state. The results show that for the α-CD and γ-CD complexes, the effects of pressure on the fluorescence parameters are similar to those in pure water, whereas the effects of pressure on the fluorescence parameters of the β-CD complex are different from those in pure water. We can interpret these results in terms of an increase in dielectric constant with increasing pressure, which results in a slight red shift in λ_{max} and a decrease in fluorescence intensity due to an increased rate of radiationless deactivation for the α-CD and γ-CD complexes. In the β-CD complex, we propose that as pressure is applied, there is an initial increase in the dielectric constant experienced by the probe leading to a (slight) red shift in λ_{max} and decrease in emission intensity, followed by a decrease in the dielectric constant leading to a blue shift.

This "turnaround" in fluorescence behavior can be explained if the conformation of the probe in the β-CD complex is more readily compressible than it is in the α-CD or γ-CD complexes, i.e., possibly because of an easier folding of the C_{11} detergent.

The order of magnitude of the microviscosity experienced by the 6-In-11^+ probe in water, typical micelles, sodium poly(styrenesulfonate) (NaPSS), and the cavity of cyclodextrins (present work), which were evaluated from various methods, is found to be as follows: H_2O (~1 cP) < SDS (~15 cP)[9,13] < HDTBr (~40 cP)[6,9] < α-CD (~80 cP) < γ-CD (~100 cP) < β-CD (~150 cP) < NaPSS (~150 cP)[13] < HDTBr + cetyl alcohol (200–300 cP)[11] < HDTBr + 1-hexadecanesulfonate (~400 cP).[11] It is clear that the apparent microviscosity of 6-In-11^+ is fairly large when it is included in cyclodextrins. The microviscosity values derived for α-CD and β-CD suggest that the location of the indolyl group is not simply "hanging free" in the water for these complexes but is weakly bound near the exterior of the cavity of the cyclodextrin via hydrophobic interactions of the side chain(s). Models suggest that the α- and β-CD cavity is too small to allow inclusions of the 11-carbon hydrocarbon group and that only the hexyl group is small enough to be inserted into the cavity. On the other hand, in the case of γ-CD, the entire probe is capable of fitting in the cavity.

Conclusion

It should be stressed that except for the NMR studies, the results of this investigation are derived from measurements of an *electronically excited probe* and not the ground state. The time scales of the measurements are sufficiently short (≲10 ns) that we expect that the results will reflect the initial general spatial location of the probes: i.e., the exit rate of the included probe is much slower than the rate of emission. However, the polarity of the electronically excited indolyl chromophore of 6-In-11^+ is expected to be different from that of the ground state, so that properties that depend on polar interactions surely will be different for the two states. Thus, the λ_{max} and τ measurements probably reflect the equilibrium position of the excited probe, and the η evaluations refer to the tumbling state.

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Registry No. 6-In-11^+, 51097-79-1; α-CD, 10016-20-3; β-CD, 7585-39-9; γ-CD, 17465-86-0.

Structure and Conformation of 8-Bromo-9-β-D-xylofuranosyladenine in the Solid State and in Solution[1]

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Abstract: The three-dimensional structure of 8-bromo-9-β-D-xylofuranosyladenine, an analogue of the antimetabolite xylofuranosyladenine, was determined by X-ray crystallography. The crystals belong to the triclinic space group $P1$, and the cell dimensions are a = 8.946 (1), b = 16.510 (8), and c = 7.140 (1) Å; α = 90.76 (3), β = 89.10 (6), and γ = 103.72 (1)°. In the unit cell there are three molecules of the nucleoside ($C_{10}H_{12}N_5O_4Br$) and two molecules of water. The structure was solved by the heavy-atom method and the refinement converged at R = 0.037 for 4200 observed reflections. All three nucleoside molecules adopt the syn conformation about the glycosidic bond. In two of the molecules the xylose ring has the C(4′)exo–C(3′)endo pucker, and there is an intramolecular O(3′)–H···N(3) hydrogen bond. In the third molecule the sugar ring pucker is C(2′)endo, and there is an O(5′)–H···N(3) intramolecular bond. The solid-state data, together with a new modified version of the Karplus relationship, were profited from to refine the results of previous NMR analyses of the solution conformations of 9-β-D-xylofuranosyladenine and its 8-bromo analogue. The new relationship, proposed by Haasnoot et al. (*Org. Magn. Reson.* **1981**, *15*, 43–52), proved distinctly superior to previous versions for conformational analyses of xylofuranosyl nucleosides.

The solution conformations of 9-β-D-xylofuranosyladenine (xyloA),[3] of some of its *O*′-methyl derivatives, and of 8-Br-xyloA have been determined with the aid of ^1H NMR spectroscopy.[4,5] The present article describes the solid-state structure and conformation of 8-Br-xyloA and a comparison with solution data. This is the first report on the solid-state structure of a β-D-xylofuranosyl nucleoside.

Purine nucleosides with bulky substituents at C(8) are usually constrained by steric hindrance to the syn conformation about the glycosidic bond. The earliest crystallographic study specifically

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(3) Abbreviations employed are the following: xyloA, 9-β-D-xylofuranosyladenine; 8-Br-xyloA, 8-bromo-9-β-D-xylofuranosyladenine.
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Table I. Fractional Atomic Coordinates[a] and Occupancy Factors

	molecule A				molecule B			molecule C		
atom	x	y	z	occ.	x	y	z	x	y	z
N(1)	4924 (5)	1887 (3)	7614 (6)		5671 (5)	5500 (3)	7204 (6)	8221 (5)	7291 (3)	2129 (6)
C(2)	3479 (6)	1826 (3)	7094 (7)		4364 (6)	5716 (3)	6907 (8)	8344 (6)	6507 (3)	2459 (8)
N(3)	2790 (4)	1489 (3)	5535 (5)		4136 (5)	6470 (3)	6555 (6)	7268 (5)	5805 (3)	2425 (6)
C(4)	3747 (5)	1185 (3)	4406 (6)		5469 (5)	7046 (3)	6556 (6)	5882 (5)	5940 (3)	2024 (6)
C(5)	5262 (5)	1192 (3)	4794 (6)		6913 (5)	6911 (3)	6813 (6)	5566 (5)	6713 (3)	1725 (6)
C(6)	5888 (5)	1580 (3)	6471 (6)		7018 (6)	6079 (3)	7138 (7)	6828 (6)	7414 (3)	1750 (6)
N(6)	7337 (5)	1647 (3)	6938 (6)		8333 (6)	5860 (3)	7380 (8)	6653 (6)	8187 (3)	1397 (8)
N(7)	5918 (4)	811 (2)	3367 (6)		8035 (4)	7655 (3)	6781 (6)	4029 (5)	6638 (2)	1417 (7)
C(8)	4825 (5)	594 (3)	2193 (6)		7246 (5)	8209 (3)	6528 (6)	3444 (6)	5841 (3)	1551 (8)
Br(8)	50000	0	0		81330 (7)	93478 (4)	63907 (10)	13672 (9)	53582 (5)	12481 (22)
N(9)	3463 (4)	803 (2)	2683 (5)		5686 (4)	7894 (2)	6337 (5)	4487 (5)	5368 (2)	1901 (6)
C(1′)	2076 (5)	703 (3)	1583 (6)		4490 (5)	8360 (3)	6275 (6)	4175 (6)	4460 (3)	2013 (8)
C(2′)	583 (5)	152 (3)	2476 (7)		3259 (5)	8071 (3)	4754 (6)	5023 (6)	4037 (3)	580 (7)
O(2′)	−191 (4)	−437 (3)	1142 (7)		3249 (5)	8784 (3)	3700 (6)	4340 (7)	3920 (3)	−1187 (7)
C(3′)	−430 (5)	773 (3)	2843 (8)		1763 (5)	7748 (3)	5876 (6)	4902 (6)	3217 (3)	1597 (7)
O(3′)	−288 (4)	1118 (3)	4654 (6)		1335 (4)	6864 (2)	5994 (5)	5932 (6)	2744 (3)	972 (6)
C(4′)	162 (7)	1414 (4)	1300 (8)		2104 (5)	8189 (3)	7783 (6)	5189 (8)	3494 (3)	3633 (7)
O(4′)	1809 (4)	1507 (2)	1305 (5)		3738 (4)	8268 (2)	8053 (5)	4644 (6)	4259 (2)	3780 (6)
C(5′)	−141 (12)	2262 (5)	1528 (14)		1225 (5)	7701 (3)	9382 (7)	6802 (11)	3655 (4)	4277 (10)
O(5′)	−1303 (11)	2379 (7)	462 (10)	0.74	1084 (4)	8215 (2)	10963 (5)	7897 (7)	4223 (4)	3161 (10)
O(5″)	−26 (5)	256 (3)	−12 (7)	0.26						
O(W1)	882 (2)	410 (1)	841 (2)	0.80						
O(W2′)	92 (3)	346 (2)	615 (4)	0.40						
O(W2″)	25 (4)	396 (2)	736 (4)	0.35						
O(W2‴)	23 (5)	462 (3)	638 (6)	0.25						

[a] The coordinates of the Br atoms were multiplied by 10^5 and those of the last five O atoms in the Table by 10^3. All other coordinates were multiplied by 10^4.

directed at this question was that of Tavale and Sobell;[6a] in these and in other X-ray analyses, 8-bromopurine nucleosides have always been found in such a syn conformation.[6] However, the results of ^1H and ^{13}C NMR spectroscopy have demonstrated that such nucleosides are predominantly, but *not exclusively*, in the syn conformation.[7] Furthermore, both 8-bromoadenosine diphosphoribose[8] and the 8-bromo analogue of NAD^+,[9] when cocrystallized with the appropriate dehydrogenase enzyme, are in the anti conformation. It is therefore to be expected that 8-Br-xyloA may also adopt such a conformation.

Apart from the intrinsic physicochemical interest of the conformation of xylonucleosides relative to those of other nucleosides, this is also of relevance to the known antimetabolic activities of xyloA, which exhibits both antiviral[10] and antitumor[11] activities. It is a substrate for adenosine deaminase and, in the presence of inhibitors of this enzyme, is readily phosphorylated in Chinese hamster ovary cells; it inhibits some process closely associated with nucleic acid synthesis at the polymer level.[12] Its ability to inhibit nuclear RNA methylation is linked to inhibition of *S*-adenosyl-L-methionine synthesis.[13] Its 5′-triphosphate interferes with formation of 5-phosphoribosyl 1-pyrophosphate and is a feedback inhibitor of purine biosynthesis.[11] Other xylofuranosylpurine nucleosides with antimetabolic activities have also been reported.[14]

Experimental Section

Crystals suitable for X-ray measurements were obtained from aqueous ethanol. They crystallize in space group $P1$. The unit cell dimensions were calculated from angular settings of 22 reflections with θ in the range 42–62°, centered on an Enraf-Nonius CAD-4 diffractometer. The following values were obtained: $a = 8.946$ (1), $b = 16.510$ (8), and $c = 7.140$ (1) Å; $\alpha = 90.76$ (3), $\beta = 89.10$ (6), and $\gamma = 103.72$ (1)°; $V = 1024.3$ Å^3, $Z = 3$, μ(Cu Kα) = 48.6 cm^{-1}, $D_m = 1.760$ (3) g cm^{-3}. The calculated density indicated the presence of water molecules in the structure; however, values calculated with two (1.741 g cm^{-3}) or three water molecules (1.771 g cm^{-3}) per unit cell were inconclusive and suggested possible disorder of water in the structure.

The crystal used for data collection had dimensions 0.075 × 0.18 × 0.25 mm. Intensities were measured with Ni-filtered Cu Kα radiation up to $2\theta = 152.6°$, using the $\omega/2\theta$ scan technique with $\Delta\omega = 1.3 + 0.15 \tan\theta$ and a maximum scan time of 150 s per reflection. Two reflections, monitored every 100 min, showed a fading in intensity due to crystal deterioration. They decreased to 73 and 79% of their initial values, respectively, at the end of data collection and were used for rescaling purposes.

Small but systematic changes of cell constants were observed during the data collection. The largest increase was noticed for b and β (0.15 and 0.23%, respectively), while c and γ remained unchanged. The overall increase in the unit cell volume was 0.23%. The cell dimensions given above are average values for the experiment, with standard deviations being indicative of long-term changes.

Out of 4281 reflections measured, 4200 had net intensities larger than $\sigma(I)$. The intensities were corrected for Lorentz and polarization factors. An analytical absorption correction was also applied, varying in the range 1.38–2.27.

The positions of the three Br atoms were determined from a Patterson map; a subsequent Fourier map revealed all nonhydrogen atoms of the nucleoside molecules. The atomic parameters were refined by the block-diagonal least-squares method, first with isotropic and then with anisotropic temperature factors. On difference Fourier maps we located two water molecules, one of them on three sites, and a disordered position for O(5′) in molecule A. Their atomic parameters, including occupancy factors, were refined with isotropic temperature factors. Of the 36 H atoms in the nucleoside molecules, 27 were located on difference Fourier maps and 9 were placed in calculated positions. All scattering factors were taken from the International Tables for X-ray Crystallography,[15] and the Br and O curves were corrected for anomalous dispersion. The following weighting scheme made the average values of $w(\Delta F^2)$ fairly

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Table II. Bond Lengths (A) and Bond Angles (Deg)[a]

	molecule A	molecule B	molecule C
N(1)–C(2)	1.331	1.321	1.349
N(1)–C(6)	1.357	1.350	1.341
C(2)–N(3)	1.331	1.336	1.320
N(3)–C(4)	1.344	1.338	1.347
C(4)–C(5)	1.385	1.377	1.390
C(4)–N(9)	1.374	1.378	1.378
C(5)–C(6)	1.410	1.421	1.413
C(5)–N(7)	1.385	1.389	1.372
C(6)–N(6)	1.322	1.325	1.349
N(7)–C(8)	1.280	1.297	1.300
C(8)–Br(8)	1.860 (4)	1.862 (4)	1.855 (5)
C(8)–N(9)	1.382	1.377	1.379
N(9)–C(1′)	1.454	1.460	1.461
C(1′)–C(2′)	1.558	1.547	1.522 (8)
C(1′)–O(4′)	1.421	1.421	1.404
C(2′)–O(2′)	1.417	1.408	1.401
C(2′)–C(3′)	1.538	1.536	1.526
C(3′)–O(3′)	1.401	1.422	1.405
C(3′)–C(4′)	1.536	1.536	1.526
C(4′)–O(4′)	1.445	1.452	1.461
C(4′)–C(5′)	1.495 (11)	1.505	1.483 (12)
C(5′)–O(5′)	1.350 (14)	1.426	1.426 (10)
C(5′)–O(5″)	1.29 (5)		
C(2)–N(1)–C(6)	119.5	120.1	118.4
N(1)–C(2)–N(3)	128.5	128.9	129.1
C(2)–N(3)–C(4)	111.9	110.8	111.5
N(3)–C(4)–C(5)	125.5	126.8	125.9
N(3)–C(4)–N(9)	128.9	127.5	128.5
C(5)–C(4)–N(9)	105.7	105.8	105.6
C(4)–C(5)–C(6)	118.0	117.5	116.9
C(4)–C(5)–N(7)	111.1	111.3	111.4
C(6)–C(5)–N(7)	131.0	131.1	131.7
N(1)–C(6)–C(5)	116.7	116.0	118.0
N(1)–C(6)–N(6)	120.6	120.2	120.5
C(5)–C(6)–N(6)	122.7	123.8	121.5
C(5)–C(7)–C(8)	103.3	103.0	103.4
N(7)–C(8)–Br(8)	123.1	123.3	123.2
N(7)–C(8)–N(9)	115.7	115.0	115.2
N(9)–C(8)–Br(8)	121.2	121.7	121.7
C(4)–N(9)–C(8)	104.3	104.8	104.5
C(4)–N(9)–C(1′)	127.2	126.7	128.3
C(8)–N(9)–C(1′)	128.3	127.5	127.1
N(9)–C(1′)–C(2′)	115.7	115.4	115.6
N(9)–C(1′)–O(4′)	107.8	106.7	107.9
C(2′)–C(1′)–O(4′)	107.3	108.1	106.2
C(1′)–C(2′)–O(2′)	110.0	105.9	114.3
C(1′)–C(2′)–C(3′)	103.4	104.0	98.6
O(2′)–C(2′)–C(3′)	106.9	113.1	112.4
C(2′)–C(3′)–O(3′)	113.5	113.1	115.4
C(2′)–C(3′)–C(4′)	100.9	103.3	103.0
O(3′)–C(3′)–C(4′)	113.5	113.6	111.4
C(3′)–C(4′)–O(4′)	103.7	104.8	104.1
C(3′)–C(4′)–C(5′)	117.9 (6)	113.3	116.7
O(4′)–C(4′)–C(5′)	107.8	108.9	109.7
C(1′)–O(4′)–C(4′)	107.2	108.7	109.6
C(4′)–C(5′)–O(5′)	113.4 (8)	112.5	115.2 (6)
C(4′)–C(5′)–O(5″)	108 (2)		

[a] Unless otherwise indicated the estimated standard deviations are 0.006–0.007 Å and 0.3–0.5°.

independent of $|F_o|$ and $\sin^2\theta$: $w = w_1w_2$, where $w_1 = 1$ for $|F_o| \leq 12$, $w_1 = 12/|F_o|$ for $|F_o| > 12$, $w_2 = (\sin^2\theta)/0.7$ for $\sin^2\theta < 0.7$, and $w_2 = 1$ for $\sin^2\theta \geq 0.7$. At convergence the discrepancy indices were $R = 0.037$ and $R_w = 0.046$ for the 4200 observed reflections. The final coordinates of the nonhydrogen atoms and their standard deviations are given in Table I.

Results and Discussion

Bond Lengths and Bond Angles. The bond lengths and bond angles for the three crystallographically independent molecules are listed in Table II. The average purine ring bond lengths, except for two, are in good agreement with those in adenosine. The exceptions are N(7)–C(8), which is shorter than in the parent adenosine, and C(8)–N(9), which is longer than in the parent adenosine. These changes are undoubtedly due to the presence of the Br substituent at C(8). A similar increase in length of the C(8)–N(9) bond has been noted in an adenosine derivative with the more bulky α-hydroxyisopropyl substituent at C(8).[16]

It is of interest to examine the exocyclic bond angles at N(9) in light of a recent report by Yasuniwa et al.,[17] who proposed a division of purine nucleosides in the syn conformation into two groups. Group A included those with $\chi_{CN} < 230°$, in which the bond angle C(8)–N(9)–C(1′) (α) is smaller than C(4)–N(9)–C(1′) (β). This was attributed to short contacts between the purine base and the sugar moiety. Nucleosides with bulky C(8) substituents (such as Br) were assigned to group B, with $\chi_{CN} \sim 240°$, and α larger than β, owing to a short contact between the substituent and H(1′). Our survey of X-ray results does not substantiate this classification. In 8-bromoadenosine ($\chi_{CN} = 241°$) and 8-bromoguanosine ($\chi_{CN} = 235°$), α and β are equal within experimental error.[6a] In the two independent molecules of 8-bromoinosine ($\chi_{CN} = 275$ and 283°), α is 6° *smaller* than β.[6d] Furthermore, since the van der Waals radius of the methyl group is similar to that of the Br atom, 8-methyladenosine 3′-phosphate, for which solid-state data are available,[17] would be expected to fall in group B. But it is classified as a member of group A, with $\chi_{CN} = 217°$ and α slightly smaller than β. Even in 8-iodoguanosine ($\chi_{CN} = 243°$), there is no difference between the two angles.[18] Only when the C(8) substituent is as bulky as $C(CH_3)_2OH$ (effective van der Waals radius 3.5–4.0 Å) is α 5° larger than β.[16] Hence it is not at all surprising that in the three molecules of 8-Br-xyloA ($\chi_{CN} = 237.4$–256.3°), α and β are essentially equal.

In the xylofuranose ring, the endocyclic angles are dependent on the ring conformation, i.e., on the phase angle of pseudorotation (*P*) and the maximum amplitude of puckering (τ_m).[19] On the basis of an analysis by Westhof and Sundaralingam,[20] we have recently derived a general equation that correlates these conformational parameters with the endocyclic angles.[21] A comparison of the calculated angles with those observed experimentally, for each of the three independent molecules, indicates that the agreement is quite good (within two standard deviations), pointing to the utility of the equation. The exocyclic angles are different in each molecule, most likely attributable to the different hydrogen-bonding patterns involving the OH groups. The distortion of each C–C–O bond angle is such as to optimize the geometry of the associated hydrogen bond.

Planarity of the Purine Ring Systems. Calculations of the least-squares planes through the nine ring atoms in each molecule reveal significant deviations from planarity of the purine rings. The largest deviations of the atoms from the planes in the three molecules are 0.025, 0.041, and 0.022 Å, respectively. The component pyrimidine and imidazole rings, particularly the latter, are more planar. As usual, the C(1′) atoms exhibit the largest displacements of substituent atoms from the purine ring planes (up to 0.201 Å). The hydrogen atoms donated to N(3) (see below) are each within 0.1 Å of the least-squares planes.

Glycosidic Torsion Angles. In all three molecules the conformation about the glycosidic bond is syn, the values of χ_{CN} [C(8)–N(9)–C(1′)–O(4′)] being in the range 237.4–256.3° (Table III). This conformation has been observed in the crystal structures of all purine nucleosides and nucleotides with bulky substituents (e.g., Br, CH_3, $C(CH_3)_2OH$) at C(8).[16,17] This finding has been rationalized on the basis of steric hindrance between such a substituent and the sugar ring, and, in fact, it has been generally

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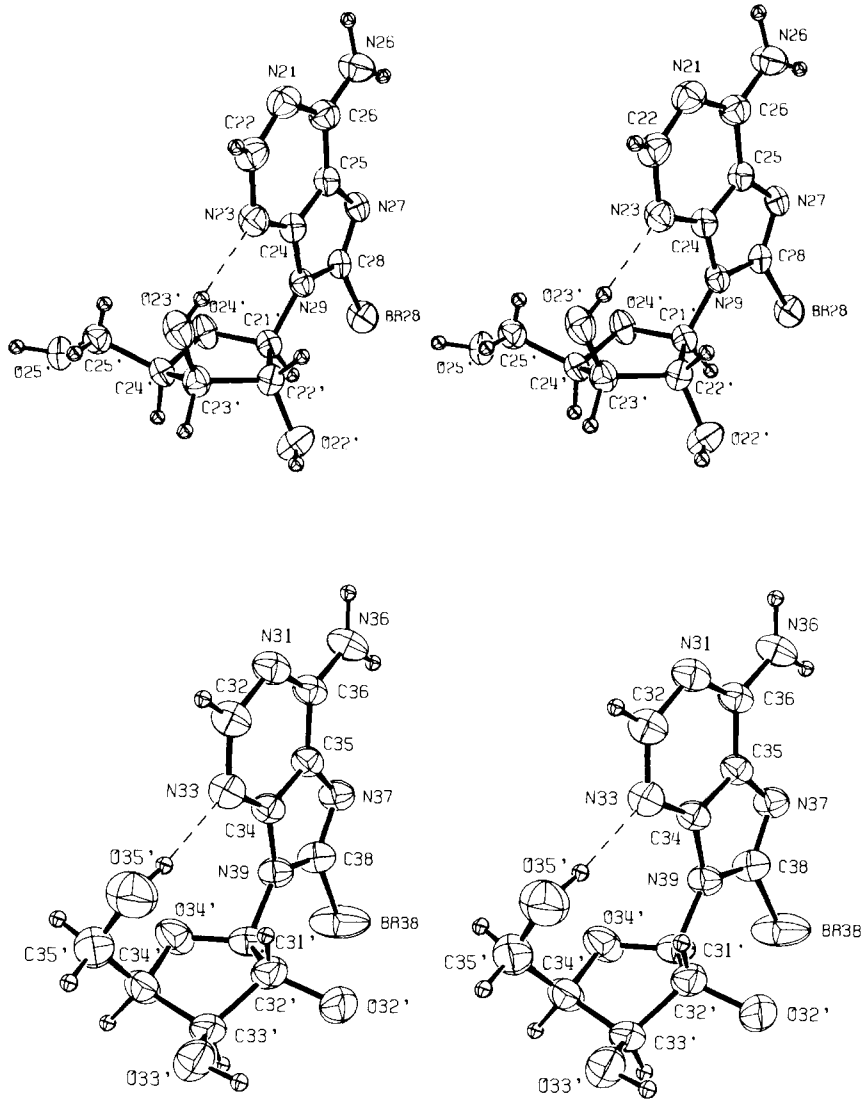

Figure 1. Stereoscopic view of molecule B (top) and molecule C (bottom). The ellipsoids correspond to 50% probability.

assumed[6a,22] that the anti conformation is not possible in such 8-substituted nucleosides. But detailed analyses of solution conformations by NMR spectroscopy of such 8-substituted nucleosides and nucleotides have shown that neither CH_3 nor Br is sufficiently bulky to exclude some contribution of the anti conformer.[7] More convincing examples are provided by crystallographic studies of complexes of dehydrogenases with 8-bromoadenosine nucleotide inhibitors,[8,9] where the 8-bromoadenine residues are found in the anti conformation. Examples of 8-substituted purine nucleosides exclusively in the syn conformation are 8-*tert*-butylguanosine and 8-(α-hydroxyisopropyl)adenosine,[7,16] where the van der Waals radii of the 8-substituents are about 4 Å, as compared to about 2 Å for CH_3 or Br.

While natural purine nucleosides in solution exhibit a preference for the anti conformation, there are now numerous examples known where interaction with various enzyme systems results in conversion to the syn conformation. Relevant to this is the finding that, in the Z form of DNA, all guanosine residues are in the syn conformation, with maintenance of normal Watson–Crick base pairing.[23]

Conformations of Sugar Moieties. The conformation of the furanose ring is different in each of the three molecules (Figure 1). In molecules A and B the pucker is C(4′)exo–C(3′)endo ($_4T^3$), with phase angles of pseudorotation (P) of 47.8 and 48.8°, respectively. The maximum amplitude of puckering in molecule A (τ_m = 41.7°) is approximately normal, but it is significantly smaller in molecule B (τ_m = 33.6°). By contrast, the sugar ring in molecule C has a C(2′)endo–C(3′)exo pucker ($^2T_3$), with P = 166.2° and τ_m = 41.9°. Additional details of the conformation are forthcoming from the values for the torsion angles, listed in Table III.

Table III. Selected Torsion Angles (Deg)

angle	molecule A	molecule B	molecule C
C(4)-N(9)-C(1′)-O(4′)	56.2	63.6	60.9
C(4)-N(9)-C(1′)-C(2′)	-63.9	-56.5	-57.8
C(8)-N(9)-C(1′)-O(4′)	-118.9	-103.7	-122.6
C(8)-N(9)-C(1′)-C(2′)	121.1	136.2	118.7
O(4′)-C(1′)-C(2′)-C(3′)	-6.1	-4.0	39.7
C(1′)-C(2′)-C(3′)-C(4′)	28.0	22.1	-40.7
C(2′)-C(3′)-C(4′)-O(4′)	-41.2	-32.9	28.7
C(3′)-C(4′)-O(4′)-C(1′)	39.2	31.7	-3.6
C(4′)-O(4′)-C(1′)-C(2′)	-20.5	-17.3	-23.3
O(4′)-C(1′)-C(2′)-O(2′)	107.7	115.4	159.1
N(9)-C(1′)-C(2′)-O(2′)	-131.9	-125.2	-81.3
O(2′)-C(2′)-C(3′)-O(3′)	150.2	144.5	76.9
C(2′)-C(3′)-C(4′)-C(5′)	-160.3	-151.4	-92.3
O(3′)-C(3′)-C(4′)-O(4′)	80.6	90.0	153.0
O(3′)-C(3′)-C(4′)-C(5′)	-38.5	-28.6	32.0

The $_4T^3$ sugar ring conformation has been observed in anhydronucleosides, in which there is an additional ring fused to the

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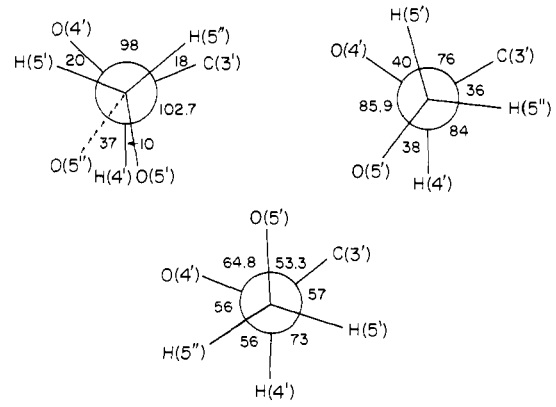

Figure 2. Newman projections along C(4')–C(5') for molecule A (top left), molecule B (top right), and molecule C (bottom). O(5") in molecule A is the minor site of the oxygen atom in the side chain.

sugar and the base,[24] as well as in nucleoside 3',5'-cyclic phosphates.[25] But it is rarely encountered in nucleosides in which the furanose ring is not fused to another ring system. Insofar as we are aware, a $_4T^3$ conformation has been reported only in adenosine 5'-(methyl phosphonate)[26] in which there is no intramolecular hydrogen bond. It is of interest that in this molecule τ_m = 33.1°, essentially identical with that in our molecule B.

In view of the foregoing, it is pertinent to examine why two of the three molecules of 8-Br-xyloA adopt this unusual ring pucker. Most likely, the major stabilizing force is the intramolecular hydrogen bond O(3')–H···N(3) (see below). The $_4T^3$ conformation is the only one in which the locations of O(3') and N(3) are such as to permit hydrogen bonding. In the C(3')endo conformation this distance is too short, and with C(2')endo it is too long. Such hydrogen bonds are possible only in purine nucleosides with an "up" 3'-OH, i.e., in xylo- and lyxonucleosides. Such compounds have hitherto not been examined in the solid state, so that the presently observed "rare" $_4T^3$ conformation is perhaps not entirely surprising.

There is also an intramolecular hydrogen bond in molecule C, viz., O(5')–H···N(3). Such a bond is usually formed when the sugar ring conformation is C(2')endo,[16] as it is in molecule C. This hydrogen bond is associated with a gauche$^+$ conformation of the CH_2OH side chain. In molecules A and B the side chains do not adopt any of the commonly observed staggered conformations. In the former, O(5') and H(4') are almost eclipsed, the torsion angle H(4')–C(4')–C(5')–O(5') being only 10° (Figure 2). This conformation can be described as approximately gauche$^-$. (When O(5') adopts its minor position, its orientation relative to C(3') is close to trans.) In molecule B the conformation of the side chain is nearly trans, but all torsion angles differ significantly from the values normally observed in fully staggered side chains (cf. molecule C). It is most likely that the individual molecules adopt these unusual conformations so as to optimize the geometries of the intermolecular hydrogen bonds in which the O(5') atoms participate.

The conformations of all three molecules are shown superimposed in Figure 3. It is interesting to see that, in spite of the different ring puckers, the oxygen atoms that donate protons to N(3) are in approximately the same position in each molecule. The flattening of the ring in molecule B (compared to molecule A) is compensated by a 15° rotation about the glycosidic bond. On the other hand, the different ring pucker in molecule C (^2E) is accompanied not only by a different conformation of the exocyclic side chain but also by an "upward" bending of the sugar moiety with respect to the purine base.

Correlations between nucleoside conformations and intramolecular hydrogen bonding are by no means new. In the complex of deoxyguanosine and 5-bromodeoxycytidine, Haschemeyer and Sobell[27] found the former in a syn conformation and suggested that it was stabilized by a possible intramolecular hydrogen bond between N(3) and O(5'). In many 8-substituted nucleosides in the solid state there is an intramolecular O(5')–H···N(3) bond, almost invariably associated with a C(2')endo sugar ring pucker and a syn conformation about the glycosidic bond.[16,17] Such a conformation, with associated intramolecular hydrogen bonding, has also been observed in solution.[28] The intramolecular hydrogen bond is, however, not a necessary condition for adoption of this conformation, since a similar solution conformation occurs with purine 5'-deoxynucleosides, where such hydrogen bonding is excluded.[7b]

With pyrimidine nucleosides in the syn conformation, one may observe, in the solid state, an intramolecular O(5')–H···O(2) bond and sugar ring conformations corresponding to values of P in the range 139–163°.[29] Such intramolecular hydrogen bonding has been found for uridine derivatives in chloroform solution with the aid of NMR, CD, and IR spectroscopy. It has been associated with a predominance of the syn conformation of the base, the gauche$^+$ conformation of the exocyclic carbinol group, and a C(2')endo conformation of the sugar ring, albeit less marked for the latter than in corresponding purine nucleosides.[30] However, the extent of hydrogen bonding appreciably decreases, as might be anticipated, in more polar solvents.

Another example is 5-(hydroxymethyl)-2'-deoxyuridine, the sugar ring which exhibits, in the solid state, the unusual C(1')exo conformation, with P = 129.0°, possibly stabilized by the previously unobserved intramolecular C(6)–H···O(4') bond.[31] Finally, the preference of the CH_2OH side chains for a gauche$^+$ conformation, in pyrimidine nucleosides with an anti conformation about the glycosidic bond, may be at least partially attributable to stabilization by a C(6)–H···O(5') bond.[32]

Hydrogen Bonding and Packing. Each molecule of 8-Br-xyloA has five protons capable of participating in hydrogen bonds. Of all these protons, only one is not involved in hydrogen bonding. Furthermore, there are the protons (which we could not locate) linked to the two water molecules, one of which has three possible positions. The hydrogen-bonding scheme is shown in Table IV. In addition to the intramolecular hydrogen bonds observed in each nucleoside molecule (see above), there are also numerous intermolecular bonds. Their strengths can best be assessed on the basis of the corrected H···A values, obtained by normalizing the bonded O–H and N–H distances to their real values of 0.97 and 1.04 Å, respectively.

The water molecules do not participate strongly in the hydrogen bond network, which may account for the positional disorder. They occupy a free space between the three nucleoside molecules (Figure 4) and are only loosely bonded to the latter. It should be noted that O(W2) is capable of forming weak O–H···O hydrogen bonds in each of its three partially occupied sites.

While there are no hydrogen bonds between purine rings, there is extensive stacking between those of molecules B and C. The planes of these bases are virtually parallel to each other, the dihedral angle between them being only 3.4°. The bases of adjacent molecules are rotated by 125°, and overlapping amounts

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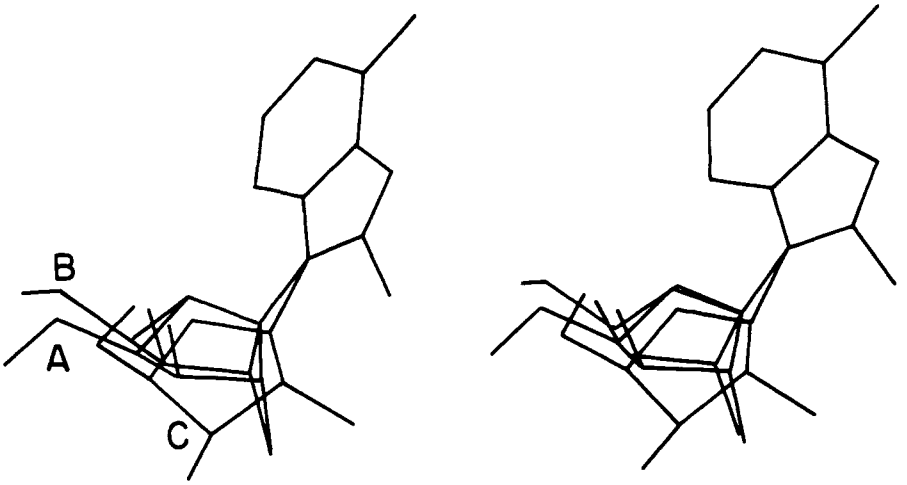

Figure 3. Superimposed stereoscopic view of molecules A, B, and C.

Table IV. Distances and Angles for Hydrogen Bonds

D···A pair	A at[a]	distances, Å			angles, deg
		D···A	H···A	H···A_{corr}	D–H···A
N(6)–H(61)A···O(3′)A	100	2.945	2.13	1.94	166
N(6)–H(62)A···O(5′)A	10$\bar{1}$	2.931	2.18	1.89	176
O(2′)–H(O2′)A···O(5′)B	0$\bar{1}\bar{1}$	2.732	1.73	1.77	172
O(3′)–H(O3′)A···N(3)A	000	2.756	1.94	1.83	162
O(5′)–H(O5′)A···O(3′)C	$\bar{1}$00	2.700	1.94	1.91	138
N(6)–H(61)B···O(3′)B	100	2.964	2.14	1.96	163
N(6)–H(62)B···O(W1)	000	3.135	2.16	2.12	166
O(2′)–H(O2′)B···O(5′)B	00$\bar{1}$	2.768	1.94	1.80	177
O(3′)–H(O3′)B···N(3)B	000	2.770	2.00	1.80	174
O(5′)–H(O5′)B···N(1)C	$\bar{1}$01	2.774	1.87	1.84	159
N(6)–H(62)C···O(2′)A	110	3.181	2.24	2.19	159
O(2′)–H(O2′)C···N(1)B	00$\bar{1}$	2.847	2.00	2.03	141
O(3′)–H(O3′)C···N(1)A	00$\bar{1}$	2.817	1.98	1.95	147
O(5′)–H(O5′)C···N(3)C	000	2.856	1.89	1.92	160
O(5″)···O(W2″)[b]	00$\bar{1}$	2.89			
O(W1)···O(W2′)[b]	1$\bar{0}$0	2.83			
O(W2‴)–H···O(5′)C	$\bar{1}$00	3.09			

[a] Translation along the x, y, and z axes. [b] It is uncertain which oxygen atom is the donor and which the acceptor.

to approximately 55%. The average distances of a purine base from its two neighbors in the stack are 3.48 and 3.53 Å. Molecule A is not involved in base stacking, its base forming a dihedral angle of 69.3° with the base of molecule B.

Solution Conformation of xyloA Analogues. The present solid-state data permit a more precise evaluation of the previous experimental data[5] on the solution conformation of xyloA analogues.

Use of the older Karplus relationship[33] with xylofuranosyl nucleosides was previously found to be of limited applicability,[4,5] and theoretical calculations showed that conformational analyses of such nucleosides, neglecting factors other than torsion angles alone, is unsatisfactory.[34] A new modification of the Karplus relation is now available[35] that takes account of most of the factors shown to be of importance by the theoretical results.[34] We have used this relationship of Haasnoot et al.[35] to evaluate the dependence of ^3J on the conformation of the xylofuranosyl ring and the results are shown in Figure 5. The experimental values of $J_{3'4'}$ for xylofuranosyl nucleosides (3.7–5.4 Hz)[4,5] are below the lowest predicted by the standard Karplus relationship.[33] The modified Haasnoot relationship corrects this and yields similar conformer populations from all three coupling constants.

Table V. Populations (%) of N-Type States in Solution for xyloA and 8-Br-xyloA

	^{3}E	$_4$E
xyloA	80,[a] 87[b]	
8-Br-xyloA	65,[a] 63[b]	80,[a] 64[b]

[a] Calculated with the aid of the standard Karplus relationship and the parametrization of Altona and Sundaralingam.[33] [b] Calculated according to the modified Karplus relationship, as described by Haasnoot et al.[35]

Previous analyses of the solution conformations of xyloA and 8-Br-xyloA[5] suggested that the N-type conformational state of the latter differs slightly from that for other xylonucleosides, being shifted from the typical ^{3}E state toward $_4$E. Since the present solid-state data show the presence of the conformer $_4$E, we have recalculated the populations of the two states, assuming the S-type state is ^{2}E and the N-type state ^{3}E (for xyloA and 8-Br-xyloA) or $_4$E (for 8-Br-xyloA). The results are shown in Table V, together with the corresponding values from the standard Karplus relationship. It will be seen that the latter gives population values differing by up to 16% from the improved Haasnoot relationship.

Table VI shows how modification of the states between which there is an equilibrium affects the values of the coupling constants calculated with the aid of Figure 5 and the simple relationship $J_{calcd} = P_N J_N + P_S J_S$. Because of the variations in values of τ_m observed in the present study in the solid-state structures of 8-Br-xyloA, the coupling constants in the table have been calculated for three values of τ_m. With the possible exception of the values

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Table VI. Comparison of Experimental Coupling Constants (Hz) for 8-Br-xyloA in Me_2SO Solution with Those Calculated from the Modified Karplus Relationship of Haasnoot et al.[35]

		calcd					
		$^2E \rightleftharpoons {}^3E$			$^2E \rightleftharpoons {}_4E$		
^3J	exptl	$\tau_m = 34°$	$\tau_m = 39°$	$\tau_m = 42°$	$\tau_m = 34°$	$\tau_m = 39°$	$\tau_m = 42°$
1',2'	3.9 ± 0.1	3.2	3.4	3.4	3.9	4.1	4.2
2',3'	2.5 ± 0.1	2.8	3.4	3.7	2.5	2.9	3.1
3',4'	5.4 ± 0.5	5.6	5.1	4.7	5.4	4.9	4.6

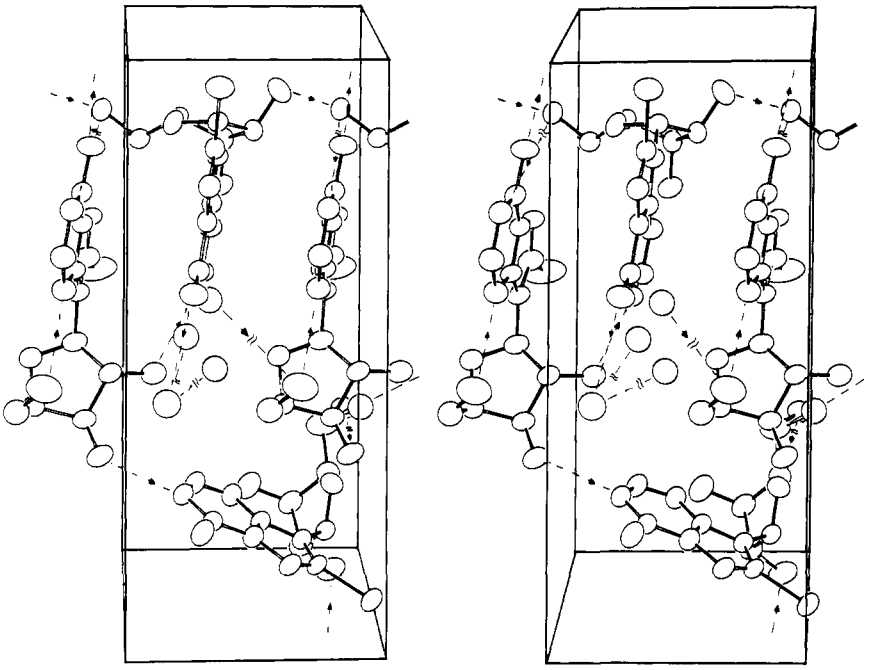

Figure 4. Stereoscopic view of the molecular packing in the crystal. Dashed lines indicate hydrogen bonds. The x axis is out of the paper, the y axis is vertical, and the z axis is horizontal.

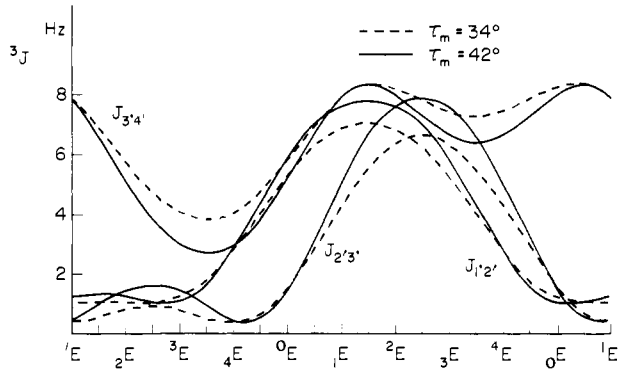

Figure 5. Dependence of proton–proton vicinal coupling constants on the conformation of xylofuranosyl rings, calculated according to Haasnoot et al.[35]

calculated for $\tau_m = 42°$, the agreement with the experimental values is reasonable, while the equilibrium $^2E \rightleftharpoons {}_4E$ provides a somewhat better approximation to the experimental values than the equilibrium $^2E \rightleftharpoons {}^3E$.

The foregoing calculations were based on the use of H–C–C–H torsion angles, calculated from the pseudorotational model with the use of trigonal projection symmetry (120° symmetry). The validity of this procedure has been questioned by Haasnoot et al.[36] when applied to five-membered rings. They introduced empirical correlations between endo- and exocyclic H–C–C–H torsion angles, profiting from solid-state data available for a large number of ribose and deoxyribose nucleosides.[37] Such a more precise analysis is at present not feasible for β-D-xylofuranosyl nucleosides since the only available data in the solid state are those for the three independent molecules of 8-Br-xyloA embraced in the present study.[38]

Table VII. Observed and Calculated Values for H–C–C–H Torsion Angles (Deg) for the Three Molecules of 8-Br-xyloA

	torsion angles								
	H(1')–C–C–H(2')			H(2')–C–C–H(3')			H(3')–C–C–H(4')		
molecule	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*
A	115	121	113	−92	−106	−94	−41	−37	−40
B	117	109	117	−98	−102	−100	−33	−27	−30
C	159	162	163	−161	−171	−166	27	29	30

[a] Calculated from pseudorotational model. [b] Observed values from the X-ray analysis (estimated standard deviations are 4–5°). [c] Calculated values from the X-ray analysis, assuming equal C–C–H and O–C–H angles (esd's are 0.4–0.6°).

In order to examine whether the assumption of trigonal projection symmetry is justified, we may compare the torsion angles calculated by this procedure with those derived from the X-ray analyses. The refined hydrogen positions can be used to calculate the H–C–C–H torsion angles; but, because of imprecise location of hydrogen atoms by X-ray diffraction, these torsion angles are not expected to be very reliable. An alternative method is to place methine hydrogens on tertiary carbon atoms in calculated positions by assuming equality of all C–C–H and O–C–H bond angles.[37]

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Table VII shows the values of both these sets of torsion angles, along with those derived from the pseudorotational model. As might have been anticipated, the agreement between set b and the other two sets is not as good as between sets a and c. The vicinal coupling constants derived from the torsion angles in sets a and c differ at most by 0.4 Hz. Hence the assumption of trigonal symmetry leads to acceptable results.

Conclusions

The present solid-state data provide support for the previously proposed[5] atypical conformational equilibrium $^2E \rightleftharpoons {}_4E$ for 8-Br-xyloA in Me_2SO solution. The conclusions regarding conformation are affected to only a minor degree for a relatively broad range of assumed τ_m values (34-42°). The modified Karplus relationship of Haasnoot et al.[36] is far superior to the standard Karplus relationship for conformational analyses of xylofuranosyl nucleosides in solution. Finally, the dependence of $J_{3'4'}$ on sugar ring conformation obtained by quantum chemical calculations[34] is similar to that given by application of the relationship of Haasnoot et al.[36]

Acknowledgments. All crystallographic computations were carried out with programs written by Ahmed et al.[39] Figures 1 and 4 were drawn with the ORTEP program of Johnson.[40] The program BMFIT(III) of Nyburg[41] was used to prepare Figure 3. We are indebted to Dr. L. Dudycz for the synthesis of 8-Br-xyloA. M.C. and I.E. thank the National Research Council of Canada for Research Associateships. Part of this investigation was supported by the Polish National Cancer Research Program (PR-6).

Registry No. 8-Br-xyloA, 15830-78-1.

Supplementary Material Available: Anisotropic temperature parameters of the nonhydrogen atoms, coordinates and isotropic temperature parameters of hydrogen atoms, comparison of observed and calculated endocyclic bond angles in the furanose rings, deviations from least-squares planes, and observed and calculated structure amplitudes (24 pages). Ordering information is given on any current masthead page.

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Isolation, Purification, and Characterization of High-Valent Complexes from a Manganese Porphyrin Based Catalytic Hydrocarbon Activation System. Crystal and Molecular Structure of μ-Oxo-bis[azido(tetraphenylporphinato)manganese(IV)]

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Abstract: High-valent complexes have been isolated from the reactions of (tetraphenylporphinato)manganese(III) derivatives, $XMn^{III}TPP$, with iodosylbenzene in hydrocarbon or halocarbon solvents. When $X = N_3^-$ or OCN^-, dimeric μ-oxo-manganese(IV) porphyrin complexes, $[XMn^{IV}TPP]_2O$, **4**, are isolated. The dimer $[N_3Mn^{IV}TPP]_2O$ has been characterized by X-ray crystallography. Intense broad absorption bands near 800 cm^{-1} in the infrared spectra of the complexes have been assigned to Mn-O-Mn bands based on ^{18}O substitution. Magnetic susceptibility measurements give $\mu_{eff} = 2.0\ \mu_B$ for $[N_3Mn^{IV}TPP]_2O$. The complexes are EPR silent. $[N_3Mn^{IV}TPP]_2O$ crystallizes as a chlorobenzene solvate in space group *Pbcn*. The unit cell has $a = 21.208$ (5) Å, $b = 16.826$ (4) Å, and $c = 22.620$ (3) Å and contains four molecules. The structure was solved by the heavy-atom method and converged with a final $R = 0.094$. The $[N_3Mn^{IV}TPP]_2O$ molecule possesses rigorous crystallographic C_2 symmetry with both Mn atoms, the bridging oxo oxygen atom, and the ligating nitrogen atoms of each N_3 ligand lying on the twofold axis. The two Mn atoms are displaced from the mean N_4 planes toward the bridging oxygen by 0.10 and 0.08 Å. The average Mn-N(porphyrin) bond distance is 2.014 (19) Å. Two antiferromagnetically coupled d^3 Mn(IV) atoms is the best description of the ground state for the dimeric complexes, **4**. On the basis of the similarity of the properties observed for both solid-state and solution samples of the complexes, their structures are probably the same in solution as in the solid state.

High-valent metalloporphyrin complexes have come under increased study in recent years because of their importance in natural systems. For example, some of the most remarkable reactions that take place in the biosphere are the hydrocarbon C-H bond activation processes catalyzed by cytochrome P-450.[1] This class of heme containing monooxygenases occurs in a variety of forms of life where they are responsible for the selective oxidation of various hydrocarbons or for the catabolism of drugs or hormones.[1] In these processes cytochrome P-450 is capable of cleaving aromatic C-H bonds and also of cleaving unactivated alkane C-H bonds regiospecifically and stereospecifically.[1] The desire to understand the mechanism(s) of cytochrome P-450-catalyzed hydrocarbon hydroxylation processes and the need for selective and effective synthetic oxygenation catalysts have recently motivated numerous investigators to examine a variety of model hydroxylation systems.[2-8] Since the initial discovery by Groves

(1) Recent review of cytochrome P-450: (a) Coon, M. J.; White, R. E. "Metal Ion Activation of Dioxygen"; Spiro, T. G., Ed.; Wiley: New York, 1980; Chapter 2. (b) Gunsalus, I. C.; Sligar, S. G. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1978**, *47*, 1. (c) Groves, J. T. In "Advances in Inorganic Biochemistry"; Eichhorn, G. L., Marzilli, L. G., Eds.; Elsevier/North Holland: New York, 1979; Vol. 1, Chapter 4. (d) Chang, C. K.; Dolphin, D. In "Bioorganic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: London, 1978; Vol. IV, p 37.

(2) Review of early work (up through 1973) on chemical model systems for oxygenase enzymes: Hamilton, G. A. In "Molecular Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974; Chapter 10.

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