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CONFORMATIONAL STUDIES ON 1-AMINO-1-DEOXYPENTITOLS*†‡

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ABSTRACT

The conformations of the four 1-amino-1-deoxy-D-pentitols and their hydrochlorides in deuterium oxide solution have been analyzed by 250-MHz, ^{1}H-n.m.r. spectroscopy. The data indicate that the D-*arabino* (**2**) and D-*lyxo* (**3**) isomers adopt extended, planar, zigzag conformations, whereas the D-*xylo* (**4**) and D-*ribo* (**1**) isomers have the carbon chain in a nonplanar, "sickle" arrangement. The conformational assignments parallel closely those previously advanced for various related series of acetylated derivatives in organic solvents, and for nonacetylated analogs in solution and in the crystalline state. The spectral changes that take place in solution upon converting the amines **1–4** into their amine-salt forms are discussed, and the conformational data are considered in relation to the reactivity of **1–4** on deamination with nitrous acid and with respect to related reactions leading to ring closure under kinetic conditions.

INTRODUCTION

Various series of investigations in our two laboratories[2–6] have been concerned with the dynamic, conformational behavior of sugars and their derivatives, both cyclic and acyclic, as a function of their stereochemistry and environment, in an effort to achieve improved understanding of the factors controlling the behavior of these molecules in chemical and biochemical processes. The latter processes involve such aspects as barriers to conformational inversion in cyclic systems and the energetics of achieving "transition-state-like" geometry for such reactions as glycoside hydrolysis, and such considerations for acyclic-sugar derivatives as the

*Dedicated to Professor Kurt Heyns on the occasion of his 70th birthday.

†For a preliminary report, see ref. 1. Part XIII of the series "Conformation of Acyclic Derivatives of Sugars". For Part XII, see ref. 2.

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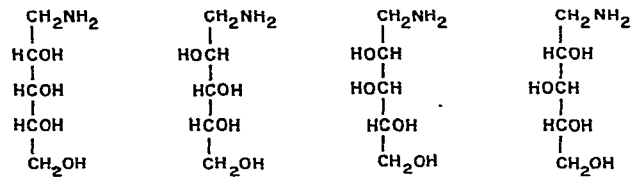
approach to transition-state geometry in cyclization reactions and the role of the ground state in reactions of very low activation-energy. Cyclization reactions that require significant activation, and which show marked variation in their course according to the stereochemistry of the acyclic precursor[5,6], have been a major theme of study in one of our laboratories as a route to derivatives containing the oxolane ring[7,8]. Both laboratories have had a common interest[9,10] in the reactions of acyclic derivatives of amino sugars upon deamination[8,11] with nitrous acid, a reaction that frequently leads to oxolane-type derivatives by a process whose activation-energy is very low and one in which the ground-state geometry of the amine precursor may play an important role in influencing the course of the reaction[12].

The present report, which describes ^{1}H-n.m.r. studies on 1-amino-1-deoxypentitols and their hydrochloride salts in deuterium oxide solution, provides experimental data on the favored conformations of these compounds in solution. The conclusions, which are in general accord with the previously established principle[3,4,13] that the extended conformation is favored except when a parallel, 1,3-interaction of substituent groups would thereby result, permit correlations between ground-state, conformational behavior and the data of Barker *et al.*[14] on the course of nitrous acid deamination of these compounds, a reaction that shows marked dependence on the relative stereochemistry of the 1-amino-1-deoxypentitol precursor.

ANALYSIS AND INTERPRETATION OF SPECTRA

General considerations. — The n.m.r.-spectral analysis of alditols and their uniformly substituted derivatives is intrinsically difficult[15], as the symmetry characteristics and limited spectral dispersion among the proton resonances impede simple, first-order analysis. The 1-amino-1-deoxypentitols offer some advantage in this respect, in that the unlike substitution at the ends of the chain introduces dissymmetry in each instance and creates magnetic anisotropy along the chain, so that the chain-terminal methylene groups cannot adopt equivalent environments. Even so, the spectral interpretations are not so readily effected as with such acyclic-sugar derivatives as the acetals[16], dithioacetals[2,3], 1,1-bis(acylamido)-1-deoxypentitols[17], and similar derivatives[4] having a single proton at C-1 of the chain, whose attribution is readily effected through its giving rise to a characteristic doublet. In contrast, for the four 1-amino-1-deoxypentitols studied [the D-*ribo* (**1**), D-*arabino* (**2**), D-*lyxo* (**3**), and D-*xylo* (**4**) stereoisomers, respectively], each gives rise, in principle, to two, non-equivalent, ABX systems resulting from H-1a, H-1b, and H-2 on the one hand, and H-5a, H-5b, and H-4 on the other. Differentiation of these methylene-group signals is not directly evident, but tentative attribution of the methylene-group signal at higher field to C-1 could be made on the basis of the observation[18] that the methine proton of the *H*CNH$_2$ group in amino sugars resonates at higher field than the methine group (*H*COH) of the corresponding neutral sugar. Firm identification of the 1-CH$_2$ resonance was made by studying the four 1-amino-1-deoxy-D-pentitols (**1**–**4**) as their hydrochloride salts (**5**–**8**, respectively) and then as the free bases in alkaline

solution generated by adding ~2 mol of NaOD/mol to solutions of each of the four hydrochloride salts in deuterium oxide. It was observed that one of the methylene-group signals showed little change in chemical shift, and this signal was thus assigned to the 5-CH_2 group; the 1-CH_2 group, already resonating at higher field than the 5-CH_2 group in acidic solution, underwent a marked shift farther upfield upon basifying the solution; the resultant deprotonation of the NH_2 group predictably leads to an increase in the electron density at C-1 and a concomitant shift upfield of the 1-CH_2 resonance.



Free bases:	1	2	3	4
HCl salts:	5	6	7	8

The net spectral-dispersions were insufficient for detailed attributions and interpretation at 60 or 100 MHz, but the spectra in deuterium oxide at 250 MHz showed sufficient first-order character for interpretation in most instances. Table I records the chemical shifts of protons of compounds **1–4** in the form of their hydrochloride salts (**5–8**, respectively) and also as the free bases **1–4** produced by addition of 2 molar equivs. of NaOD; the corresponding, first-order spin-couplings are given in Table II.

As in previous, related studies[3], it is assumed that rotameric interconversion for these acyclic derivatives is rapid, and that vicinal pairs of protons in antiparallel disposition give rise to large (~9 Hz) couplings, whereas those in gauche disposition give small (1.5–2.0 Hz for *gauche-trans*[19]; 3.0–3.5 for *gauche-cis*) couplings. Variations outside these limits may be attributed to (*a*) the effects of substituent electronegativity[20], (*b*) the adoption of favored, minimum-energy conformations wherein the dihedral angles of vicinal protons are perturbed significantly from nominal 60 or 180° values, and (*c*) the incidence of conformational equilibria in which there is time-averaging of couplings from two or more conformers that exist in substantial proportions in rapid equilibrium.

In comparing a series of closely related compounds, as in this instance, the effect of substituent electronegativity will be small, and may be disregarded unless a completely quantitative interpretation is attempted; in the absence of a solid, theoretical basis for relating coupling constants to exact dihedral angles, quantitative interpretations of this type are considered unsound[3,21], literature precedents for such attempts notwithstanding. Minor variations from the idealized, 60° staggering of substituents along each carbon–carbon bond are to be expected, and are supported by

TABLE I

PROTON CHEMICAL-SHIFT DATA (250 MHz) FOR 1-AMINO-1-DEOXY-D-PENTITOLS AND THEIR HYDROCHLORIDES IN DEUTERIUM OXIDE AT ~25°

Compound	*Configuration*	*Chemical shifts of protons*[a] (*δ values relative to DSS*)						
		H-1a	*H-1b*	*H-2*	*H-3*	*H-4*	*H-5a*	*H-5b*
1-HCl (5)	*ribo*	3.126 q	3.324 q	4.103 oct	3.836 dd	— 3.624	— 3.802 m[b] —	
1[c]	*ribo*	2.652 q	2.872 q	←		3.597 — 3.832[b]	→	
2-HCl (6)	*arabino*	3.286 q	3.383 q	4.322 oct	3.554 dd	3.771 oct	3.871 q	3.693 q
2[c]	*arabino*	2.697 q	2.855 q	4.001 oct	3.524 dd	3.744 oct	3.818 q	3.644 q
3-HCl (7)	*lyxo*	3.064 q	3.408 q	3.987 m[d]	3.604 dd	3.944 m[d]	— 3.684 d[e] —	
3[c]	*lyxo*	2.660 q	2.928 q	3.612 m[f]	3.488 dd	3.918 m	— 3.668 d[e] —	
4-HCl (8)	*xylo*	3.174 q	3.264 q	4.066 sx	3.682 dd	3.856 sx	3.678 q	3.770 q
4[c]	*xylo*	2.672 q	2.760 q	←		3.544 — 3.808[b]	→	

[a]The protons at C-1 and C-5 resonating at higher field are denoted as H-1a and H-5a; those resonating at lower field are denoted H-1b and H-5b, respectively. [b]Overlapping signals showing second-order behavior. [c]After addition of 2 molar equivs. of NaOD to the solution. [d]Overlapped peaks. [e]The C-5 protons have the same chemical shift. [f]High-field transition of multiplet.

TABLE II

FIRST-ORDER, PROTON–PROTON, SPIN-COUPLING DATA (250 MHz) FOR 1-AMINO-1-DEOXY-D-PENTITOLS AND THEIR HYDROCHLORIDES IN DEUTERIUM OXIDE AT ~25°

Compound	*Configuration*	*Spin couplings*[a] *(Hz)*							
		$J_{1a,1b}$	$J_{1a,2}$	$J_{1b,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
1-HCl (5)	*ribo*	13.5	8.75	2.75	3.75	~9	[b]	[b]	[b]
1[c]	*ribo*	13.5	8.5	3.0		[b]	[b]	[b]	[b]
2-HCl (6)	*arabino*	13	9.5	3.5	1.5	8.5	~5.7	2.2	11.2
2[c]	*arabino*	12.5	8.5	4.25	2.0	7.5	5.5	3.5	11.0
3-HCl (7)	*lyxo*	13	9.25	3.25	8.0	1.75	(6.3)[d]		
3[c]	*lyxo*	13	7.75	3.0	8.0	2.0	(6.3)[d]		
4-HCl (8)	*xylo*	13.2	8.7	3.6	3.7	5.3	4.2	6.5	12.5
4[c]	*xylo*	13.2	7.7	4.5		[b]	[b]	[b]	[b]

[a]The protons at C-1 and C-5 resonating at higher field are denoted as H-1a and H-5a, and those resonating at lower field as H-1b and H-5b, respectively. [b]Not determined, because of second-order effects. [c]After addition of 2 molar equivs. of NaOD to the solution. [d]Observed spacing of doublet.

X-ray crystallographic data for acyclic-sugar derivatives in the solid state[21,22]. The qualitatively observed difference between *gauche-trans* and *gauche-cis* vicinal protons, where the nominal angle is 60° in each instance, has ample precedent[4,23] in cyclic-sugar systems[19], and a similar principle appears valid with respect to acyclic systems from a comparative examination of the data for examples given in this series of studies[2,3].

So long as the analysis is restricted essentially to a qualitative treatment, spin-coupling values that are clearly intermediate between the limiting values noted may be taken as indicative of the presence of conformational mixtures in solution, and are so interpreted in the following analyses.

*1-Amino-1-deoxy-*D*-arabinitol* (**2**). — The 250-MHz, ^{1}H-n.m.r. spectrum of **2** and its hydrochloride salt (**6**) are shown in Fig. 1. The spectra are essentially first-order, and the salt **6** shows at highest field (δ ~3.4) an eight-line pattern for the AB portion of an ABX system that was attributed to the 1-CH_2 group, because of the marked upfield-shift (by ~0.6 p.p.m.) observed upon basification of the solution. The spacings allowed determination of the first-order $J_{1a,2}$, $J_{1b,2}$, and $J_{1a,1b}$ values (the higher-field proton of each methylene group is arbitrarily designated "a", and the lower-field one, "b", in each instance), and permitted assignment, in turn, of the H-2 signal, observed at lowest field in the spectrum as a narrow, eight-line pattern of total width equal to $J_{1a,2}+J_{1b,2}+J_{2,3}$. The value of $J_{2,3}$ thereby determined permitted identification of the signal for H-3, resonating at higher field than the other two methine protons.

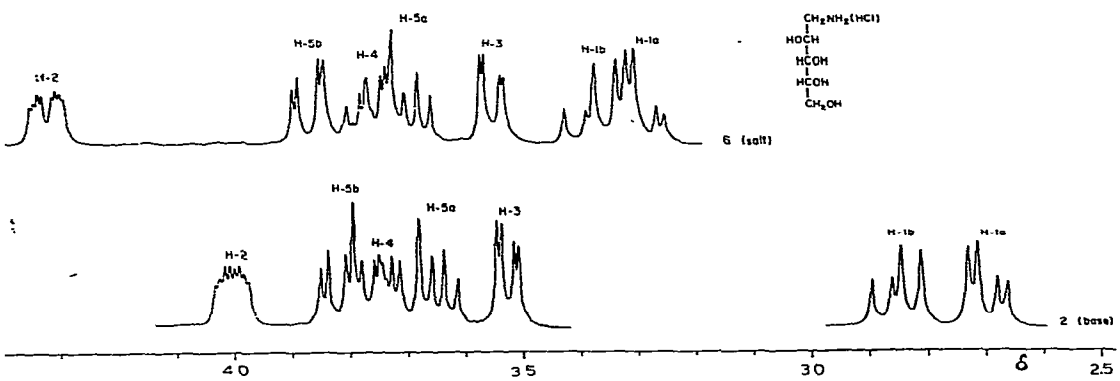


Fig. 1. The 250-MHz, ^{1}H-n.m.r. spectrum of 1-amino-1-deoxy-D-arabinitol hydrochloride (**6**) in deuterium oxide solution (upper trace). The lower trace shows the spectrum corresponding to the free base (**2**) after the addition of ~2 mol of NaOD per mol. Chemical shifts are relative to sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS).

The remaining three protons (H-4 and the two of the 5-CH_2 group) give rise to a pattern that is sufficiently resolved for an approximate AMX analysis; four-line patterns at the low-field and high-field ends of the remaining group of signals may be

assigned to the nonequivalent protons at C-5, and the intermediate pattern assigned to H-4 displays the strong $J_{3,4}$ coupling and the additional multiplicity arising through coupling to the C-5 protons; the proximity of the H-4 and H-5b patterns leads to the incidence of some second-order character, even at 250 MHz, and the spacing recorded for $J_{4,5a}$ must be regarded as only an approximation to the true coupling.

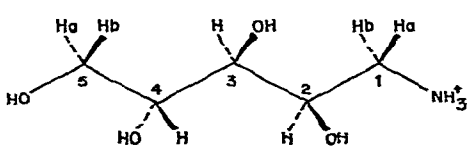
The lower trace in Fig. 1 shows the effect of adding ~2 molar equivalents of NaOD to the solution, to generate the free base **2** in alkaline solution. In addition to the pronounced, upfield shift of the 1-CH_2 signals already noted, it may be observed that the H-1a and H-1b signals become further separated as a result of a stronger upfield-shift of H-1b than of H-1a. Minor changes in certain patterns are observed as the result of small changes in some of the coupling constants, and the pattern for H-4 and the 5-CH_2 protons becomes more closely a first-order AMX pattern with the clear separation of all three multiplets. The shielding effect on the C-1 protons brought about by removing the positive charge from N-1 is also transmitted to C-2, as evidenced by the upfield shift (by 0.32 p.p.m.) of the H-2 signal of **2** as compared with that of **6**.

In conformational terms, the observed coupling-data for the salt **6** and its free base **2** are in clear accord with the planar, extended, zigzag conformation (**6a**) shown, which is as expected, as this conformer has maximal staggering of small–medium–large groups along each carbon–carbon bond, and no parallel 1,3-interactions (*β*-interactions) of chain substituents. The values for the salt **6** are closer to the anticipated extreme values for *gauche*- and *trans*-disposed, vicinal protons than they are for the base **2**, suggesting that **6** has higher conformational homogeneity as conformer **6a** than has **2** as the corresponding conformer, although both molecules strongly favor the conformation indicated. The coupling data suggest that the nitrogen atom does not significantly populate the other rotameric states about the C-1–C-2 bond, whereas there is greater freedom about C-4–C-5, permitting O-5 to populate to some extent the rotameric state wherein it is parallel to H-3.

1-Amino-1-deoxy-D-*lyxitol* (**3**). — The spectra of the salt **7** and the free base **3** were analyzed straightforwardly (see Tables I and II). High-field quartets observed at δ 3.064 and 3.408 for the salt **7** are readily assigned to H-1a and H-1b, respectively, because of their pronounced upfield-shift upon basification of the solution. The H-2 and H-4 multiplets are partially superposed in the spectrum of **7**, but are fully separated in the spectrum of **3**, because the H-2 resonance for **3** lies ~0.4 p.p.m. to higher field than for **7**; this shift parallels the inductive effect of the $-NH_3^+$ group on H-2, as already described for the *arabino* series. The H-3 signal appears as a doublet of doublets whose spacings provide the key couplings for establishing the conformation of the compound. The attributions of H-1a, 1b, 2, and 3 were confirmed by spin-decoupling. The signals for H-5a and H-5b appear as a doublet, because of the fortuitous, chemical-shift equivalence of these protons, and thus it was not possible to extract the true couplings of the AA′X system for H-4,5a,5b; the observed spacing (6.3 Hz) of the H-5 doublet may be regarded as the average of the estimated values of $J_{4,5\,anti}$ (~9 Hz) and $J_{4,5\,gauche}$ (~2 Hz). Identical chemical-shifts for the C-5 protons

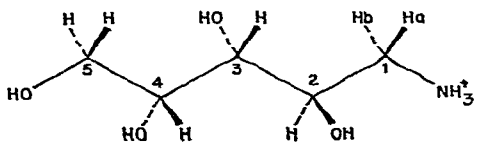
have been observed for related *lyxo* derivatives, namely, lyxose diethyl and diphenyl dithioacetals[3].

The observed couplings are consonant with the fully extended conformation depicted (7a); this was derived from consideration of the values of $J_{1a,2}$, $J_{1b,2}$, $J_{2,3}$, and $J_{3,4}$, all of which are extreme values for either antiparallel or gauche dispositions. These values are as expected, because there are no parallel, 1,3-interactions of substituents generated in this conformation. Little significant difference is observed between the spin couplings for the free base **3** and those for the hydrochloride salt **7**.



D-*arabino*

6a (planar zigzag)



D-*lyxo*

7a (planar zigzag)

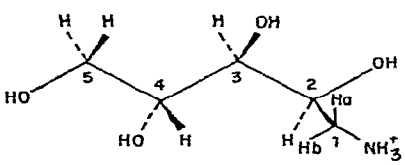
1-Amino-1-deoxy-D-*ribitol* (**1**). — As with the preceding two examples, the signals of H-1a and H-1b are readily identified by their strong deshielding for the salt (**5**) as compared with the free base (**1**); the downfield shift is ~0.5 p.p.m. The spectrum of the hydrochloride salt (**5**) shows the H-2 signal clearly separated to low field as an 8-line multiplet, from which the small $J_{2,3}$ coupling may be determined. The remaining signals for **5** appear as an envelope of peaks displaying a complex, ABC type of pattern for H-4, 5a, and 5b, with the H-3 signal separated at slightly lower field as a doublet of doublets showing some second-order perturbation; an approximate value of 9 Hz was estimated for $J_{3,4}$. The spectrum of the free base (**1**) was more difficult to analyze, because the H-2 signal is shifted upfield into the envelope of signals for H-3, 4, 5a, and 5b, so that some of the couplings could not be determined by inspection.

The small value observed for the $J_{2,3}$ coupling indicates that the salt **5** does not adopt a planar, extended, zigzag conformation, which would require H-2 and H-3 to be antiparallel and would generate a 1,3-interaction between O-2 and O-4. Rotation about C-2–C-3 to the sickle conformer ($_2G^-$*, **5a**) indicated would accommodate the observed low value of $J_{2,3}$ without simultaneously generating another 1,3-interaction (as between C-1 and O-3 in the other C-2–C-3 rotamer possible). The large value of $J_{3,4}$ establishes the essential coplanarity of the C-2–C-5 chain, but the rotameric disposition of O-5 is not directly assignable. Although the $J_{2,3}$ coupling for the free base **1** was not readily determinable from the spectrum, it is very probable that this compound adopts a conformation essentially similar to that of its salt **5**. In each instance, it may be assumed that there is considerable freedom for conformational

*See ref. 3 for definition of this terminology.

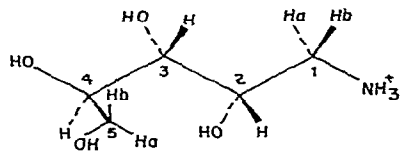
interconversion, but with favored population of the $_2G^-$ conformation (**5a**) and avoidance of the planar, extended conformation.

1-Amino-1-deoxy-D-*xylitol* (**4**). — The spectrum of the hydrochloride salt (**8**) shows sufficient dispersion to permit detailed analysis; as before, the H-1a and H-1b signals undergo large upfield-shifts upon conversion into the free base **4**, and the H-2 signal, well separated to low field in the spectrum of **8**, is shifted upfield into the multiplet for H-3, 4, 5a, and 5b in the spectrum of **4**. The quartet signals for H-1a and H-1b in **8** allow measurement of $J_{1a,2}$ and $J_{1b,2}$, and the $J_{2,3}$ coupling (3.7 Hz) is then evident from the width of the H-2 multiplet; this spacing is also found in the H-3 doublet of doublets located within the ABX group of signals for H-4, 5a, 5b. The H-3 signal also gives the $J_{3,4}$ value (5.3 Hz), and the latter may also be retrieved from the H-4 signal that falls on the low-field side of the signals for H-5a and H-5b. In the free base **4**, the upfield shift of H-2 leads to overlapping of the H-2,3,4,5a,5b signals, precluding simple analysis.



D - *ribo*

5a ($_2G^-$)



D - *xylo*

8a ($_3G^+$)

The vicinal couplings observed for the salt **8** are indicative of conformational instability, as the values of $J_{2,3}$ and $J_{3,4}$ in particular (3.7 and 5.3 Hz, respectively) are intermediate between those expected for exclusive population of gauche, and antiparallel, rotameric states. These couplings show a favored, but not exclusive, tendency for the molecule to adopt a conformation having H-2 and H-3 gauche-disposed and H-3 and H-4 antiparallel; such an arrangement would accord with the $_3G^+$ sickle conformation (**8a**) derived from the planar, extended conformation (which would have an unfavorable, parallel interaction between O-2 and O-4) by counter-clockwise rotation of C-5 along the C-3–C-4 bond. That this is far from the exclusive conformer is evident from the relatively low $J_{3,4}$ value, and the conformational instability is further manifested from the couplings of H-2 and H-4 with their respective, neighboring, methylene protons; these also exhibit non-extreme values indicative of population by more than one rotameric state.

Little direct conformational information is provided by the spectrum of the free base **4**; it may be presumed that this compound displays conformational instability of the same type as that of the salt **8**.

DISCUSSION

The conformational tendencies displayed by the 1-amino-1-deoxypentitols show good overall correlation with the tabulated[3]*, solution-conformational behavior of various classes of *acetylated* 1,2,3,4-tetrahydroxybutyl derivatives having the four relative configurations of the pentitols; the literature on corresponding *unsubstituted* derivatives is much more sparse, but similar general correlations are again evident when the present results are compared with the behavior of the aldopentose diethyl (and diphenyl) dithioacetals[3]. The near identity of the behavior of the D-*arabino* and D-*lyxo* derivatives **2** (**6**) and **3** (**7**) is to be expected from considerations of symmetry and the assumption that the chain-terminal groups, OH and NH_2 (NH_3^+), do not exert significantly different conformation-directing effects; both compounds strongly favor the extended, planar, zigzag conformation, in which there are no parallel, 1,3-interactions of substituents.

The conformation ($_2G^-$) favored by the *ribo* derivative (**5**) as well as that ($_3G^+$ with considerable conformational instability) displayed by the *xylo* derivative (**8**) likewise show good correlation with the collected data for series of related compounds, including unsubstituted dithioacetals of D-ribose and D-xylose[3].

1-Amino-1-deoxy-D-ribitol (**1**) is noteworthy, as it constitutes a model for the acyclic-sugar side-chain of riboflavin and the oxidation–reduction coenzyme, flavine adenine dinucleotide (FAD). It is noteworthy that the same $_2G^-$ conformation that is favored in aqueous solution for the salt **5** is also the conformation adopted by the 1-amino-1-deoxy-D-ribitol component of riboflavin in the crystalline state, as is revealed by inspection of the crystallographic data of Tanaka *et al.*[24]. Their data** show that the dihedral angle of C-1 and C-4 along the C-2–C-3 bond is 62°, and that of C-2 and C-5 along C-3–C-4 is 167°; these values are close to the idealized angles for the $_2G^-$ sickle conformation depicted for 1-amino-1-deoxy-D-ribitol and its hydrochloride. The favored disposition of this alditol chain may have significant implications as regards the shape of FAD and its binding to receptor sites.

It is of interest to compare the conformational properties of the 1-amino-1-deoxypentitols with their behavior in chemical reactions. In reactions of appreciable activation-energy that lead to more than one product, the conformation of the ground state is not a significant factor in influencing product-distribution, as the relative energies of possible transition-states govern the outcome of the reaction (Curtin–Hammett principle)[25]. However, in reactions of zero, or very low, activation-energy, the ground-state conformation may play the principal or a significant role in determining the course of reaction. The present conformational information for the salts **5**–**8** may be compared with the data of Barker *et al.*[14] on their reaction with aqueous nitrous acid at 0°. This reaction takes place[8,11] with very low activation-

*In Table I of ref. 3 (first paper), the reference numbers cited in the final column should all be raised by 4.

**The crystallographic structure depicted[24] shows the L enantiomer, but the natural, D-*ribo* derivative was presumably the form studied.

energy, by way of a diazonium ion, and involves the attack of oxygen from the solvent, or the molecule itself, either on the diazonium ion directly, or on a "hot" carbonium ion derived from it by loss of nitrogen. Three products are formed in this reaction, the 1,4-anhydroalditol arising by attack of O-4 on C-1, the 2,5-anhydroalditol produced with inversion of configuration at C-2 (presumably by way of an intermediate 1,2-epoxide), and the alditol, formed by attack of solvent (water). The data of Barker *et al.*[14] are given in Table III, where it may be seen that the products of intramolecular reaction are preponderant with all four configurations, but that substantial differences exist between the ratio of cyclized to acyclic products, according to the stereochemistry of the precursor.

On considering the favored, ground-state conformations established here for **5–8**, and examining the yields of alditols in Table III, a correlation is evident between

TABLE III

NITROUS ACID DEAMINATION OF 1-AMINO-1-DEOXY-D-PENTITOLS[a]

Configuration	*1,4-Anhydride*	*2,5-Anhydride (C-2 inverted)*	*Total anhydrides*	*Alditol*
lyxo	55	24	79	20
arabino	78	9	86	14
ribo	78	15	93	7
xylo	89	9	98	2

[a]Data from ref. 14 for the reaction: $HOCH_2(CHOH)_3CH_2NH_3^+Cl^- \xrightarrow[0°]{HNO_2}$ 1,4-anhydroalditol + 2,5-anhydroalditol + alditol.

the tendency to adopt the extended conformation (*lyxo* and *arabino*) and the appreciable yield of alditol (20 and 14%, respectively); in contrast, those configurations (*ribo* and *xylo*) that favor non-extended conformations give far less of the intermolecular reaction-product (7 and 2% of alditol, respectively) and correspondingly greater proportions of cyclized products (93 and 98%, respectively). It should be noted, however, that intramolecular cyclization still furnishes the major products in all of these reactions, indicating that, even though there is a *relative* tendency favoring the alditol product for those reactants that favor the extended ground-state, there is nevertheless a net preponderance of products that must arise through conformational change during the reaction. This result indicates that the postulated diazonium-ion (or carbonium-ion) intermediate has a long enough lifetime (that is, it requires sufficient activation energy), relative to the time required for rotameric interconversion, to allow conformational change toward a suitable transition-state for cyclization in the majority of reaction encounters. The molecules that favor non-extended conformations at the outset (*ribo*, *xylo*) show the greatest propensity for cyclization, although it should be recognized that nonextended conformers other than

the preponderant, lowest-energy forms in these conformationally mobile molecules must be the immediate precursors of the cyclized products.

A parallel exists between these results and those on the nitrous acid deamination of amino alcohols of the type $ArAr'C(OH)CH(NH_2)R$, where the rate of the deamination is comparable to the rate of conformational rotation about the central C–C bond[26].

As intramolecular reactions leading to five-membered, cyclic products generally take place much more readily than comparable, competing reactions occurring intermolecularly, the preponderance of cyclized products in the deamination of all four 1-amino-1-deoxypentitols is not surprising; it may nevertheless be concluded that there exists a significant influence of ground-state, conformational control in the deamination reactions of these acyclic polyhydroxyamines. At this stage, it would be speculative to enlarge on the conformational implications involved in forming the two types of anhydride, as firm information to support the mechanism proposed[14] for formation of the C-2-inverted 2,5-anhydride is not available.

The results may be contrasted with those of other reactions leading to cyclization of pentitol precursors, in which the activation energies are much higher, and the reaction rates are governed by a substantial difference between ground-state and transition-state energy. Thus, the rates[14] of acid-catalyzed dehydration of pentitols to their 1,4-anhydrides fall in the order (relative rates in parentheses) *ribo* (50) > *xylo* (29) > *arabino* (10) > *lyxo* (1); these rates reflect the relative stabilities of the respective transition-states, coupled with favored ground-states that facilitate access to transition-state geometry. Related considerations apply in the methanolysis of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonylpentofuranoses leading to 2,5-anhydropentose dimethyl acetals[6], and in the 2,5-cyclization of pentose dialkyl dithioacetals upon attempted 5-*O*-*p*-toluenesulfonylation[5].

EXPERIMENTAL

^1H-N.m.r. spectra. — Spectra were recorded at 250 MHz with a CAMECA-250 spectrometer (Thomson CSF, Paris) with solutions (5–10%) of the hydrochloride salts[14] **5–8** in deuterium oxide containing sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) as the internal standard. The temperature was ~20°. Detailed analyses were made from spectra recorded at 300-Hz sweep-width. After the spectra had been recorded, each salt was converted into its corresponding free base (**1–4**) by addition of a solution (~10%) of NaOD in deuterium oxide in ~2 mol/mol proportion to the salt used, and the spectra of the free bases were then recorded.

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REFERENCES

1 J. DEFAYE, D. HORTON, AND M. MUESSER, *Abstr. Pap. Am. Chem. Soc. Meet.*, 168 (1974) CARB-1.
2 M. BLANC-MUESSER, J. DEFAYE, AND D. HORTON, *J. Org. Chem.*, 43 (1978) 3053–3055.
3 D. HORTON AND J. D. WANDER, *J. Org. Chem.*, 39 (1974) 1859–1863, and previous papers in this series; see also, J. D. WANDER AND D. HORTON, *Adv. Carbohydr. Chem. Biochem.*, 32 (1976) 16–123.
4 P. L. DURETTE, D. HORTON, AND J. D. WANDER, *Adv. Chem. Ser.*, 117 (1973) 147–176; *Ann. N.Y. Acad. Sci.*, 222 (1973) 884–914 and papers cited therein; see also P. L. DURETTE AND D. HORTON, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 49–125.
5 J. DEFAYE AND D. HORTON, *Carbohydr. Res.*, 14 (1970) 128–132.
6 J. DEFAYE, D. HORTON, AND M. MUESSER, *Carbohydr. Res.*, 20 (1971) 305–318.
7 P. ANGIBEAUD, J. DEFAYE, H. FRANCONIE, AND M. BLANC-MUESSER, *Carbohydr. Res.*, 49 (1976) 209–223 and earlier papers in this series; see also J. DEFAYE AND V. RATOVELOMANANA, *ibid.*, 17 (1971) 57–65.
8 J. DEFAYE, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 181–228.
9 J. DEFAYE, D. HORTON, T. NAKAMURA, AND K. D. PHILIPS, *Carbohydr. Res.*, 16 (1971) 133–144.
10 P. ANGIBEAUD, C. BOSSO, J. DEFAYE, AND D. HORTON, *Abstr. Pap. Am. Chem. Soc. Meet.*, 168 (1974) CARB-6.
11 S. PEAT, *Adv. Carbohydr. Chem.*, 2 (1946) 37–77; J. M. WILLIAMS, *Adv. Carbohydr. Chem. Biochem.*, 31 (1975) 9–70.
12 E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, AND G. A. MORRISON, *Conformational Analysis*, Wiley, New York, 1965, p. 21.
13 D. HORTON, H. S. EL KHADEM, AND T. F. PAGE, JR., *J. Org. Chem.*, 33 (1968) 734–740.
14 D. D. HEARD, B. G. HUDSON, AND R. BARKER, *J. Org. Chem.*, 35 (1970) 464–467.
15 S. J. ANGYAL, R. LE FUR, AND D. GAGNAIRE, *Carbohydr. Res.*, 23 (1972) 121–134; compare J. A. MILLS, *Aust. J. Chem.*, 27 (1974) 1433–1446; S. J. ANGYAL, D. GREEVES, AND J. A. MILLS, *ibid.*, 27 (1974) 1447–1456.
16 J. DEFAYE, D. GAGNAIRE, D. HORTON, AND M. MUESSER, *Carbohydr. Res.*, 21 (1972) 407–416.
17 B. COXON, R. S. TIPSON, M. ALEXANDER, AND J. O. DEFERRARI, *Carbohydr. Res.*, 35 (1974) 15–31.
18 D. HORTON, J. B. HUGHES, J. S. JEWELL, K. D. PHILIPS, AND W. N. TURNER, *J. Org. Chem.*, 32 (1967) 1073–1080; D. HORTON, W. E. MAST, AND K. D. PHILIPS. *ibid.*, 32 (1967) 1471–1474.
19 B. COXON, *Tetrahedron*, 21 (1965) 3481–3503.
20 P. L. DURETTE AND D. HORTON, *Org. Magn. Reson.*, 3 (1971) 417–427.
21 A. DUCRUIX, C. PASCARD-BILLY, D. HORTON, AND J. D. WANDER, *Carbohydr. Res.*, 29 (1973) 276–279.
22 Compare G. A. JEFFREY AND H. S. KIM, *Carbohydr. Res.*, 14 (1970) 207–216; N. G. PANAGIOTOPOULOS, G. A. JEFFREY, S. J. LA PLACA, AND W. C. HAMILTON, *Acta Crystallogr. Sect. B*, 30 (1974) 1421–1430.
23 P. L. DURETTE AND D. HORTON, *J. Org. Chem.*, 36 (1971) 2658–2669.
24 N. TANAKA, T. ASHIDA, Y. SASADA, AND M. KAKUDO, *Bull. Chem. Soc. Jpn.*, 42 (1969) 1546–1554.
25 See E. L. ELIEL, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, pp. 149–156.
26 J. C. MARTIN AND W. G. BENTRUDE, *J. Org. Chem.*, 24 (1959) 1902–1905.