the phosphonate analog of GpU (**8**)[29] at 90 °C

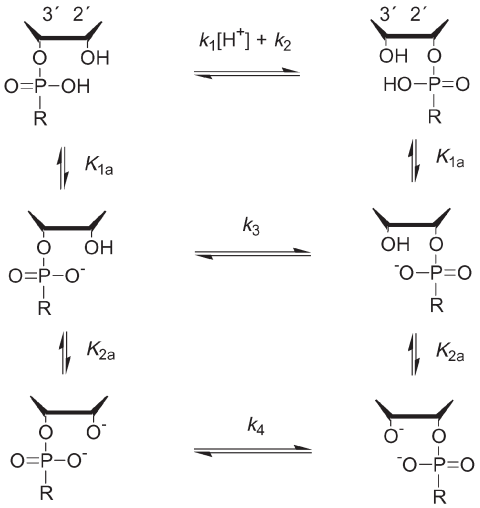
ates derived from 2′-deoxyadenosine (*S*,*R*)-**5** do not undergo any reaction besides degradation of the adenine moieties at pH > 9 and fast depurination at pH < 5.

As seen from Table I, the migration of the C5′-phosphonate group occurs at equal rate in both directions, i.e. from 3′- to 2′-oxygen atom and from 2′- to 3′-oxygen atom. All the rate constants listed can be taken as buffer-independent rate constants, since no buffer catalysis has been observed at the low buffer concentrations (0.05 mol l^{-1}) employed.

It has been previously shown that the pH-profiles for the acid-catalyzed cleavage and isomerization of dinucleoside-3′,5′-monophosphates[2] and simple ribonucleoside 3′-alkyl phosphates[27] exhibit, depending on pH, both the first- and second-order dependence of the rate on the hydroxonium ion concentration. A similar binomial dependence of the rate on acidity applies to fitting of the kinetic data for the acid-catalyzed reactions of the phosphonate analogs. Accordingly, the observed pseudo-first-order rate constant for the isomerization of unsubstituted C5′-phosphonates **3** and **4** can be expressed by Eq. (*4*) that takes into account reactions of substrate monocation, neutral form and monoanion. To fit the data obtained with the C5′-hydroxyphosphonates (*R*)-**1** and (*R*)-**2**, a kinetically significant dianionic form has additionally to be taken into account (Eq. (*5*)). In other words, the isomerization of the unsubstituted C5′-phosphonates **3** and **4** takes place via three and the isomerization of the C5′-hydroxyphosphonates (*R*,*S*)-**1** and (*R*,*S*)-**2** via four different ionic forms (Scheme 2). Table II records the pK_a values of various ionic forms (cf. Scheme 2) and the rate constants (k_f + k_r) for their isomerization.

$$k_{obs} = \frac{\frac{k_1}{K_{1a}}[H^+]^2 + \frac{k_2}{K_{1a}}[H^+] + k_3}{\frac{[H^+]}{K_{1a}} + 1} \qquad (4)$$

$$k_{obs} = \frac{\frac{k_1}{K_{1a}}[H^+]^2 + \frac{k_2}{K_{1a}}[H^+] + k_3 + \frac{k_4 K_W K_{2a}}{[H^+]}}{\frac{[H^+]}{K_{1a}} + 1 + \frac{K_{2a}}{[H^+]}} \qquad (5)$$



SCHEME 2

TABLE II
Acidity constants for various ionic forms of the C5′-phosphonate analogs of ApA **1**–**4** and rate constants for mutual isomerization of the 3′,5′- **1**, **3** and 2′,5′-isomers **2**, **4**[a]

	pK_{a1}	pK_{a2}	k_1, 10^{-2} M^{-1} s^{-1}	k_2, 10^{-4} s^{-1}	k_3, 10^{-5} s^{-1}	k_4, 10^{8} l mol^{-1} s^{-1}
(*R*)-**1** = (*R*)-**2**	0.5 ± 0.2	10.7 ± 0.2	6.2 ± 1.5	2.2 ± 1.6	3.4 ± 0.2	7.1 ± 0.8
3 = **4**	0.9 ± 0.4		4.0 ± 1.0	15 ± 2	0.95 ± 0.14	

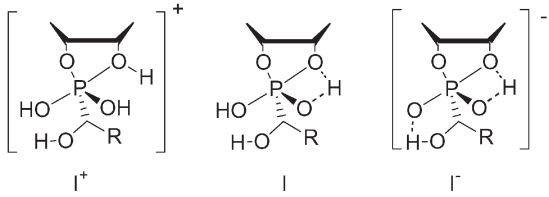
[a] At 90 °C, I = 1.0 mol l^{-1} with $NaNO_3$. The ionic product of water is 3.78×10^{-13} mol l^{-1} under the experimental conditions. The second-order rate constants for the oxonium-ion-catalyzed depurination and hydroxide-ion-catalyzed degradation of the adenine moieties are $(9.2 \pm 1.6) \times 10^{-3}$ and $(6.8 \pm 1.6) \times 10^{-4}$ l mol^{-1} s^{-1}, respectively.

DISCUSSION

Figure 1 shows, in addition to the pH-rate profiles obtained in the present work for the isomerization of the C5′-hydroxyphosphonate **1** and **2** and unsubstituted C5′-phosphonate analogs of ApA **3** and **4**, the rate profiles reported previously for the isomerization of uridylyl-3′,5′-uridine (UpU, **6**)[2], uridine 3′-methylphosphonate (**7**)[28] and the phosphonate analog of guanylyl-3′,5′-uridine (**8**)[29] having the 5′-oxygen atom replaced with a carbon atom. As seen, all the phosphonates are isomerized under neutral conditions faster than UpU and the C5′-hydroxyphosphonates **1** and **2** react faster than the other phosphonates (**3**, **4**, **7** and **8**) that do not bear a hy-

droxy function on the phosphorus-bound carbon atom. The reaction most likely proceeds as indicated in Scheme 1. Concerted proton transfer from the 2′-hydroxy group to the phosphoryl oxyanion and attack of the developing 2′-oxyanion on phosphorus give a phosphorane intermediate. The entering 2′-oxygen atom initially adopts an apical position forcing the 3′-oxygen atom into an equatorial position. Among the three other ligands, the C5′-atom and the oxyanion take an equatorial position and the hydroxy ligand an apical position. Proton transfer from the hydroxy ligand to the oxyanion may, however, take place and this allows pseudorotation, which transfers the 3′-oxygen to an apical position and, hence, results in isomerization. It is not clear which one of the steps is rate-limiting, formation/breakdown of the phosphorane intermediate or its pseudorotation. The faster isomerization of phosphonates compared to phosphates, however, makes the pseudorotation step an attractive candidate. With phosphonates, the 3′-oxygen ligand does not have to compete for an apical position with the 5′-ligand, since the C5′-atom is locked into an equatorial position. This may well enhance isomerization, assuming that the pseudorotation is at least partially rate-liming.

As mentioned above, the C5′-hydroxyphosphonate analogs of ApA **1** and **2** are isomerized even more readily than the other phosphonates **3**, **4**, **8** and **9**. We have shown previously that an appropriately situated hydroxy function may stabilize the phosphorane intermediate by donating a hydrogen bond to anionic oxygen in the phosphorane[16,17]. With C5′-hydroxyphosphonates, this kind of stabilization is possible by formation of a five-membered ring (I^- in Scheme 3).



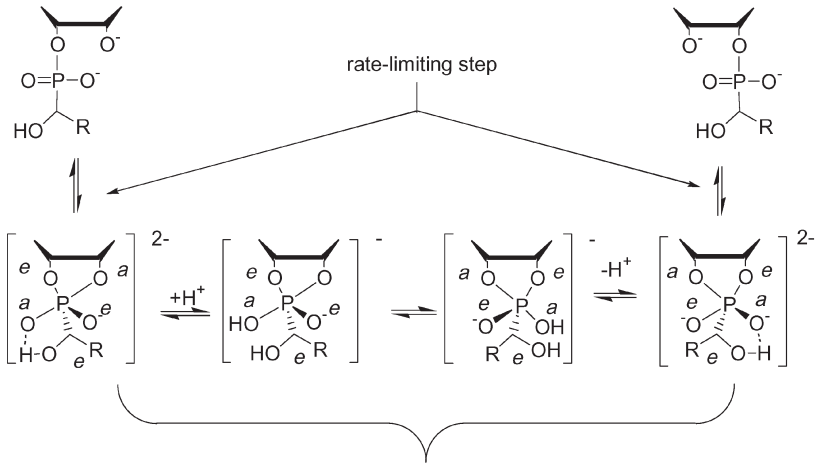
I^+ I I^-

SCHEME 3

The acid-catalyzed isomerization is in all likelihood mechanistically quite similar to the pH-independent reaction discussed above. Either the 2′-hydroxy group attacks on a fully protonated monocationic phosphonate diester linkage (I^+ in Scheme 3), or a neutral phosphonate diester linkage is attacked concerted with a proton transfer from the attacking 2′-hydroxy group to the developing phosphorane oxyanion (I in Scheme 3). Neither of

the phosphoranes obtained contain an anionic oxy ligand. Accordingly, stabilization of the phosphorane by intramolecular hydrogen-bonding of the C5′-hydroxy group does not play a role any more and, hence, C5′-hydroxyphosphonates and their unsubstituted counterparts are isomerized at equal rates in acid. It is also worth noting that the reactivity difference between phosphonates and phosphates is under acidic conditions much smaller than in neutral solutions. A possible explanation is that a more electrophilic compound is less basic and, hence, increased susceptibility to nucleophilic attack on phosphorus is partially cancelled by decreased amount of the protonated substrate.

Interestingly, C5′-hydroxyphosphonates **1** and **2** exhibit a hydroxide-ion-catalyzed isomerization around pH 11. This kind of reaction has not been observed with ribonucleoside 3′-phosphodiesters or 3′-phosphonate diesters. The hydroxide-ion-catalyzed reaction must proceed via a dianionic transition state, since the predominant ionic form of the starting material at pH < 10.5 (at 90 °C) is monoanion. Dianionic phosphorane has been argued to be only marginally stable[19,20] and it cannot undergo pseudorotation, since the two oxyanion ligands are locked to equatorial position. Evidently the C5′-hydroxy function is able, as a hydrogen-bond donor, to stabilize the dianionic phosphorane to such an extent that the phosphorane may undergo a thermodynamically favored protonation to a monoanion which is able to pseudorotate, in contrast to a dianionic phosphorane (Scheme 4). It should be noted that the second pK_a value of the



SCHEME 4

phosphorane probably is higher than 14 at room temperature[4,30,31]. Accordingly, protonation of the dianionic phosphorane is thermodynamically allowed under the conditions of the present study. If the pseudorotation is not rate-limiting, this protonation remains kinetically invisible, and hydroxide-ion-catalyzed isomerization is observed.

The pK_{2a} value of 3′,5′-UpU (**6**) has been reported to be 11.5 at 90 °C (I = 0.1 mol l^{-1})[2]. Application of Eq. (*5*) to the kinetic data obtained with (*R*)-**1** gives a pK_{2a} value of 10.7. Part of this difference may be accounted for by different base moiety structure: 3′,5′-ApA is at 60 °C by 0.3 logarithmic units more acidic than 3′,5′-UpU [2]. In addition, the high ionic strength used in the present work may well enhance the dissociation.

The mechanisms of the two side reactions observed, viz. depurination and degradation of the adenine moieties, are in all likelihood similar to those described previously for adenosine. Depurination proceeds by rapid initial protonation of one of the adenine bases to a N^1-protonated or N^1,N^7-diprotonated species, depending on pH [32,33]. The protonated base then undergoes a unimolecular departure, giving a ribosyl oxocarbenium ion, which is rapidly trapped by water. Under alkaline conditions, adenine bases are in all likelihood degraded along a multistage pathway that is initiated by an attack of hydroxide ion on the C8 atom[34]. This gives a 5-formamidopyrimidine intermediate, which undergoes two subsequent reactions: either deformylation to N^4-ribosyl-4,5,6-triaminopyrimidine or recyclization to N^6-ribosyladenine by an attack of the original 6-amino group on the formamido carbon. These intermediates finally yield 4,5,6-triaminopyrimidine and adenine as chromophoric products.

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