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Three-state models of furanose pseudorotation

Wilma K.Olson

Department of Chemistry, Rutgers University, New Brunswick, NJ 08903, USA

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ABSTRACT

A general procedure is described to treat the pseudorotation of the furanose ring in terms of a three-state conformational equilibrium. In addition to the principal n (C3'-endo) and s (C2'-endo) puckering domains, the unusual e (O1'-endo) intermediate is included in the analysis. Each of these three conformational categories is represented by a blend of five closely related puckered forms rather than by a single rotational isomeric state. Using this model together with experimentally measured nmr coupling constants, the puckering populations of various nucleic acid analogs are estimated. The conventional two-state n/s equilibria is confirmed in ordinary ribose and deoxyribose systems. The e domain, however, is found to be of major importance in several chemically modified furanoses including certain pyrimidine deoxynucleosides damaged by radiation and various nucleosides and nucleotides forced by bulky substituents on the base into unusual syn glycosyl arrangements. The "free" pseudorotation of these modified systems is not detected by conventional two-state puckering analyses.

INTRODUCTION

Comparisons of potential energy with experimental data[1] clearly demonstrate that the pseudorotation of ribose and deoxyribose is not "free" as recently suggested.[2] X-ray,[3-6] nmr,[7-9] and potential energy[2,10-15] studies indicate that the motion of the furanose is confined to only a small portion of the theoretically available pseudorotation space. The majority of X-ray structures fall into two distinct categories of puckering (n or C3'-endo and s or C2'-endo described by pseudorotation phase angles P of approximately 0 and π radians, respectively [1]). In both domains (illustrated for a model ribose in Fig. 1) the amplitude of puckering τ_m remains constant at approximately 40°.[5] The X-ray data and computed potential energies additionally reveal that the pentose oscillates between these two preferred states via only one of the two theoretically possible intermediate forms (cf. Fig. 1). While the unusual e-puckered intermediate with $P \sim \pi/2$ radians occurs in at least 9 different furanose crystal structures,[16-24] there are no solid-state

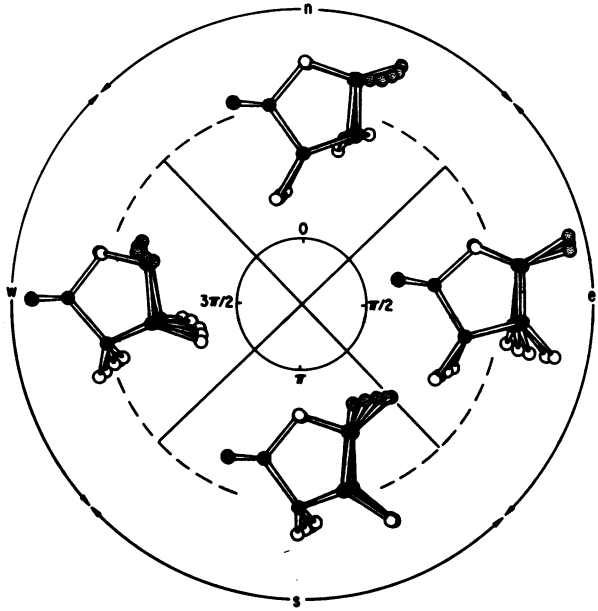

Figure 1
Principal categories of ring puckering on the pathway of furanose pseudorotation of a model ribose (without protons). Each of the domains is described by a blend of five discrete states separated by phase angle P increments of 0.1π radians. To emphasize the continuity of pseudorotational motions, states representative of each domain are superimposed in a common reference frame. The median structures of the four ranges (n, e, s, w) are located respectively at P = 0, π/2, π, and 3π/2 radians. Atomic designations are: solid spheres = carbon, open spheres = oxygen, stippled spheres = nitrogen.

examples (in appropriate ribose or deoxyribose analogs) of the w-puckered form where P ~ 3π/2 radians. The sterically hindered w state entails excessive energies in all potential energy surfaces reported to date.[2,10-15] The less encumbered e pucker apparently predominates only in chemically modified furanose systems. With the exception of one structure,[17] the X-ray examples of e puckering involve either unusual bases,[16,18,20,22-24] altered exocyclic substituents,[21] or transition metal complexation.[19] In addition, five out of seven of the e-puckered compounds entail a deoxyribose sugar.[16,17,20-24] According to potential energy studies that best reproduce nmr coupling constants of ordinary ribonucleosides and -nucleotides,[1] the potential barrier of the e-puckered ring lies between 2.5 and 5.0 kcal/mole.

The replacement of the 2'-hydroxyl of ribose by hydrogen in deoxyribose lowers the barrier slightly to the 1.5-3.0 kcal/mole range. In both ribose and deoxyribose the magnitude of the pseudorotation barrier is great enough to suppress significant occurrences of intermediate forms. The conformational transition between n and s puckerings, however, is somewhat easier for deoxyribose than for ribose.

The relative importance of the n, e, and s ranges of pentose pseudorotation in solution can be estimated by a direct analysis of measured coupling constants. All previous treatments of the furanose nmr data have been interpreted in terms of an equilibrium of n and s states only.[7-9] According to these studies, the n and s conformers are equally favored in ribose while the s form is predominant in deoxyribose. It has been recently suggested, however, that the intermediate e puckering may assume some importance in the solution behavior of certain nucleosides and nucleotides involving unusual bases and modified substituents.[21,22] Indeed, the set of nmr coupling constants associated with the unusual nucleoside, 5-iodo-5'-amino-2',5'-dideoxyuridine (5I-5'NH_3-dU), is described almost as well by a 25:20:55 equilibrium mixture of rigid n, e, and s conformers as by a 36:64 blend of the n and s rotational isomeric states alone.[21] Such a three-state model is consistent, in addition, with the nmr properties of 5-hydroxymethyl-2'-deoxyuridine (5-CH_2OH-dU).[22]

In this brief report we outline a general treatment of furanose pseudorotation in terms of a three-state conformational equilibrium. We represent each of the three major conformational categories (n, e, and s) by a blend of closely related puckered forms (illustrated in Fig. 1) rather than by a single rotational isomeric state. This averaged rotational picture accounts more satisfactorily for the local flexibility of the pentose suggested by (1) the range of puckerings noted in the X-ray crystallographic examples,[3-6] (2) the magnitudes of nmr parameters of allegedly rigid structures (e.g., the 3'-5'-cyclic nucleotide monophosphates),[25-27] and (3) the broad minima of the published pseudorotation potential energies.[2,10-15] Using this model together with experimentally measured coupling constants, we estimate the populations of the three principal puckerings in various furanose systems. We relate the various coupling constants to the local conformation of the sugar using a combination of Karplus-like relationships[7,9,28] and molecular orbital theory predictions.[29] Our numerical results describing ribose and deoxyribose differ slightly from fractional populations reported previously in rotational isomeric state computations.[7-9] Our data, however, confirm the con-

ventional two-state n/s interpretation of sugar puckering in normal polynucleotides. The study additionally reveals several chemically modified furanose systems where the e conformation assumes major importance. These systems include pyrimidine deoxynucleosides damaged either by ionizing radiations to 5,6-dihydro derivatives or by UV radiation to photodimers as well as various systems (both ribose and deoxyribose, purine and pyrimidine, nucleosides and nucleotides) forced by bulky substituents on the base into unusual syn glycosyl arrangements. The unusual (e-type) puckering preferences of these systems escapes detection in conventional two-state analyses of pentose pseudorotation.

METHODS AND RESULTS

The relative populations of the n, e, and s quadrants of pseudorotation may be computed on the basis of two equations of the form

$$J_{OBS} = \sigma_n J_n + \sigma_e J_e + \sigma_s J_s \quad (1)$$

that relate two experimental coupling constants J_{OBS} to the fractional populations of the three domains (σ_q, q = n, e, or s) and the respective mean couplings expected for the domains (J_q, q = n, e, or s) together with the equation

$$1 = \sigma_n + \sigma_e + \sigma_s \quad (2)$$

that accounts for the total population of puckered states. The regional J's appearing in Eq. 1 are evaluated here from published Karplus-like and molecular orbital variations[1,7,9,28] of J with P at increments of 0.1π radians in P over the specified quadrants. For simplicity, the five states chosen within each pseudorotation range (cf. Fig. 1) are assigned equal weighting in the computation of J_q. Values of J_q computed in this manner are listed in Table 1 for all three-bond proton couplings in ribose and deoxyribose. Also reported in Table 1 are the mean experimental couplings J_{OBS} of these two sugars.

Pseudorotation populations consistent with the observed coupling constants of ribose and deoxyribose systems are listed in Table 2. Values of σ_q are obtained using Eqs. 1 and 2 for all possible pairwise combinations of the measured coupling constants (i.e., J_{OBS}). Experimental data not employed in each application of Eq. 1 are compared with coupling constant values J_P predicted by the resultant set of σ_q. The J_P are obtained with Eq. 1 using the computed σ_q together with the relevant J_q from Table 1. The extent to which these predictions deviate from observed data is reported in the ΔJ

Table 1. Conformationally-weighted regional coupling constants

Constants	Experimental value, Hz	Regional value, Hz n	e	s
	Ribose			
$J_{1'2'}$	4.5	0.2	6.8	9.0
$J_{2'3'}$	5.2	4.9	7.9	5.5
$J_{3'4'}$	5.0	9.3	7.1	0.1
	Deoxyribose			
$J_{1'2'}$	7.4	0.3	7.8	10.0
$J_{1'2''}$	6.5	7.7	8.3	6.2
$J_{2'3'}$	6.5	7.0	10.3	6.3
$J_{2''3'}$	3.3	11.3	4.8	1.1
$J_{3'4'}$	3.1	9.3	7.1	0.1

columns of Table 2, where $\Delta J = J_P - J_{OBS}$. The ΔJ values are a measure of the reliability of the computed pseudorotation populations (σ_q).

Ribose. As evident from Table 2, the computed population distributions depend dramatically upon the pair of experimental parameters utilized in Eq. 1. For ribose the value of σ_e approximately equals zero when the computation is based on either the $J_{1'2'}/J_{2'3'}$ or the $J_{2'3'}/J_{3'4'}$ experimental pairs; the probability of the same domain, however, increases to 0.04 when the $J_{1'2'}/J_{3'4'}$ pair is utilized. All three population distributions satisfactorily reproduce the observed coupling constants. The value of $J_{2'3'}$ computed on the basis of the $J_{1'2'}/J_{3'4'}$ result ($\sigma_n = 0.50$, $\sigma_e = 0.04$, $\sigma_s = 0.46$) deviates only 0.1 Hz from the observed data. The $J_{1'2'}$ and $J_{3'4'}$ values computed on the basis of the two other ribose distributions vary just 0.2 Hz from the experimental values. The very low values of σ_e reported in Table 2 confirm the conventional interpretation of ribose pseudorotation as a two-state equilibrium of n and s puckering. Best fit to the mean ribose coupling constants comes from an approximately 50:50 distribution of our

Table 2. Three-state pseudorotation analysis

Deviations from experiment in Hz					Populations		
$\Delta J_{1'2'}$	$\Delta J_{1'2''}$	$\Delta J_{2'3'}$	$\Delta J_{2''3'}$	$\Delta J_{3'4'}$	σ_n	σ_e	σ_s
		Ribose[†]					
r*		r		-0.2	0.51	0.0	0.49
r		0.1		r	0.50	0.04	0.46
-0.2		r		r	0.53	0.01	0.46
		Deoxyribose[‡]					
r	r	-0.2	0.5	-0.8	0.28	-0.06	0.78
r	0.1	r	0.5	-0.5	0.27	0.0	0.73
r	-0.6	-1.5	r	-2.4	0.36	-0.39	1.03
r	0.3	0.4	0.7	r	0.24	0.11	0.65
0.9	r	r	-0.4	-1.3	0.17	0.02	0.81
0.5	r	-0.1	r	-1.1	0.22	-0.01	0.79
-1.6	r	-0.7	1.9	r	0.48	-0.20	0.72
0.5	0.0	r	r	-1.0	0.21	0.01	0.78
-0.6	0.2	r	1.2	r	0.33	0.0	0.67
0.9	0.5	1.0	r	r	0.12	0.27	0.61

[†]See Table 1 for mean experimental coupling constants.
*The populations are determined on the basis of pairs of reference experimental coupling constants denoted by r.

flexible n and s states. The known ±1.5 Hz variations of $J_{1'2'}$ and $J_{3'4'}$ in ribose[1,7-9] affect the computed proportions of n and s states but do not alter the population of the e domain. As $J_{1'2'}$ and $J_{3'4'}$ vary between 3.0 and 6.0 Hz and between 6.5 and 3.5 Hz, respectively, the n/s ratio varies between 30:70 and 70:30 with σ_e always less than 0.01.

Deoxyribose. Regardless of the pair of experimental coupling constants utilized, the computed distribution of pseudorotation states in deoxyribose is biased toward the s domain. According to Table 2, σ_s is never smaller

than 0.61. In nine of ten cases examined, the σ_n parameter is greater than σ_e. The value of σ_e, however, is seen to range from the relatively large value of 0.27 to the unrealistic value of -0.39 in the various computations. The most reliable fit of the experimental data is obtained from the computation based on the $J_{1'2'}/J_{2'3'}$ experimental data. The $J_{1'2''}$, $J_{2''3''}$, and $J_{3'4'}$ coupling constants computed on the basis of this distribution (σ_n = 0.27, σ_e = 0.0, σ_s = 0.73) are all within 0.5 Hz of observed values. The deoxyribose data can also be fit within 0.7 Hz by the $J_{1'2'}/J_{3'4'}$ analysis where σ_n = 0.24, σ_e = 0.11, and σ_s = 0.65. In view of the somewhat larger values of σ_e found in deoxyribose compared to ribose, the potential barrier to pseudorotation is clearly lowered upon removal of the 2'-hydroxyl group. The barrier, however, is not low enough to permit free pseudorotational motions. Unfortunately, the precise magnitudes of the energy barriers cannot be deduced from the computed statistical weights in Table 2. The σ_e values based upon the ribose nmr data, however, are comparable to those obtained through PCILO[12] and semiempirical[11,13-14] computations where the pseudorotation barrier is 3-5 kcal/mole. The σ_e values for deoxyribose are similar to those based upon semiempirical computations[13] where the pseudorotation barrier is about 2 kcal/mole.

Chemically modified furanoses. The pseudorotation populations that best reproduce the proton coupling constants in various nucleosides and nucleotides[1,7-9,21,22,30-37,43] are listed in Table 3. The σ_q are mean values of all solutions to Eqs. 1-2 that fit the experimental data within 1.0 Hz. The extent to which the averaged σ_q reproduce the coupling constants is apparent from the list of ΔJ in Table 3. In general the models are more satisfactory for ribose than for deoxyribose systems. The average discrepancy in the ribose data is only 0.1 Hz while that in the deoxyribose results is 0.5 Hz.

As noted above, the pseudorotation of common (unmodified) ribo- and deoxyribonucleosides and nucleotides[1,7-9] is consistent with a two-state equilibrium of n- and s-puckered conformations. According to our analysis in terms of flexible pucker families, the motions of 5I-5'NH_3-dU in solution are also limited to these two domains. In constrast to the recent three-state treatment of this derivative by Birnbaum et al.[21] where an intermediate e pucker predominates, σ_e here is only 0.07. The former computations, however, are based upon a rigid rotational isomeric state approximation together with a set of coupling constants designed to model ribose motions.[9] The data in Table 3 are obtained for our more flexible model using coupling constants developed for the deoxyribose ring.[38] According to our calculations, the

Table 3. Pseudorotation populations of selected furanoses

System	Population			Deviations from experiment in Hz				
	σ_n	σ_e	σ_s	$\Delta J_{1'2'}$	$\Delta J_{1'2''}$	$\Delta J_{2'3'}$	$\Delta J_{2''3'}$	$\Delta J_{3'4'}$
Ribose								
unmodified[a,1,7-9]	0.52	0.01	0.47	-0.1		0.0		-0.1
orotidine[30]	0.49	0.38	0.13	0.3		-0.2		0.3
β-cyanuric acid[30]	0.44	0.35	0.21	0.5		-0.3		0.0
6Me-U[31]	0.52	0.25	0.23	0.6		-0.4		0.0
8Br-A[32]	0.22	0.03	0.75	-0.1		0.0		-0.1
8Br-5'Amp[32]	0.23	0.38	0.39	0.0		0.0		-0.1
8MeS-5'Amp[32]	0.22	0.36	0.42	0.0		0.0		0.0
8MeNH-5'Amp[34]	0.07	0.19	0.74	0.0		0.0		0.0
8Me_2N-5'Amp[34]	0.17	0.38	0.45	0.0		0.0		0.0
Deoxyribose								
unmodified[a,1,8]	0.26	0.05	0.69	0.0	0.2	0.2	0.6	-0.3
5I-5'NH_3-dU[21]	0.30	0.07	0.63	0.2	0.4	0.1	1.1	-0.4
5-CH_2OH-dU[22]	0.33	0.04	0.63	0.0	0.2	0.2	0.8	-0.7
6Me-dU[35]	0.36	0.36	0.28	0.4	-0.9	-0.3	0.6	0.0
6Me-5'dUmp[35]	0.32	0.37	0.31	0.5	-0.7	-0.1	0.5	-0.2
6Me-3'dUmp[35]	0.42	0.31	0.27	0.6	-1.0	-0.6	0.4	0.0
p[]T of Tp[]T[b,c,33]	0.10	0.31	0.59	-0.3	1.4	0.0	-0.2	-1.0
p[]dU of Tp[]dU[b,37]	-0.02	0.53	0.49	0.0	1.3	0.0	-0.4	-
5,6-dihydro pyrimidine derivatives[36,43]	0.16	0.23	0.61	0.0	0.5	0.7	0.1	-0.1

[a] Computations based on mean coupling constants.
[b] cis-syn photodimer; the 3'-residue of the dimer exhibits a strong preference for s puckering.
[c] Coupling constants reported in ref. 37 for this compound do not match data of ref. 31.

motions of 5-CH_2OH-dU in solution are also described by a two-state equilibrium, rather than by a three-state scheme.

Major chemical modifications that force the base away from its normal anti orientation into the syn glycosyl conformation apparently disrupt normal furanose pseudorotation. The intermediate e domain assumes major importance in both syn pyrimidines (orotidine,[30] β-cyanuric acid,[30] 6Me-U,[31] 6Me-dU,[35] 6Me-5'dUmp,[35] 6Me-3'dUmp[35]) and syn purines (8Br-5'Amp,[32] 8MeS-5'Amp,[32] 8MeNH-5'Amp,[34] 8Me_2N-5'Amp[34]). In addition, the pentose of these systems moves almost freely over the n, e, and s regions of pseudorotation space. The pseudorotation of 8Br-A, however, does not follow this pattern but rather resembles the hindered motions of the commonly occurring deoxyribonucleosides and nucleotides. The possible formation of an intramolecular hydrogen bond between the N3 of the syn adenine and the free 5'-hydroxyl group of the s-puckered pentose may account for the unique behavior of 8Br-A;[32] such stabilizing effects cannot occur with syn pyrimidines systems or in syn purine nucleotides. On the other hand, pyrimidine nucleosides damaged by ionizing radiation to saturated 5,6-dihydro derivatives[36,43] contain large proportions of e puckering and undergo "free" pentose pseudorotation in solution. The 5'-ends of the cis-syn pyrimidine photodimers Tp[]T[33] and Tp[]dU[37] formed by UV irradiation also show a strong preference for e puckering; however, these sugars flip rapidly between e and s puckerings with relatively little preference for the n range. The conformational similarities between radiation damaged bases and syn bases do not surface in a conventional two-state analysis of pentose pseudorotation. The standard analyses[30-37] emphasize the different proportions of n and s puckering in various systems rather than the intermediate e puckering and the "free" pseudorotational surfaces that accompany certain chemical modifications of the nucleic acid bases.

DISCUSSION

A conformational blend of n- and s-puckered units satisfactorily accounts for the coupling constants of the sugar protons in a majority of low molecular weight nucleic acid analogs. The conventional interpretation of pseudorotation, however, eliminates the possibility of the unusual puckerings exhibited by a number of chemically modified nucleosides in recent solid state studies[16-24] and also suggested by various potential energy estimates.[2,11-15] Through adoption of a rotational isomeric state approximation, the standard models additionally ignore the broad range of local flexibility associated with each of the preferred pseudorotational domains. These fluctuations,

however, assume importance in systems, such as the furanose, characterized by relatively large regions of low (i.e., ≤ RT) energy.

The three-state analysis of pseudorotation detailed above is a more general description of pentose flexibility. The scheme is designed to include the "rare" e range of sugar puckering and also to reflect the restrained flexibility within each of the three families of pentose conformations. Using this approach, an unusual extreme flexibility is revealed in certain chemically modified nucleosides and nucleotides. Until now the unusual solution properties of nucleic acid analogs possessing syn bases or saturated base derivatives (e.g., 5-6-dihydropyrimidines and pyrimidine photo dimers) were rationalized in terms of the degree or amplitude (τ_m) of sugar puckering[23,31-33] rather than in terms of an alternate pseudorotational range. According both to available X-ray examples[3-6] and to potential energy surfaces,[2,11-15] the most probable path of pentose pseudorotation is one close to constant τ_m. Indeed, very few examples of ring flattening, where τ_m decreases to values of 30° or less, are found in the X-ray literature.[6,23] The three-state model of sugar puckering offered here with τ_m = 38° is very likely a more realistic interpretation of the motions in most nucleic acid derivatives. The present analysis, however, is not consistent with the nmr properties of 5I-5'NH_3-dU and 5CH_2OH-dU in solution despite the unusual e-puckered form of these compounds in the solid state.[21,22] The coupling constants of 5I-5'NH_3-dU and 5CH_2OH-dU are better matched here by a standard n/s equilibrium.

The extreme deformation found from this analysis of certain rare nucleosides and nucleotides could profoundly alter the physical and biological properties of naturally occurring nucleic acids. If the "free" pseudorotation of syn and saturated bases persists at the polymer level, the occurrences of rare bases could introduce extremely flexible links into the polynucleotide backbone. A single such link could readily deform the chain into an unusually bent structure. Furthermore, a series of modified residues might describe structures drastically different from the A and B helices associated, respectively, with standard n and s pentose puckerings. Indeed, the freely rotating pentoses could describe a continuum of helix and coil regions in rapid equilibrium with one another. On the other hand, the pseudorotation within the 8Br-A polynucleotide does not appear to parallel the free motions associated with corresponding modifications at the nucleotide level.[39] Poly 8Br-A forms a self-complementary double helix that has been suggested to resemble standard A-type structures.[40] Several alternative

double helical models, however, appear to reproduce the solution properties of this complex (D. Plick and W. K. O., unpublished data).

The similar "free" pseudorotation associated with saturated pyrimidine derivatives and various syn bases may possibly relate to the common carcinogenic effects of radiation and specific chemicals. The syn nucleotides are well known models of the major covalent adduct formed by acetylaminofluorene (AAF), a potent hepatic carcinogen, at the C8 purine positions of native DNA and RNA.[41,42] Because the radiation-damaged bases generally assume the anti glycosyl conformation characteristic of unmodified DNA and RNA,[16,20,36,37,43] their conformational similarity to syn systems is generally ignored.

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