complexes in Pyrex tubes were degassed, sealed, and irradiated (48 h) with a Hanovia 450-W medium-pressure mercury arc lamp. To obtain an uniform exposure of light the sample tubes were rotated periodically.

The photoproducts were extracted with a chloroform–water mixture. The products were analyzed with a Chemito gas chromatograph fitted with either 5% or 10% SE-30 columns (adsorbed on chromosorb P 5 ft × $^1/_8$ in.) and characterized by their spectral properties. Among the photoproducts from **1–8**, acetophenone was a commonly available one, and the other product, the cyclobutanol, from **1**, **2**, and **6–8** has already been reported and has been characterized.[15] The IR and ^{1}H NMR spectra of the cyclobutanols derived from **1**, **2**, and **6–8** in this study match well with the reported values.[16] The photoproducts derived from **9–14** are substituted acetophenones and aryl-substituted cyclobutanols. The substituted acetophenones were identified by comparison with authentic samples obtained from Aldrich. The cyclobutanols derived from **9–14** were spectrally characterised after obtaining pure samples (as per GLC) via preparative photolysis followed by preparative TLC. The IR and ^{1}H NMR spectra of cyclobutanols derived from **5** and **9–14** are provided below.

1-Phenyl-2-decylcyclobutan-1-ol: IR (neat) (a) 3600–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) [cis] δ 0.86 (3 H, t), 1.00–1.40 (18 H, m), 1.62 (2 H, m), 2.00–2.28 (2 H, m), 2.65 (1 H, m), 7.20–7.50 (5 H, m), [trans] 0.87 (3 H, t), 1.20–1.25 (18 H, m), 1.85 (1 H, m), 1.97 (1 H, m), 2.17 (1 H, m), 2.40 (1 H, m), 2.63 (1 H, m), 7.15–7.50 (5 H, m).

1-(4-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3620–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (3 H, t), 1.09–1.32 (6 H, m), 2.01–2.23 (3 H, m), 2.35 (3 H, s), 2.60–2.69 (2 H, m), 7.26 (4 H, AB q).

1-(4-Methylphenyl)-2-hexylcyclobutan-1-ol: IR (neat) 3625–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (3 H, t), 1.09–1.40 (10 H, m), 2.01–2.23 (3 H, m), 2.35 (3 H, s), 2.60–2.70 (2 H, m), 7.26 (4 H, AB q).

1-(3-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3640–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, t), 1.35 (6 H, m), 1.60 (1 H, m), 2.20 (1 H, m), 2.40 (3 H, s), 2.53 (1 H, t), 2.85 (1 H, m), 3.27 (1 H, t), 7.20–7.91 (4 H, m).

1-(3-Methylphenyl)-2-nonylcyclobutan-1-ol: IR (neat) 3640–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, t), 1.35 (16 H, m), 1.60 (1 H, m), 2.20 (1 H, m), 2.40 (3 H, s), 2.52 (1 H, t), 2.85 (1 H, m), 3.25 (1 H, t), 7.20–7.90 (4 H, m).

1-(2-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3630–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.05–1.60 (6 H, m), 2.0–2.25 (3 H, m), 2.45 (3 H, s), 2.60–2.70 (2 H, m), 6.9–7.5 (4 H, m).

1-(2-Methylphenyl)-2-nonylcyclobutan-1-ol: IR (neat) 3630–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.05–1.60 (16 H, m), 2.0–2.28 (3 H, m), 2.45 (3 H, s), 2.60–2.75 (2 H, m), 6.9–7.50 (4 H, m).

Analytically pure samples (>98%) of cyclobutanols could not be obtained for elemental analysis.

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Effects of Cyclonucleoside Formation on the Rates of Glycosidic Hydrolyses in Purine Ribonucleosides

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Received March 2, 1987

Syntheses of several carbon-bridged purine cyclonucleosides are reported, along with kinetic data on their rates of glycosidic hydrolysis. We find that 5′,8-bridged nucleosides hydrolyze less than 10 times more slowly than analogous nucleoside models, but that the 3,5′-bridged adenosine hydrolyzes 29 000 times more slowly than does 3-methyladenosine at 25 °C in 0.1 N HCl. This surprising stability can be rationalized on the basis of (1) an electrostatic effect resulting from the presence of an ammonium group at the 5′-carbon and (2) the existence of a nonideal geometry for lone-pair stabilization of the transition structure. On the basis of these results, the previously reported slow rates of hydrolysis in 3,5′-cycloguanosine and 3,5′-cyclowyosine can be rationalized.

Glycosidic hydrolysis (glycolysis, depurination) of purine deoxyribonucleosides is a fundamental process in the chemistry of DNA both in vivo[1] and in vitro.[2-10] In vivo depurination of methylated nucleotides is accomplished with the DNA glycosylases, which are important in a major pathway by which damaged or misreplicated DNA is repaired.[11] We have recently proposed a mechanism for glycosylase enzymes that involves the repulsion of lone-pair electrons on the substrate and the enzyme.[12a] In order to test our hypothesis under conditions that model the enzymatic reaction as we suggest, we have looked first to glycolysis in cycloribonucleosides. The use of *ribo*nucleosides allows us to take advantage of the vicinal diol group for the positioning of catalytic groups;[12b] mechanistically, acid-catalyzed ribonucleoside hydrolysis (Scheme I)[13] is identical with that of deoxyribonucleoside hydrolysis, albeit slower. The rationale for the use of *cyclo*ribonucleosides is shown in Scheme II. While adenosine (or guanosine) can relieve a potential electrostatic repulsion via a ribose "envelope inversion" (**1a** → **1b**), the corresponding cyclonucleoside (**2**) cannot. This, coupled with the fact that forming a ring between C-8 and C-5′ does not introduce a large electronic perturbation of the sugar or base rings, makes cyclonucleosides appropriate models for

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(2) Brown, D. M. In *Basic Principles in Nucleic Acid Chemistry*; Ts'o, P. O. P., Ed.; Academic Press: New York, 1974; Vol. II, Chapter 1.
(3) Walker, R. T. *Annu. Rep. Chem. Soc.* **1972**, *69B*, 531.
(4) Romero, R.; Stein, R.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 7620.
(5) Garrett, E. R.; Mehta, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 8532.
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(7) Cordes, E. H.; Bull, H. G. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 429–465 (especially pp 456–458).
(8) Zoltewicz, J. A.; Clark, D. F. *J. Org. Chem.* **1972**, *37*, 1193.
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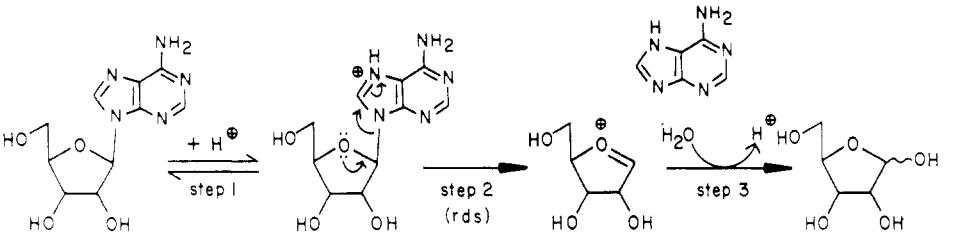
(11) For a recent review, see: Pegg, A. E.; Bennett, R. A. In *Enzymes of Nucleic Acid Synthesis and Modification*; Jacob, S. T., Ed.; CRC Press: Boca Raton, FL, 1983; Vol. I, Chapter 6.

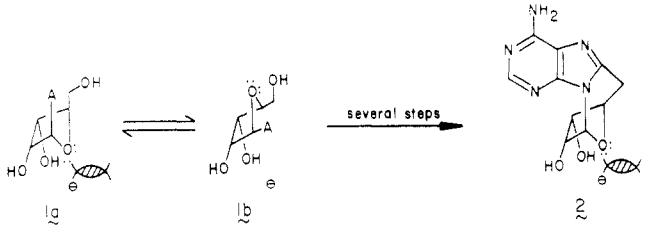
(12) (a) 191st Meeting of the American Chemical Society, New York, April 13–18, 1986, abstract 200 (organic division); *Tetrahedron Lett.*, in press. (b) Bakthavachalam, V.; Lin, L.-G.; Cherian, X. M.; Czarnik, A. W. *Carbohydr. Res.*, in press.
(13) Although the first site of protonation in adenosine is N^1, N^1-methyladenosine does not hydrolyze much faster than does adenosine itself (cf. ref 44). The site of protonation that leads to productive glycosidic cleavage is not known; we have arbitrarity depicted hydrolysis via N7 protonation in Scheme I.

0022-3263/87/1952-3113$01.50/0

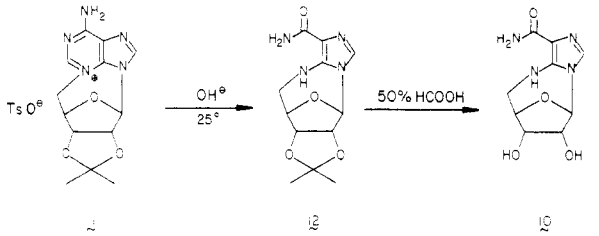
Scheme I



Scheme II



Scheme III

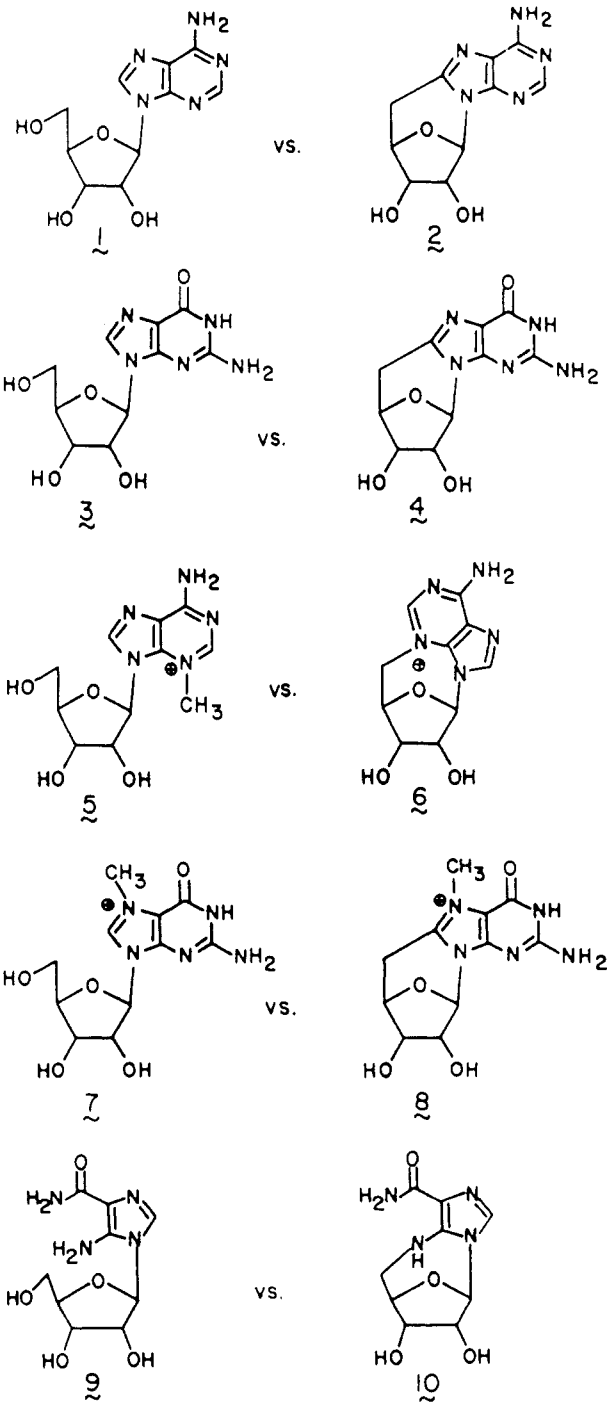


"rigid" enzyme-bound nucleosides. While kinetic studies on the hydrolysis rates of both neutral and alkylated nucleosides have been reported,[5,14-19] much less work has been done using cyclonucleosides. Several studies have subjected cyclonucleosides (or their protected derivatives) to acidic conditions and have identified the products as resulting from glycosidic bond cleavage.[20-22,50] Prior to our enzyme modelling work, we have had to answer some fundamental questions concerning cyclonucleoside hydrolysis that have not been addressed in the literature to date. We can now report, based on careful kinetic and product analysis studies, that most cyclonucleosides do undergo glycosidic hydrolysis; however, the predicted loss of ring strain in the hydrolysis does not increase the rate of this process, as might have been expected. Furthermore, cyclization of the 5′-position onto the adenosine N-3 nitrogen results in a decrease in its rate of hydrolysis by a factor of 29 000 at 25 °C.

Synthetic Methods

For this work, we required cyclonucleosides **2**, **4**, **6**, **8**, and **10** in addition to the noncyclic, naturally occurring nucleosides (**1**, **3**, **5**, **7**, and **9**) to which they have been compared (Chart I). Adenosine (**1**), guanosine (**3**), AICAR (**9**), and 5′-amino-5′-deoxyadenosine, *p*-toluenesulfonic acid salt (**13**) were available commercially.[23] Both 5′,8-cycloadenosine **2** and 5′,8-cycloguanosine **4** (as its isopropylidene derivative) were prepared by using literature procedures[24,25]

Chart I



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(22) Ikehara, M.; Kaneko, M. *J. Am. Chem. Soc.* **1968**, *90*, 497.

(23) Purchased from Sigma Chemical Company, St. Louis, MO.

Table I. First-Order Rate Constants for Glycosidic Hydrolysis in Selected Nucleosides and Corresponding Cyclonucleosides[a]

compd	reactn condtns	$10^5 k_1$ (s^{-1})	$t_{1/2}$ (min)
1	0.1 N HCl, 99 °C	164.5	7.02
1	0.1 N HCl, 89.5 °C	51.1	22.6
2	0.1 N HCl, 89.5 °C	8.3	139
3	0.1 N HCl, 77 °C	14.3	80.8
3	0.1 N HCl, 87 °C	39.9	28.9
4	0.1 N HCl, 87 °C	13.2	87.7
5	0.1 N HCl, 25 °C	66.7[b]	17.2
6	0.1 N HCl, 25 °C	0.0023[c]	50200
6	0.1 N HCl, 75.5 °C	2.21	523
6	0.1 N HCl, 80 °C	4.05	285
6	0.1 N HCl, 87 °C	8.99	128
6	0.1 N HCl, 91.5 °C	14.2	81.3
6	0.1 N HCl, 95.5 °C	19.9	58.0
7	pH 5, 87 °C	9.42	123
	0.1 N HCl, 88 °C	60.7	19.0
8	pH 5, 87 °C	*d*	*d*
8	0.1 N HCl, 86 °C	6.69	173
9	0.1 N HCl, 89.5 °C	4.73	244
10	0.1 N HCl, 88 °C	*e*	*e*
13	0.1 N HCl, 88 °C	0.714	1620

[a] All reactions were followed by HPLC using the conditions described in the Experimental Section. [b] Rate constant taken from the literature (ref 13–15 and 44). [c] Calculated value based on the activation parameters reported in the text. [d] The rate of glycosidic hydrolysis in compound 8 is sufficiently slowed at pH 5 that ring-opening becomes the predominant reaction. [e] The rate of glycosidic hydrolysis in compound 10 is sufficiently slowed at pH 1 that several side reactions become predominant.

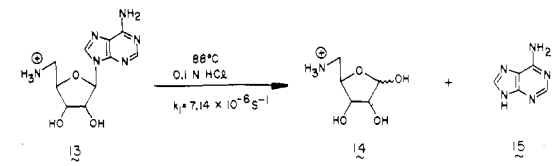
based on the cyclization of a carbon radical at the 5′-position. 3-Methyladenosine (**5**)[16] and 7-methylguanosine (**7**)[26] have been prepared previously. The heretofore unknown N^3,5′-cycloadenosine salt **6** was obtained by partial hydrolysis of the known isopropylidene derivative,[27] and 7-methyl-5′,8-cycloguanosine (**8**) was prepared by methylation of compound **4** with methyl *p*-toluenesulfonate. The cyclic AICAR derivative **10** was also an unknown compound, although the preparation and characterization of isopropylidene derivative **12** has been reported.[28] We have prepared cyclonucleoside **10** by an analogous base-catalyzed ring opening of cycloadenosine salt **11**, followed by acid-catalyzed removal of the isopropylidene group (Scheme III).

Results

While depurination reactions have been followed using a variety of methods, we monitored these glycolyses conveniently using HPLC[29] and an internal standard for reference. The results of our kinetic studies are summarized in Table I. In every case we have examined, the cyclonucleoside hydrolyzes more slowly than does its corresponding noncyclic counterpart, but the relative differrence depends strikingly on the specific type of cyclization. For example, forming a bridge between the ribose 5′-carbon and C-8 of the base seems to have a relatively small effect. At pH 1 and 88 ± 2 °C cycloadenosine **2** hydrolyzes about 6 times more slowly than does adenosine (**1**), cycloguanosine **4** hydrolyzes 3 times more slowly than does guanosine (**3**), and 7-methylcycloguanosine **8** hydrolyses 9 times more slowly than does 7-methylguanosine (**7**) itself. In each of these cases, the difference in hydrolysis rates is less than an order of magnitude.

Alternatively, forming a bridge between the ribose 5′-carbon and N-3 of the base slows the rate of depurination by an enormous amount. Cycloadenosine salt **6** hydrolyzes more slowly at pH 1 *and reflux* than does the analogous 3-methyladenosine (**5**) at room temperature! By carrying out the hydrolysis of compound **6** at a variety of temperatures, we calculated the activation parameters for this reaction to be $\Delta H^{\ddagger} = 27.4 \pm 0.9$ kcal/mol and $\Delta S^{\ddagger} = -1.4 \pm 2.6$ eu. An extrapolation of 25 °C then yields a rate constant of 2.3×10^{-8} s^{-1} for the hydrolysis of **6** at pH 1, which is 29 000 times slower than that of 3-methyladenosine under the same conditions. A similar comparison between AICAR (**9**) and the cycloAICAR **10** unfortunately fails, because glycosidic hydrolysis in compound **10** becomes so slow that reactions other than glycolysis predominate.

Scheme IV



13 **14** **15**

To determine the effect of a strongly electron withdrawing group at the 5′-position of the ribose ring (such as is found in derivatives **6**, **19**, and **21**), we measured the rate of glycosidic hydrolysis of 5′-amino-5′-deoxyadenosine (**13**) as shown in Scheme IV. Under acidic conditions, the 5′-amino group is fully protonated and is a good model for the quaternary ammonium group in **6**, **19**, and **21**. In 0.1 N HCl and at 88 °C, nucleoside **13** hydrolyzes with a rate constant of 7.14×10^{-6} s^{-1}; the HPLC analysis used demonstrated the clean conversion of starting material to adenine, verifying the locus of cleavage.

Discussion

Purine Cyclonucleosides Related to Adenosine. What is the reason for the observed sensitivity of hydrolysis rate to starting material structure? We should first note that the failure to observe an *increase* in the rate of cyclonucleoside hydrolysis as compared to nucleoside hydrolysis is somewhat unexpected. Strained acetals contained in three-[30] and four-membered[31] rings are reported to open up to 500 000 times more quickly than analogous acyclic acetals. On the basis of this precedent, all cyclonucleosides might have been expected to open more quickly than the analogous naturally occurring nucleosides. That they did not suggests there is an important difference between simple strained acetals and the cyclonucleosides. One obvious difference is that we are comparing acetal with aminal hydrolysis, but the A-1 mechanisms are virtually identical, forming oxonium ion intermediates in each instance and varying only in the nature of the leaving group.

One obvious difference between cycloadenosine **6** and the other cyclonucleoside derivatives involves the substituent at the 5′-position. The presence of an electron-withdrawing immonium group in **6** might be expected to decrease its glycosidic hydrolysis rate, by inductively removing electron density for the ribose ring oxygen. As a model, we measured the hydrolysis rate in 5′-amino-5′-

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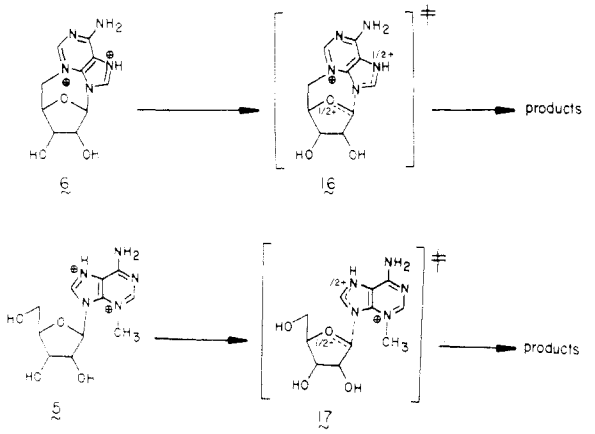
(26) Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1963**, *85*, 193.
(27) Clark, V. M.; Todd, A. R.; Zussman, J. *J. Chem. Soc.* **1951**, 2952.
(28) Anzai et al. *Agric. Biol. Chem.* **1973**, *37*, 301, 2431; **1976**, *40*, 373.
(29) Examples: (a) UV, see ref 9. (b) HPLC, Fujii, T.; Saito, T. *Heterocycles* **1982**, *17*, 117. (c) Thin-layer densitometry, Golankiewicz, B.; Zielonacka-Lis, E. *J. Chromatogr. Sci.* **1982**, *20*, 386.
(30) (a) Mori, A. L.; Porzio, M. A.; Schaleger, L. L. *J. Am. Chem. Soc.* **1972**, *94*, 5034, (b) 5039.
(31) Atkinson, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 819.

Scheme V



deoxyadenosine (13); under the conditions of the reaction (0.1 N HCl), the amine group will exist completely in the ammonium form and should mimic the effect predicted in 13. When the HPLC method already described is used, the pseudo-first-order rate constant for hydrolysis was determined to be 7.14×10^{-6} s^{-1} ($t_{1/2}$ = 27 h) at 88 °C, representing an approximately 70-fold deceleration as compared to adenosine itself under the same condtions. A similar retarding effect in the glucopyranoside series has been previously noted.[49]

Still, the inductive effect does not explain the rate difference between compounds 5 and 6 completely, and a geometric explanation for the rate differences must also be considered. We suggest that the generation of an "anti-Bredt transition structure", as suggested in Scheme V, must be a contributing factor in all the cyclonucleosides we have examined to an extent determined by their respective geometries. The A-1 pathway formally requires partial double bond character in the oxonium ion-like transition structure (16) that has an energetically nonideal geometry for oxygen stabilization of the adjacent carbenium ion. Such a scenario does not exist with the natural nucleosides, which do not require formation of double bond character at any bridgehead position as in transition structure 17. To the best of our knowledge, the hydrolysis of cyclonucleoside 6 represents the first case of a reaction that passes through an anti-Bredt transition structure but does not generate any anti-Bredt products or intermediates along the way. The results of molecular mechanics calculations on cycloadenosine derivatives 2 and 6 are also instructive as pertains to relative geometric alignments of antiperiplanar electrons. Molecular models confirm that the frameworks of these compounds are locked into single conformations, and our molecular mechanics calculations[32] on cycloadenosine 2 indicate that the dihedral angle defined by [N-9/C-1'/O/antiperiplanar lone electron pair] is almost exactly 180° (179.8° calculated), which should be optimal for O-assisted bond cleavage.[33] On the other hand, a molecular mechanics calculation on cycloadenosine salt 6 predicts a dihedral angle of 167°, or 13° from the optimal. We cannot, of course, quantitatively predict how a variation of this kind will affect the rate of the glycolysis. Indeed, the concept of stereoelectronic control in acetal hydrolyses has been strongly criticized,[34] although a recent paper by Kirby clearly demonstrates its significance in an extreme case.[35]

Chart II

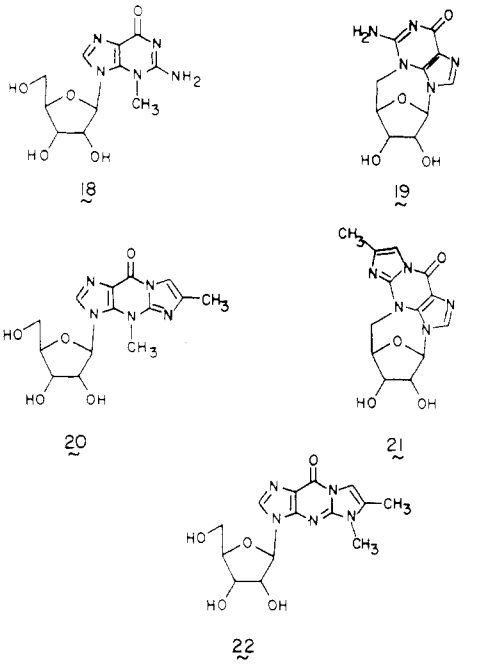


Table II. First-Order Rate Constants for Glycosidic Hydrolysis in Selected Guanine Nucleosides and Corresponding Cyclonucleosides

compd	reactn condtns	$10^5 k_1$ (s^{-1})	$t_{1/2}$ (min)
18	0.1 N HCl, 25 °C[43]	1600	0.72
19	0.9 N HCl, 37 °C[36]	>9.5[a]	<122
20	0.1 N HCl, 25 °C[43]	730	1.58
21	0.9 N HCl, 37 °C[36]	ca. 0.37[a]	ca. 3120
21	0.1 N HCl, 85 °C[43]	10	116
22	0.1 N HCl, 25 °C[43]	0.00047[b]	2460000
22	0.1 N HCl, 85 °C[43]	5.5	210

[a] Estimated based on thin layer chromatography observation of the hydrolysis reaction in ref 36. [b] Calculated value based on the activation parameters reported in ref 43.

Purine Cyclonucleosides Related to Guanosine. At this point, it is useful to summarize previous work on the glycosidic hydrolyses of other carbon-bridged cyclonucleosides, which is limited to the guanosine series. Cycloguanosine 19 (Chart II) was synthesized and hydrolyzed originally by Robins[20] and used later by Reese[36] to estimate the stability of its glycosidic linkage. No kinetics were performed, but it was reported that 100% glycosidic hydrolysis had occurred after 27 h at 37 °C in 0.9 N HCl; no attempt at product structure assignment was reported, but rather the loss of starting material was apparently followed.[20] This compound is directly analogous to our cycloadenosine derivative 6, but at the time the reference 3-methylguanosine was unknown, so a comparison of glycolysis rates could not be made. 3-Methylguanosine (18) was subsequently synthesized[37,38] and the rate of its acid-

(32) Molecular mechanics programs adapted from Allinger's MMP1 were obtained from Serena Software, 489 Serena Lane, Bloomington, IN, 47401. This version (name: MMPM) with the accompanying graphics routine was run on an IBM-AT microcomputer. Energies as a function of glycosidic torsion angle were obtained by using the dihedral angle driver option of this program.

(33) Page, M. I. In *Organic Reaction Mechanisms 1983*; Knipe, A. C.; Watts, W. E., Eds.; Wiley: New York, 1985; p 1.

(34) Sinnott, M. L. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; pp 389–431 (especially pp 396–397).

(35) Evans, C. M.; Glenn, R.; Kirby, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 4706.

(36) Reese, C. B.; Whittall, N. *Nucleic Acids Res.* **1976**, *3*, 3439.

(37) (a) Nakatsuki, S.; Goto, T. "Abstracts of Papers", The Symposium of the Society of Synthetic Organic Chemistry, Japan, Tokyo, June 22, 1977. (b) Nakatsuki, S.; Goto, T. "Abstracts of Papers", 26th International Congress of Pure and Applied Chemistry, Tokyo, September 9, 1977; p 1127.

(38) Itaya, T.; Ogawa, K. *Tetrahedron Lett.* **1978**, 2907.

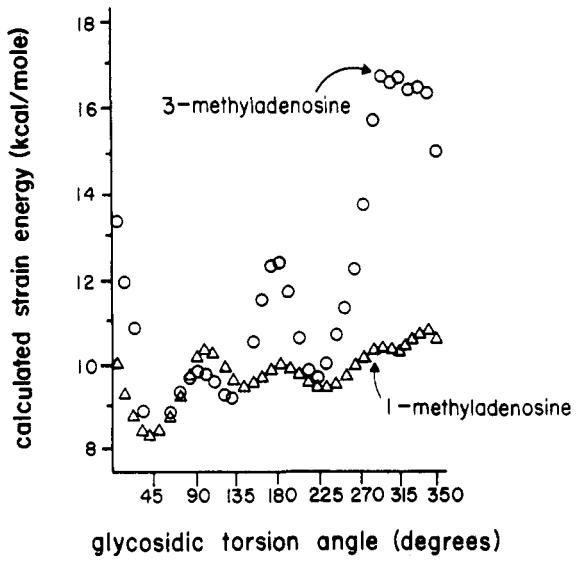


Figure 1. Energetics of glycosidic bond rotation in methyladenosines as calculated by using molecular mechanics methods.[32]

catalyzed glycosidic hydrolysis determined to be extremely fast, with a half-life of 42 s at 25 °C in 0.1 N HCl;[39] this is clearly many orders of magnitude faster than that of cycloguanosine **19** inasmuch as its synthesis required stirring overnight at 25 °C in 1.0 N HCl.[20]

Considerable discussion exists concerning the similarly rapid glycosidic hydrolyses in 3-methylguanosine (**18**) and wyosine (**20**),[40] a fluorescent nucleoside isolated[41,42] from various $tRNA^{Phe}$'s and preparatively hydrolyzed under acidic conditions,[21] and a detailed kinetic comparison was reported in 1980.[39] Two groups[21,36] almost simultaneously reported the synthesis of cyclowyosine **21** (or its isopropylidene derivative) by different methods and described its hydrolysis on a preparative scale, but kinetic studies of some detail did not appear until later.[43] The data from these studies are summarized in Table II. Because of the extremely rapid hydrolysis of wyosine (**20**) as compared to its structural isomer **22** or to cyclowyosine **21**, it has been proposed that the position of the methyl group in both 3-methylguanosine (**18**) and in wyosine (**20**) induces a steric repulsion between the heterocyclic base and ribose moieties that accelerates their dissociation.[43,50] A steric repulsion of this type was assumed to be much less in either **21** or **22**.

It does not seem likely to us that the N-methyl group of **20** can exert much of a steric repulsion with the ribose ring; rotation about the glycosidic bond insures that the nucleoside can adopt a conformation that relieves this interaction. To illustrate this point, we have carried out molecular mechanics calculations to predict the energetics of rotation about the glycosidic linkage for the related methylated purines 1-methyladenosine and 3-methyladenosine (Figure 1). Inasmuch as we are comparing closely related structural isomers, comparisons of calculated strain energies are valid; we do not suggest that absolute energies are quantitative. The results as shown in Figure 1 indicate that 3-methyladenosine does experience a substantial amount of strain in some conformations. For example, at a dihedral angle (O4′–C1′–N9–C8; looking down the C1′–N9 bond, a clockwise rotation of C8 results in a positive angle change) of around 300°, a local energy maximum is observed owing to a strong steric repulsion between the N3 methyl group and the H2′ hydrogen; this repulsion is seen to be much less in 1-methyladenosine owing to the displacement of the methyl group. Alternatively, both 1-methyl- and 3-methyladenosines have energy minima at an angle of about 45°, which falls in the anti conformation region. X-ray structures of both purine mononucleotides[47] and of purine-containing self-complementary dinucleoside monophosphates[48] exhibit glycosidic angles near 45°. This energy minimum in the anti conformation required for base-pairing seems reasonable inasmuch as alkylating agents are able to attack adenosine's N3 position in the duplex form.[11] In addition, methylation of an ethenoguanosine locked in an anti conformation occurs to a substantial extent at the N3 position even when an alternative methylation site is available.[50] At the 45° angle, both 1-methyl- and 3-methyladenosines can occupy a conformation of low and approximately equal energy; this conclusion is also reached on the basis of examination of CPK space-filling molecular models, which does not indicate any bad contacts at the 45° angle. Inasmuch as each compound can be expected to populate the low energy conformations, release of strain energy cannot be used to explain the enhanced reactivity toward glycosidic hydrolysis.

In our view, any type of alkylation of either guanosine at the N3 position or of wyosine at the corresponding nitrogen would increase the rate of hydrolysis as compared to guanosine itself, but in both cycloguanosine **19** and cyclowyosine **21** this alkylation concommitantly both places an electron-withdrawing group at the 5′-position and forces the hydrolysis reaction to pass through an "anti-Bredt transition structure" like that depicted for 3,5′-cycloadenosine **6** in Scheme V. The opposing effects nearly cancel, so that the hydrolysis rates in cyclowyosine **21** and in guanosine (**3**) are within an order of magnitude of each other;[43] we have seen essentially the same occurrence in the present study (compare the hydrolysis rates of adenosines **1** and **6**). The very unexpectness of this dramatic retarding effect forced then uncomfortable (but correct) conclusions and incorrect predictions to be drawn in one study.[36] Finally, we explain the equally dramatic retarding effect of moving the N-methyl group in **20** to the position occupied in structural isomer **22** based not on steric grounds but on electronic grounds, by analogy to the known effect of positional methylation on the hydrolysis of adenosine derivatives. While methylation of an *endo*cyclic nitrogen on adenosine (e.g., 3-methyladenosine) increases the hydrolysis rate by several orders of magnitude, methylation of an *exo*cyclic nitrogen (i.e., N^6-methyladenosine) leaves the hydrolysis rate virtually unaffected.[5] The same pattern is almost certain to be followed by guanosine, so that N^2-methylguanosine is predicted to hydrolyze at about the same rate as does guanosine itself even though 7-methylguanosine (in which no steric re-

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pulsion is possible) hydrolyzes much more quickly than guanosine near neutral pH. An extension to wyosine (**20**) and its structural isomer **22** then leads to correct predictions regarding their hydrolysis rates.

Conclusion

Cyclonucleosides undergo acid-catalyzed glycosidic hydrolysis more slowly than corresponding nonbridged nucleosides. Two effects are likely responsible: (1) bridged nucleosides involving reaction at the purine N3 position experience a strong inductive effect as a result of the ammonium group near the ribose ring oxygen and (2) the A-1 pathway formally requires partial double bond character in the oxonium ion-like transition structures that has an energetically nonideal geometry for oxygen stabilization of the adjacent carbenium ion. Furthermore, the extent to which such an "anti-Bredt transition structure" results in slower hydrolysis depends on the initial geometry of the conformationally locked cyclonucleoside. N3-methylated purine nucleosides hydrolyze quickly, but the reason is not a steric one inasmuch as a nonstrained conformation exists.

We are interested in cyclonucleosides that undergo glycosidic hydrolysis at reasonable rates above pH 5 as enzyme models, inasmuch as we require a nearby carboxylic acid group to exist as its carboxylate ion under the conditions of the glycolysis. Consequently, we are most interested in alkylated cyclonucleoside models for 3-methyladenosine (**5**) and 7-methylguanosine (**7**); such alkylation precludes the need to protonate the heterocyclic base, and spontaneous glycolyses of compounds **5** and **7** have been documented to proceed at pH 7[44] and 5[45], respectively. It is not possible, however, to methylate cycloadenosine at N3 directly; this reaction gives the N1 isomer as does adenosine,[26] which hydrolyzes at about the same rate as adenosine itself.[44] Our hypothesis that cycloadenosine salt **6**, which is both rigid and selectively alkylated at N3, would undergo glycolysis at a reasonable rate at pH 7 was, unfortunately, incorrect on the basis of the work contained in this paper. 7-Methylcycloguanosine **8** experiences base ring-opening reactions at pH 5, but at pH 1 it undergoes glycolysis only 9 times more slowly than does 7-methylguanosine itself. All of this suggests that a 7-methylcycloguanosine with a somewhat longer bridge length between C-8 and the 5′-position may well meet our criteria, and we are in the process of synthesizing this currently unknown class of guanosine derivative.

Experimental Section

General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, B.C. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. FT NMR spectra at 11.75 T (500 MHz) or 7.0 T (300 MHz) were obtained on equipment funded in part by NIH Grant No.1 S10 RR01458-01A1. We thank Mr. Richard Weisenberger and Dr. C. E. Cottrell for their assistance in obtaining mass and high-field ^{1}H NMR spectra, respectively, at The Ohio State University Chemical Instrumentation Center, and Mr. Carl Engelman for other NMR assistance. The determination of first-order rate constants was accomplished by using the computer program LSTSQ, available from Serena Software, 489 Serena Lane, Bloomington, IN, 47401. Glycolysis reactions were carried out in either 0.1 N HCl, 0.15 M sodium acetate buffer (pH 5), or 0.05 M sodium phosphate buffer (pH 7). Adenosine (**1**), guanosine (**3**), 7-methylguanosine (**7**), aminoimidazolecarboxamide riboside (AICAR, **9**), 5′-amino-5′-deoxyadenosine (*p*-toluenesulfonic acid salt; **13**), adenine, guanine, 7-methylguanine, and AICA were all purchased from Sigma Chemical Co., St. Louis, MO.

5′,8-Cyclo-5′-deoxyguanosine (4). A mixture of the known isopropylidene derivative[25] (500 mg, 1.6 mmol) in 0.1 N HCl (75 mL) was stirred at 85 °C for 1 h, after which a clear solution was obtained. The reaction was cooled and made alkaline with concentrated NH_4OH. Cooling in an ice bath gave a pale tan solid within 2 h, which was filtered, washed with water and acetone, and dried to afford the deprotected cyclonucleoside (300 mg, 69%): mp >300 °C; R_f 0.2 (1-butanol/acetic acid/water, 4:1:1, on cellulose; ^{1}H NMR ($(CD_3)_2SO$) δ 3.11–3.14 (d, 1, 5′-H), 3.45–3.50 (m, 1, 5′-H), 4.25–4.29 (m, 2, 3′- and 4′-H), 4.67 (d, 1, 2′-H), 5.94 (s, 1, 1′-H), 7.4 (br s, 2, NH_2), 11.58 (br s, 1, NH); FAB mass spectrum, m/e 266 ($C_{10}H_{12}N_5O_4^+$).

3,5′-Cyclo-5′-deoxyadenosinium Chloride (6). A solution of the known[27] isopropylidene derivative of compound **6** (1 g, 2.1 mmol) in 50 mL of 0.1 N HCl was heated at 80 °C for 2 h. The reaction mixture was cooled, neutralized with ammonium hydroxide, and evaporated to dryness in vacuo. The residue was taken up in 75 mL of methanol; 25 mL of acetone was added to this and was concentrated to 50 mL. The white solid precipitated was isolated and was recrystallized from acetone–methanol to afford the deprotected cyclonucleoside (500 mg): mp 245–246 °C; UV λ_{max} 276 nm (CH_3OH, ϵ 20 500), 274 nm (0.1 N HCl), 272 nm (pH 7 buffer), unstable in 0.1 N NaOH; ^{1}H NMR ($(CD_3)_2SO$) δ 3.95–3.96 (m, 1, 5′-H), 4.27–4.28 (m, 1, 5′-H), 4.59–4.63 (m, 1, 3′-H), 4.72–4.73 (m, 1, 4′-H), 4.99–5.02 (m, 1, 2′-H), 5.64 (br s, 1, OH), 5.77 (br s, 1, OH), 6.42 (s, 1, 1′-H), 8.48 (s, 1, Ar H), 8.72 (s, 1, Ar H), 9.30 (br s, 2, NH_2); ^{13}C NMR ($(CD_3)_2SO$) δ 58.2 (t), 70.0 (d), 75.5 (d), 83.3 (d), 93.2 (d), 119.5 (s), 139.3 (d), 139.4 (s), 149.2 (d), 156.6 (s); FAB mass spectrum, m/e 250 ($C_{10}H_{12}N_5O_3^+$).

Anal. Calcd for $C_{10}H_{12}N_5O_3Cl$: C, 42.04; H, 4.23; N, 24.51; Cl, 12.41. Found: C, 42.04; H, 4.20; N, 24.29; Cl, 12.11.

8,5′-Cyclo-5′-deoxy-7-methylguanosine *p*-Toluenesulfonate (8). A heterogeneous mixture of cycloguanosine 4[25] (400 mg, 1.5 mmol), dimethylacetamide (5 mL), and methyl *p*-toluenesulfonate (320 mg, 1.7 mmol) was stirred at 75 °C for 4 h. The clear reaction mixture was treated with acetone (200 mL) and was chilled at −25 °C overnight to afford, after filtration and washing with acetone, a cream-colored solid (410 mg, 60%). An analytical sample was obtained by recrystallization from acetone–methanol: mp 260–262 °C; UV λ_{max} 260 (CH_3OH, ϵ 9900) and 286 (8900), 258 and 282 (sh) (0.1 N HCl), 258 and 284 (pH 7 buffer), 258 and 284 (unstable, 0.1 N NaOH); ^{1}H NMR ($(CD_3)_2SO$) δ 2.28 (s, 3, tosyl CH_3), 3.82 (s, 3, N^7-CH_3), 4.22–4.23 (m, 1, 5′-H), 4.28–4.30 (s, 1, 5′-H), 4.76 (d, 1, 4′-H), 5.44 (d, 1, 2′- or 3′-H), 5.57 (d, 1, 2′- or 3′-H), 6.19 (s, 1, 1′-H), 7.11 (d, 2, tosyl Ar H), 7.2 (br s, 2, NH_2), 7.47 (d, 2, tosyl Ar H), 11.64 (br s, 1, N_1-H); ^{13}C NMR ($(CD_3)_2SO$) δ 20.70 (CH_3), 26.02 (CH_2), 32.53 (CH_3), 73.17 (CH), 75.71 (CH), 80.61 (CH), 88.40 (CH), 106.29, 125.39 (CH), 127.96 (CH), 137.59, 142.51, 145.58, 146.99, 153.27, 155.56; FAB mass spectrum, m/e 280 ($C_{11}H_{14}N_5O_4^+$).

Anal. Calcd for $C_{18}H_{21}N_5O_7S$: C, 47.89; H, 4.69; N, 15.51; S, 7.10. Found: C, 47.78; H, 4.71; N, 15.09; S, 6.93.

5-Amino-5′,N^5-cyclo-5′-deoxy-1-(2′,3′-*O*-isopropylideneribosyl)imidazole-4-carboxamide (12). A solution of compound 11[27] (8.0 g, 17.3 mmol) in 300 mL of 0.2 N KOH was left at 25 °C for 3 days. The reaction mixture was acidified with 1 N HCl and then was extracted with chloroform (5 × 100 mL). The chloroform extract was dried ($MgSO_4$) and was concentrated to a small volume in vacuo. The chloroform solution was loaded onto a column of silica gel and was eluted with chloroform–methanol (95:5, 2000 mL); pooled fractions on evaporation gave **12** as a colorless foamy solid (2.8 g, 58%): R_f 0.4 (chloroform/methanol, 90:10); mp, softens to a glass above 70 °C and melts to a clear liquid at ca. 135 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3, CH_3), 1.54 (s, 3, CH_3), 3.27–3.30 (m, 1, 5′-H), 3.35–3.39 (m, 1, 5′-H), 4.59 (d, 1, 3′-H), 4.66–4.67 (m, 1, 4′-H), 4.92 (d, 1, 2′-H), 5.50 (br s, 1, NH), 5.77 (s, 1, 1′-H), 6.31 (br d, 1, NH), 6.66 (br s, 1, NH), 7.09 (s, 1, C2-H); ^{13}C NMR ($CDCl_3$) δ 24.49 (CH_3), 26.08 (CH_3), 49.58 (C-5′), 82.30 (C-4′), 85.81 (C-2′ and C-3′), 90.91 (C-1′), 112.82 (acetal-C), 116.53 (C-4), 128.66 (C-2), 144.54 (C-5), 166.90 (CO-NH_2); mass spectrum, m/e (relative intensity) 280 (100); high resolution mass spectrum, calcd for $C_{12}H_{16}N_4O_4$ 280.1171, found 280.1171.

5-Amino-5′,N^5-cyclo-5′-deoxy-1-β-D-ribosylimidazole-4-carboxamide (10). A solution of the isopropylidene compound **12** (300 mg, 1.1 mmol) in aqueous HCOOH (50%, 10 mL) was heated at 80 °C for 6 h and the reaction mixture was concentrated to 3 mL in vacuo. Water (15 mL) was added and was concentrated

to 3 mL again; this was repeated three times and the mixture was finally evaporated to dryness. The residue was dissolved in 100 mL of warm methanol, silica gel (2 g) was added to the methanolic solution, and the solution was evaporated to dryness. The residue was loaded onto a column of silica gel and was eluted with $CHCl_3$–MeOH (9:1). Pooled fractions on evaporation gave **10** as a colorless solid (100 mg, 39%): R_f 0.1 ($CHCl_3$–MeOH, 9:1); mp 244–245 °C; UV λ_{max} (nm) 270 (CH_3OH, ϵ 12900), 264 (0.1 N HCl), 274 (pH 7 buffer), 276 (0.1 N NaOH); ^1H NMR ($(CD_3)_2SO$) δ 2.93–2.96 (m, 1, 5′-H), 3.41–3.45 (m, 1, 5′-H), 3.94 (d, 1, 4′-H), 4.20 (d, 1, 3′-H), 4.35 (m, 1, 2′-H), 5.1–5.4 (br s, 2, OH's), 5.81 (s, 1, 1′-H), 6.33–6.34 (m, 1, NH), 6.86 and 6.99 (br s, 2, NH_2), 7.42 (s, 1, C2-H); ^{13}C NMR ($(CD_3)_2SO$) δ 49.37 (t, C-5′), 71.52 (d, C-4′), 76.99 (s, C-3′), 87.69 (d, C-2′), 92.42 (d, C-1′), 115.72 (br s, $CONH_2$), 128.97 (d, C-2), 143.80 (s, C-5), 166.38 (s, C-4); mass spectrum, m/e 240 ($C_6H_{12}N_4O_4^+$).

Anal. Calcd for $C_9H_{12}N_4O_4 \cdot 0.5H_2O$: C, 43.37; H, 5.26; N, 22.48. Found: C, 43.57; H, 4.97; N, 22.13.

Conditions Used for the HPLC Separation of Nucleosides, Cyclonucleosides, and Their Hydrolysis Products. HPLC was carried out on an IBM LC/9533 system using an IBM C-18 reversed phase column and a 20-μL injection loop. Elution was carried out with continuous UV detection of the eluant at 254 nm as follows. Solvent A (5% methanol in 0.1 M ammonium dihydrogen phosphate solution (no adjustment to pH made), flow rate 2.0 mL/min) gives adenine (5.2 min), adenosine (13.9 min), cycloadenosine (4.8 min) and its hydrolysis product (14.6 min), guanine (3.1 min), guanosine (5.1 min), cycloguanosine (5.3 min) and its hydrolysis product (2.6 min), 7-methylguanosine (2.1 min), 7-methylguanine (6.2 min), and 7-methylcycloguanosine (3.3 min) and its hydrolysis product (7.4 min). Solvent B (1% methanol in 0.1 M ammonium dihydrogen phosphate solution, flow rate 0.5 mL/min) gives cycloadenosine salt (10.7 min) and its hydrolysis product (11.7 min) and guanine (16.0 min). Solvent C (1% methanol in 0.1 M ammonium dihydrogen phosphate solution, flow rate 2.0 mL/min) gives AICAR (13.3 min) and AICA (4.8 min).

Product Characterization of Glycosidic Hydrolysis Reactions. For preparative scale reactions using the cyclonucleosides, the hydrolyses were repeated at higher concentrations and allowed to proceed for at least 6 half-lives, after which the homogeneity of the product was determined by HPLC. UV absorption spectra of each product solution was taken at acidic, neutral, and basic pH's and compared to spectra of analogous purine standards as described. Finally, each reaction mixture was lyophilized to provide solid samples that were characterized by fast atom bombardment mass spectrometry. Unless specifically mentioned, every hydrolysis product appeared as a single peak on HPLC.

Glycosidic hydrolysis product from 5′,8-cycloadenosine (2): UV λ_{max} (nm) 268 (0.1 N HCl), 266 (pH 7 buffer), 272 (0.1 N NaOH) [compare to adenine 263 (0.1 N HCl), 261 (pH 7 buffer), 269 (0.1 N NaOH)]; FAB mass spectrum, m/e 268 ($C_{10}H_{14}N_5O_4^+$).

Glycosidic hydrolysis product from 5′,8-cycloguanosine (4): UV λ_{max} (nm) 254 (0.1 N HCl), 236 (pH 7 buffer), 276 (0.1 N NaOH) [compare to guanine 250 (0.1 N HCl), 244 (pH 7 buffer), 276 (0.1 N NaOH)]; FAB mass spectrum, m/e 284 ($C_{10}H_{14}N_5O_5^+$).

Glycosidic Hydrolysis Product from 3,5′-Cycloadenosine Salt 6. This reaction product has previously been prepared and characterized.[20] Our reaction product proved identical with that reported.

Glycosidic hydrolysis product from 7-methyl-5′,8-cycloguanosine (8): UV λ_{max} (nm) 256 (0.1 N HCl), 250 (pH 7 buffer), 282 (0.1 N NaOH) [compare to 7-methylguanine 252 (0.1 N HCl), 250 (pH 7 buffer), 282 (0.1 N NaOH)]; FAB mass spectrum, m/e 298 ($C_{11}H_{16}N_5O_5^+$). To insure that the purine ring system was not undergoing acid-catalyzed hydration (as is known to occur under basic conditions), we heated a sample of 7,9-dimethylguanine[46] at 90 °C in 0.1 N HCl for 24 h; during this time, no change was observed in the solution's HPLC trace, which was identical with that obtained by using a solution of 7,9-dimethylguanine itself.

Glycosidic Hydrolysis Product from Cyclo-AICAR Derivative 10. HPLC of this reaction performed in 0.1 N HCl does not reveal the clean conversion of starting material and concurrent formation of a single product seen in all other reactions, but rather demonstrated the production of at least three reaction products all forming on about the same time frame.

Glycosidic Hydrolysis Product from 5′-Amino-5′-deoxyadenosine. The UV absorbing product of glycosidic cleavage, namely adenine, eluted identically with that of authentic adenine in several solvent systems.

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Skeletal Deformation in 4,5-Disubstituted 9,10-Dihydrophenanthrenes and 4,5-Disubstituted Phenanthrenes

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Single-crystal X-ray structures were determined for six 9,10-dihydro-4,5-di-X-phenanthrenes (**1**, X = H, F, OMe, Cl, Me, CF_3) and four 4,5-di-X-phenanthrenes (**2**, X = F, Cl, Me, CF_3). Skeletal deformation in both series appears to be simply related to the apparent overlap between the X groups.

We have previously proposed a simple measure of steric stress (apparent overlap, Σr^*)[1] and shown that it correlates well with the energy required to overcome the stress in rotation in biphenyls,[1] *meso*-tetraarylporphyrins,[2] 9,10-dihydrophenanthrenes,[3] and *N*-arylsuccinimides.[4]

Examination of models reveals that intramolecular distances between substituents at C-4 and C-5 in both phenanthrenes and dihydrophenanthrenes are shorter than the sums of their van der Waals radii, even for the case of hydrogen[5] and this was expected to cause distortions

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